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

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2. SYNOPSIS

Name of Sponsor/ Company: Alkermes, Inc.	
Name of Investigational Product: ALKS 3831	
Name of Active Ingredients: samidorphan and olanzapine	
Title of Study: 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	
No. of Study Centers: This is a multi-center study	
Studied Period: Estimated date first patient consented: June 2013 Estimated date last patient completed: June 2015	**Phase of development:** 2

Objectives:

The objectives of this study are to evaluate 3 doses of samidorphan co-administered with olanzapine (ALKS 3831) in subjects with schizophrenia to (1) evaluate ALKS 3831 as a treatment for schizophrenia, (2) assess the safety and tolerability of ALKS 3831, and (3) characterize the impact of the samidorphan component of ALKS 3831 on weight and other metabolic factors.

Methodology:

This is a Phase 2, randomized, placebo-controlled multicenter study, which will be conducted in 2 parts: Part A and Part B. Part A will begin with screening and will include a 1-week olanzapine lead-in period followed by a 12-week double-blind, placebo-controlled treatment period where subjects will receive samidorphan or placebo (in addition to the olanzapine prescribed on Study Day 1). Part B will include an additional 12-week treatment period where all subjects will receive active olanzapine + samidorphan (ie, ALKS 3831). At the end of Part B, samidorphan dosing will stop, but olanzapine dosing will continue uninterrupted through the 4-week follow-up period, which includes 2 safety visits.

This study will use an independent Data Safety Monitoring Board (DSMB) to monitor for tolerability of study drug. After at least 1 week of safety data has been collected for 40 randomized subjects, the DSMB will review the accumulated safety data for all subjects. After at least 1 week of safety data has been collected for 150 randomized subjects, the DSMB will review the accumulated safety data for all subjects. Complete details of the membership and functioning of this board will be available in the DSMB Charter.

During clinic visits, assessments of psychotic symptoms using measures such as the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impressions-Severity (CGI-S) will occur. Body weight will be measured using consistent methods at every visit. Alcohol and drug use will be monitored throughout the study. Concentrations of samidorphan, RDC-9986 (primary metabolite of samidorphan), and olanzapine will be determined in plasma samples collected at Visits 2-23.

Part A (Screening, Olanzapine Lead-in, and Double-blind Treatment Period)

Screening assessments will occur in the 30-day period before subjects report to the clinic for verification of eligibility and initiation of olanzapine treatment (Study Day 1). On Study Day 1 (Visit 2), all eligible subjects will be initiated on olanzapine. Olanzapine dose will be selected and titrated by the principal investigator (PI) based upon individual subject needs and consistent with current clinical practice. Subjects will return one week later (ie, Study Day 8, Visit 3) for a 2-night inpatient stay and the start of the 12-week double-blind placebo-controlled treatment period. At this visit, subjects will be randomized in a 1:1:1:1 ratio to receive samidorphan (5, 10, or 20 mg) or placebo. Olanzapine dosing will continue uninterrupted. Thus, the Part A treatment groups will be as follows:

- Olanzapine + Samidorphan (5 mg)
- Olanzapine + Samidorphan (10 mg)
- Olanzapine + Samidorphan (20 mg)
- Olanzapine + Placebo

All study drug will be taken once daily by mouth. Olanzapine and samidorphan/placebo tablets should be taken together (ie, at the same time). Randomization will be stratified by the amount of weight change during the olanzapine lead-in period (ie, from Day 1 to Day 8), with subjects grouped into the following 3 strata:

- Weight change ≤0 kg
- Weight increase >0 to <1 kg
- Weight increase ≥1 kg

Subjects will be discharged from the inpatient unit on Study Day 10 (Visit 5) and will return on Study Day 15 (Visit 6).

Subjects are not required to be taking any antipsychotic medication at the time of screening or Visit 2. However, those who are will be tapered off of their prior antipsychotic medication within two weeks after initiation (ie, by Study Day 15, Visit 6). This cross-taper from prior antipsychotic treatment to olanzapine will be conducted under the care and discretion of the PI and consistent with current clinical practice.

After Study Day 15 subjects will return to the clinic weekly through the first month of double-blind treatment (ie, Study Day 36) and then every 2 weeks thereafter for the remainder of Part A. Any subject who prematurely discontinues during Part A will be asked to return to the clinic for an early termination (ET) visit and will be asked to return for follow-up visits 2 and 4 weeks later.

Part A Visit Schedule

	Screening	Olanzapine Lead-In	Double-Blind Placebo-Controlled Treatment Period										Transition*
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Day	**-30 to -1**	**1**	**8**	**9**	**10**	**15**	**22**	**29**	**36**	**50**	**64**	**78**	**92**
Week			**1**			**2**	**3**	**4**	**5**	**7**	**9**	**11**	**13**

* Transition (Visit 13) is the end of Part A and the beginning of Part B (Part B begins with dosing at Visit 13).
Shaded cells represent inpatient stays.

Assessments prior to study drug administration at Visit 13 (the transition visit) will serve as end of Part A assessments; dosing and post-dose assessments will be considered Part B assessments.

Part B (Active ALKS 3831 Treatment and Safety Follow-up Periods)

After completion of Part A (ie, at Visit 13), subjects will transition into Part B and will continue onto a 12-week active treatment period during which all subjects will receive ALKS 3831 (ie, olanzapine plus samidorphan). Subjects who had been receiving ALKS 3831 during the double-blind period will continue on the same dose for the 12-week active treatment period. Subjects who had been receiving olanzapine + placebo in the double-blind period will continue on the same dose of olanzapine and will be transitioned from placebo to samidorphan (at the highest dose).

At Visit 13 (Study Day 92), subjects will be admitted for a 2-night inpatient stay (Visits 13-15, Study Days 92-94) to allow for monitoring following initiation of samidorphan dose in subjects originally assigned to the olanzapine + placebo group. The inpatient stay is required for all subjects. After discharge (Study Day 94), subjects will return 5 days later for Visit 16 (Study Day 99). After Visit 16, subjects will be seen weekly for the next 3 weeks (Visits 17-19) and then at 2-week intervals for the remainder of the study (Visits 20-25).

The subject will take the final samidorphan dose the night before Visit 23 (Study Day 176). No samidorphan dose will be administered onsite during Visit 23. Olanzapine dosing will continue uninterrupted through a 4-week follow-up period: A safety follow-up visit will occur 2 weeks after and

4 weeks after Visit 23. Any subject who prematurely discontinues from the study during Part A or Part B will be asked to return to the clinic for an ET visit and follow-up visits 2 and 4 weeks after the ET visit.

Part B Visit Schedule

	Transition*	Active ALKS 3831 Treatment Period										Follow-Up	
Visit	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23/ET**	**24**	**25**
Day	**92**	**93**	**94**	**99**	**106**	**113**	**120**	**134**	**148**	**162**	**176**	**190**	**204**
Week	**13**			**14**	**15**	**16**	**17**	**19**	**21**	**23**	**25**	**27**	**29**

* Transition (Visit 13) is the end of Part A and the beginning of Part B (Part B begins with dosing at Visit 13)
Shaded cells represent inpatient stays.

Number of subjects (planned): Approximately 280 subjects will be randomized.

Diagnosis and main criteria for inclusion:

Adults (18-50 years of age) with stable schizophrenia who may benefit from olanzapine treatment, who have a body mass index (BMI) of 17-30 kg/m^2, who have maintained a stable body weight for at least 3 months prior to screening (change ≤5%) and from screening to Visit 2 (change ≤1 kg), and who have not been exposed to olanzapine, clozapine, mesoridazine, chlorpromazine, or thioridazine for more than 1 week within the past year or at any time in the 3 months prior to screening will be considered for participation. Complete eligibility criteria are listed in Section 7.1 and Section 7.2.

Investigational product dosage and mode of administration:

ALKS 3831 refers to the combination of olanzapine and samidorphan. In this study, olanzapine and samidorphan will be co-administered. Commercially available olanzapine for oral administration will be supplied or arranged for dispensing by the investigative site.

Samidorphan will be provided by the sponsor. Each tablet contains samidorphan (2.5, 5 or 10 mg). Subjects will take 2 tablets per day by mouth (ie, doses of samidorphan will be 5, 10, or 20 mg).

Samidorphan is a Schedule II controlled substance according to the United States Drug Enforcement Agency and will require proper handling.

Reference product dosage and mode of administration:

Placebo consists of tablets identical in size and appearance to the samidorphan tablets, but without active samidorphan. Subjects will take 2 tablets per day by mouth.

Duration of study: The study duration for each subject will be approximately 33 weeks and will include 25 study visits. This includes up to one month for screening, a 1-week lead-in period of olanzapine dosing, two 12-week treatment periods (a 12-week double-blind placebo-controlled period and a 12-week period where all subjects get active ALKS 3831), and safety follow-up visits which occur 2 and 4 weeks after Visit 23.

Criteria for evaluation:

Safety Assessments

Safety will be evaluated based on the following measures:

- Incidence of Adverse events (AEs)
- Clinical laboratory test (chemistry, hematology, and urinalysis) results
- Vital signs including blood pressure

- Electrocardiograms (ECGs)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Laboratory parameters including HDL, LDL, total cholesterol, triglycerides, fasting glucose and insulin, ratio of fasting glucose to fasting insulin, hemoglobin A1c (HbA1c), C-reactive protein, leptin, bicarbonate, and carbohydrate deficient transferrin (CDT)

Reported AE terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) preferred terms and system organ classes. Concomitant medications will be categorized using the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system.

Pharmacokinetic Assessments

For all subjects, plasma samples will be collected according to the schedule in Table 1 and Table 2 for quantifying olanzapine, samidorphan, and RDC-9986 (primary metabolite of samidorphan) concentrations. Pharmacokinetic (PK) data may be used to assess compliance with study drug administration and/or in a subsequent population PK evaluation conducted outside of this study.

Efficacy Assessments

Efficacy will be evaluated based on following measures:

- Positive and Negative Syndrome Scale (PANSS)
- Body weight
- Waist circumference
- Clinical Global Impressions-Severity (CGI-S)
- Impact of Weight on Quality of Life – Lite Questionnaire (IWQOL-Lite)
- Personal and Social Performance Scale (PSP)
- Timeline Follow-Back (TLFB) assessment of alcohol drinking
- Food Craving Inventory (FCI)

Other Assessments:

Pharmacogenetic assessments to explore the relationship between olanzapine-induced weight gain and genotype and identify people susceptible to weight gain

Endpoints:

Primary Endpoint: Absolute change in PANSS total score from randomization to the end of Part A

Secondary Endpoints:

- Percent change in body weight
- Number and percentage of subjects with adverse events from randomization to the end of Part A
- Absolute change in body weight
- Proportion of subjects exhibiting significant weight gain (definition of weight gain will include body weight gain greater than 7%)
- Absolute change in CGI-S

Additional Endpoints:

- Change in waist circumference
- Change in blood lipid concentrations including LDL, HDL, total cholesterol and triglycerides
- Change in assessments related to glucose regulation including fasting glucose and insulin, fasting glucose to fasting insulin ratio, HbA1c, C-reactive protein, leptin and bicarbonate
- Change in vital signs including blood pressure
- Change in IWQOL-Lite scales (physical function, self-esteem, sexual life, public distress and work) and total score
- Change in PSP
- Change in FCI
- Change in alcohol and drug use

Statistical methods:

Once all subjects have completed Part A of the study, an unblinded analysis of the 12-week placebo-controlled data will be performed. This analysis may be conducted prior to the completion of Part B of the study.

Safety

All subjects who receive at least 1 dose of study drug (olanzapine, samidorphan, or placebo) will be included in the safety analysis. The secondary endpoint, number and percentage of subjects with adverse events from randomization to the end of Part A, will be analyzed descriptively by treatment group. Adverse events will be summarized overall and by MedDRA® preferred terms and system organ class as well as by severity and by relationship to study drug. Additional analysis of safety assessments will include summary statistics including mean, median, interquartile range, minimum, and maximum for continuous variables and number and percent for categorical variables. These statistics will be provided for the following: AEs, ECG parameters, laboratory test results, vital signs, and C-SSRS results during the entire study.

Efficacy

The efficacy analysis will be conducted on 2 full analysis set (FAS) populations:

- The FAS 1 population will include all subjects who are randomized, receive at least one dose of study drug, and have at least one post-baseline PANSS assessment.
- The FAS 2 population will include all FAS 1 subjects who gained weight during the initial week of olanzapine treatment prior to randomization and have at least one post-baseline weight assessment.

The primary endpoint is the absolute change in PANSS total score from randomization to the end of Part A (ie, the end of the 12-week, placebo-controlled double-blind treatment period) and will be evaluated by treatment group (ALKS 3831 vs. the placebo group [olanzapine alone]) using a 2-sided mixed-model for repeated measures (MMRM) to test for equivalence at an alpha level of 0.05. The primary analysis will be conducted in the FAS 1 population. More details about this analysis will be provided in the statistical analysis plan (SAP).

The secondary endpoint, percent change in weight from randomization to the end of Part A, will be evaluated by treatment group using an MMRM approach similar to that of the primary endpoint. However, this will be a superiority analysis. Each treatment group will be compared to the placebo

group with a 2-sided hypothesis test to test for superiority at an alpha level of 0.05. The secondary efficacy analysis will also be conducted in the FAS 1 population. More details about this analysis will be provided in the SAP.

Analysis of other secondary endpoints and additional endpoints will include inferential analyses and descriptive analyses by visit (mean, standard deviation, median, minimum, and maximum for continuous variables and number and percent for categorical variables), as appropriate.

Analyses for the primary and secondary endpoints will be repeated in the FAS 2 population as sensitivity analyses when applicable. Additional details regarding these analyses will be provided in the SAP.

Sample size considerations

Sample size calculations are based on the primary endpoint of absolute change in PANSS total score. These calculations assume 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 provide 95% power to detect equivalence on the primary endpoint (absolute PANSS total score change from randomization to the end of Part A) with a 2-sided test at an alpha level of 0.05. 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 3 ALKS 3831 treatment groups will be pooled for comparison with placebo. 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.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

LIST OF TABLES

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4. LIST OF ABBREVIATIONS

Abbreviation or term	Explanation
AE	adverse event
ALK-P	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical [classification system]
BMI	Body Mass Index
BUN	blood urea nitrogen
ECG	electrocardiogram
C-SSRS	Columbia Suicide Severity Rating Scale
C-VISA™	Clinical Validation Inventory for Study Admission
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CDT	carbohydrate deficient transferrin
CGI-S	Clinical Global Impressions-Severity
CNS	central nervous system
CPK	creatine phosphokinase
CRO	Contract Research Organization
CTA	Clinical Trial Agreement
CDT	carbohydrate deficient transferrin
CYP	cytochrome P450
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSMB	Data Safety Monitoring Board
eCRF	electronic case report form
EDC	electronic data capture
ECT	Electroconvulsive Therapy
ECG	Electrocardiogram
ET	early termination
FAS	full analysis set
FCI	Food Craving Inventory

Abbreviation or term	Explanation
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
HbA1c	hemoglobin A1c
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IWQOL-Lite	Impact of Weight on Quality of Life-Lite
IWRS	Interactive Web Response System
LDH	lactic dehydrogenase
MedDRA©	Medical Dictionary for Regulatory Activities
MMRM	mixed-model for repeated measures
OTC	over-the-counter
PANSS	Positive and Negative Syndrome Scale
PI	principal investigator
PK	Pharmacokinetic(s)
PSP	Personal and Social Performance Scale
QTcF	QT Interval-Frederica Formula
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOP	standard operating procedure
TLFB	Timeline Follow Back
US	United States
WHO	World Health Organization

5. INTRODUCTION

5.1. Background

Olanzapine is regarded as one of the most effective antipsychotics with well-recognized efficacy and other advantages such as decreased incidence of extrapyramidal symptoms. However, it also has safety and tolerability limitations which have been demonstrated to affect compliance and retention of patients on olanzapine therapy [Lieberman, 2005]. In particular, results of the CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) study identify olanzapine as an effective atypical antipsychotic agent associated with the highest weight gain (4.2 kg over up to 18 months of treatment and an overall >7% body weight in 30% of subjects) and a comparatively higher discontinuation rate due to increases in body weight and metabolic effects than other antipsychotic agents [Lieberman, 2005]. Further, it is estimated that between 40-60% of people with schizophrenia abuse alcohol and/or illicit drugs [Lubman, 2010], and these "dual diagnosis" patients have worse outcomes on a variety of measures [Batki, 2009;Dixon 1999].

ALKS 3831 is a combination drug under investigation for treatment of schizophrenia. The principle active component in ALKS 3831 is olanzapine. The other active component is samidorphan, a new chemical entity that clinical studies have shown to limit the weight gain caused by olanzapine alone. This effect was first seen in a proof-of- concept study conducted in healthy adults (Study ALK33-301). This effect appears to be specific to antipsychotic weight gain because samidorphan did not cause meaningful changes in weight when administered as a single agent in adults with binge eating disorder (Study ALK33-101).

As stated previously, despite being regarded as one of the most effective antipsychotics for the treatment of schizophrenia, safety and tolerability limitations have affected compliance and retention of patients on olanzapine therapy. As a result, many patients are switched from olanzapine to other antipsychotics to address tolerability issues even if the alternative antipsychotic is regarded as less effective. The presence of samidorphan in ALKS 3831 is to enhance the benefit and decrease the risk of the principal ingredient, olanzapine.

In addition to enhancing the safety of olanzapine, samidorphan may help with substance abuse in schizophrenia. Comorbid substance abuse is regarded as a considerable obstacle in the treatment and management of many patients with schizophrenia. Samidorphan (also referred to as ALKS 33 or RDC-0313) is structurally derived from naltrexone and like naltrexone, acts as an antagonist at μ-opioid receptors with mixed agonist/antagonist activity at both κ and δ receptors. In laboratory animals and in humans, samidorphan is a potent μ-antagonist. Clinical data have shown that samidorphan blocked both the subjective and physiological effects of the opioid agonist remifentanil (Study ALK33-004). In adults with alcohol dependence, samidorphan was associated with a reduction in drinking behavior (Study ALK33-005).

Thus, the combination of samidorphan and olanzapine (ie, ALKS 3831) as a fixed-dose combination may result in an enhanced therapeutic agent for the treatment of patients with schizophrenia. ALKS 3831 could thereby address the need for antipsychotics with improved benefit/risk profiles for schizophrenia patients for whom olanzapine is the optimal antipsychotic choice as well as dual diagnosis patients and expand the population of patients for whom olanzapine is the antipsychotic of choice.

5.2. Study Drugs

In this study, samidorphan and olanzapine will be co-administered oral tablets. The following sections provide an overview of samidorphan and olanzapine. Detailed information about the study drugs can be found in the ALKS 3831 Investigator's Brochure (IB) and Zyprexa® (olanzapine) United States (US) Package Insert [2011] respectively.

5.2.1. Samidorphan

Samidorphan is a new chemical entity in clinical development by Alkermes. It is an opioid modulator which acts primarily as an antagonist at μ opioid receptors, with mixed agonist/antagonist activity at δ and κ receptors. It is currently being investigated as a single agent for the treatment of reward disorders, in combination with buprenorphine for the treatment of major depressive disorder and for the treatment of cocaine dependence, and in combination with olanzapine for the treatment of schizophrenia. Based on its chemical structure, samidorphan is a Schedule II controlled substance according to the US Drug Enforcement Agency and will require proper handling (see Section 10).

Ten clinical studies of samidorphan have been conducted to date, 8 of which included subjects that received samidorphan alone (not in combination with another product). Overall, approximately 600 subjects have been exposed to samidorphan. Commonly reported adverse events (AEs) observed across all studies included nausea, fatigue, and somnolence. Overall, no trends or clinically meaningful changes have been observed in clinical laboratory analytes, vital sign parameters, or electrocardiogram (ECG) data.

5.2.2. Olanzapine

Olanzapine has been available in the US since 1996 and was originally approved for the treatment of schizophrenia, but has since been approved for other indications including the treatment of schizophrenia in adolescents and bipolar disorder. The safety and tolerability profile of olanzapine is well documented, and adverse event labeling is supported by an extensive safety database that includes over 8,500 adult patients [2011]. Commonly reported AEs consistent across all or most dosage forms in short-term, placebo controlled trials include somnolence, constipation, dry mouth, accidental injury, weight gain, postural hypotension, dizziness, asthenia, fever and abnormal gait.

5.3. Study Rationale

Schizophrenia is a lifelong illness and changes in medication are often made to better manage evolving symptoms and to control side effects and/or tolerability issues. Similar to what was done in the landmark CATIE study [Lieberman, 2005], this study is seeking to enroll patients that are psychiatrically stable, where stability is largely defined by the absence of significant fluctuations or an acute exacerbation of symptoms. In these patients, stability may still reflect a sub-optimal condition that could be improved by transitioning to a different medication. Other patients may be well-controlled on their current antipsychotic, but may be experiencing unpleasant or intolerable side effects such as hyperprolactinemia or extrapyramidal symptoms. These patients may also benefit from switching to a different medication.

In this Phase 2 study, such patients will be transitioned to olanzapine which is widely regarded as one of the most efficacious antipsychotics currently available. Patients with stable symptoms who are not currently taking an antipsychotic, but who may benefit from treatment with olanzapine, are also eligible to participate in this study. In addition to olanzapine, subjects will also receive samidorphan. Samidorphan may offer a range of potential benefits when administered with olanzapine for patients with schizophrenia including attenuated weight gain and a reduction in concomitant substance abuse. Both of these benefits have the potential to increase patient retention on therapy and improve long term outcomes.

One Phase 1 study, ALK33-301, has been conducted in healthy adults (N = 106) to determine the safety, tolerability, and efficacy of samidorphan taken with olanzapine to mitigate olanzapine-induced weight gain. The co-administration of samidorphan (5 mg) and olanzapine when administered once daily for 3 weeks to healthy volunteers was generally well tolerated and resulted in significantly less weight gain compared with subjects administered olanzapine alone. Aside from a positive effect on weight gain, samidorphan did not appear to impact the adverse event profile of olanzapine in this Phase 1 study. The co-administration of samidorphan and olanzapine did not impact the pharmacokinetics (PK) of either individual drug.

Alkermes refers to the combination of olanzapine and samidorphan as ALKS 3831. The current Phase 2 study in adults with schizophrenia will assess the efficacy of ALKS 3831 on psychiatric symptoms, the safety and tolerability of ALKS 3831, and whether subjects receiving ALKS 3831 gain less weight than subjects receiving placebo.

Future studies will explore other anticipated benefits conferred by ALKS 3831 opioid modulation.

5.4. Dose Rationale

Commercially available olanzapine will be administered at the dose selected by the principal investigator (PI) based on the individual subject's clinical condition.

Clinical studies investigating the safety, tolerability, PK, and exploratory efficacy with samidorphan have found this compound to be safe and generally well tolerated following single oral doses of 1-55.7 mg and up to 12-weeks of once daily oral or sublingual (1-10 mg) administration (see ALKS 3831 IB). The samidorphan dose levels (oral administration) in the current trial (5, 10, and 20 mg) were selected based on PK, pharmacologic, and safety considerations. It is expected that these doses will be sufficient to establish a therapeutic dose range and inform dose selection for future studies.

Based on the divergent metabolic pathways of samidorphan and olanzapine, and supported by the results of a prior clinical trial and an in vitro investigation, no PK drug-drug interactions are anticipated in the patient population.

6. OBJECTIVES

The objectives of this study are to evaluate 3 doses of samidorphan co-administered with olanzapine (ALKS 3831) in subjects with schizophrenia to (1) evaluate ALKS 3831 as a treatment for schizophrenia (2) assess the safety and tolerability of ALKS 3831; and (3) characterize the impact of the samidorphan component of ALKS 3831 on weight and other metabolic factors.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Subject Inclusion Criteria

Each subject must meet all of the following inclusion criteria to be qualified to participate in this study.

1. Subject is willing and able to provide informed consent; subject has signed the main informed consent form (ICF) before initiation of any study specific procedures (see Section 17.3)
2. Subject is age 18 to 50 years, inclusive, at screening
3. Subject has a body mass index (BMI) of 17.0-30.0 kg/m^2, inclusive, at screening
4. Subject has a diagnosis of schizophrenia (based on Diagnostic and Statistical Manual of Mental Disorders [DSM] criteria) that is clinically stable as evidenced by both of the following:
   - No hospitalizations for acute exacerbations of schizophrenia within 2 months before screening
   - Clinical Global Impressions-Severity (CGI-S) score of ≤3 (mild) at screening and Visit 2
5. Subject has a total Positive and Negative Syndrome Scale (PANSS) score ≤80 at screening and Visit 2
6. Subject has stable positive symptoms as shown by a score ≤4 on PANSS for items related to delusion, hallucination, conceptual disorganization, and unusual thought content, at screening and Visit 2.
7. Subject currently resides in a stable residence or living arrangement, has been in this residence/living arrangement for at least 8 weeks prior to screening, and the residence/living arrangement is not anticipated to change during the study.
8. Subject agrees to maintain current level of fitness or exercise regimen for the duration of the study
9. Subject reports a stable body weight for at least 3 months prior to screening (change ≤5%) and from screening to Visit 2 (change ≤1 kg)
10. Subject agrees to use an acceptable method of contraception for the duration of the study (as described in Section 8.4.2).
11. Subject must have an informant or caregiver who meets the following criteria:
    a. Informant or caregiver will be in contact with the subject several times per week.
    b. If necessary, the informant or caregiver will accompany the subject to visits.
    c. Informant or caregiver will help ensure maximum subject adherence to study procedures.

12. Subject is fluent in the language (oral and written) in which assessments will be made, and can be reliably rated.

7.2. Subject Exclusion Criteria

Subjects with any of the following conditions will be excluded from participation in this study.

1. Subject does not meet duration of illness eligibility requirements for one of the following reasons:
   - Subject initiated first antipsychotic treatment within the past 12 months.
   - Subject has had symptoms lasting <2 years.
2. Subject presents with comorbid neuropsychiatric disorders including the following:
   - Axis I (according to DSM criteria) diagnosis of schizoaffective disorder or bipolar disorder, or current major depressive disorder that is untreated and/or unstable. Current major depressive disorder that is treated and stable is *not* a criterion for exclusion.
   - Clinically significant cognitive difficulties including dementia, delirium, or amnestic syndromes, or any other cognitive disorder present within the past 2 years that could interfere with participation in the study
   - Drug induced or toxic psychosis
   - Any other psychiatric condition that could interfere with participation in the study
3. Subject has a diagnosis (based on DSM-5 criteria) of moderate or severe alcohol or drug use disorder currently or at any time during the 3 months prior to screening. Nicotine and caffeine use are allowed.
4. Subject poses a current suicide risk as confirmed by the baseline Columbia-Suicide Severity Rating Scale (C-SSRS) by a response of "Yes" to question #4 or 5 with ideation or suicidal behavior occurring in the past year
5. Subject reports positive human immunodeficiency virus (HIV) status at screening
6. Subject has diabetes or meets any of the following criteria:
   - Hemoglobin A1c (HbA1c) ≥6.5% at Visit 1
   - Fasting plasma glucose ≥126 mg/dL (7.0 mmol/L) at Visit 2
   - A random plasma glucose ≥200 mg/dL (11.1 mmol/L) at Visit 1
7. Subject has a clinically significant or unstable medical illness, condition, or disorder that would be anticipated to potentially compromise subject safety or adversely affect the evaluation of efficacy, including (but not necessarily limited to) the following:
   - Clinically significant hypotension or hypertension not controlled by medical therapy
   - Unstable thyroid dysfunction in the past 6 months (eg, hypothyroidism, hyperthyroidism, or thyroiditis that was untreated, or discovered and treatment was

initiated within the 6 months prior to screening) or a TSH value outside of the normal range (high or low) at screening

- Personal or family history of neuroleptic malignant syndrome
- Dyslipidemia, defined for this study as total cholesterol >280 mg/dL or triglycerides >500 mg/dL, at screening
- Inflammatory bowel disease or any other gastrointestinal (GI) disorder associated with weight loss, anorexia nervosa, bulimia nervosa, or binge eating disorder
- Neurologic conditions including the following:
  - History of seizure disorder or a condition associated with seizures
  - History of brain tumor, subdural hematoma or other clinically significant neurological condition within the 12 months prior to screening
  - Head trauma with loss of consciousness within the 12 months prior to screening
  - Active acute or chronic central nervous system (CNS) infection
  - Stroke within the 6 months prior to screening

8. Subject has a cardiac condition that might confound the results of the study or pose additional risk when administering the investigational agents to the subject or preclude successful completion of the study. Such conditions include the following:
   - Clinically significant cardiac arrhythmia, cardiomyopathy, or cardiac conduction defect; a history of myocardial infarction or unstable angina; or clinically significant ECG abnormality at Visit 1 or Visit 2.
   - QT interval >450 msec for men and >470 msec for women, as corrected by the Fridericia formula (QTcF), observed at Visit 1 or Visit 2.
9. Subject has a laboratory abnormality that would compromise the well-being of the subject, or has any of the following specific laboratory results at Visit 1 or Visit 2:
   - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) value ≥3 times the upper limit of the laboratory normal reference range
   - Absolute neutrophil count (ANC) $\leq 1.5 \times 10^3$ per µL at Visit 1 and $<1.0 \times 10^3$ per µL at Visit 2
   - Platelet count $\leq 75 \times 10^3$ µL
   - Serum creatinine >2.5 mg/dL
   - Positive pregnancy test result
10. Subject is pregnant or breastfeeding or is planning to become pregnant within 60 days of the last study drug administration
11. Subject has had any GI surgical procedures within one year prior to screening
12. Subject has had a surgical procedure for weight loss or is planning to have liposuction during the study

13. Subject has had significant changes in diet or exercise regimen within the 6 weeks prior to screening or plans to join a weight management program during the study.
14. Subject has started a smoking cessation program within the 6 months prior to screening or anticipates quitting smoking during the study
15. Subject requires or has had electroconvulsive therapy (ECT) treatment in the 2 month period prior to randomization
16. Subject has a positive urine drug screen for benzodiazepines, opioids, amphetamine/ methamphetamine, or cocaine at screening (Exception: A positive screen for benzodiazepine may not be exclusionary if the PI or designated investigator confirms that such medication was medically indicated and consults the PPD Medical Monitor before enrolling a subject with such a finding)
17. Subject has taken opioid medications within the 14 days prior to screening and/or anticipates a need to take opioid medication during the study period
18. Subject has a history of hypersensitivity to or intolerance of olanzapine
19. Subject has used olanzapine, clozapine, mesoridazine, chlorpromazine, or thioridazine for more than one week during the past year or at any time during the past 3 months
20. Subject is currently on a statin medication (an HMG-CoA reductase inhibitor) that was initiated or has had the dose changed within the 3 months prior to screening
21. Subject has current or pending legal charges with the potential for incarceration that could interfere with the study scheduling
22. Subject is currently participating in or has recently participated in another clinical trial in which the subject received an experimental or investigational drug or agent within the 3 months prior to screening
23. Subject is employed by Alkermes or its affiliates (including permanent, temporary contract worker, or designee responsible for the conduct of the study) or is an immediate family member* of an Alkermes or affiliate employee
24. Subject is investigator-site personnel or an immediate family member* of investigator-site personnel

* Immediate family is defined as a spouse, parent, child, or sibling whether biological or legally adopted.

7.3. Subject Withdrawal

A subject may be discontinued from the study at any time if the subject, PI (or designee), or sponsor determines that it is not in the best interest of the subject to continue participation. If a subject has an ANC<1.0 $\times 10^3$ per µL at anytime from Visit 2 to Visit 25, the PI (or designee) should discontinue the subject from participation immediately.

If a subject withdraws from the study for any reason, any ongoing AEs and/or a low ANC will be followed until resolution, until deemed stable by the PI, or until the subject is deemed by the PI to be lost to follow-up. If, in the opinion of the PI, it is necessary to monitor a subject beyond the

safety follow-up visit, the follow-up period may be extended as necessary. In such instances, the sponsor and the PI will agree to an acceptable follow-up schedule.

In the event that a subject chooses to withdraw from the study, the PI (or designee) should make a reasonable effort to ascertain the reason(s) for withdrawal while fully respecting the subject's rights. The subject should complete an ET visit when possible and subjects should be encouraged to return for follow-up visits 2 and 4 weeks after the ET visit. If the subject fails or refuses to return to the study center, an attempt must be made to contact the subject by telephone in order to assess as many safety and efficacy parameters as possible. All data collected over the telephone must be documented and kept in the subject's record.

The PI must maintain a record of all subjects who fail to complete the study. A full explanation of the reason for study discontinuation will be made on the appropriate electronic case report form (eCRF). If a subject is lost to follow-up, a reasonable attempt to contact the subject must be made and documented.

7.4. Replacement of Subjects

Subjects who withdraw from the study after randomization will not be replaced.

8. STUDY DESIGN

8.1. Overall Study Design and Plan

It is not unusual for prescribing physicians to consider a change in a patient's antipsychotic medication (see Section 5.3). Reasons for considering a change often include insufficient control of symptoms and/or tolerability issues. In some cases, patients who are apparently adequately controlled may wish to change therapies in hopes of even better control or fewer side effects. This study will include subjects who have a diagnosis of schizophrenia who have not been exposed to olanzapine, clozapine, mesoridazine, chlorpromazine, or thioridazine for more than one week within the past year or at any time in the 3 months prior to screening.

This is a Phase 2, randomized, placebo-controlled multicenter study, which will be conducted in two parts: Part A and Part B. Part A will begin with screening and will include a 1-week olanzapine lead-in period followed by a 12-week double-blind, placebo-controlled treatment period where subjects will receive samidorphan or placebo (in addition to the olanzapine prescribed on Study Day 1). Part B will include an additional 12-week treatment period where all subjects will receive active olanzapine + samidorphan (ie, ALKS 3831). At the end of Part B, samidorphan dosing will stop, but olanzapine dosing will continue uninterrupted through the 4-week follow-up period, which includes 2 safety visits.

This study will use an Independent Data Safety Monitoring board (DSMB) to monitor for tolerability of study drug. After at least one week of safety data has been collected for 40 randomized subjects, the DSMB will review the accumulated safety data for all subjects. After at least one week of safety data has been collected for 150 randomized subjects, the DSMB will review the accumulated safety data for all subjects. Complete details of the membership and functioning of this board will be available in the DSMB Charter.

This is Alkermes' first study of the co-administration of olanzapine and samidorphan in a population of adults with schizophrenia. In addition, this study includes higher doses of samidorphan than the 5-mg dose that was used in a prior study (ALK33-301). Samidorphan has been associated with somnolence, and olanzapine has been associated with orthostatic hypotension. In ALK33-301, there was no apparent additive effect of the co-administration on either of these adverse effects. However, because the current study involves higher doses of samidorphan than studied previously, it was desired to take a conservative approach by monitoring subjects in an inpatient setting for 2 nights following randomization (Visit 3) and transition (Visit 13).

During clinic visits, assessments of psychotic symptoms using measures such as the PANSS and CGI-S will occur. Body weight will be measured using consistent methods at every visit. Alcohol and drug use will be monitored throughout the study. Concentrations of samidorphan, RDC-9986 (primary metabolite of samidorphan), and olanzapine will be determined in plasma samples collected at Visits 2-23.

8.1.1. Part A (Screening, Olanzapine Lead-In, and Double-Blind Placebo-Controlled Treatment Period)

Screening assessments will occur in the 30-day period before subjects report to the clinic for verification of eligibility and initiation of olanzapine treatment (Study Day 1). On Study Day 1 (Visit 2), all eligible subjects will be initiated on olanzapine. Olanzapine dose will be selected and titrated by the PI based upon individual subject needs and consistent with current clinical practice. Subjects will return one week later (ie, Study Day 8, Visit 3) for a 2-night inpatient stay and the start of the 12-week double-blind placebo-controlled treatment period. At this visit, subjects will be randomized in a 1:1:1:1 ratio to receive samidorphan (5 mg, 10 mg, or 20 mg) or placebo. Olanzapine dosing will continue uninterrupted. Thus, the Part A treatment groups will be as follows:

- Olanzapine + Samidorphan (5 mg)
- Olanzapine + Samidorphan (10 mg)
- Olanzapine + Samidorphan (20 mg)
- Olanzapine + Placebo

All study drug will be taken once daily, by mouth, at the same time. Subjects will be encouraged to take study drug in the evening or at bedtime. Study drug administration may be adjusted to accommodate study procedures. Randomization will be stratified by the amount of weight change during the olanzapine lead-in period (ie, from Day 1 to Day 8), with subjects grouped into the following 3 strata:

- Weight change ≤0 kg
- Weight increase >0 to <1 kg
- Weight increase ≥1 kg

This stratification will be used for analyses of secondary endpoints as specified in the statistical analysis plan (SAP).

Subjects will be discharged from the clinic on Study Day 10 (Visit 5), and will return on Study Day 15 (Visit 6).

Subjects are not required to be taking any antipsychotic medication at the time of screening or Visit 2. However, those who are will be tapered off of their prior antipsychotic medication within 2 weeks after initiation (ie, by Study Day 15, Visit 6). This cross-taper from prior antipsychotic

treatment to olanzapine will be conducted under the care and discretion of the PI and consistent with current clinical practice.

After Study Day 15 subjects will return to the clinic weekly through the first month of double-blind treatment (ie, Study Day 36) and then every 2 weeks thereafter for the remainder of Part A. Any subject who prematurely discontinues during Part A will be asked to return to the clinic immediately for an ET visit and after 2 and 4 weeks for follow-up visits.

Assessments prior to study-drug administration at Visit 13 (the transition visit) will serve as end of Part A assessments; dosing and post-dose assessments will be considered Part B assessments.

8.1.2. Part B (Active ALKS 3831 Treatment and Safety Follow-up Periods)

After completion of Part A (ie, at Visit 13), subjects will transition into Part B and will continue onto a 12-week active treatment period during which all subjects will receive ALKS 3831 (ie, olanzapine + samidorphan). Subjects who had been receiving ALKS 3831 during the double-blind period will continue on the same dose for the 12-week active treatment period. Subjects who had been receiving olanzapine + placebo in the double-blind period will continue on the same dose of olanzapine and will be transitioned from placebo to samidorphan (at the highest dose).

At Visit 13 (Study Day 92), subjects will be admitted for a 2-night inpatient stay to allow for monitoring following initiation of samidorphan dose in subjects originally assigned to the olanzapine + placebo group. Because treatment assignments in the double-blind period must remain blind until all subjects have completed Part A or been discontinued from the study, the inpatient stay is required for all subjects. After discharge (Study Day 94), subjects will return 5 days later for Visit 16 (Study Day 99). After Visit 16, subjects will be seen weekly for the next 3 weeks (Visits 17-19) and then at 2-week intervals for the remainder of the study (Visits 20-25).

The subject will take the final samidorphan dose the night before Visit 23 (Study Day 176). No samidorphan dose will be administered onsite during Visit 23. Olanzapine dosing will continue uninterrupted. Two safety follow-up visits will occur 2 and 4 weeks after Visit 23. Any subject who prematurely discontinues from the study during Part B will be asked to return to the clinic for an ET visit and follow-up visits 2 and 4 weeks after the ET visit.

8.2. Schedule of Visits and Assessments

The schedule of visits and assessments for Part A is shown in Table 1. The schedule of visits and assessments for Part B is shown in Table 2.

Because fasting glucose and insulin levels will be measured at some visits, subjects will be instructed not to eat or drink for 8 hours before these visits: Visit 2, Visit 3, Visit 13, and Visit 23/ET (see Table 1 and Table 2). Random glucose and insulin levels will be measured at visits where glucose and insulin measurements are indicated, but fasting is not required.

For a missed visit, the site should attempt to contact the subject to reschedule.

Premature discontinuation procedures are provided in Section 7.3.

Figure 1: Study Design Schematic

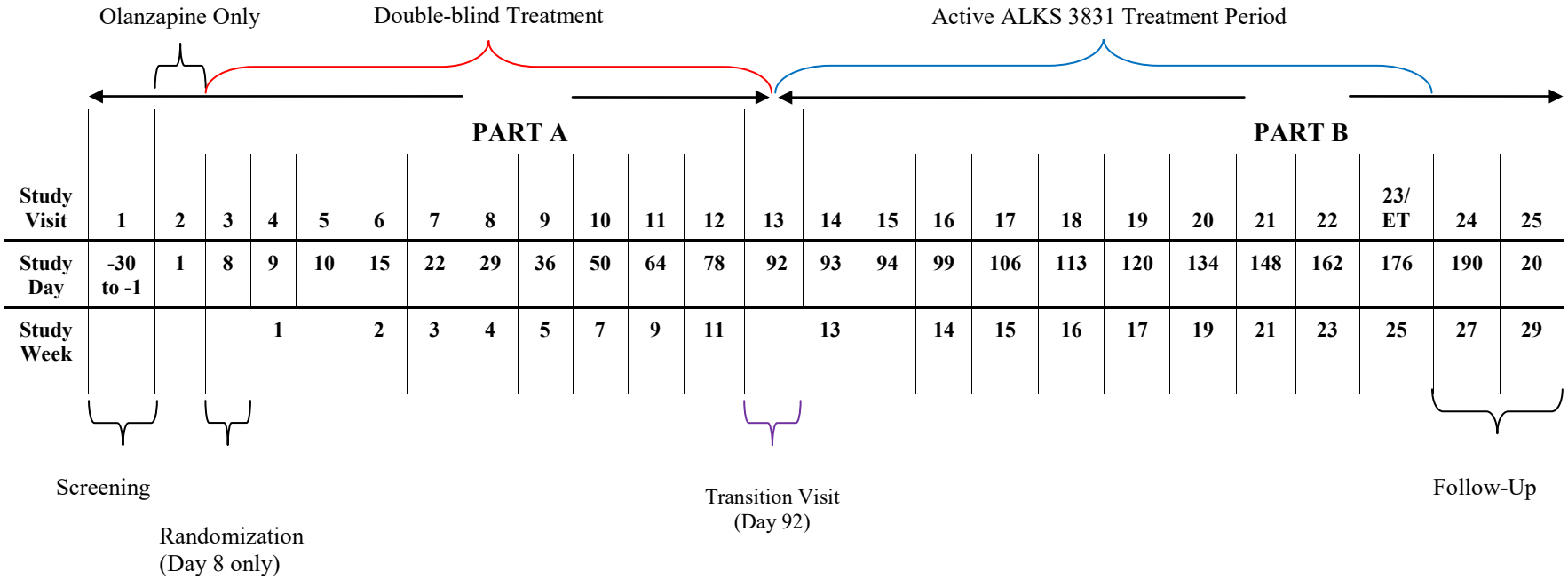

Table 1: Schedule of Assessments (Part A)

	Screening	Olanza-pine	Double-Blind Placebo-Controlled Treatment Period										Transition[1]
	Outpatient Visits		Inpatient Stay			Outpatient Visits							Inpatient Stay[2]
Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13
Study Day	-30 to -1	1	8 (±1)	9 (±1)	10 (±1)	15 (±1)	22 (±2)	29 (±2)	36 (±2)	50 (±2)	64 (±2)	78 (±2)	92 (±2)
Study Week			1			2	3	4	5	7	9	11	13
Informed Consent	X												
Demographics, Medical/Psychiatric History	X												
Height, Weight, and Waist Circumference[3]	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test[4]	X	X											X
Drug Screens[5]	X	X	X	X	X	X	X	X	X	X	X	X	X
Timeline Follow-Back (TLFB)[6]	X	X								X			X
Vital Signs[7]	X	X	X[8]	X[8]	X[8]	X[8]	X	X	X	X	X	X	X[8]
Blood and urine samples for clinical labs[9]	X	X	X		X	X			X		X		X
Hemoglobin A1c, C-reactive protein, leptin	X	X	X								X		X
Carbohydrate Deficient Transferrin (CDT)	X	X									X		X
Electrocardiogram (ECG)[10]	X	X[11]	X		X	X							X
Physical Examination[12]	X	X	X										X
Columbia Suicide Severity Rating Scale (C-SSRS)[13]	X	X	X	X	X	X	X	X	X	X	X	X	X

	Screening	Olanza-pine	Double-Blind Placebo-Controlled Treatment Period										Transition[1]
	Outpatient Visits		Inpatient Stay			Outpatient Visits							Inpatient Stay[2]
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Study Day	**-30 to -1**	**1**	**8 (±1)**	**9 (±1)**	**10 (±1)**	**15 (±1)**	**22 (±2)**	**29 (±2)**	**36 (±2)**	**50 (±2)**	**64 (±2)**	**78 (±2)**	**92 (±2)**
Study Week			**1**			**2**	**3**	**4**	**5**	**7**	**9**	**11**	**13**
Positive and Negative Syndrome Scale (PANSS)	X	X	X			X	X		X		X		X
Clinical Global Impressions-Severity (CGI-S)	X	X	X			X	X		X		X		X
Eligibility Criteria Review	X	X	X										
Randomization			X										
Dispense Emergency Treatment Card					X								
Pharmacogenetic blood sample			X										
Blood samples for PK		X	X	X	X	X	X	X	X	X	X	X	X
Personal and Social Performance Scale (PSP)		X	X							X			X
Food Craving Inventory (FCI)		X	X			X							X
Impact of Weight on Quality of Life – Lite Questionnaire (IWQOL-Lite)		X	X										X
Interactive Web Response System (IWRS)			X	X	X	X	X	X	X	X	X	X	X
Olanzapine Dosing		X	X	X	X	X	X	X	X	X	X	X	X
Double-Blind Samidorphan/ Placebo Dosing[14]			X	X	X	X	X	X	X	X	X	X	
Adverse Event (AE) Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X

	Screening	Olanza-pine	Double-Blind Placebo-Controlled Treatment Period										Transition[1]
	Outpatient Visits		Inpatient Stay			Outpatient Visits							Inpatient Stay[2]
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Study Day	**-30 to -1**	**1**	**8 (±1)**	**9 (±1)**	**10 (±1)**	**15 (±1)**	**22 (±2)**	**29 (±2)**	**36 (±2)**	**50 (±2)**	**64 (±2)**	**78 (±2)**	**92 (±2)**
Study Week			**1**			**2**	**3**	**4**	**5**	**7**	**9**	**11**	**13**
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Validation Inventory for Study Admission (C-VISA™)	X												

[1] Transition Visit = the end of Part A and the beginning of Part B. Assessments at this visit are included in both schedules for convenience.
[2] All measures should be taken pre-dose at Visit 13 except where indicated
[3] Height will be measured at screening only; weight and waist circumference will measured at all indicated visits
[4] Serum pregnancy test at screening; urine pregnancy test at other time points
[5] Centralized drug screen testing at screening, local drug screen testing via dipstick at other time points. The urine drug screen includes benzodiazepines, opioids, amphetamine/methamphetamine, and cocaine.
[6] Alcohol use only
[7] Orthostatic blood pressure and heart rate measurements will be taken anytime pre-dose and approximately 1 hour post-dose at Visits 3 - 6 and Visit 13 only. At all other dosing visits, routine vital sign assessments will be conducted anytime pre-dose. At all other visits (when no dosing occurs) assessments will be conducted anytime.
[8] Collect pre-dose and post-dose data
[9] An overnight fast is required for labs at Visit 2, Visit 3, and Visit 13. Thyroid stimulating hormone should be assessed at screening only.
[10] ECG will be measured anytime pre-dose and approximately 3 hours post-dose except for Visit 1 and Visit 2 where only 1 ECG will be done. For Visit 2, the ECG should be completed before dosing. For Visit 6, dosing may be done earlier than normal to accommodate post-dose procedure.
[11] Collect data pre-dose
[12] Full physical examination at screening; brief physical examination at all other scheduled time points
[13] At screening, the "Baseline" version will be administered, and at all other visits the "Since Last Visit" version will be administered.
[14] During inpatient visits, study drug will be administered by the study staff. Otherwise, study drug will be dispensed for self-administration by the subject

Table 2: Schedule of Assessments (Part B)

	Transition[1]	**Active ALKS 3831 Treatment Period**										**Follow-Up**	
	Inpatient Stay			**Outpatient Visits**									
Study Visit	**13**[2]	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23/ET**	**24**	**25**
Study Day:	**92 (±2)**	**93 (±2)**	**94 (±2)**	**99 (±1)**	**106 (±2)**	**113 (±2)**	**120 (±2)**	**134 (±2)**	**148 (±2)**	**162 (±2)**	**176 (±2)**	**190 (±2)**	**204 (±2)**
Study Week	**13**			**14**	**15**	**16**	**17**	**19**	**21**	**23**	**25**	**27**	**29**
Weight and Waist Circumference	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test[3]	X												
Drug Screens[4]	X		X	X	X	X	X	X	X	X	X	X	X
Timeline Follow-Back (TLFB)[5]	X							X			X		X
Vital Signs[6]	X[7]	X[7]	X[7]	X[7]	X	X	X	X	X	X	X	X	X
Blood and urine samples for clinical labs[8]	X		X	X			X		X		X		X
Hemoglobin A1c, C-reactive protein, leptin	X								X		X		X
Carbohydrate Deficient Transferrin (CDT)	X							X			X		
Blood samples for PK	X	X	X	X	X	X	X	X	X	X	X		
Physical Examination	X				X						X	X	X
Electrocardiogram (ECG)[9]	X		X	X							X	X	
Positive and Negative Syndrome Scale (PANSS)	X			X			X		X		X		
Personal and Social Performance Scale (PSP)	X							X			X		

	Transition[1]	Active ALKS 3831 Treatment Period										Follow-Up	
	Inpatient Stay			Outpatient Visits									
Study Visit	**13**[2]	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23/ET**	**24**	**25**
Study Day:	**92 (±2)**	**93 (±2)**	**94 (±2)**	**99 (±1)**	**106 (±2)**	**113 (±2)**	**120 (±2)**	**134 (±2)**	**148 (±2)**	**162 (±2)**	**176 (±2)**	**190 (±2)**	**204 (±2)**
Study Week	**13**			**14**	**15**	**16**	**17**	**19**	**21**	**23**	**25**	**27**	**29**
Columbia Suicide Severity Rating Scale (C-SSRS)	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Global Impressions-Severity (CGI S)	X			X			X		X		X		
Food Craving Inventory (FCI)	X			X	X						X		X
Impact of Weight on Quality of Life – Lite Questionnaire (IWQOL-Lite)	X							X			X		
Interactive Web Response System (IWRS)	X	X	X	X	X	X	X	X	X	X	X		
Olanzapine Dosing[10]	X	X	X	X	X	X	X	X	X	X	X	X	X
Samidorphan Dosing[11]	X	X	X	X	X	X	X	X	X	X			
Collect Emergency Treatment Card											X		
Adverse Event (AE) Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X

[1] Transition Visit (end of Part A and beginning of Part B). Assessments at this visit are included in both schedules for convenience.
[2] All data should be collected pre-dose at Visit 13 except where indicated
[3] Urine pregnancy test
[4] Local drug screen testing via dipstick. The urine drug screen includes benzodiazepines, opioids, amphetamine/methamphetamine, and cocaine. Additional drug tests may be conducted at the discretion of the investigator.
[5] Alcohol use only
[6] Orthostatic blood pressure and heart rate measurements will be taken pre-dose and approximately 1 hour post-dose at Visits 13 – 16. At all other dosing visits, routine vital sign assessments will be conducted anytime pre-dose. At all other visits (when no dosing occurs) assessments will be conducted anytime.
[7] Collect pre-dose and post-dose data.

[8] An overnight fast is required for labs on Visit 13 and Visit 23/ET
[9] ECG will be measured anytime pre-dose and approximately 3 hours post-dose except for Visit 23/ET and Visit 24 where no dosing occurs. For Visit 16, dosing may be done earlier than normal to accommodate post-dose procedure.
[10] The subject will take olanzapine uninterrupted through Visit 25
[11] The subject will take the final samidorphan dose the night before Visit 23

8.3. Study Procedures Descriptions

Details of the study procedures are described below.

8.3.1. Informed Consent

The nature of the study and its risks and benefits will be explained to the subject (and caregiver as required) by the PI or designee as described in the site-specific ICF approved by the overseeing Institutional Review Board (IRB)/Independent Ethics Committee (IEC) (see Section 17.3).

8.3.2. Demographics, Medical and Psychiatric History

Demographic data and medical/psychiatric history will be reviewed and documented according to the schedule shown in Table 1.

8.3.3. Drug Testing

A urine drug test for prohibited substances, including benzodiazepines, opioids, amphetamine/ methamphetamine, and cocaine, will be performed at the time points specified in Table 1 and Table 2.

8.3.4. Timeline Follow-Back

Alcohol use will be recorded using the Timeline Follow-Back (TLFB) method [Sobell and Sobell 1992] at the time points specified in Table 1 and Table 2. At each visit where TLFB is to be performed, alcohol use data will be collected for the prior 30-day period.

8.3.5. Concomitant Medication Review

Concomitant medications will be reviewed at every visit. The medications include prescription and nonprescription medications, vitamins, and supplements.

Study staff will record the following data on all medications used by the subject: name, dose, regimen, route of administration, start and stop dates, and the indication for use.

8.3.6. Vital Signs

Vital signs (ie, blood pressure, heart rate, respiratory rate, and oral body temperature) will be assessed at every visit. Blood pressure and heart rate will be measured after the subject has been resting in a seated or supine position for at least 5 minutes.

An effort will be made to consistently use the same arm (preferably the subject's dominant arm) to measure blood pressure and heart rate throughout the study. The blood pressure cuff will be calibrated per study site standard operating procedures (SOP). Automated measurement is preferred, but if performed manually, heart rate will be measured in the brachial artery for at least 30 seconds.

Orthostatic blood pressure and heart rate will be measured according to the schedule shown in Table 1 and Table 2. Orthostatic blood pressure and heart rate will be collected in the following manner:

- Allow subject to be in a supine position for at least 5 minutes
- Measure blood pressure and heart rate
- Have subject stand for 2 minutes
- Measure blood pressure and heart rate

For Part A, orthostatic blood pressure and heart rate measurements will be taken anytime pre-dose and approximately 1 hour post-dose at Visits 3 - 6 and Visit 13 only. At all other dosing visits, routine vital sign assessments will be conducted anytime pre-dose. At all other visits (when no dosing occurs) assessments will be conducted anytime.

For Part B, orthostatic blood pressure and heart rate measurements will be taken pre-dose and approximately 1 hour post-dose at Visits 13 - 16. At all other dosing visits, routine vital sign assessments will be conducted anytime pre-dose. At all other visits (when no dosing occurs) assessments will be conducted anytime.

8.3.7. Physical Examination, Height

A physical examination will be performed according to the schedule shown in Table 1 and Table 2.

Height will be measured at Visit 1 only.

8.3.8. Body Weight and Waist Circumference

Body weight will be measured 3 times at every visit. The median weight will be calculated by an Interactive Web Response System (IWRS) system at Visit 2 and Visit 3 to calculate the change in weight during the first week of olanzapine exposure. At Visit 2, as part of the eligibility assessment, the PI or designee must ensure that the subject's body weight has not changed by greater than 1 kg. Body weight will also be measured prior to discharge from the inpatient stay.

Subjects should be asked to void immediately prior to the body weight measurement. Subjects should be weighed on the same scale for each measurement under the same conditions. Subjects should remove all personal items, such as watches and jewelry, prior to body weight measurement. Subjects should be weighed in hospital gowns with a consistent amount of undergarments for each measurement. Subjects will be weighed 3 times. The median weight will be calculated by an IWRS system as described above at Visit 2 and Visit 3 and entered into an electronic data capture (EDC) system at all other visits.

Waist circumference will be measured according to the schedule shown in Table 1 and Table 2.

8.3.9. 12-Lead Electrocardiogram

A 12-lead ECG will be conducted according to the schedule shown in Table 1 and Table 2. For Part A, ECG will be measured anytime pre-dose and approximately 3 hours post-dose except for Visit 1 and Visit 2 where only 1 ECG will be done. For Visit 2, the ECG should be completed

before dosing. For Visit 6, dosing may be done earlier than normal to accommodate post-dose procedures.

For Part B, ECG will be measured anytime pre-dose and approximately 3 hours post-dose except for Visit 23/ET and Visit 24 where no dosing occurs. For Visit 16, dosing may be done earlier than normal to accommodate post-dose procedure.

8.3.10. Adverse Event Monitoring

AEs will be monitored continuously from the time a subject signs the informed consent document until the completion of the final study visit. AEs and serious adverse events (SAEs) are defined in Sections 13.2 and 13.3, respectively. Section 13.5 provides guidance on the monitoring and reporting requirements for AEs. Section 13.6 provides guidance on the reporting requirements for SAEs.

8.3.11. Laboratory Assessments

Blood and urine samples for laboratory assessments will be collected according to the schedule shown in Table 1 and Table 2. Overnight fasting (no eating or drinking for 8 hours before the visit) will be required for labs at Visit 2, Visit 3, Visit 13, and Visit 23/ET. Otherwise, samples will be collected in accordance with the site's usual procedures and analyzed by a central laboratory. Follow-up samples may be obtained for repeat testing as clinically indicated.

Specific hematology, biochemistry, and urinalysis assessments are listed in Table 3. Overnight fasting is required for some visits because fasting glucose and insulin levels (value and absolute change from baseline) will be measured. Otherwise, random glucose and insulin levels will be taken.

Table 3: Clinical Laboratory Assessments

Hematology	Biochemistry	Urinalysis
• Hematocrit • Hemoglobin • Red blood cell count • Total and differential (absolute) white blood cell count • Platelets	• Sodium • Potassium • Bicarbonate • Glucose[1] • Creatinine • Total protein • Blood urea nitrogen (BUN) • Albumin • Albumin/globulin ratio • Total bilirubin • Alanine transferase (ALT) • Aspartate transferase (AST) • Lactic dehydrogenase (LDH) • Gamma-glutamyl transferase (GGT) • Alkaline phosphatase (ALK-P) • Creatine phosphokinase (CPK) • Insulin[1] • Triglyceride • Total, HDL and LDL cholesterol • Prolactin • Thyroid stimulating hormone (TSH)[2]	• Color • pH • Specific gravity • Ketones • Protein • Glucose[1] • Bilirubin • Nitrite • Urobilinogen • Occult blood • Cotinine • Microscopic examination of sediment, *only if urinalysis dipstick results are abnormal*

[1] Requires fasting where indicated on Table 1 and Table 2 (see also Section 8.3.11)
[2] Assessed at screening only

8.3.11.1. Specialty Laboratory Assessments

In addition to the clinical laboratory assessments listed in Table 3, HbA1c, C-reactive protein, leptin, and carbohydrate deficient transferrin (CDT) will be assessed at select visits, as indicated in Table 1 and Table 2.

A blood sample for pharmacogenetic analyses exploring the relationship between olanzapine-induced weight gain and genotype will be collected according to the schedule in Table 1. This sample will be stored by a third party for up to 10 years after study completion (instructions will be given for shipping to storage facility). Note: This sample should only be taken if subjects have

agreed to it by signing a separate DNA consent form (see Section 17.3). Subjects may be enrolled in the study without consenting to this procedure, in which case it should not be done.

8.3.11.2. Pregnancy Screening

A pregnancy test will be performed on all women according to the schedule in Table 1 and Table 2. At screening, a serum pregnancy test will be performed. A urine pregnancy test will be performed at all other scheduled time points. A positive result at any time will necessitate the subject's withdrawal from the study.

8.3.12. Pharmacokinetic Assessments

Samidorphan, RDC-9986 (primary metabolite of samidorphan), and olanzapine concentrations will be determined from plasma samples collected according to the schedule in Table 1 and Table 2. The time of last study drug administration and the associated PK blood draw must both be recorded in each subject's appropriate source documents. PK samples will be stored at -20°C ± 10°C.

Pharmacokinetic data may be used to assess compliance with study drug administration and/or included in a subsequent population PK analysis conducted outside of this study.

8.3.13. Clinical Global Impressions-Severity

The PI or designee will complete the CGI-S (Appendix A) scale at the time points shown in Table 1 and Table 2.

8.3.14. Columbia Suicide Severity Rating Scale

The PI or designee will complete the C-SSRS (Appendix B) according to the schedule in Table 1 and Table 2. At Screening, the "Baseline" version will be administered, and at all other visits, the "Since Last Visit" version will be administered.

8.3.15. Positive and Negative Syndrome Scale

The PI or designee will complete the PANSS (Appendix C) according to the schedule in Table 1 and Table 2.

8.3.16. Personal and Social Performance Scale

The PI or designee will complete the 5-point PSP scale (Appendix D) according to the schedule in Table 1 and Table 2.

8.3.17. Food Craving Inventory

The subject will complete the Food Craving Inventory (Appendix E) according to the schedule in Table 1 and Table 2.

8.3.18. Impact of Weight on Quality of Life - Lite

The subject will complete the Impact of Weight on Quality of Life - Lite (Appendix F) questionnaire according to the schedule in Table 1 and Table 2.

8.3.19. Audio Recording

The screening interview and administration of assessments may be recorded using an audio digital pen. A third party may review these recordings for quality assurance and confirmation of subject eligibility.

8.3.20. Olanzapine Administration

Subjects will receive olanzapine for once daily administration according to the schedule in Table 1 and Table 2. The dose will be at the discretion of the PI.

Initiation on olanzapine, including transition from another antipsychotic (as applicable), is a highly individualized process. Formalizing the potential clinical scenarios may pose undue burden and/or risk to subjects. Clinical judgment is essential, and for this reason, the details of this process are left to the discretion of the treating physician, who will follow current clinical practice.

8.3.21. Randomization

After confirming eligibility on Visit 3, and after a 1-week olanzapine lead-in period, subjects will be randomized as outlined in Section 9.3.

8.3.22. Drug Dispensation and Reconciliation

Section 9 provides information related to drug dispensing procedures. The study drug use and storage information will be explained to/reviewed with the subject.

Study drugs include samidorphan and matching placebo tablets, and olanzapine tablets, all for oral administration. Samidorphan is a Schedule II substance, and should be stored, dispensed, and otherwise handled in accordance with the associated regulations.

Olanzapine will be prescribed by the PI and dispensed for oral administration by study staff.

During the inpatient stays, study drug will be dispensed once daily, and the time of administration will be at the discretion of study staff. Time of administration at any visit (inpatient or outpatient) may be adjusted as needed to accommodate post-dose measurements. Before being discharged from each inpatient stay, and at each post-randomization outpatient visit until Visit 23/ET, all subjects will receive blister cards containing samidorphan or placebo for self administration. Subjects will be instructed to take 2 tablets per day from the blister card in addition to their olanzapine tablet(s) once daily in the evening or at bedtime until Visit 23. The subject will take the final samidorphan dose the night before Visit 23. No samidorphan dose will be administered onsite during Visit 23. Olanzapine dosing will continue uninterrupted. Two safety follow-up visits will occur 2 and 4 weeks after Visit 23. Any subject who prematurely discontinues from the study during Part B will be asked to return to the clinic for an ET visit and follow-up visits 2 and 4 weeks after the ET visit.

Subjects will be instructed to keep all unused tablets in their blister card and not to mix tablets between blister cards and bottles.

Subjects will be instructed to return the original containers and any remaining study drug at each subsequent visit. Study drug accountability will be documented as the number of tablets

dispensed, dosed, lost/missing, or remaining. If applicable, the site will discuss noncompliance with the subject.

8.3.23. Emergency Treatment Card

An emergency treatment card will be distributed to each subject prior to discharge at Visit 5. The card will indicate that the subject may be receiving an opioid antagonist and/or olanzapine and will include the PI's contact information, a suggested pain management plan, and information regarding opiate blockade. Subjects will be instructed to keep the emergency treatment card with them at all times. Study personnel will confirm that the subjects have the card in their possession at each study visit. The treatment cards will be collected at Visit 23/ET.

8.3.24. Clinical Validation Inventory for Study Admission

The PI or designee will complete the Diagnostic Validation Workbook as part of the Clinical Validation Inventory for Study Admission (C-VISA™) at Visit 1. This workbook is a structured method for assessing and documenting study eligibility based on the criteria given in Section 7.

8.4. Study Requirements and Restrictions

8.4.1. Prohibited Medications

Use or expected use of any of the following medications (including generic equivalents or alternative brand names) within 60 days prior to screening or during the study period is prohibited.

- All prescription or over-the-counter (OTC) agents taken for the purpose of weight reduction, including (but not limited to) the following anti-obesity agents:
  - Prescription drugs such as orlistat (Xenical), sibutramine (Meridia), Belviq (lorcaserin); and phentermine (Adipex-P, Ionamin, Pro-Fast SA, Pro-Fast SR, Fastin, Oby-Trim, Zantryl, Teramine, Phentride, Phentercot, Obephen, Oby-cap), Qsymia (phentermine and topiramate)
  - Over-the-counter anti-obesity agents (eg, herbal supplements or other alternative remedies such as Cortislim, Dexatrim, Acutrim, Orlistat)
- Systemic steroids administered by oral, intravenous, or intramuscular route
- Antipsychotic agents including clozapine, mesoridazine, chlorpromazine, or thioridazine
- Zyprexa oral disintegrating tablets, Zyprexa Relprevv™ intramuscular injection (long-acting), or Zyprexa IntraMuscular injection (short-acting)
- Topiramate (Topamax®); Calcitonin (eg, Miacalcin®), Exenatide (Byetta®); Sulfonylureas (eg, Diamicron®, Amaryl®, Glucotrol®, Micronase®); Meglitinides (eg, Starlix®, Prandin®); Metformin or any hypoglycemic agent

Use of opioid agonists (eg, codeine, oxycodone, tramadol, or morphine) within 14 days before screening is prohibited. Use of opioid antagonists, including naltrexone (any formulations) and

naloxone within 60 days before screening through the follow-up visit is prohibited. Note: during the study period, opioid agonists should be avoided (refer to Section 8.4.4).

Use of hypnotic agents for insomnia (eg, benzodiazepines, zolpidem, trazodone) is permissible. Short half-life benzodiazepines are preferable for the treatment of insomnia over long half-life benzodiazepines due to the potential for lingering effects on daytime functioning and study assessments.

Treatment of agitation and/or anxiety with benzodiazepines is permissible, but the dose should be kept as stable as possible throughout the study so as not to interfere with daytime functioning and study assessments. Special care should be taken with dosing of benzodiazepines on study visit days so as not to influence efficacy ratings (eg, PANSS); doses of benzodiazepines should be withheld if scheduled to be taken within several hours of a PANSS rating.

Use of moderate to strong inducers or inhibitors of cytochrome P450 (CYP) 3A4 (prescription medications, OTC medications, or dietary supplements) within 30 days before randomization through follow-up is prohibited. A partial list of CYP3A4 modulators is provided in Appendix G.

Medications that are contraindicated with olanzapine use or exhibit drug-interaction potential with olanzapine will be defined and prohibited at the discretion of the PI.

See Section 8.3.5 for details regarding the concomitant medication review.

8.4.2. Contraception

All subjects must agree to use an acceptable method of contraception for the duration of the study. Subjects who are abstinent must agree to use an acceptable contraceptive method should they become sexually active. The following are considered acceptable methods:

- Condom (barrier method) plus
  - Intrauterine device (IUD)

    or
  - Hormonal contraceptive (such as birth control pills or patches, a vaginal ring, or a contraceptive implant)

Sexually active male subjects must agree use a condom in addition to his partner's normal use of contraception.

Exemptions: Subjects who are surgically sterile are exempt from the requirement to use contraception. Women who have undergone a hysterectomy, bilateral tubal ligation, or bilateral salpingo-oophorectomy are considered surgically sterile. Men who have undergone a vasectomy are considered surgically sterile. In addition, women who are postmenopausal are also exempt from the requirement to use contraception.

8.4.3. Other Restrictions

Subjects will be instructed to maintain their normal caffeine intake as well as normal activity/exercise throughout the study. Subjects are prohibited from participating in a weight management program for the duration of the study.

8.4.4. Pain Management

Because ALKS 3831 contains samidorphan, a μ-opioid receptor antagonist, patients may experience reduced or ineffective analgesia when taking an opioid analgesic agent concurrently with ALKS 3831, including several days after last dosing of ALKS 3831.

In the event of an emergency, pain management of the subject should include the following:

- Regional analgesia or use of non-opioid analgesics
- If opiate anesthesia or analgesia is required, the subject should be continuously monitored, in an anesthesia care setting, by persons not involved in the conduct of the surgical or diagnostic procedure. The opioid therapy must be provided by individuals specifically trained in the use of anesthetic drugs and the management of the respiratory effects of potent opioids, specifically the establishment and the maintenance of a patent airway and assisted ventilation.
- Close monitoring by appropriately trained personnel in a setting equipped and staffed for cardiopulmonary resuscitation

For subjects requiring emergency opioid analgesics prior to dosing, the study drug should not be administered. If opioid analgesics are required after the study drug has been dosed, it may take several days for opiate sensitivity to be restored, since samidorphan is an opioid antagonist and could interfere with opioid-mediated pain management.

9. TREATMENT OF SUBJECTS

9.1. Study Drug Dose and Administration

Study drugs include samidorphan and matching placebo tablets, and olanzapine tablets, all for oral administration. Samidorphan is a Schedule II substance, and should be stored, dispensed, and otherwise handled in accordance with the associated regulations.

Olanzapine will be prescribed by the PI and will be dispensed for oral administration by study staff.

During the inpatient stays, study drug will be dispensed once daily, and the time of administration will be at the discretion of the clinic staff. Time of administration at any visit (inpatient or outpatient) may be adjusted as needed to accommodate post-dose measurements. Before being discharged from each inpatient stay, and at each outpatient post-randomization study visit until Visit 23/ET, all subjects will receive blister cards containing samidorphan or placebo for self administration. Subjects will be instructed to take 2 tablets per day from the blister card and their olanzapine tablet(s) once daily in the evening or at bedtime until Visit 23. The subject will take the final samidorphan dose the night before Visit 23. No samidorphan dose will be administered onsite during Visit 23/ET. Olanzapine dosing will continue uninterrupted. Two safety follow-up visits will occur 2 and 4 weeks after Visit 23. Any subject who prematurely discontinues from the study during Part B will be asked to return to the clinic for an ET visit and follow-up visits 2 and 4 weeks after the ET visit.

Subjects should take all study drug tablets (olanzapine and samidorphan/placebo) orally and at the same time. Subjects should be advised that somnolence may occur with dosing and thus they should avoid driving or operating heavy machinery until they have determined how the study drug affects them.

Subjects will be instructed to keep all unused tablets in their blister card and not to mix tablets between blister cards and bottles. Subjects will also be instructed to return unused tablets to the site when they return for their next visit. If dosing occurs at this visit, the dose should be taken from subjects' next blister card. The dose should not be taken from the blister card the subjects are returning.

If a dose is missed or forgotten, subjects will be instructed to resume the regular dosing schedule the following evening. Subjects will be instructed not to take a double dose to try to "make up" for a missed dose.

9.2. Treatment Compliance

As described in Section 8.3.22, study personnel will assess treatment compliance at every visit from first dose of study drug at Visit 2 through Visit 23/ET accounting for the dispensed tablets (samidorphan, olanzapine, and placebo accounting for dosed, lost/missing, or remaining tablets). Additional measures of compliance may be used; these will be described in the Operational Plan as necessary. Study drug accountability will be performed using an EDC system. Subjects who have demonstrated compliance during the first week of olanzapine study will be randomized to double-blind treatment (samidorphan or placebo).

Noncompliance will be discussed with the subject as needed.

9.3. Randomization and Blinding

Part A of this study will be conducted in a double-blind fashion. On Day 8 (Visit 3), subjects will be randomized to receive one of the following regimens in a 1:1:1:1 ratio:

- Olanzapine + Samidorphan (5 mg)
- Olanzapine + Samidorphan (10 mg)
- Olanzapine + Samidorphan (20 mg)
- Olanzapine + Placebo

Randomization will be performed centrally through an IWRS system and will be stratified by the amount of weight change during the olanzapine lead-in period (ie, from Day 1 to Day 8), with subjects grouped into the following 3 strata:

- Weight change ≤0 kg
- Weight increase >0 to <1 kg
- Weight increase ≥1 kg

Alkermes staff, clinical staff, and subjects will remain blinded to treatment assignment until Part A of the study is complete. All PPD staff will remain blinded except when their study function requires unblinding (eg, drug supply management, IWRS operation, DSMB operation, etc). These unblinded staff will follow procedures designed to ensure that study integrity is maintained.

9.4. Breaking Study Blind

The PI is responsible for all trial-related medical decisions. Emergency unblinding may be done without contacting a medical monitor. Any premature unblinding should be promptly documented and explained to the medical monitor within 24 hours following disclosure of study drug assignment. Breaking the blind for a single subject will not affect the blind for the remaining subjects.

Once Part A of the study is complete (ie, the final subject has completed the final Part A assessment), the Part A data will be locked, unblinded, and the Part A data analyses will be conducted. This may occur prior to the completion of Part B of the study; however individual treatment assignments will remain blinded to the sites.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

Commercially available olanzapine will be supplied or arranged for dispensing by the investigative site.

Samidorphan will be provided by the sponsor. Each tablet contains 2.5, 5, or 10 mg. Subjects will take 2 tablets per day (ie, doses of samidorphan will be 5, 10, or 20 mg) by mouth.

Samidorphan is a Schedule II substance and will require proper handling, storage, and accountability in accordance with local, regulations, and operating procedures.

Placebo consists of tablets, identical in size and appearance to the samidorphan tablets. Subjects will take 2 tablets per day by mouth.

10.2. Packaging and Labeling

Samidorphan and placebo will be packaged in blister packs. Blister packs will be provided in weekly or biweekly configurations. The weekly blister pack will contain 18 tablets, which provides one week of dosing with sufficient overage to allow for 2 additional once daily doses. The biweekly packs will contain 32 tablets, providing 2 weeks of dosing with sufficient overage to allow for 2 additional once daily doses.

Blister pack labels will meet all applicable local and regulatory requirements.

10.3. Storage

Under the US Controlled Substances Act, samidorphan is considered a Schedule II substance because it is derived from opium alkaloids. Therefore, samidorphan and/or blinded study drug must be stored in accordance with restrictions related to Schedule II substances. The site will take adequate precautions, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance.

10.4. Accountability

The clinical site is required to maintain current drug dispensation and accountability logs throughout the study. All unused supplies will be checked against the drug movement records during the study and/or at the end of the study.

Refer to Section 9 for additional study drug reconciliation procedures.

10.5. Handling and Disposal

Following completion and verification of accountability logs, all unused and used packages must be destroyed in accordance with regulations for controlled substances. Study drug destruction will occur only at the end of the trial and upon notification/approval by the sponsor. Packages may be destroyed on site according to Good Clinical Practice (GCP), site procedures and in accordance with all regulations for controlled substances. Alternatively, the sponsor may arrange

for destruction with a third party vendor operating in accordance with GCP. Redispensation or disposal of drug product during the course of the trial is prohibited.

11. ASSESSMENT OF EFFICACY

11.1. Primary Endpoint

The primary endpoint is the absolute change in PANSS total score from randomization to the end of Part A.

11.2. Secondary Endpoints

- Percent change in body weight
- Absolute change in body weight
- Proportion of subjects exhibiting significant weight gain (definition of weight gain will include body weight gain greater than 7%)
- Absolute change in CGI-S

11.3. Additional Endpoints

- Change in waist circumference
- Change in IWQOL-Lite scales (physical function, self-esteem, sexual life, public distress and work) and total score
- Change in PSP
- Change in FCI
- Change in alcohol and drug use

12. PHARMACOKINETIC/ PHARMACODYNAMIC ASSESSMENTS

For all subjects, samidorphan, RDC-9986 (primary metabolite of samidorphan) and olanzapine concentrations will be determined from plasma samples collected according to the schedule in Table 1 and Table 2. PK data may be used to assess compliance with study drug administration and/or included in a subsequent population PK analysis conducted outside of this study.

13. ASSESSMENT OF SAFETY

Safety will be assessed from randomization to the end of Part A. Part B data will be used to examine longer-term safety. The number and percentage of subjects with AEs from randomization to the end of Part A is included as a secondary endpoint. In addition to this secondary endpoint, safety will be evaluated based on AEs, vital signs, clinical laboratory assessments (hematology, blood clinical biochemistry, and urinalysis), 12-lead ECG findings, and data from C-SSRS surveys.

13.1. Safety Endpoints

- Number and percentage of subjects with adverse events from randomization to the end of Part A
- Change in blood lipid concentrations including LDL, HDL, total cholesterol and triglycerides
- Change in assessments related to glucose regulation including fasting glucose and insulin, fasting glucose to fasting insulin ratio, HbA1c, c-reactive protein, leptin and bicarbonate
- Change in vital signs including blood pressure

13.2. Definition of Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product. The occurrence, which may or may not have a causal relationship with the investigational treatment, may include any clinical or laboratory change that does not commonly occur in that subject and is considered clinically significant.

Illnesses present prior to the subject signing the main ICF are considered to be pre-existing conditions and are documented on the medical history eCRF. Pre-existing conditions that worsen during the study are entered on the AE eCRF.

All out-of-range laboratory values will be deemed as clinically significant or not clinically significant by the PI (or designated investigator). Clinically significant values will be considered AEs and recorded as such on the eCRFs.

13.3. Definition of Serious Adverse Event

A serious adverse event (SAE) is any AE, occurring at any dose and regardless of causality that meets one or more of the following criteria:

- Results in death
- Is life-threatening. The subject is at immediate risk of death from the reaction as it occurs. This does not include reaction that, had it occurred in a more severe form, might have caused death.

- Requires inpatient hospitalization or prolongation of existing hospitalization. Hospital admission for elective surgery scheduled prior to study entry is not considered an SAE.
- Results in disability/incapacity (eg, a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/ birth defect

Important medical events that may not result in death, be immediately life threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require intervention to prevent one of the other outcomes listed above.

At Visits 3 and 13, subjects are admitted for a 2-night inpatient stay at the study site, per the protocol. If prolongation of this protocol-required stay is necessary for the management of the subject's schizophrenia **without a worsening of the subject's baseline clinical status or the development of new signs or symptoms**, and is confirmed as such by the medical monitor, the event should be categorized as an AE, not an SAE.

Admission to an inpatient unit or hospital for a non-medical reason (ie, social-stay admission) during the trial is considered an AE, not an SAE.

13.4. Relationship to Study Drug

The assessment of study drug relationship to each AE will be reported on the appropriate source document (and SAE form, in the event of an SAE) by the PI (or designated investigator) according to his/her best clinical judgment. The criteria listed in Table 4 should be used to guide this assessment. Please note that not all criteria must be present to be indicative of a particular drug relationship. All study drugs are considered "test drugs" for the purposes of the definitions listed in the table. However, relationship and action taken will be separated out in the EDC to assess for olanzapine and samidorphan/placebo separately. The PI (or designated investigator) can attribute relationship to olanzapine, samidorphan/placebo or both.

Table 4: Causality Guidelines

Relationship[1]	Criteria for assessment
Definitely related	There is evidence of exposure to the test drug. AND The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause. Dechallenge (if performed) is positive. Rechallenge (if feasible) is positive. The AE shows a pattern consistent with previous knowledge of the test drug or test drug class.
Probably related	There is evidence of exposure to the test drug. AND The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause. Dechallenge (if performed) is positive.
Possibly related	There is evidence of exposure to the test drug. AND The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE could have been due to another equally likely cause. Dechallenge (if performed) is positive.
Probably not related	There is evidence of exposure to the test drug. AND There is another more likely cause of the AE. Dechallenge (if performed) is negative or ambiguous. Rechallenge (if performed) is negative or ambiguous.
Definitely not related	The subject did not receive the test drug. OR Temporal sequence of the AE onset relative to administration of the test drug is not reasonable. OR There is another obvious cause of the AE.

[1] Relationship will be assessed twice: once for olanzapine and once for samidorphan/placebo

13.4.1. Adverse Events of Special Interest

PIs or their designees will be required to record additional details for AEs of special interest related to abuse liability. These AEs fall into general categories including (but not limited to)

substance-related disorders, euphoria, sedation, stimulation, hallucinations, motor impairment, and cognitive impairment. More details on these AEs will be provided outside of this protocol.

13.5. Monitoring and Recording of Adverse Events

AE data collection will begin after a subject signs the main ICF and will continue until completion of the safety follow-up visit. Any AE or SAE having an onset after the safety follow-up visit will not be collected or reported unless the PI (or designated investigator) feels that the event may be related to the study drug.

Subjects will be instructed by the PI (or designee) to report the occurrence of any AE. All volunteered, elicited, and observed AEs are to be recorded on the AE eCRFs.

The PI (or designated investigator) will assess all AEs regarding any causal relationship to the study drug (see Section 13.4), the intensity (severity) of the event, action taken, and subject outcome.

The following criteria should be used to guide the assessment of intensity (severity):

- **Mild:** Causes awareness of sign or symptom, but is easily tolerated; does not interfere with usual activities
- **Moderate:** Causes discomfort enough to interfere with usual activities
- **Severe:** Is incapacitating; results in inability to work or perform usual activities

All AEs will be followed until resolution, until deemed stable by the PI, or until the subject is deemed by the PI to be lost to follow-up.

For clinical study safety reporting purposes, the most recent version of the IB will be used as the reference document to designate event expectedness.

Withdrawal from the study as a result of an AE and any therapeutic measures that are taken shall be at the discretion of the PI (or designated investigator). If a subject withdraws from the study for any reason, any ongoing AEs will be followed until resolution, until deemed stable by the PI, or until the subject is deemed by the PI to be lost to follow-up.

13.6. Reporting of Serious Adverse Events

All SAEs must be reported to PPD within 24 hours of discovery, by faxing the report to the following:

Attention: PPD Medical Monitor

US Fax Number: PPD

EU Fax Number: PPD

The written report should be submitted on the SAE form provided for this purpose. The report must include the PI's (or designated investigator's) opinion as to whether the event is study drug-related. If this relationship is determined to be possibly, probably, or definitely related to study drug, evidence to support this assessment must also be provided. This assessment will be done twice: once for olanzapine and once for samidorphan/placebo. The report submitted will include both assessments.

14. STATISTICS

14.1. Sample Size Considerations

Sample size calculations are based on the primary endpoint of absolute change in PANSS total score. These calculations assume 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 provide 95% power to demonstrate equivalence on the primary endpoint (absolute PANSS total score change from randomization to the end of Part A) with a 2-sided test at an alpha level of 0.05. 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 3 ALKS 3831 treatment groups will be pooled for comparison with placebo. 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.

14.2. General Statistical Methodology

The statistical analysis methods are described below. Additional details will be provided in the statistical analysis plan to be finalized before database lock and unblinding. In general, summary statistics, including n, mean with (SD), median, minimum, and maximum for continuous variables and number (%) of subjects in each category for categorical variables will be provided by treatment group for all variables.

Source data for the summary tables and statistical analyses will be presented as subject data listings.

All statistical tests and CIs, unless stated otherwise, will be 2-sided and will be set at $\alpha = 0.05$.

14.2.1. Efficacy Population

The efficacy analysis will be conducted on 2 analysis populations:

- The FAS 1 population will include all subjects who are randomized, receive at least one dose of study drug, and have at least one post-baseline PANSS assessment.
- The FAS 2 population will include all FAS 1 subjects who gained weight during the initial week of olanzapine treatment prior to randomization and have at least one post-baseline weight assessment.

14.2.2. Safety Population

The safety population, defined as all randomized subjects who receive at least 1 dose of study drug (olanzapine, samidorphan, or placebo), will be used in the safety analyses.

14.3. Demographics and Baseline Data

Demographics and baseline characteristics such as gender, age, race, ethnicity, weight, BMI will be summarized with descriptive statistics to assess the comparability of the study groups.

If there are heterogeneities between treatment groups in any of the subject characteristics that are of clinical importance or could affect the treatment outcome, the impact of the imbalances will be investigated and, if necessary, appropriate adjustments will be considered in the efficacy and safety analyses.

Medical history will be summarized for the safety population using the number of observations and percentage of subjects by body system.

14.4. Efficacy Analyses

The primary endpoint is the absolute change in PANSS total score from randomization to the end of Part A (ie, the end of the 12-week, placebo-controlled double-blind treatment period) and will be evaluated by treatment group (ALKS 3831 vs. the placebo group [olanzapine alone]) using a 2-sided mixed-model for repeated measures (MMRM) to test for equivalence at an alpha level of 0.05. The primary analysis will be conducted in the FAS 1 population. More details about this analysis will be provided in the SAP.

The secondary endpoint, percent change in weight from randomization to the end of Part A, will be evaluated by treatment group using an MMRM approach similar to that of the primary endpoint. However, this will be a superiority analysis. Each treatment group will be compared to the placebo group with a 2-sided hypothesis test to test for superiority at an alpha level of 0.05. The secondary efficacy analysis will also be conducted in the FAS 1 population. More details about this analysis will be provided in the SAP.

Analysis of other secondary endpoints and additional endpoints will include inferential analyses and descriptive analyses by visit (mean, SD, median, minimum, and maximum for continuous variables and number and percent for categorical variables), as appropriate.

Analyses for the primary and secondary endpoints will be repeated in the FAS 2 population as sensitivity analyses when applicable. Additional details regarding these analyses will be provided in the SAP.

14.5. Pharmacokinetic/Pharmacodynamic Analyses

For all subjects, plasma samples will be collected on Visits 2-23 to quantify the concentrations of olanzapine, samidorphan, and RDC-9986 (primary metabolite of samidorphan). Pharmacokinetic data may be used to assess compliance and/or included in subsequent population PK evaluation conducted outside of this study.

14.6. Safety and Tolerability Analyses

Reported AE terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA©) preferred terms and system organ classes. Descriptive summary statistics will be provided for AEs, laboratory tests, and vital signs and will include mean, SD, median, minimum and maximum for continuous variables and number and percent for categorical variables.

The incidence of AEs, including clinically significant abnormal laboratory tests or ECG values, will be summarized for each treatment group and overall, by severity and by relationship to study drug. The summary tables will include the number and percent of subjects with AEs overall, by

system organ class, and by preferred terms within each system organ class. AEs resulting in treatment discontinuation or modification will be identified.

Laboratory tests will be summarized by visit for the absolute value itself and for change from baseline. Tables showing the shift from baseline will also be presented.

ECG findings will be summarized by visit. Concomitant medications will be categorized and presented using the World Health Organization (WHO) drug Anatomical Therapeutic Chemical (ATC) classification system.

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

15.1. Study Monitoring

Monitoring of the study site (including, but not limited to, reviewing eCRFs for accuracy and completeness) will be performed by an Alkermes monitor or designee. A paper copy of the laboratory reports will be generated and will remain with the source documents at the site.

15.2. Audits and Inspections

By signing the protocol, the PI agrees that, within local regulatory restrictions and institutional and ethical considerations, authorized representatives of Alkermes, a regulatory authority, and/or an IRB/IEC may visit the site to perform audits or inspections, including the drug storage area, study drug stocks, drug accountability records, subject charts and source documents, and other records relative to study conduct. The purpose of an Alkermes audit or inspection is to systematically and independently examine all study-related activities and documents (eg, laboratory reports, workbooks, subjects' medical records) to determine whether these activities were conducted, and data recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements.

The PI (or designee) should contact Alkermes immediately if contacted by a regulatory agency regarding an inspection.

15.3. Institutional Review Board/ Independent Ethics Committee

The PI must obtain IRB/IEC approval for the investigation. Initial IRB/IEC approval as well as all materials approved by the IRB/IEC for this study, including the subject consent forms and recruitment materials (and as required, caregiver consent forms), must be maintained by the PI and made available for inspection.

16. QUALITY CONTROL AND QUALITY ASSURANCE

This study will be conducted under GCP and all applicable regulatory requirements. To ensure compliance, Alkermes may conduct a quality assurance audit. Please see Section 15.2 for details regarding the audit process.

16.1. Case Report Forms

This study will use eCRFs. All eCRFs will be completed by the clinic staff prior to review by the Alkermes monitor or designated representative. All eCRFs will be reviewed by the PI, as noted by his or her electronic signature, after review by the Alkermes monitor or designated representative.

The Alkermes monitor or designated representative will review source records on-site and compare them to the data collected on the eCRF.

16.2. Confidentiality of Data

By signing this protocol, the PI affirms to Alkermes that he or she will maintain in confidence information furnished to him or her by Alkermes and will divulge such information to his or her respective IRB or IEC under an appropriate understanding of confidentiality with such board. All data will be considered the sole property of Alkermes. Please refer to the Clinical Trial Agreement (CTA) for details.

17. ETHICAL CONSIDERATIONS

17.1. Ethics Review

The clinical site's IRB/IEC must meet all relevant regulatory requirements. The study protocol and ICFs will be reviewed by the IRB/IEC prior to enrolling subjects into the study; written approval from the committee must be received by Alkermes before drug will be released to the PI. The protocol must be re-approved by the IRB/IEC upon receipt of amendments and annually, as local regulatory requirements require.

The PI is responsible for submitting all protocol changes and SAE reports to the IRB/IEC according to local procedures. At a minimum, all SAEs requiring an investigational new drug safety report must be immediately reported.

In accordance with applicable local regulatory requirements, the PI may be obligated to provide periodic safety updates on the conduct of the study at his or her site and notification of study closure to the IRB/IEC. Such periodic safety updates and notifications are the responsibility of the PI and not of the sponsor.

All relevant correspondence from the IRB/IEC will be forwarded by the respective study site to the sponsor in a timely fashion.

17.2. Ethical Conduct of the Study

This study will be conducted in accordance with the protocol, the ICH Guideline E6, and all applicable local regulatory requirements. GCP is an international ethical and scientific quality standard used for designing, conducting, recording, and reporting studies involving the participation of human subjects. Alkermes is committed to complying with this standard to provide assurance that the rights, safety, and well-being of study subjects will be protected, consistent with the principles having their origin in the Declaration of Helsinki.

17.3. Written Informed Consent

The PI (or authorized designee) at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, potential and possible risks and benefits of the study. Each prospective subject will receive an IRB-approved ICF that summarizes all pertinent study information (the main ICF) and a separate IRB-approved ICF that summarizes only the pharmacogenetic testing (the DNA ICF) and will be given ample time to read the forms and ask questions about the study. All information is to be provided in a language understandable to the subject and must not include any language that waives the subject's legal rights. Prospective subjects must also be informed of their right to withdraw consent without prejudice at any time during the study. If the subject chooses to participate, he must sign the main ICF before any study-specific procedures are conducted. The subject does not need to sign the DNA ICF to participate in the main study, but the pharmacogenetic testing outlined in Section 8.3.11.1 should not be conducted unless the subject signs the DNA ICF.

All subjects will be informed of their rights to privacy and will be made aware that the study data will be submitted to Alkermes, the IRB, the CRO (Contract Research Organization) if applicable,

and to regulatory authorities for review and evaluation for the duration of the study and until the project has been approved for marketing, or is withdrawn from investigation. They will also be informed that the study monitor may inspect their medical records to verify the accuracy and completeness of the study records and results.

Significant changes to the protocol or product safety information may require a revision of the ICFs, which must be reviewed and signed by all applicable study participants.

The time that informed consent is obtained must be documented. The PI must maintain original, signed ICFs in the subject's source documents. Original, signed ICFs also must be given to the subject.

18. DATA HANDLING AND RECORDKEEPING

An overview of study data handling and recordkeeping procedures and restrictions is provided in the subsequent sections; please refer to the CTA for further details. Principal investigators are responsible for handling data in a manner consistent with local and international regulations on personal data (including health information) collection and protection (eg, in the Czech Republic: Act No. 101/2000 Coll. on personal data protection).

18.1. Data Capture

As stated in Section 16.1, this study will use eCRFs for capturing data. All entries, corrections, and alterations will be made by the PI or designee. Data entries will be verified for accuracy and correctness by independent monitors. The electronic data capture system maintains a full audit trail.

When available, a paper copy of all laboratory reports will remain with the source documents at the study site. All out of range laboratory values will be deemed as clinically significant or not clinically significant by the PI (or designated investigator). Any out of range laboratory values that meet the definition of an adverse event (see Section 13) will be documented accordingly.

AEs will be coded using MedDRA. Concomitant medications will be categorized using the WHO-ATC classification system.

18.2. Inspection of Records

Alkermes or its representative will be allowed to conduct site visits to the investigational facilities for the purpose of monitoring any aspect of the study. The PI agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and source documents, and other records relative to study conduct.

18.3. Retention of Records

Retention and storage of essential clinical study documents (eg, worksheets, drug accountability forms, and other administrative documentation) shall be governed by the terms and conditions of the site's CTA. If the CTA does not state specific document retention terms, then the site shall keep essential clinical study documentation for the longer of

- Ten years after discontinuation of the study, or
- Two years following the date a marketing application is approved for the study drug for the indication for which it is being investigated pursuant to the study, or
- If no application is to be filed or if the application is not approved for such indication, until 2 years after the date the study is terminated.

Subjects' medical files should be retained in accordance with the applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution, or private practice. A third-party blood-sample storage facility will retain blood samples for genotyping for up to ten years after discontinuation of the study.

18.4. Use of Information and Publication Policy

Data generated in this study are proprietary information that is the sole property of Alkermes. Results of the study are to be held in confidence by both the PIs and the sponsor. Please refer to the CTA for details on the procedures for publishing and presenting data.

19. REFERENCES

Batki SL, Meszaros ZS, Strutynski K, Dimmock JA, Leontieva L, Ploutz-Snyder R, Canfield K, Drayer RA (2009) Medical comorbidity in patients with schizophrenia and alcohol dependence. Schizophr Res 107:139-146

Dixon L (1999) Dual diagnosis of substance abuse in schizophrenia: prevalence and impact on outcomes. Schizophr Res 35 Suppl:S93-100

Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK (2005) Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 353:1209-1223

Lubman DI, King JA, Castle DJ (2010) Treating comorbid substance use disorders in schizophrenia. Int Rev Psychiatry 22:191-201

Sobell LC, Sobell MB (1992) Timeline Follow-Back: A technique for assessing self-reported alcohol consumption. In: Litten RZ, Allen JP eds. Measuring Alcohol Consumption: Psychosocial and Biological Methods. The Humana Press, Totowa, NJ, pp. 41-72

Zyprexa [Package Insert]. Indianapolis, IN: Eli Lilly,& Co.; 2011.

APPENDIX A. SAMPLE CLINICAL GLOBAL IMPRESSIONS-SEVERITY (CGI-S) SCALE

Clinical Global Impression (CGI)

Reference: **Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare**

Rating Clinician-rated

Administration time Varies with familiarity with patient

Main purpose To provide a global rating of illness severity, improvement and response to treatment

Population Adults

Commentary

Amongst the most widely used of extant brief assessment tools in psychiatry, the CGI is a 3-item observer-rated scale that measures illness severity (CGIS), global improvement or change (CGIC) and therapeutic response. The illness severity and improvement sections of the instrument are used more frequently than the therapeutic response section in both clinical and research settings. The Early Clinical Drug Evaluation Program (ECDEU) version of the CGI (reproduced here) is the most widely used format, and asks that the clinician rate the patient relative to their past experience with other patients with the same diagnosis, with or without collateral information. Several alternative versions of the CGI have been developed, however, such as the FDA Clinicians' Interview-Based Impression of Change (CIBIC), which uses only information collected during the interview, not collateral. The CGI has proved to be a robust measure of efficacy in many clinical drug trials, and is easy and quick to administer, provided that the clinician knows the patient well.

Scoring

The CGI is rated on a 7-point scale, with the severity of illness scale using a range of responses from 1 (normal) through to 7 (amongst the most severely ill patients). CGI-C scores range from 1 (very much improved) through to 7 (very much worse). Treatment response ratings should take account of both therapeutic efficacy and treatment-related adverse events and range from 0 (marked improvement and no side-effects) and 4 (unchanged or worse and side-effects outweigh the therapeutic effects). Each component of the CGI is rated separately; the instrument does not yield a global score.

Versions

CGI for bipolar disorder (CGI-BD), FDA Clinicians' Interview-Based Impression of Change (CIBIC), Clinicians' Interview-Based Impression of Change-Plus (CIBIC+), NYU CIBIC+, Parke-Davis Pharmaceuticals Clinical Interview-Based Impression (CIBI); the CGI has been translated into most languages.

Additional references

Leon AC, Shear MK, Klerman GL, Portera L, Rosenbaum JF, Goldenberg I. A comparison of symptom determinants of patient and clinician global ratings in patients with panic disorder and depression. J Clin Psychopharmacol 1993; 13(5):327–31.

Spearing MK, Post RM, Leverich GS, Brandt D, Nolen W. Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): the CGI-BP. Psychiatry Res 1997; 73(3):159–71.

Zaider TI, Heimberg RG, Fresco DM, Schneier FR, Liebowitz MR. Evaluation of the clinical global impression scale among individuals with social anxiety disorder. Psychol Med 2003; 33(4):611–22.

Address for correspondence

Not applicable – the CGI is in the public domain.

Clinical Global Impression (CGI)

1. **Severity of illness**
   Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?
   0 = Not assessed
   1 = Normal, not at all ill
   2 = Borderline mentally ill
   3 = Mildly ill
   4 = Moderately ill
   5 = Markedly ill
   6 = Severely ill
   7 = Among the most extremely ill patients

2. **Global improvement:** Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.
   Compared to his condition at admission to the project, how much has he changed?
   0 = Not assessed
   1 = Very much improved
   2 = Much improved
   3 = Minimally improved
   4 = No change
   5 = Minimally worse
   6 = Much worse
   7 = Very much worse

3. **Efficacy index:** Rate this item on the basis of **drug effect only**.
   Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect.
   EXAMPLE: Therapeutic effect is rated as 'Moderate' and side effects are judged 'Do not significantly interfere with patient's functioning'.

Therapeutic effect		**Side effects**			
		None	*Do not significantly interfere with patient's functioning*	*Significantly interferes with patient's functioning*	*Outweighs therapeutic effect*
Marked	Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
Moderate	Decided improvement. Partial remission of symptoms	05	06	07	08
Minimal	Slight improvement which doesn't alter status of care of patient	09	10	11	12
Unchanged or worse		13	14	15	16

Not assessed = 00

Reproduced from Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare

APPENDIX B. SAMPLE COLUMBIA SUICIDE SEVERITY RATING SCALE (C-SSRS)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended for use by trained clinicians. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidality depends on clinical judgment.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact PPD *New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact* PPD

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes," ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Lifetime: Time He/She Felt Most Suicidal

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?

If yes, describe:

Yes ☐ **No** ☐

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g. *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan.
Have you actually had any thoughts of killing yourself?

If yes, describe:

Yes ☐ **No** ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…..and I would never go through with it".*
Have you been thinking about how you might do this?

If yes, describe:

Yes ☐ **No** ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".*
Have you had these thoughts and had some intention of acting on them?

If yes, describe:

Yes ☐ **No** ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?

If yes, describe:

Yes ☐ **No** ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.

Most Severe Ideation: _____ _____

Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day

____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

____

Controllability
Could /can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts

____

Deterrents
Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others.
(2) Mostly to get attention, revenge or a reaction from others.
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain.
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling).
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling).
(0) Does not apply

____

SUICIDAL BEHAVIOR

(Check all that apply, so long as these are separate events; must ask about all types)

Lifetime

Actual Attempt:

A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt.

Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.

Have you made a suicide attempt?

Have you done anything to harm yourself?

Have you done anything dangerous where you could have died?

What did you do?

Did you_____ as a way to end your life?

Did you want to die (even a little) when you_____?

Were you trying to end your life when you _____?

Or did you think it was possible you could have died from_____?

Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)? (Self-Injurious Behavior without suicidal intent)

If yes, describe:

Yes ☐ **No** ☐

Total # of Attempts _____

Yes ☐ **No** ☐

Has subject engaged in Non-Suicidal Self-Injurious Behavior?

Interrupted Attempt:

When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).*

Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so.

Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?

If yes, describe:

Yes ☐ **No** ☐

Total # of interrupted _____

Aborted Attempt:

When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else.

Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?

If yes, describe:

Yes ☐ **No** ☐

Total # of aborted _____

Preparatory Acts or Behavior:

Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note).

Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?

If yes, describe:

Yes ☐ **No** ☐

Suicidal Behavior:

Suicidal behavior was present during the assessment period?

Yes ☐ **No** ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g. surface scratches). 1. Minor physical damage (e.g. lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g. comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g. comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended for use by trained clinicians. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidality depends on clinical judgment.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact PPD *, New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact* PPD

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes," ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead — Yes ☐ No ☐

Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.

Have you wished you were dead or wished you could go to sleep and not wake up?

If yes, describe:

2. Non-Specific Active Suicidal Thoughts — Yes ☐ No ☐

General, non-specific thoughts of wanting to end one's life/commit suicide (e.g. *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.

Have you actually had any thoughts of killing yourself?

If yes, describe:

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act — Yes ☐ No ☐

Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…..and I would never go through with it".*

Have you been thinking about how you might do this?

If yes, describe:

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan — Yes ☐ No ☐

Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u>, as opposed to *"I have the thoughts but I definitely will not do anything about them".*

Have you had these thoughts and had some intention of acting on them?

If yes, describe:

5. Active Suicidal Ideation with Specific Plan and Intent — Yes ☐ No ☐

Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.

Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?

If yes, describe:

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe

Most Severe Ideation: _____ _____

Type # (1-5) ***Description of Ideation***

Frequency ____

How many times have you had these thoughts?

(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day

Duration ____

When you have the thoughts, how long do they last?

(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

Controllability ____

Could /can you stop thinking about killing yourself or wanting to die if you want to?

(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts

Deterrents ____

Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?

(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

Reasons for Ideation ____

What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?

(1) Completely to get attention, revenge or a reaction from others.
(2) Mostly to get attention, revenge or a reaction from others.
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain.
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling).
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling).
(0) Does not apply

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** ☐ **No** ☐ Total # of Attempts _____ **Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐
Completed Suicide:	**Yes** ☐ **No** ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g. surface scratches). 1. Minor physical damage (e.g. lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g. comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g. comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

APPENDIX C. SAMPLE POSITIVE AND NEGATIVE SYNDROME SCALE (PANSS)

PANSS

Positive and Negative Syndrome Scale

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Abraham Fiszbein, M.D.

Rating Criteria

MHS

Positive Scale (P)

P1. Delusions. Beliefs which are unfounded, unrealistic, and idiosyncratic. *Basis for rating:* thought content expressed in the interview and its influence on social relations and behavior as reported by primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Presence of one or two delusions, which are vague, uncrystallized, and not tenaciously held. Delusions do not interfere with thinking, social relations, or behavior.
4	Moderate	Presence of either a kaleidoscopic array of poorly formed, unstable delusions or a few well-formed delusions that occasionally interfere with thinking, social relations, or behavior.
5	Moderate	Presence of numerous well-formed delusions that are tenaciously held and occasionally interfere with thinking, social relations, or behavior.
6	Severe	Presence of a stable set of delusions which are crystallized, possibly systematized, tenaciously held, and clearly interfere with thinking, social relations, and behavior.
7	Extreme	Presence of a stable set of delusions which are either highly systematized or very numerous, and which dominate major facets of the patient's life. This frequently results in inappropriate and irresponsible action, which may even jeopardize the safety of the patient or others.

Positive Scale (P)

P2. Conceptual disorganization. Disorganized process of thinking characterized by disruption of goal-directed sequencing, e.g., circumstantiality, tangentiality, loose associations, non-sequiturs, gross illogicality, or thought block. *Basis for rating*: cognitive-verbal processes observed during the course of interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Thinking is circumstantial, tangential, or paralogical. There is some difficulty in directing thoughts toward a goal, and some loosening of associations may be evidenced under pressure.
4	Moderate	Able to focus thoughts when communications are brief and structured, but becomes loose or irrelevant when dealing with more complex communications or when under minimal pressure.
5	Moderate Severe	Generally has difficulty in organizing thoughts, as evidenced by frequent irrelevancies, disconnectedness, or loosening of associations even when not under pressure.
6	Severe	Thinking is seriously derailed and internally inconsistent, resulting in gross irrelevancies and disruption of thought processes, which occur almost constantly.
7	Extreme	Thoughts are disrupted to the point where the patient is incoherent. There is marked loosening of associations, which results in total failure of communication, e.g., "word salad" or mutism.

Positive Scale (P)

P3. Hallucinatory behavior. Verbal report or behavior indicating perceptions which are not generated by external stimuli. These may occur in the auditory, visual, olfactory, or somatic realms. *Basis for rating*: verbal report and physical manifestations during the course of interview as well as reports of behavior by primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	One or two clearly formed but infrequent hallucinations, or else a number of vague abnormal perceptions, which do not result in distortions of thinking or behavior.
4	Moderate	Hallucinations occur frequently but not continuously, and the patient's thinking and behavior are affected only to a minor extent.
5	Moderate Severe	Hallucinations are frequent, may involve more than one sensory modality, and tend to distort thinking and/or disrupt behavior. Patient may have delusional interpretation of these experiences and respond to them emotionally and, on occasion, verbally as well.
6	Severe	Hallucinations are present almost continuously, causing major disruption of thinking and behavior. Patient treats these as real perceptions, and functioning is impeded by frequent emotional and verbal responses to them.
7	Extreme	Patient is almost totally preoccupied with hallucinations, which virtually dominate thinking and behavior. Hallucinations are provided a rigid delusional interpretation and provoke verbal and behavioral responses, including obedience to command hallucinations.

Positive Scale (P)

P4. Excitement. Hyperactivity as reflected in accelerated motor behavior, heightened responsivity to stimuli, hypervigilance, or excessive mood lability. *Basis for rating*: behavioral manifestations during the course of interview as well as reports of behavior by primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Tends to be slightly agitated, hypervigilant, or mildly overaroused throughout the interview, but without distinct episodes of excitement or marked mood lability. Speech may be slightly pressured.
4	Moderate	Agitation or overarousal is clearly evident throughout the interview, affecting speech and general mobility, or episodic outbursts occur sporadically.
5	Moderate Severe	Significant hyperactivity or frequent outbursts of motor activity are observed, making it difficult for the patient to sit still for longer than several minutes at any given time.
6	Severe	Marked excitement dominates the interview, delimits attention, and to some extent affects personal functions such as eating and sleeping.
7	Extreme	Marked excitement seriously interferes in eating and sleeping and makes interpersonal interactions virtually impossible. Acceleration of speech and motor activity may result in incoherence and exhaustion.

Positive Scale (P)

P5. Grandiosity. Exaggerated self-opinion and unrealistic convictions of superiority, including delusions of extraordinary abilities, wealth, knowledge, fame, power, and moral righteousness. *Basis for rating*: thought content expressed in the interview and its influence on behavior as reported by primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Some expansiveness or boastfulness is evident, but without clear-cut grandiose delusions.
4	Moderate	Feels distinctly and unrealistically superior to others. Some poorly formed delusions about special status or abilities may be present but are not acted upon.
5	Moderate Severe	Clear-cut delusions concerning remarkable abilities, status, or power are expressed and influence attitude but not behavior.
6	Severe	Clear-cut delusions of remarkable superiority involving more than one parameter (wealth, knowledge, fame, etc.) are expressed, notably influence interactions, and may be acted upon.
7	Extreme	Thinking, interactions, and behavior are dominated by multiple delusions of amazing ability, wealth, knowledge, fame, power, and/or moral stature, which may take on a bizarre quality.

Positive Scale (P)

P6. Suspiciousness/persecution. Unrealistic or exaggerated ideas of persecution, as reflected in guardedness, a distrustful attitude, suspicious hypervigilance, or frank delusions that others mean one harm. *Basis for rating:* thought content expressed in the interview and its influence on behavior as reported by primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Presents a guarded or even openly distrustful attitude, but thoughts, interactions, and behavior are minimally affected.
4	Moderate	Distrustfulness is clearly evident and intrudes on the interview and/or behavior, but there is no evidence of persecutory delusions. Alternatively, there may be indication of loosely formed persecutory delusions, but these do not seem to affect the patient's attitude or interpersonal relations.
5	Moderate Severe	Patient shows marked distrustfulness, leading to major disruption of interpersonal relations, or else there are clear-cut persecutory delusions that have limited impact on interpersonal relations and behavior.
6	Severe	Clear-cut pervasive delusions of persecution which may be systematized and significantly interfere in interpersonal relations.
7	Extreme	A network of systematized persecutory delusions dominates the patient's thinking, social relations, and behavior.

Positive Scale (P)

P7. Hostility. Verbal and nonverbal expressions of anger and resentment, including sarcasm, passive-aggressive behavior, verbal abuse, and assaultiveness. *Basis for rating:* interpersonal behavior observed during the interview and reports by primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Indirect or restrained communication of anger, such as sarcasm, disrespect, hostile expressions, and occasional irritability.
4	Moderate	Presents an overtly hostile attitude, showing frequent irritability and direct expression of anger or resentment.
5	Moderate Severe	Patient is highly irritable and occasionally verbally abusive or threatening.
6	Severe	Uncooperativeness and verbal abuse or threats notably influence the interview and seriously impact upon social relations. Patient may be violent and destructive but is not physically assaultive toward others.
7	Extreme	Marked anger results in extreme uncooperativeness, precluding other interactions, or in episode(s) of physical assault toward others.

Negative Scale (N)

N1. Blunted affect. Diminished emotional responsiveness as characterized by a reduction in facial expression, modulation of feelings, and communicative gestures. *Basis for rating*: observation of physical manifestations of affective tone and emotional responsiveness during the course of interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Changes in facial expression and communicative gestures seem to be stilted, forced, artificial, or lacking in modulation.
4	Moderate	Reduced range of facial expression and few expressive gestures result in a dull appearance.
5	Moderate Severe	Affect is generally "flat," with only occasional changes in facial expression and a paucity of communicative gestures.
6	Severe	Marked flatness and deficiency of emotions exhibited most of the time. There may be unmodulated extreme affective discharges, such as excitement, rage, or inappropriate uncontrolled laughter.
7	Extreme	Changes in facial expression and evidence of communicative gestures are virtually absent. Patient seems constantly to show a barren or 'wooden" expression.

Negative Scale (N)

N2. Emotional withdrawal. Lack of interest in, involvement with, and affective commitment to life's events. *Basis for rating*: reports of functioning from primary care workers or family and observation of interpersonal behavior during the course of interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Usually lacks initiative and occasionally may show deficient interest in surrounding events.
4	Moderate	Patient is generally distanced emotionally from the milieu and its challenges but, with encouragement, can be engaged.
5	Moderate Severe	Patient is clearly detached emotionally from persons and events in the milieu, resisting all efforts at engagement. Patient appears distant, docile, and purposeless but can be involved in communication at least briefly and tends to personal needs, sometimes with assistance.
6	Severe	Marked deficiency of interest and emotional commitment results in limited conversation with others and frequent neglect of personal functions, for which the patient requires supervision.
7	Extreme	Patient is almost totally withdrawn, uncommunicative, and neglectful of personal needs as a result of profound lack of interest and emotional commitment.

Negative Scale (N)

N3. Poor rapport. Lack of interpersonal empathy, openness in conversation, and sense of closeness, interest, or involvement with the interviewer. This is evidenced by interpersonal distancing and reduced verbal and nonverbal communication. *Basis for rating:* interpersonal behavior during the course of interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Conversation is characterized by a stilted, strained, or artificial tone. It may lack emotional depth or tend to remain on an impersonal, intellectual plane.
4	Moderate	Patient typically is aloof, with interpersonal distance quite evident. Patient may answer questions mechanically, act bored, or express disinterest.
5	Moderate Severe	Disinvolvement is obvious and clearly impedes the productivity of the interview. Patient may tend to avoid eye or face contact.
6	Severe	Patient is highly indifferent, with marked interpersonal distance. Answers are perfunctory, and there is little nonverbal evidence of involvement. Eye and face contact are frequently avoided.
7	Extreme	Patient is totally uninvolved with the interviewer. Patient appears to be completely indifferent and consistently avoids verbal and nonverbal interactions during the interview.

Negative Scale (N)

N4. Passive/apathetic social withdrawal. Diminished interest and initiative in social interactions due to passivity, apathy, anergy, or avolition. This leads to reduced interpersonal involvements and neglect of activities of daily living. *Basis for rating:* reports on social behavior from primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Shows occasional interest in social activities but poor initiative. Usually engages with others only when approached first by them.
4	Moderate	Passively goes along with most social activities but in a disinterested or mechanical way. Tends to recede into the background.
5	Moderate Severe	Passively participates in only a minority of activities and shows virtually no interest or initiative. Generally spends little time with others.
6	Severe	Tends to be apathetic and isolated, participating very rarely in social activities and occasionally neglecting personal needs. Has very few spontaneous social contacts.
7	Extreme	Profoundly apathetic, socially isolated, and personally neglectful.

Negative Scale (N)

N5. Difficulty in abstract thinking. Impairment in the use of the abstract-symbolic mode of thinking, as evidenced by difficulty in classification, forming generalizations, and proceeding beyond concrete or egocentric thinking in problem-solving tasks. *Basis for rating:* responses to questions on similarities and proverb interpretation, and use of concrete vs. abstract mode during the course of the interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Tends to give literal or personalized interpretations to the more difficult proverbs and may have some problems with concepts that are fairly abstract or remotely related.
4	Moderate	Often utilizes a concrete mode. Has difficulty with most proverbs and some categories. Tends to be distracted by functional aspects and salient features.
5	Moderate Severe	Deals primarily in a concrete mode, exhibiting difficulty with most proverbs and many categories.
6	Severe	Unable to grasp the abstract meaning of any proverbs or figurative expressions and can formulate classifications for only the most simple of similarities. Thinking is either vacuous or locked into functional aspects, salient features, and idiosyncratic interpretations.
7	Extreme	Can use only concrete modes of thinking. Shows no comprehension of proverbs, common metaphors or similes, and simple categories. Even salient and functional attributes do not serve as a basis for classification. This rating may apply to those who cannot interact even minimally with the examiner due to marked cognitive impairment.

Negative Scale (N)

N6. Lack of spontaneity and flow of conversation. Reduction in the normal flow of communication associated with apathy, avolition, defensiveness, or cognitive deficit. This is manifested by diminished fluidity and productivity of the verbal-interactional process. *Basis for rating*: cognitive-verbal processes observed during the course of interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Conversation shows little initiative. Patient's answers tend to be brief and unembellished, requiring direct and leading questions by the interviewer.
4	Moderate	Conversation lacks free flow and appears uneven or halting. Leading questions are frequently needed to elicit adequate responses and proceed with conversation.
5	Moderate Severe	Patient shows a marked lack of spontaneity and openness, replying to the interviewer's questions with only one or two brief sentences.
6	Severe	Patient's responses are limited mainly to a few words or short phrases intended to avoid or curtail communication. (E.g., "I don't know," "I'm not at liberty to say.") Conversation is seriously impaired as a result, and the interview is highly unproductive.
7	Extreme	Verbal output is restricted to, at most, an occasional utterance, making conversation impossible.

Negative Scale (N)

N7. Stereotyped thinking. Decreased fluidity, spontaneity, and flexibility of thinking, as evidenced in rigid, repetitious, or barren thought content. *Basis for rating:* cognitive-verbal processes observed during the interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Some rigidity shown in attitudes or beliefs. Patient may refuse to consider alternative positions or have difficulty in shifting from one idea to another.
4	Moderate	Conversation revolves around a recurrent theme, resulting in difficulty in shifting to a new topic.
5	Moderate Severe	Thinking is rigid and repetitious to the point that, despite the interviewer's efforts, conversation is limited to only two or three dominating topics.
6	Severe	Uncontrolled repetition of demands, statements, ideas, or questions which severely impairs conversation.
7	Extreme	Thinking, behavior, and conversation are dominated by constant repetition of fixed ideas or limited phrases, leading to gross rigidity, inappropriateness, and restrictiveness of patient's communication.

General Psychopathology Scale (G)

G1. Somatic concern. Physical complaints or beliefs about bodily illness or malfunctions. This may range from a vague sense of ill being to clear-cut delusions of catastrophic physical disease. *Basis for rating:* thought content expressed in the interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Distinctly concerned about health or somatic issues, as evidenced by occasional questions and desire for reassurance.
4	Moderate	Complains about poor health or bodily malfunction, but there is no delusional conviction, and over-concern can be allayed by reassurance.
5	Moderate Severe	Patient expresses numerous or frequent complaints about physical illness or bodily malfunction, or else patient reveals one or two clear-cut delusions involving these themes but is not preoccupied by them.
6	Severe	Patient is preoccupied by one or a few clear-cut delusions about physical disease or organic malfunction, but affect is not fully immersed in these themes, and thoughts can be diverted by the interviewer with some effort.
7	Extreme	Numerous and frequently reported somatic delusions, or only a few somatic delusions of a catastrophic nature, which totally dominate the patient's affect and thinking.

General Psychopathology Scale (G)

G2. Anxiety. Subjective experience of nervousness, worry, apprehension, or restlessness, ranging from excessive concern about the present or future to feelings of panic. *Basis for rating*: verbal report during the course of interview and corresponding physical manifestations.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Expresses some worry, over-concern, or subjective restlessness, but no somatic and behavioral consequences are reported or evidenced.
4	Moderate	Patient reports distinct symptoms of nervousness, which are reflected in mild physical manifestations such as fine hand tremor and excessive perspiration.
5	Moderate Severe	Patient reports serious problems of anxiety, which have significant physical and behavioral consequences, such as marked tension, poor concentration, palpitations, or impaired sleep.
6	Severe	Subjective state of almost constant fear associated with phobias, marked restlessness, or numerous somatic manifestations.
7	Extreme	Patient's life is seriously disrupted by anxiety, which is present almost constantly and, at times, reaches panic proportion or is manifested in actual panic attacks.

General Psychopathology Scale (G)

G3. Guilt feelings. Sense of remorse or self-blame for real or imagined misdeeds in the past. *Basis for rating:* verbal report of guilt feelings during the course of interview and the influence on attitudes and thoughts.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Questioning elicits a vague sense of guilt or self-blame for a minor incident, but the patient clearly is not overly concerned.
4	Moderate	Patient expresses distinct concern over his or her responsibility for a real incident in his or her life but is not preoccupied with it, and attitude and behavior are essentially unaffected.
5	Moderate Severe	Patient expresses a strong sense of guilt associated with self-deprecation or the belief that he or she deserves punishment. The guilt feelings may have a delusional basis, may be volunteered spontaneously, may be a source of preoccupation and/or depressed mood, and cannot be allayed readily by the interviewer.
6	Severe	Strong ideas of guilt take on a delusional quality and lead to an attitude of hopelessness or worthlessness. The patient believes he or she should receive harsh sanctions for the misdeeds and may even regard his or her current life situation as such punishment.
7	Extreme	Patient's life is dominated by unstable delusions of guilt, for which he or she feels deserving of drastic punishment, such as life imprisonment, torture, or death. There may be associated suicidal thoughts or attribution of others' problems to one's own past misdeeds.

General Psychopathology Scale (G)

G4. *Tension.* Overt physical manifestations of fear, anxiety, and agitation, such as stiffness, tremor, profuse sweating, and restlessness. *Basis for rating:* verbal report attesting to anxiety and, thereupon, the severity of physical manifestations of tension observed during the interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Posture and movements indicate slight apprehensiveness, such as minor rigidity, occasional restlessness, shifting of position, or fine rapid hand tremor.
4	Moderate	A clearly nervous appearance emerges from various manifestations, such as fidgety behavior, obvious hand tremor, excessive perspiration, or nervous mannerisms.
5	Moderate Severe	Pronounced tension is evidenced by numerous manifestations, such as nervous shaking, profuse sweating, and restlessness, but conduct in the interview is not significantly affected.
6	Severe	Pronounced tension to the point that interpersonal interactions are disrupted. The patient, for example, may be constantly fidgeting, unable to sit still for long, or show hyperventilation.
7	Extreme	Marked tension is manifested by signs of panic or gross motor acceleration, such as rapid restless pacing and inability to remain seated for longer than a minute, which makes sustained conversation not possible.

General Psychopathology Scale (G)

G5. Mannerisms and posturing. Unnatural movements or posture as characterized by an awkward, stilted, disorganized, or bizarre appearance. *Basis for rating:* observation of physical manifestations during the course of interview as well as reports from primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Slight awkwardness in movements or minor rigidity of posture.
4	Moderate	Movements are notably awkward or disjointed, or an unnatural posture is maintained for brief periods.
5	Moderate Severe	Occasional bizarre rituals or contorted posture are observed, or an abnormal position is sustained for extended periods.
6	Severe	Frequent repetition of bizarre rituals, mannerisms, or stereotyped movements, or a contorted posture is sustained for extended periods.
7	Extreme	Functioning is seriously impaired by virtually constant involvement in ritualistic, manneristic, or stereotyped movements or by an unnatural fixed posture which is sustained most of the time.

General Psychopathology Scale (G)

G6. Depression. Feelings of sadness, discouragement, helplessness, and pessimism. *Basis for rating*: verbal report of depressed mood during the course of interview and its observed influence on attitude and behavior as reported by primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Expresses some sadness or discouragement only on questioning, but there is no evidence of depression in general attitude or demeanor.
4	Moderate	Distinct feelings of sadness or hopelessness, which may be spontaneously divulged, but depressed mood has no major impact on behavior or social functioning, and the patient usually can be cheered up.
5	Moderate Severe	Distinctly depressed mood is associated with obvious sadness, pessimism, loss of social interest, psychomotor retardation, and some interference in appetite and sleep. The patient cannot be easily cheered up.
6	Severe	Markedly depressed mood is associated with sustained feelings of misery, occasional crying, hopelessness, and worthlessness. In addition, there is major interference in appetite and/or sleep as well as in normal motor and social functions, with possible signs of self-neglect.
7	Extreme	Depressive feelings seriously interfere in most major functions. The manifestations include frequent crying, pronounced somatic symptoms, impaired concentration, psychomotor retardation, social disinterest, self-neglect, possible depressive or nihilistic delusions, and/or possible suicidal thoughts or actions.

General Psychopathology Scale (G)

G7. Motor retardation. Reduction in motor activity as reflected in slowing or lessening of movements and speech, diminished responsiveness to stimuli, and reduced body tone. *Basis for rating:* manifestations during the course of interview as well as reports by primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Slight but noticeable diminution in rate of movements and speech. Patient may be somewhat underproductive in conversation and gestures.
4	Moderate	Patient is clearly slow in movements, and speech may be characterized by poor productivity, including long response latency, extended pauses, or slow pace.
5	Moderate Severe	A marked reduction in motor activity renders communication highly unproductive or delimits functioning in social and occupational situations. Patient can usually be found sitting or lying down.
6	Severe	Movements are extremely slow, resulting in a minimum of activity and speech. Essentially the day is spent sitting idly or lying down.
7	Extreme	Patient is almost completely immobile and virtually unresponsive to external stimuli.

General Psychopathology Scale (G)

G8. Uncooperativeness. Active refusal to comply with the will of significant others, including the interviewer, hospital staff, or family, which may be associated with distrust, defensiveness, stubbornness, negativism, rejection of authority, hostility, or belligerence. *Basis for rating:* interpersonal behavior observed during the course of interview as well as reports by primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Complies with an attitude of resentment, impatience, or sarcasm. May inoffensively object to sensitive probing during the interview.
4	Moderate	Occasional outright refusal to comply with normal social demands, such as making own bed, attending scheduled programs, etc. The patient may project a hostile, defensive, or negative attitude but usually can be worked with.
5	Moderate Severe	Patient frequently is incompliant with the demands of his or her milieu and may be characterized by others as an "outcast' or having "a serious attitude problem." Uncooperativeness is reflected in obvious defensiveness or irritability with the interviewer and possible unwillingness to address many questions.
6	Severe	Patient is highly uncooperative, negativistic, and possibly also belligerent. Refuses to comply with most social demands and may be unwilling to initiate or conclude the full interview.
7	Extreme	Active resistance seriously impacts on virtually all major areas of functioning. Patient may refuse to join in any social activities, tend to personal hygiene, converse with family or staff, and participate even briefly in an interview.

General Psychopathology Scale (G)

G9. Unusual thought content. Thinking characterized by strange, fantastic, or bizarre ideas, ranging from those, which are remote or atypical to those which are distorted, illogical, and patently absurd. *Basis for rating*: thought content expressed during the course of interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Thought content is somewhat peculiar or idiosyncratic, or familiar ideas are framed in an odd context.
4	Moderate	Ideas are frequently distorted and occasionally seem quite bizarre.
5	Moderate Severe	Patient expresses many strange and fantastic thoughts (e.g., being the adopted son of a king, being an escapee from death row) or some which are patently absurd (e.g., having hundreds of children, receiving radio messages from outer space through a tooth filling).
6	Severe	Patient expresses many illogical or absurd ideas or some, which have a distinctly bizarre quality (e.g., having three heads, being a visitor from another planet).
7	Extreme	Thinking is replete with absurd, bizarre, and grotesque ideas.

General Psychopathology Scale (G)

G10. Disorientation. Lack of awareness of one's relationship to the milieu, including persons, place, and time, which may be due to confusion or withdrawal. *Basis for rating*: responses to interview questions on orientation.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	General orientation is adequate but there is some difficulty with specifics. For example, patient knows his or her location but not the street address; knows hospital staff names but not their functions; knows the month but confuses the day of week with an adjacent day; or errs in the date by more than two days. There may be narrowing of interest evidenced by familiarity with the immediate but not extended milieu, such as ability to identify staff but not the Mayor, Governor, or President.
4	Moderate	Only partial success in recognizing persons, places, and time. For example, patient knows he or she is in a hospital but not its name; knows the name of his or her city but not the borough or district, knows the name of his or her primary therapist but not many other direct care workers; knows the year and season but is not sure of the month.
5	Moderate Severe	Considerable failure in recognizing persons, place, and time. Patient has only a vague notion of where he or she is and seems unfamiliar with most people in his or her milieu. He or she may identify the year correctly or nearly so but not know the current month, day of week, or even the season.
6	Severe	Marked failure in recognizing persons, place, and time. For example, patient has no knowledge of his or her whereabouts; confuses the date by more than one year; can name only one or two individuals in his or her current life.
7	Extreme	Patient appears completely disoriented with regard to persons, place, and time. There is gross confusion or total ignorance about one's location, the current year, and even the most familiar people, such as parents, spouse, friends, and primary therapist.

General Psychopathology Scale (G)

G11. Poor attention. Failure in focused alertness manifested by poor concentration, distractibility from internal and external stimuli, and difficulty in harnessing, sustaining, or shifting focus to new stimuli. *Basis for rating:* manifestations during the course of interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Limited concentration evidenced by occasional vulnerability to distraction or faltering attention toward the end of the interview.
4	Moderate	Conversation is affected by the tendency to be easily distracted, difficulty in long sustaining concentration on a given topic, or problems in shifting attention to new topics.
5	Moderate Severe	Conversation is seriously hampered by poor concentration, distractibility, and difficulty in shifting focus appropriately.
6	Severe	Patient's attention can be harnessed for only brief moments or with great effort, due to marked distraction by internal or external stimuli.
7	Extreme	Attention is so disrupted that even brief conversation is not possible.

General Psychopathology Scale (G)

G12. Lack of judgment and insight. Impaired awareness or understanding of one's own psychiatric condition and life situation. This is evidenced by failure to recognize past or present psychiatric illness or symptoms, denial of need for psychiatric hospitalization or treatment, decisions characterized by poor anticipation of consequences, and unrealistic short-term and long-range planning. *Basis for rating*: thought content expressed during the interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Recognizes having a psychiatric disorder but clearly underestimates its seriousness, the implications for treatment, or the importance of taking measures to avoid relapse. Future planning may be poorly conceived.
4	Moderate	Patient shows only a vague or shallow recognition of illness. There may be fluctuations in acknowledgment of being ill or little awareness of major symptoms, which are present, such as delusions, disorganized thinking, suspiciousness, and social withdrawal. The patient may rationalize the need for treatment in terms of its relieving lesser symptoms, such as anxiety, tension, and sleep difficulty.
5	Moderate Severe	Acknowledges past but not present psychiatric disorder. If challenged, the patient may concede the presence of some unrelated or insignificant symptoms, which tend to be explained away by gross misinterpretation or delusional thinking. The need for psychiatric treatment similarly goes unrecognized.
6	Severe	Patient denies ever having had a psychiatric disorder. He or she disavows the presence of any psychiatric symptoms in the past or present and, though compliant, denies the need for treatment and hospitalization.
7	Extreme	Emphatic denial of past and present psychiatric illness. Current hospitalization and treatment are given a delusional interpretation (e.g., as punishment for misdeeds, as persecution by tormentors, etc.), and the patient may thus refuse to cooperate with therapists, medication, or other aspects of treatment.

General Psychopathology Scale (G)

G13. Disturbance of volition. Disturbance in the willful initiation, sustenance, and control of one's thoughts, behavior, movements, and speech. *Basis for rating:* thought content and behavior manifested in the course of interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	There is evidence of some indecisiveness in conversation and thinking, which may impede verbal and cognitive processes to a minor extent.
4	Moderate	Patient is often ambivalent and shows clear difficulty in reaching decisions. Conversation may be marred by alteration in thinking, and in consequence verbal and cognitive functioning are clearly impaired.
5	Moderate Severe	Disturbance of volition interferes in thinking as well as behavior. Patient shows pronounced indecision that impedes the initiation and continuation of social and motor activities, and which also may be evidenced in halting speech.
6	Severe	Disturbance of volition interferes in the execution of simple, automatic motor functions, such as dressing and grooming, and markedly affects speech.
7	Extreme	Almost complete failure of volition is manifested by gross inhibition of movement and speech, resulting in immobility and/or mutism.

General Psychopathology Scale (G)

G14. Poor impulse control. Disordered regulation and control of action on inner urges, resulting in sudden, unmodulated, arbitrary, or misdirected discharge of tension and emotions without concern about consequences. *Basis for rating:* behavior during the course of interview and reported by primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Patient tends to be easily angered and frustrated when facing stress or denied gratification but rarely acts on impulse.
4	Moderate	Patient gets angered and verbally abusive with minimal provocation. May be occasionally threatening, destructive, or have one or two episodes involving physical confrontation or a minor brawl.
5	Moderate Severe	Patient exhibits repeated impulsive episodes involving verbal abuse, destruction of property, or physical threats. There may be one or two episodes involving serious assault, for which the patient requires isolation, physical restraint, or p.r.n. sedation.
6	Severe	Patient frequently is impulsively aggressive, threatening, demanding, and destructive, without any apparent consideration of consequences. Shows assaultive behavior and may also be sexually offensive and possibly respond behaviorally to hallucinatory commands.
7	Extreme	Patient exhibits homicidal attacks, sexual assaults, repeated brutality, or self-destructive behavior. Requires constant direct supervision or external constraints because of inability to control dangerous impulses.

General Psychopathology Scale (G)

G15. Preoccupation. Absorption with internally generated thoughts and feelings and with autistic experiences to the detriment of reality orientation and adaptive behavior. *Basis for rat*ing: interpersonal behavior observed during the course of interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Excessive involvement with personal needs or problems, such that conversation veers back to egocentric themes and there is diminished concern exhibited toward others.
4	Moderate	Patient occasionally appears self-absorbed, as if daydreaming or involved with internal experiences, which interferes with communication to a minor extent.
5	Moderate Severe	Patient often appears to be engaged in autistic experiences, as evidenced by behaviors that significantly intrude on social and communicational functions, such as the presence of a vacant stare, muttering or talking to oneself, or involvement with stereotyped motor patterns.
6	Severe	Marked preoccupation with autistic experiences, which seriously delimits concentration, ability to converse, and orientation to the milieu. The patient frequently may be observed smiling, laughing, muttering, talking, or shouting to himself or herself.
7	Extreme	Gross absorption with autistic experiences, which profoundly affects all major realms of behavior. The patient constantly may be responding verbally and behaviorally to hallucinations and show little awareness of other people or the external milieu.

General Psychopathology Scale (G)

G16. Active social avoidance. Diminished social involvement associated with unwarranted fear, hostility, or distrust. *Basis for rating:* reports of social functioning by primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Patient seems ill at ease in the presence of others and prefers to spend time alone, although he or she participates in social functions when required.
4	Moderate	Patient grudgingly attends all or most social activities but may need to be persuaded or may terminate prematurely on account of anxiety, suspiciousness, or hostility.
5	Moderate Severe	Patient fearfully or angrily keeps away from many social interactions despite others' efforts to engage him. Tends to spend unstructured time alone.
6	Severe	Patient participates in very few social activities because of fear, hostility, or distrust. When approached, the patient shows a strong tendency to break off interactions, and generally he or she appears to isolate himself or herself from others.
7	Extreme	Patient cannot be engaged in social activities because of pronounced fears, hostility, or persecutory delusions. To the extent possible, he or she avoids all interactions and remains isolated from others.

APPENDIX D. SAMPLE PERSONAL AND SOCIAL PERFORMANCE (PSP) SCALE

Personal and Social Performance (PSP) Scale and points scale.

(1) Make note of the patient's level of dysfunction during the *past month* for the 4 main areas below. **t**he *functioning criteria* below must be used to determine the level of dysfunction. Note that there are some common criteria for areas a-c and other criteria specifically for area d.

	Absent	Mild	Manifest	Marked	Severe	Very severe
a) Self-care	☐	☐	☐	☐	☐	☐
b) Personal and social relationships	☐	☐	☐	☐	☐	☐
c) Socially useful activities, including work and study	☐	☐	☐	☐	☐	☐
d) Disturbing and aggressive behaviour	☐	☐	☐	☐	☐	☐

Level of severity: areas a-c

(i) Absent

(ii) Mild: only recognised by someone who is very close to the person

(iii) Manifest: difficulties that are clearly visible to anybody, although they do not substantially interfere with the person's ability to perform a role in this area, taking into account his/her socio-cultural context, age, sex and level of education.

(iv) Marked: difficulties considerably hinder the person from performing his/her role in this area. **t**he person is still capable of performing some tasks, although insufficiently and occasionally, without professional or social help. If the person is helped by someone, s/he may qualify for the previous level of functioning.

(v) Severe: difficulties that make the person unable to perform any role in this area if not helped by a professional, or the person has a destructive role, however, there are no survival risks

(vi) Very severe: deterioration and extreme difficulties which may put the person's survival at risk

Levels of severity: area d

(i) Absent

(ii) Mild: being rude, unsociable or slight complaints

(iii) Manifest: speaking too loudly or speaking to others in a too familiar manner, or eating in a socially unacceptable way

(iv) Marked: insulting other people in public, breaking or throwing objects, frequently behaving in a socially unacceptable way, but not dangerous way (e.g. undressing or urinating in public)

(v) Severe: frequent verbal threats or physical attacks without intention or possible serious injuries

(vi) Very severe: frequent aggressive acts, aimed to cause serious injuries

(2) Choose a 10-point range. **T**he 10-point range is based on the level of dysfunction for the 4 main areas: (a) socially useful activities, including work and study; (b) personal and social relationships;(c) self-care; and (d) disturbing and aggressive behavior.

100-91	Excellent functioning in all 4 areas. **T**he person is held in high consideration for his/her good qualities, adequately copes with life's problems, and is involved in a wide range of interests and activities
90-81	Good functioning in all 4 areas, only has common problems or difficulties
80-71	Mild difficulties for 1 or more a-c areas
70-61	Manifest but not marked difficulties in 1 or more a-c areas or mild difficulties in d
60-51	Marked difficulties for 1 or more a-c areas or manifest difficulties in d
50-41	Marked difficulties in 2 or more areas, or severe difficulties in 1 or more a-c areas, with or without marked difficulties in d
40-31	Severe difficulties in 1 area and marked difficulties in at least 1 of the a-c areas, or marked difficulties in d
30-21	Severe difficulties in 2 a-c areas, or severe difficulties in d, with or without deterioration in a-c areas
20-11	Severe difficulties in all a-d areas or very severe difficulties in d with or without deterioration in general a-c areas. If the person reacts to provocative stimuli, the suggested rating is 20-16; if not, 15-11.
10-1	Lack of independence for basic functioning, with extreme behaviour, but with no risk to survival (6-10) or with risk to survival, e.g. death risk due to malnutrition, dehydration, infections, inability to recognise manifest dangerous situations (1-5)

(3) Adjustment within the 10-point range

- The level of dysfunction in other areas should be taken into consideration, adding points within the 10-point range (e.g. from 31 to 40). Consider:
  - taking care of physical and psychological health
  - Accommodation, place of residence, looking after living space
  - Contributing to housekeeping activities, participating in family life or at day centre/halls of residence
  - Personal and sexual relationships
  - Looking after children
  - Social network, friends and co-workers
  - Adjusting to social norms
  - General interests
  - Using transport, telephone
  - Strategies for coping with crisis situations
- Risk and suicidal behaviour are not taken into account on this scale

(4) Write the final score (0-100):_____

APPENDIX E. SAMPLE FOOD CRAVING INVENTORY (FCI)

Food Craving Inventory-II

For each of the foods listed below (Items 1 – 28), please mark the appropriate bubble using the following scale.

A craving is defined as an intense desire to consume a particular food (or food type) that is difficult to resist.

Over the past month, how often have you experienced a craving for the food?

	Never	Rarely (once or twice)	Sometimes	Often	Always/ Almost every day
1. Cake	☐	☐	☐	☐	☐
2. Pizza	☐	☐	☐	☐	☐
3. Fried Chicken	☐	☐	☐	☐	☐
4. Gravy	☐	☐	☐	☐	☐
5. Sandwich Bread	☐	☐	☐	☐	☐
6. Sausage	☐	☐	☐	☐	☐
7. French fries	☐	☐	☐	☐	☐
8. Cinnamon Rolls	☐	☐	☐	☐	☐
9. Rice	☐	☐	☐	☐	☐
10. Hot dog	☐	☐	☐	☐	☐
11. Hamburger	☐	☐	☐	☐	☐
12. Biscuits	☐	☐	☐	☐	☐
13. Ice cream	☐	☐	☐	☐	☐
14. Pasta	☐	☐	☐	☐	☐
15. Fried fish	☐	☐	☐	☐	☐
16. Cookies	☐	☐	☐	☐	☐
17. Chocolate	☐	☐	☐	☐	☐
18. Pancakes or waffles	☐	☐	☐	☐	☐
19. Corn bread	☐	☐	☐	☐	☐
20. Chips	☐	☐	☐	☐	☐
21. Rolls	☐	☐	☐	☐	☐
22. Cereal	☐	☐	☐	☐	☐
23. Donuts	☐	☐	☐	☐	☐
24. Candy	☐	☐	☐	☐	☐
25. Brownies	☐	☐	☐	☐	☐
26. Bacon	☐	☐	☐	☐	☐
27. Steak	☐	☐	☐	☐	☐
28. Baked potato	☐	☐	☐	☐	☐

APPENDIX F. SAMPLE IMPACT OF WEIGHT ON QUALITY OF LIFE-LITE (IWQOL-LITE) QUESTIONNAIRE

Impact of Weight on Quality of Life Questionnaire—Lite Version (IWQOL-Lite)

Please answer the following statements by circling the number that best applies to you in the past week. Be as open as possible. There are no right or wrong answers.

Physical Function		ALWAYS TRUE	USUALLY TRUE	SOMETIMES TRUE	RARELY TRUE	NEVER TRUE
1.	Because of my weight I have trouble picking up objects.	5	4	3	2	1
2.	Because of my weight I have trouble tying my shoes.	5	4	3	2	1
3.	Because of my weight I have difficulty getting up from chairs.	5	4	3	2	1
4.	Because of my weight I have trouble using stairs.	5	4	3	2	1
5.	Because of my weight I have difficulty putting on or taking off my clothing.	5	4	3	2	1
6.	Because of my weight I have trouble with mobility.	5	4	3	2	1
7.	Because of my weight I have trouble crossing my legs.	5	4	3	2	1
8.	I feel short of breath with only mild exertion.	5	4	3	2	1
9.	I am troubled by painful or stiff joints.	5	4	3	2	1
10.	My ankles and lower legs are swollen at the end of the day.	5	4	3	2	1
11.	I am worried about my health.	5	4	3	2	1
Self-esteem		ALWAYS TRUE	USUALLY TRUE	SOMETIMES TRUE	RARELY TRUE	NEVER TRUE
1.	Because of my weight I am self-conscious.	5	4	3	2	1
2.	Because of my weight my self-esteem is not what it could be.	5	4	3	2	1
3.	Because of my weight I feel unsure of myself.	5	4	3	2	1
4.	Because of my weight I don't like myself.	5	4	3	2	1
5.	Because of my weight I am afraid of being rejected.	5	4	3	2	1
6.	Because of my weight I avoid looking in mirrors or seeing myself in photographs.	5	4	3	2	1
7.	Because of my weight I am embarrassed to be seen in public places.	5	4	3	2	1

Direct all correspondence to PPD Obesity and Quality of Life Consulting,
1004 Norwood Avenue, Durham, NC 27707 USA; email: PPD fax: PPD

Sexual Life		ALWAYS TRUE	USUALLY TRUE	SOMETIMES TRUE	RARELY TRUE	NEVER TRUE
1.	Because of my weight I do not enjoy sexual activity.	5	4	3	2	1
2.	Because of my weight I have little or no sexual desire.	5	4	3	2	1
3.	Because of my weight I have difficulty with sexual performance.	5	4	3	2	1
4.	Because of my weight I avoid sexual encounters whenever possible.	5	4	3	2	1

Public Distress		ALWAYS TRUE	USUALLY TRUE	SOMETIMES TRUE	RARELY TRUE	NEVER TRUE
1.	Because of my weight I experience ridicule, teasing, or unwanted attention.	5	4	3	2	1
2.	Because of my weight I worry about fitting into seats in public places (e.g. theaters, restaurants, cars, or airplanes).	5	4	3	2	1
3.	Because of my weight I worry about fitting through aisles or turnstiles.	5	4	3	2	1
4.	Because of my weight I worry about finding chairs that are strong enough to hold my weight.	5	4	3	2	1
5.	Because of my weight I experience discrimination by others.	5	4	3	2	1
Work (Note: For homemakers and retirees, answer with respect to your daily activities.)		ALWAYS TRUE	USUALLY TRUE	SOMETIMES TRUE	RARELY TRUE	NEVER TRUE
1.	Because of my weight I have trouble getting things accomplished or meeting my responsibilities.	5	4	3	2	1
2.	Because of my weight I am less productive than I could be.	5	4	3	2	1
3.	Because of my weight I don't receive appropriate raises, promotions or recognition at work.	5	4	3	2	1
4.	Because of my weight I am afraid to go on job interviews.	5	4	3	2	1

APPENDIX G. PARTIAL LIST OF PROHIBITED CYTOCHROME P450 (CYP) 3A4 INDUCERS AND MODERATE-TO-STRONG INHIBITORS

Partial List of Cytochrome P450 3A4 (CYP3A4) Inhibitors and Inducers (This is not an exhaustive list.)

Moderate to Strong CYP3A4 inhibitors:

Amprenavir

Aprepitant

Atazanavir

Boceprevir

Ciprofloxacin

Clarithromycin

Conivaptan

Crizotinib

Darunavir/ ritonavir

Diltiazem

Erythromycin

Fosamprenavir

Fluconazole

Imatinib

Indinavir

Itraconazole

Ketoconazole

Lopinavir/ ritonavir

Nefazodone

Nelfinavir

Posaconazole

Ritonavir

Saquinavir

Telaprenavir

Telithromycin

Troleandomycin

Verapamil

Voriconazole

Partial List of Moderate to Strong CYP3A4 inducers:

Bosentan

Carbamazepine

Efavirenz

Etravirine

Modafinil

Nafcillin

Nevirapine

Phenobarbital

Phenytoin

Rifampin

Rifabutin

St. John's Wort