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

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CLINICAL STUDY PROTOCOL

ALK3831-A303

Study Title:	A Phase 3 Study to Evaluate Weight Gain of ALKS 3831 Compared to Olanzapine in Adults with Schizophrenia	
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	Original Protocol:	17 Sep 2015
Sponsor:	Alkermes, Inc. 852 Winter Street Waltham, MA 02451 USA	

CONTACT INFORMATION

Table 1: Study Contact Information

Role in Study	Name	Address and Telephone
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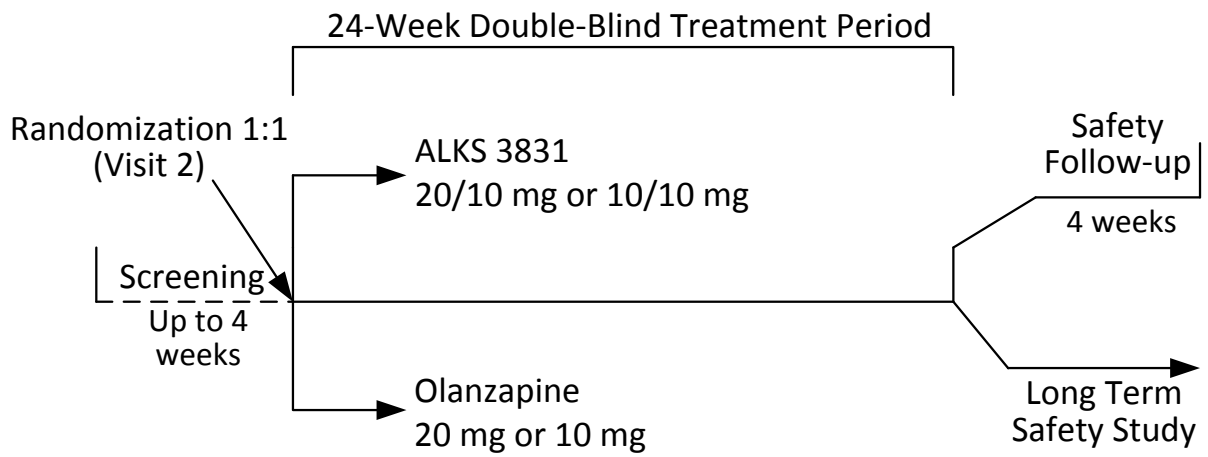
Alkermes Global Safety Officer	PPD	Alkermes, Inc. 852 Winter Street Waltham, MA 02451 Phone: PPD
Clinical Research Organization (CRO) Medical Monitor and 24-Hour Emergency Contact	PPD	PPD PPD PPD Del Mar, CA 92014 Mobile: PPD Office: PPD

2. SYNOPSIS

Name of Sponsor/Company: Alkermes, Inc.	
Name of Investigational Product: ALKS 3831	
Name of Active Ingredient: Olanzapine and samidorphan	
Title of Study: A Phase 3 Study to Evaluate Weight Gain of ALKS 3831 Compared to Olanzapine in Adults with Schizophrenia	
Investigators: This is a multicenter study.	
Study Period: Estimated date of first subject's consent: Q1 2016 Estimated date of last subject's last visit: Q1 2018	**Phase of Development:** 3
Objectives: **Primary:** To evaluate weight gain of ALKS 3831 (a fixed-dose combination of olanzapine and samidorphan) compared to olanzapine in adults with schizophrenia **Secondary:** To evaluate the safety and tolerability of ALKS 3831 in adults with schizophrenia	
Methodology: This is a Phase 3, multicenter, randomized, double-blind, study in adults with schizophrenia. Subjects will be screened at Visit 1, up to 30 days prior to randomization. At Visit 2, eligible subjects will be randomized 1:1 to ALKS 3831 (olanzapine/10 mg samidorphan) or olanzapine treatment groups and receive study drug for up to 24 weeks. Subjects are not excluded from the study if they are taking other antipsychotic medication. However they must be tapered off this medication and switched onto ALKS 3831 or olanzapine by the end of Week 2, Visit 4. This is an outpatient study in which subjects will visit the study site weekly for the first 6 weeks, then biweekly for the remaining 18 weeks. Study drug will be provided as coated bilayer tablets dispensed to the subjects in blister packs at each visit to be taken at home, one tablet by mouth each day, preferably at bedtime. For the first week, subjects will receive 10 mg olanzapine per dose: either ALKS 3831 10/10 (10 mg olanzapine/10 mg samidorphan) or OLZ 10 (10 mg olanzapine), according to treatment assignment. At the end of Week 1, the dose will escalate to 20 mg: ALKS 3831 20/10 (20 mg olanzapine/10 mg samidorphan) or OLZ 20. Following this increase, the dose may be decreased back to 10 mg at the end of Week 2, 3, or 4 according to investigator discretion. No further dose adjustments will be allowed beyond Week 4 and the dose will remain fixed for the remaining 20 weeks of the study. Body weight and metabolic parameters (including fasting triglycerides, cholesterol, and glucose) will be measured throughout the 24-week treatment period. Psychiatric symptoms will also be evaluated using PANSS and CGI. A schematic summarizing study design is presented below.	



Subjects completing this study will be eligible to enroll in a long-term safety study (ALK3831-A304). Subjects not continuing in the long-term safety study or subjects prematurely discontinuing from the study will enter the 4-week safety follow-up period.

Number of Subjects Planned: Approximately 400 or 540 randomized (200 or 270 per treatment group)

Main Criteria for Inclusion: Men and women 18 through 55 years of age (inclusive), with a body mass index (BMI) of 18.0 to 30.0 kg/m^2 (inclusive) and with a Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnosis of schizophrenia who meet sponsor criteria for symptom stability.

Main Criteria for Exclusion: Subjects may be excluded based on diagnosis of additional psychiatric conditions, use of prohibited or contraindicated drugs and medications, pre-existing medical conditions, abnormal lab results during screening, participation in any recent clinical trials or previous clinical trials of ALKS 3831 or samidorphan, pregnancy, and relationship to an employee of the study sponsor or CRO.

Investigational Product, Dosage, Duration, and Mode of Administration: ALKS 3831 will be supplied as a coated bilayer tablet containing either 10 mg or 20 mg olanzapine and 10 mg samidorphan. The tablet is to be taken by mouth once daily, preferably at bedtime.

Reference Therapy, Dosage, Duration, and Mode of Administration: Olanzapine will be supplied as an identical bilayer tablet manufactured by Alkermes, Inc., containing either 10 mg or 20 mg of olanzapine only and no additional active ingredients. Olanzapine tablets will be taken by mouth once daily, preferably at bedtime.

Duration of Study: The total duration of this study is approximately 32 weeks (8 months) including a 4 week (1 month) screening period, a 24-week (6 month) treatment period, and a 4 week (1 month) follow-up period.

Criteria for Evaluation:

Efficacy:

- Body Weight (Primary Endpoint)

Antipsychotic Efficacy:

- Positive and Negative Symptom Scale (PANSS)
- Clinical Global Impression – Severity (CGI-S)

- Clinical Global Impression – Improvement (CGI-I)

Other Assessments:

- Cigarette Use Questionnaire
- Impact of Weight on Quality of Life – Lite Questionnaire (IWQOL-Lite)
- EuroQol-5D (EQ-5D)
- Substudy: an exploratory substudy will measure body composition (using Bioelectrical Impedance Analysis [BIA]) in subjects at a subset of sites participating in the main ALK3831-A303 study; see Addendum A for substudy details

Safety: The following assessments will be collected to measure safety and tolerability throughout the study:

- Adverse events (AEs)
- Waist Circumference
- Clinical laboratory parameters including chemistry, hematology, and urinalysis
- Vital signs (oral temperature, respiratory rate, orthostatic blood pressure, and heart rate)
- Electrocardiogram parameters (Uncorrected QT, QTcF, QTcB, PR, RR, and QRS intervals)
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Abnormal Involuntary Movement Scale (AIMS)
- Simpson-Angus Scale (SAS)
- Barnes Akathisia Rating Scale (BARS)

Pharmacokinetics/Pharmacodynamics: Concentrations of olanzapine, samidorphan, and metabolites of interest will be determined from plasma samples collected according to the schedule in Table 3. Pharmacokinetic (PK) data from these samples may be included in a subsequent population PK analysis or other post-hoc analyses conducted outside of this study.

Statistical Methods:

Study Populations:

Safety Population: The safety population includes all randomized subjects who receive at least one dose of study drug (ALKS 3831 or olanzapine).

Efficacy Population: The efficacy population includes:

- Full analysis set (FAS) population: all subjects in the safety population who have at least one postbaseline weight assessment
- Early weight gain population: all subjects in the FAS population who gain weight (>0 kg) at Week 1

Efficacy:

Primary Endpoints: The primary endpoints are:

- Percent change from baseline in body weight at Week 24 in the FAS population

- Proportion of subjects with ≥10% weight gain at Week 24 in the FAS population

For percent change from baseline in body weight at Week 24, the primary analysis will be carried out using an analysis of covariance (ANCOVA) method based on multiple imputation for missing data. The model will include treatment group, race, and baseline age as factors, and baseline weight as a covariate.

For proportion of subjects with ≥10% weight gain at Week 24, the primary analyses will be carried out using a logistic regression model based on multiple imputation for missing data. The model will include treatment group, race, and baseline age as factors, and baseline weight as a covariate.

Key Secondary Endpoint: The key secondary endpoint is:

- Proportion of subjects with ≥7% weight gain at Week 24

The key secondary endpoint will be analyzed similarly to the primary endpoints.

A fixed sequence approach will be used to control overall Type I error rate. First, both primary endpoints will be tested at an alpha level of 0.05. If both primary endpoints are statistically significant, the key secondary endpoint will be tested at an alpha level of 0.05.

Other Endpoints: Other endpoints are:

- Percent change from baseline in body weight at Week 24 in the early weight gain population
- Proportion of subjects with ≥10% weight gain at Week 24 in the early weight gain population
- Change from baseline in fasting lipids (fasting triglycerides, LDL, HDL, total cholesterol), fasting glucose, fasting insulin, and HbA1c by visit
- Absolute change in body weight by visit
- Change from baseline in waist circumference by visit
- Change from baseline in PANSS total score and subscales by visit
- Change from baseline in CGI-S by visit
- CGI-I score by visit
- Change from baseline in IWQOL-Lite total score and subscales by visit
- Change from baseline in EQ-5D score by visit

Safety: All safety analyses will be based on observed data only, and no missing values will be imputed.

Reported adverse event terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by preferred term and system organ class categories.

Observed values and change from baseline in BMI, waist circumference, laboratory parameters, vital signs, and ECG parameters will be summarized by treatment group and study visit.

Prior and concomitant medication use will be summarized by World Health Organization Drug Dictionary Anatomical Therapeutic Class code and treatment group.

Pharmacokinetics/Pharmacodynamics: Concentrations of olanzapine, samidorphan, and metabolites of interest will be provided as by-subject listings.

Sample Size Considerations: The target sample size is 400 randomized subjects (200 per treatment group). This sample size will provide at least 90% power to detect a significant difference in mean percent change in body weight at Week 24 of 4% or more (3% on ALKS 3831 vs 7% on olanzapine group with standard deviation of 9%) and a 13% difference in proportion of subjects with ≥10% weight gain at Week 24 (14% on ALKS 3831 vs 27% on olanzapine group).

One unblinded interim analysis will be conducted by an independent statistical center (ISC) when 50% of subjects (N=200) have completed the double-blind treatment period or have discontinued from the study to determine if the final sample size will be increased to 540 (270 subjects per treatment group).

Interim Analysis: The details regarding the conduct of unblinded interim analyses will be specified in the interim analysis operational plan and the statistical testing methodology will be specified in the interim analysis plan (IAP). There will be no early stopping for efficacy or futility. The sponsor will not be informed with any unblinded interim analysis results except for a recommendation to either increase the sample size or to leave the sample size unchanged.

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4. LIST OF ABBREVIATIONS

The following abbreviations are used in this study protocol.

Table 2: List of Abbreviations and Definitions of Terms

Abbreviation or Term	Explanation or Definition
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical [classification system]
BARS	Barnes Akathisia Rating Scale
BMI	Body mass index
CGI-I	Clinical Global Impression - Improvement
CGI-S	Clinical Global Impression - Severity
CNS	Central nervous system
CP	Conditional power
CRO	Contract research organization
CSA	Clinical Study Agreement
C-SSRS	Columbia-Suicide Severity Rating Scale
DSM-5	Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition
IEC	Independent Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
ECT	Electroconvulsive therapy
EQ-5D	EuroQol five dimensions questionnaire
EOT	End of treatment
EPS	Extra pyramidal symptoms
ET	Early termination
FAS	Full analysis set
GCP	Good Clinical Practice

Table 2: List of Abbreviations and Definitions of Terms (Continued)

Abbreviation or Term	Explanation or Definition
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HbA1C	Hemoglobin A1c
HDL	High-density lipoprotein
IAP	Interim analysis plan
ICF	Informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ISC	Independent statistical center
IUD	Intrauterine device
IWQOL	Impact of Weight on Quality of Life
IRB	Institutional Review Board
LDL	Low-density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MINI	Mini International Neuropsychiatric Interview
MMRM	Mixed model with repeated measurements
OLZ	Olanzapine
PANSS	Positive and Negative Syndrome Scale
PCP	Phencyclidine
PCS	Potentially clinically significant
PK	Pharmacokinetic
QTcB	QT corrected with Bazett formula
QTcF	QT corrected with Fridericia formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Simpson-Angus Scale
SCI-PANSS	Structured Clinical Interview for the PANSS
TEAE	Treatment-emergent adverse event
WHO	World Health Organization

5. INTRODUCTION

5.1. Background

Schizophrenia is a chronic, severe disease with debilitating psychotic symptoms, physical and psychiatric comorbidities and increased mortality. Despite the availability of a range of FDA-approved medicines, the disease is still inadequately treated and associated with enormous human and economic cost. Life expectancy is reduced by 19 years in men and 16 years in women with schizophrenia compared to the general population (Harris and Barraclough 1998; Lambert et al, 2010; Tiihonen et al, 2009). The decreased life expectancy is due to a combination of direct effects of the disease, eg increased rates of suicide and violence (Hodgins 2008; Kuo et al, 2005), as well as indirect causes including increased incidence of obesity and cardiovascular disease (Nasrallah et al, 2006; Saha et al, 2007).

The goal of treatment in schizophrenia is to achieve the maximal reduction in positive and negative symptoms and increase functionality. Unfortunately, even with regular administration of currently available antipsychotic medications at full therapeutic dose levels, the overwhelming majority of patients continue to exhibit residual active symptomatology. For physicians and patients, in many cases the current treatment paradigm involves an efficacy/tolerability trade-off, where use of the most efficacious agents is avoided or delayed in order to avoid known safety issues. As such, there is a need for more efficacious therapies with better tolerability.

Olanzapine is regarded as one of the most effective antipsychotic agents with well-recognized efficacy and decreased incidence of extrapyramidal symptoms. However, its efficacy is compromised by safety and tolerability limitations that affect compliance and retention of patients on olanzapine therapy (Lieberman et al, 2005). In particular, results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), identify olanzapine as an effective atypical antipsychotic associated with the highest weight gain (9.4 kg over a treatment period up to 18 months and ≥7% body weight in 30% of subjects) and a comparatively higher discontinuation rate compared to other antipsychotic agents due to weight gain and metabolic effects. As a result of these limitations surrounding safety, tolerability, adherence and retention, the risk of olanzapine therapy can outweigh the benefit and patients are often switched to alternative antipsychotic agents even if they are less effective.

ALKS 3831 is a fixed-dose combination product of olanzapine and samidorphan (also referred to as ALKS 33 or RDC-0313, see Section 5.2.1 for more information on samidorphan) under investigation for the treatment of schizophrenia. Phase 1 and Phase 2 studies demonstrated that coadministration of samidorphan with olanzapine attenuates the weight gain experienced with olanzapine alone. Results from these studies are described in more detail in Section 5.3. In addition, ALKS 3831 may have the further benefit of controlling substance abuse in patients with schizophrenia. Comorbid substance use disorder is a well-recognized obstacle to patient care. An estimated 1 out of every 3 patients with schizophrenia (33.7%) meet or have met criteria for alcohol use disorder (Regier et al, 1990). Patients with both schizophrenia and alcohol use disorder represent a common variant of the schizophrenia spectrum that is difficult to treat and is associated with an extremely poor prognosis (Dixon 1999; Koekkoek et al, 2006). In clinical studies, samidorphan has been shown to block both the subjective and physiological effects of

the opioid agonist remifentanil (ALK33-004) and it is correlated with reduced drinking behavior in adults with alcohol dependence (ALK33-005). ALK3831-401 is an ongoing clinical study designed to evaluate the effect of ALKS 3831 on drinking behavior in adult subjects with schizophrenia and alcohol use disorder.

In summary, ALKS 3831 is being explored as a therapeutic agent for the treatment of schizophrenia designed to combine the antipsychotic efficacy of olanzapine with a reduced risk of weight gain and associated metabolic deficits. Development of ALKS 3831 as a fixed-dose combination of olanzapine and samidorphan has the potential to improve upon the benefit/risk profile of olanzapine alone and address a significant clinical need for patients that are currently forced to choose between treatment efficacy vs safety.

5.2. Study Drugs

In this study a fixed dose combination of olanzapine and samidorphan will be administered in a single bilayer tablet. The following sections provide an overview of samidorphan and olanzapine. Detailed information about the study drugs can be found in the current ALKS 3831 Investigator's Brochure (IB).

5.2.1. Samidorphan

Samidorphan is a new molecular entity in clinical development by Alkermes. It is an opioid modulator that functions as an antagonist at μ-opioid receptors and as a low intrinsic activity agonist at κ- and δ-opioid receptors. It is currently being investigated in combination with buprenorphine for the treatment of major depressive disorder (ALKS 5461) and in combination with olanzapine for the treatment of schizophrenia. Based on its chemical structure, samidorphan is considered a Schedule II controlled substance according to the US Drug Enforcement Agency and will require proper handling (see Section 10.5). At least 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). 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 (Zyprexa®) 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 (Eli Lilly and Company 2016). 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

The rationale for this Phase 3 study is based on the promising efficacy and safety results from prior Phase 1 and Phase 2 studies of ALKS 3831.

A Phase 1 study conducted in healthy males (Study ALK33-301), demonstrated that 3 weeks of treatment with ALKS 3831 resulted in 29% less weight gain compared with subjects who received olanzapine alone. Based on the results of this study, a two-part (Part A and Part B), Phase 2 study (ALK3831-302) was conducted to evaluate the antipsychotic efficacy and body weight effect of ALKS 3831 in subjects with schizophrenia. In Part A (a 12-week, double-blind, randomized, olanzapine-controlled phase), ALKS 3831 demonstrated similar antipsychotic efficacy compared with olanzapine based on Positive and Negative Syndrome Scale (PANSS) total score. ALKS 3831 also led to clinically and statistically significant less body weight gain compared to olanzapine. Specifically, treatment with ALKS 3831 led to a 37% lower mean percent weight gain from baseline compared with olanzapine, and a 2.7-fold reduction in the risk of gaining 10% or more of baseline body weight in the full study population. Moreover, in the population of subjects (63% of total) that gained weight during the 1-week olanzapine lead-in period (referred to as the early weight gain population), ALKS 3831 treatment led to a 51% lower mean percent weight gain compared with olanzapine, and a 4.1-fold reduction in the risk of gaining 10% or more of baseline body weight. Data from Part B (a 12-week all-active, extension) indicated maintenance of the beneficial effect on weight observed in Part A, while maintaining stable PANSS scores over the 12 week extension period.

The current Phase 3 study will further evaluate weight gain of ALKS 3831 compared to olanzapine in adults with schizophrenia over a 24 week period.

5.4. Dose Rationale

The selected doses of ALKS 3831 (20/10 [20 mg olanzapine/10 mg samidorphan] and 10/10 [10 mg olanzapine/10 mg samidorphan]) are within the approved olanzapine therapeutic dose range for the treatment of schizophrenia (Eli Lilly and Company 2016). Olanzapine doses of 10 and 20 mg will bracket the lowest and highest approved maintenance doses for the treatment of schizophrenia and provide adequate coverage for the intended commercial maintenance dose range of ALKS 3831, 10 to 20 mg.

The 10 mg samidorphan dose was identified as the minimally effective dose based on the robust efficacy, with optimal safety profile observed in ALK3831-302 at this dose. A fixed dose of samidorphan was selected due to the fact that data from this study demonstrated no correlation between the ratio of samidorphan/olanzapine dose and percent change from baseline in body weight, indicating that even with higher olanzapine doses, a fixed dose of samidorphan is sufficient to achieve maximal effect on reducing olanzapine-induced weight gain.

6. OBJECTIVES

6.1. Primary Objective

The primary objective of this study is to evaluate weight gain of ALKS 3831 (a fixed-dose combination of olanzapine and samidorphan) compared to olanzapine in adults with schizophrenia.

6.2. Secondary Objective

The secondary objective is to evaluate the safety and tolerability of ALKS 3831 in adults with schizophrenia.

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 written informed consent
2. Subject is age 18 to 55 years, inclusive, at screening (Visit 1)
3. Subject has a body mass index (BMI) of 18.0 to 30.0 kg/m^2, inclusive, at Visit 1 and Visit 2
4. Subject meets the DSM-5 criteria for a primary diagnosis of schizophrenia, confirmed with the Mini International Neuropsychiatric Interview (MINI) at Visit 1
5. Subject is outpatient at Visits 1 and 2
6. Subject is appropriate for outpatient treatment as evidenced by the following:
   - No hospitalizations for acute exacerbations of schizophrenia within 6 months before Visit 1
   - PANSS total score of 50 to 90 (inclusive) at Visits 1 and 2
   - Clinical Global Impression of Severity (CGI-S) score of ≤4 at Visits 1 and 2
7. Subject has maintained a stable body weight (change ≤5%) for at least 3 months prior to Visit 1 based on self-report
8. Subject agrees to abide by the contraception requirements specified in the protocol
9. Subject is willing and able to provide government-issued identification

7.2. Subject Exclusion Criteria

Each subject must not meet any of the following criteria to be qualified to participate in this study.

7.2.1. Psychiatric Criteria

1. Subject does not meet antipsychotic treatment or duration of illness eligibility requirements for one or more of the following reasons:
   - Subject initiated first antipsychotic treatment within the past 12 months
   - <1 year has elapsed since the initial onset of active-phase of schizophrenia symptoms
   - Subject is antipsychotic naïve

2. Subject has any of the following psychiatric conditions per DSM-5 criteria, as assessed by the MINI. Conditions not assessable by the MINI should be assessed by clinical judgment:
    - Diagnosis of schizoaffective disorder or bipolar I or II disorder, or current, untreated or unstable major depressive disorder (according to DSM-5 criteria)
    - 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 poses a current suicide risk at Visit 1 or Visit 2 in the opinion of the investigator and as confirmed by the following:
    - Answers "Yes" on items 4 or 5 from the Columbia-Suicide Severity Rating Scale (C-SSRS) with ideation or suicidal behavior occurring within the past year

7.2.2. Criteria Based on Treatment History

4. Subject has a history of treatment resistance, defined as failure to respond to 2 adequate trials of different antipsychotic medications (a minimum of 4 week at the subject's maximum tolerated dose)
5. Subject has a history of poor or inadequate response to treatment with olanzapine
6. Subject has used clozapine within 6 months prior to Visit 1 and has any history of clozapine use for treatment-resistant schizophrenia
7. Subject has used olanzapine, chlorpromazine, or thioridazine at any time during the 6 months prior to Visit 1 or long-acting injectable antipsychotic medication in the last 6 months with the exception of 3-month paliperidone which must not have been received within the past 12 months
8. Subject requires or has had electroconvulsive therapy (ECT) treatment in the 6-month period prior to Visit 1

7.2.3. Criteria Based on Drug/Alcohol Use and Concomitant Meds

9. Subject has a diagnosis (based on DSM-5 criteria, as assessed by the MINI) of alcohol or drug use (with the exception of nicotine) disorder, moderate or severe, currently or at any time during the 3 months prior to Visit 1
10. Subject has a positive drug screen for opioids, phencyclidine (PCP), amphetamine/ methamphetamine, or cocaine at Visit 1 or Visit 2
11. Subject has taken opioid agonists (eg, codeine, oxycodone, tramadol, or morphine) within the 14 days prior to Visit 1 and/or anticipates a need to take opioid medication during the study period (eg, planned surgery), or has taken opioid antagonists including naltrexone (any formulations) and naloxone within 60 days prior to Visit 1

12. Subject is currently taking any contraindicated medications as per the approved labeling for olanzapine
13. Subject is currently on a statin medication (an HMG-CoA reductase inhibitor) that was initiated or has had a dose adjustment within the 3 months prior to Visit 1
14. Subject is taking any weight loss agents or hypoglycemic agents at Visit 1

7.2.4. Criteria Based on Medical Conditions/Medical History

15. Subject has a known or suspected intolerance, allergy or hypersensitivity to olanzapine or opioid antagonists at Visit 1
16. 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 stabilized 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)
    - Personal or family history of neuroleptic malignant syndrome, has a history of clinically significant extrapyramidal symptoms when taking olanzapine, or has had clinically significant tardive dyskinesia
    - Neurologic conditions including the following:
        - History of seizure disorder or a condition associated with seizures (exception: history of febrile seizures)
        - History of brain tumor, subdural hematoma, stroke, or other clinically significant neurological condition within the 12 months prior to Visit 1
        - Head trauma with loss of consciousness within the 12 months prior to Visit 1
        - Active acute or chronic central nervous system (CNS) infection
    - 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 including the following:
        - Clinically significant cardiac arrhythmia, cardiomyopathy, or cardiac conduction defect, a history of myocardial infarction or unstable angina within 6 months prior to Visit 1
17. Subject has inflammatory bowel disease or any other gastrointestinal (GI) disorder associated with weight loss, anorexia nervosa, bulimia nervosa, or binge eating disorder
18. Subject has had any GI surgical procedures within 1 year prior to Visit 1
19. Subject has had a surgical procedure for weight loss or is planning to have liposuction during the study

20. Subject has joined a weight management program or had significant changes in diet or exercise regimen within the 6 weeks prior to Visit 1 or plans to join a weight management program during the study
21. Subject has started a smoking cessation program within the 6 months prior to Visit 1 or anticipates quitting smoking during the study
22. Subject has a history of diabetes
23. Subject has had a significant blood loss (>500 mL) or blood or blood product donation (including platelets or plasma) within 60 days of Visit 1 or anticipated blood or blood product donation at any time during the study period

7.2.5. Criteria Based on Laboratory Assessments

24. 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:
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) value ≥2 times the upper limit of the laboratory normal reference range
    - Absolute neutrophil count (ANC) $\leq 1.5 \times 10^3$ µL
    - Platelet count $\leq 75 \times 10^3$ µL
    - Serum creatinine >2.5 mg/dL
    - Positive pregnancy test result
25. Subject has a positive serology test for hepatitis B surface antigen, hepatitis C antibody confirmed by RNA testing, or human immunodeficiency virus (HIV) antibody at Visit 1
26. Subject has dyslipidemia, defined for this study as total fasting cholesterol >280 mg/dL or fasting triglycerides >500 mg/dL, at Visit 1
27. Subject has a Hemoglobin A1c (HbA1c) ≥6.0% at Visit 1
28. Subject has a fasting plasma glucose ≥126 mg/dL (7.0 mmol/L) at Visit 1
29. Subject has a clinically significant ECG abnormality at Visits 1 or 2
    – Subject has a QT interval >450 msec for men and >470 msec for women, as corrected by the Fridericia formula (QTcF), observed at Visits 1 or 2

7.2.6. General Criteria

30. Subject is currently pregnant or breastfeeding or is planning to become pregnant within 60 days of the last study drug administration
31. Subject has any finding that, in the view of the investigator, would compromise the subject's ability to fulfill the protocol visit schedule or study requirements
32. Subject has participated in another clinical trial in which the subject received an experimental or investigational drug or agent within 3 months before Visit 1 by self-report or through confirmation using an clinical trial subject registry
33. Subject has participated in a prior clinical study of ALKS 3831 or samidorphan

34. Subject is employed by Alkermes, CRO, or study site (permanent, temporary contract worker, or designee responsible for the conduct of the study) or is immediate family[1] of an Alkermes, CRO, or study site employee

7.3. Subject Withdrawal

A subject may be discontinued from the study at any time if the subject, investigator, or sponsor determines that it is not in the best interest of the subject to continue participation. If a subject has an ANC $<1.0 \times 10^3$ µL or HbA1c ≥6.5% at any time from Visit 2 to Visit 17, the PI (or designee) should discontinue the subject from participation immediately. Other reasons for discontinuation include:

- Adverse Event
- Lack of Efficacy
- Lost to Follow-up
- Withdrawal by Subject
- Protocol Deviation (non-compliance with study drug or study procedures)
- Pregnancy
- Study Terminated by Sponsor
- Other

Following premature discontinuation, subjects can be started on another antipsychotic at the discretion of their prescribing physician.

If a subject withdraws from the study for any reason, they will be asked to return to the clinic for an early termination (ET) visit. The early termination visit should be scheduled as close as possible to the subject's last dose and will mimic the assessments scheduled to be conducted at the EOT visit (Visit 17). Randomized subjects who discontinue study drug but are willing to come in for further assessments will be asked to complete the ET visit followed by 2 safety follow-up visits 2 and 4 weeks after the ET visit (same assessments as Visits 18 and 19 in Table 3. They will then be asked to return to the study center for monthly visits until end of planned treatment, to collect the following information: weight, adverse events, and new antipsychotics.

Any ongoing AEs at the time of discontinuation will be followed until resolution, until deemed stable by the investigator, or until the subject is deemed by the investigator to be lost to follow-up.

If, in the opinion of the investigator, 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 investigator will agree to an acceptable follow-up schedule.

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

In the event that a subject chooses to withdraw from the study, the investigator should make a reasonable effort to ascertain the reason(s) for withdrawal, while fully respecting the subject's rights.

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 investigator must maintain a record of all subjects who fail to complete the study. A full explanation of the reason for study discontinuation will be documented and made on the appropriate electronic case report form (eCRF). In addition, the eCRF will also record if weight gain contributed to premature discontinuation from the study. If a subject is lost to follow-up, a reasonable attempt to contact the subject must be made and documented.

Randomized subjects completing all scheduled visits through Visit 17 will be considered study completers.

7.4. Replacement of Subjects

Subjects prematurely discontinued from the study post-randomization will not be replaced.

8. STUDY DESIGN

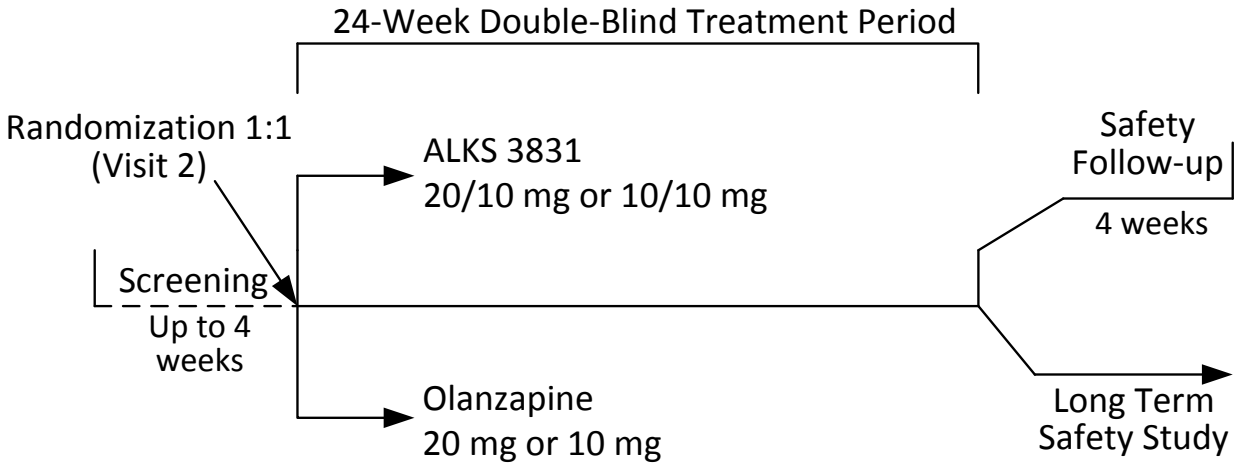
8.1. Overall Study Design and Plan

This is a Phase 3, multicenter, randomized, double-blind, study in adults with schizophrenia.

Subjects will be screened at Visit 1, up to 30 days prior to randomization. Eligible subjects will be randomized at Visit 2 in a 1:1 fashion to the following 2 treatment groups: ALKS 3831 (olanzapine/10 mg samidorphan) or olanzapine. For all subjects, the initial olanzapine dose will be 10 mg given as either ALKS 3831 10/10 (10 mg olanzapine/10 mg samidorphan) or OLZ 10 (10 mg olanzapine), according to treatment assignment. Subjects will be titrated up to 20 mg (ALKS 3831 20/10 [20 mg olanzapine/10 mg samidorphan] or OLZ 20 [20 mg olanzapine]) at the end of Week 1 of treatment. Following this dose increase, the dose may be decreased to ALKS 3831 10/10 or OLZ 10 at the end of Week 2, 3, or 4 if there are tolerability issues based on the judgment of the investigator. Reasons for down-titration will be documented in the electronic case report form (eCRF). No further dose adjustments will be allowed beyond week 4 and the dose will remain fixed for the remaining 20 weeks of the study.

This is an outpatient study. Subjects will be seen weekly for the first 6 weeks (Visits 3-8), then biweekly for the remaining 18 weeks (Visits 9-17/end of treatment [EOT]). Body weight and metabolic parameters (including fasting triglycerides, cholesterol, and glucose) will be measured throughout the 24-week treatment period. Psychiatric symptoms will also be evaluated using the assessments listed in Section 11. A schematic summarizing study design is presented in Figure 1. The details of study visits and assessments are provided in Table 3.

Figure 1: ALK3831-A303 Study Design Schematic



Subjects completing this study will be eligible to enroll in a long-term safety study (ALK3831-A304). Subjects not continuing in the long-term safety study or subjects prematurely discontinuing from the study will enter the 4-week safety follow-up period.

Subjects taking antipsychotic medication at study entry must be tapered off their medication and titrated onto ALKS 3831 or olanzapine (in accordance with the randomized allocation) within 2 weeks after randomization (by Visit 4). This cross-taper from prior antipsychotic treatment to

double-blind study medication will be conducted under the care and discretion of the principal investigator and consistent with current clinical practice.

8.2. Schedule of Visits and Assessments

The schedule of assessments is shown in Table 3.

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

Premature discontinuation procedures are provided in Section 7.3. Any subject that prematurely discontinues study drug but agrees to return for further assessments must first complete an ET visit (same assessments as Visit 17) and two safety follow-up visits 2 and 4 weeks following the ET visit (same assessments as Visits 18 and 19 respectively). Following completion of these follow-up visits, subjects will be asked to return to the study center for monthly visits until the end of planned treatment, to collect the following information: weight, adverse events, and new antipsychotics.

Table 3: Schedule of Assessments

	Screening	24-Week Double-Blind Treatment																Safety Follow-up[a]		Monthly Visits[b]
Visit	**1**	**2[c]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17/ET**	**18**	**19**	**20 to 24**
Study Week (Visit Window of ±2 Days for Visits 3-24)			**1**	**2**	**3**	**4**	**5**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	
Qualification/ Diagnostic Assessments																				
Informed Consent	X																			
Eligibility Criteria Review	X	X																		
Demographics and Medical/ Psychiatric History Review	X																			
Mini International Neuropsychiatric Interview (MINI)	X																			
Height	X																			
Qualification/ Safety Assessments																				
Serology Testing[d]	X																			
Pregnancy Test[e]	X	X									X									
Drug Screen[f]	X	X																		
Physical Exam[g]	X	X															X			
12-lead Electrocardiogram	X	X									X						X			
Abnormal Involuntary Movement Scale (AIMS)	X	X				X					X						X			
Simpson-Angus Scale (SAS)	X	X				X					X						X			
Barnes Akathisia Rating Scale (BARS)	X	X				X					X						X			

Table 3: Schedule of Visits and Assessments (Continued)

	Screening	24-Week Double-Blind Treatment																Safety Follow-up[a]		Monthly Visits[b]
Visit	**1**	**2[c]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17/ET**	**18**	**19**	**20 to 24**
Study Week (Visit Window of ±2 Days for Visits 3-24)			**1**	**2**	**3**	**4**	**5**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	
Biochemistry, Urinalysis, and Hematology Samples[h]	X	X	X	X		X			X		X		X		X		X			
Vital Signs[i]	X	X	X	X		X		X	X		X		X		X		X		X	
Body Weight and Waist Circumference[j]	X	X	X	X		X		X	X		X		X		X		X	X	X	X[j]
AE Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[k]
Concomitant Medication Review[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[m]
C-SSRS[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Psychiatric Efficacy/ Lifestyle/ Quality of Life Assessments																				
PANSS[o]	X	X		X		X		X	X		X		X		X		X			
CGI-S	X	X		X		X		X	X		X		X		X		X			
CGI-I				X		X		X	X		X		X		X		X			
Cigarette Use Questionnaire		X				X		X	X		X		X		X		X			
IWQOL-Lite		X				X					X						X			
EQ-5D		X				X					X						X			

Table 3: Schedule of Visits and Assessments (Continued)

Visit	Screening Day -30 to -1	24-Week Double-Blind Treatment																Safety Follow-up[a]		Monthly Visits[b]
	1	2[c]	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17/ET	18	19	20 to 24
Study Week (Visit Window of ±2 Days for Visits 3-24)			1	2	3	4	5	6	8	10	12	14	16	18	20	22	24	26	28	
Other/ General Procedures																				
Randomization		X																		
Genotype Sample	X																			
PK Labs[p]		X	X	X		X			X		X		X		X		X			
Study Drug Dispensation		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Study Drug Return and Adherence Review			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Emergency Treatment Card[q]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			

Abbreviations: AE=adverse event; CGI-I=Clinical Global Impression-Improvement; CGI-S=Clinical Global Impression-Severity; C-SSRS=Columbia-Suicide Severity Rating Scale; ET=early termination; EQ-5D=EuroQol five dimensions questionnaire; IWQOL-Lite=Impact of Weight on Quality of Life – Lite Questionnaire; PANSS=Positive and Negative Syndrome Scale; PK=pharmacokinetics

[a] The Safety Follow-up Period is not required for subjects entering ALK3831-A304.

[b] Up to 5 additional weight assessments following premature discontinuation.

[c] All assessments conducted at Visit 2 are to be done predose.

[d] Serology testing to include hepatitis B surface antigen, anti-hepatitis C antibodies, and anti-human immunodeficiency virus (HIV) antibodies. A positive hepatitis C antibody test must be confirmed by RNA testing.

[e] Serum pregnancy test at screening; urine pregnancy test at subsequent specified visits. The urine pregnancy test may be repeated at any time during the study based on the investigator's judgment.

[f] Centralized drug testing at screening; local drug testing (via dipstick) at other timepoints. The drug panel includes opiates, amphetamine/methamphetamine, phenylcyclidine (PCP), and cocaine. The urine drug screen may be repeated at any point during the study based on the investigator's discretion.

[g] Full physical exam at screening; brief physical at all other indicated visits

[h] Blood samples to be collected after an overnight (at least 8 hour) fast with no food or drink except water.

[i] Vital signs include orthostatic blood pressure and heart rate, respiratory rate, and oral body temperature. Blood pressure, pulse rate, and respiratory rate will be taken after the subject has been supine for 5 minutes and once again after the subject has stood for 2 minutes.

[j] Body weight and waist circumference to be measured in triplicate at all indicated visits. Body weight will also be measured in subjects prematurely discontinuing study drug and returning for weight assessments for the additional follow-up visits 20 through 24.

[k] Adverse events will be recorded for subjects prematurely discontinuing study drug and returning for weight assessments for additional follow-up visits 20 through 24.

[l] All medications (prescription and over the counter, including vitamins and herbal supplements) taken within 60 days will be recorded at screening. Any changes will be recorded at subsequent visits.

[m] Only new antipsychotic medications are to be recorded at visits 20 through 24 for subjects prematurely discontinuing study drug and returning for weight assessments for additional follow-up visits.

[n] "Baseline/Screening" version to be completed at screening. "Since Last Visit" version to be completed at subsequent timepoints.

[o] To be completed by the PI or designee using the Structured Clinical Interview for the PANSS (SCI-PANSS). The PANSS should be administered before any other psychiatric assessment or questionnaire.

[p] One PK draw to occur during each indicated visit. When PK and safety blood samples are scheduled to be collected on the same day, efforts should be made to collect during the same draw.

[q] Dispense card at Visit 2; confirm possession of card and redispense another card as necessary at all subsequent visits. Collect card at Visit 17/ET or Visit 19 as applicable.

8.3. Study Procedures Descriptions

Details of the study procedures are described below. The overall schedule of assessments is provided in Table 3.

8.3.1. Informed Consent

The nature of the study and its risks and benefits will be explained to the subject by the principal investigator or designated study personnel as outlined in Section 17.3.

Prior to the administration of any study-specific procedures, authorized study personnel will obtain written informed consent from each potential subject.

8.3.2. Eligibility Review

An eligibility review will be conducted by the investigator at the visits specified in Table 3 using the subject inclusion criteria in Section 7.1 and exclusion criteria in Section 7.2.

8.3.3. Demographics and Medical History

Subject's demographic data and medical history will be reviewed and documented at the timepoints specified in Table 3.

8.3.4. Concomitant Medication Review

All medications (prescription and non-prescription, including vitamins and herbal supplements) taken by a given subject within 60 days of screening through follow-up will be recorded.

At each study visit (see Table 3), the investigator or designee 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. Note: for subjects prematurely discontinuing study drug and returning for weight assessments for additional follow-up visits 20 to 24, only new antipsychotic medications will be recorded.

8.3.5. Vital Signs

Vital signs (ie, blood pressure, heart rate, respiratory rate, and oral body temperature) will be assessed at the timepoints specified in Table 3. 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 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

Vital signs may be collected at any time during a scheduled visit, unless otherwise noted.

8.3.6. Physical Examination

A physical examination will be performed at the timepoints specified in Table 3. A full physical will be performed at screening and a brief physical at subsequent visits.

8.3.7. Height, Body Weight, and Waist Circumference

Height will be measured at screening only and body weight and waist circumference will be measured at all the timepoints specified in Table 3. Subjects who discontinue prematurely will be asked to return to the clinic for weight measurements as outlined in Section 7.3 and Table 3.

For weight measurements, subjects should be asked to void immediately prior to measurement and should be dressed in a hospital gown with consistent under-attire for each measurement. Subjects should remove all personal items such as watches and jewelry and they should be weighed on the same scale for each measurement under the same conditions.

Both weight and waist circumference will be measured three consecutive times at each assessment and all measurements will be recorded in the eCRF.

8.3.8. 12-Lead Electrocardiogram

A 12-lead electrocardiogram (ECG) will be conducted at the timepoints specified in Table 3. All scheduled ECGs must be performed after the subject has rested quietly for at least 5 minutes in the supine position.

A qualified clinician will conduct ECGs and assess ECG results using equipment that has been calibrated according to the site's standard operating procedures. The following ECG parameters will be collected: pulse, RR, PR, QRS, QT, QT interval corrected using the Fridericia formula (QTcF), and QT interval corrected using the Bazett formula (QTcB).

The ECGs will also be evaluated by a central reader.

8.3.9. Structured Interviews and Questionnaires

Brief descriptions of each of the interviews and questionnaires to be distributed are available below. All interviews and questionnaires will be administered by trained and qualified study personnel.

Table 3 provides information on the timepoints at which each assessment should be administered.

At screening the medical and psychiatric history and MINI diagnostic interview must be conducted prior to the PANSS. For all other visits where assessments overlap, the PANSS should be administered first before any other psychiatric assessment.

8.3.9.1. Diagnostic Assessments

8.3.9.1.1. Mini International Neuropsychiatric Interview

The MINI is a short, clinician-administered, structured diagnostic interview, with an administration time of approximately 15 minutes (Sheehan et al, 1998). The MINI has been validated against the much longer Structured Clinical Interview for DSM Diagnoses (SCID). The MINI will be used at screening only as indicated in Table 3.

8.3.9.2. Antipsychotic Efficacy Assessments

For assessments performed at multiple visits, every effort should be made to pair the same clinician/rater with the same subject across visits.

8.3.9.2.1. Clinical Global Impression-Severity

The PI or designee will complete the CGI-Severity (CGI-S, Appendix B) scale at the timepoints specified in Table 3. The CGI-S measures mental illness severity. Clinicians are asked to rate subjects based on their prior experience working with individuals in a similar patient population (Guy 1976).

8.3.9.2.2. Clinical Global Impression-Improvement

The PI or designee will complete the CGI-Improvement (CGI-I, Appendix B) at the timepoints specified in Table 3. The CGI-I measures improvement from the first assessment (Guy 1976).

8.3.9.2.3. Positive and Negative Syndrome Scale

The PI or designee will complete the PANSS (Appendix C) (Kay et al, 1987) according to the schedule in Table 3. The Structured Clinical Interview for the PANSS (SCI-PANSS) will be used to administer the PANSS.

8.3.9.3. Safety Assessments

8.3.9.3.1. Abnormal Movement Rating Scales

The PI or designee will complete the following abnormal movement rating scales: The Abnormal Involuntary Movement Scale (AIMS, Appendix D) (Guy 1976), the Barnes Akathisia Rating Scale (BARS, Appendix E) (Barnes 1989), and the Simpson-Angus Scale (SAS, Appendix F) (Simpson and Angus 1970) at the timepoints specified in Table 3.

After administration of the first dose of study drug, if a subject complains of extrapyramidal symptoms on a day when abnormal movement scale assessments are not scheduled, an unscheduled abnormal movement assessment should be performed.

8.3.9.3.2. Columbia-Suicide Severity Rating Scale

The PI or designee will administer the C-SSRS (Appendix G) according to the schedule in Table 3. The “Baseline/Screening” version is to be completed at Visit 1 and the “Since Last Visit” version is to be completed at all subsequent scheduled timepoints. The C-SSRS should be administered by a qualified clinician trained in assessing and managing suicidal ideation and behavior (Posner et al, 2011).

8.3.9.4. Other Assessments

8.3.9.4.1. Cigarette Use Questionnaire

Data on cigarette use will be collected using the question: “How many packs of cigarettes did you smoke over the past 7 days?” at the timepoints specified in Table 3.

8.3.9.4.2. Impact of Weight on Quality of Life – Lite

Subjects will complete the IWQOL-Lite questionnaire (Appendix H) at the timepoints specified in Table 3.

8.3.9.4.3. EuroQol-5D

Subjects will complete the EQ-5D (Appendix I) at the timepoints specified in Table 3. This scale provides an indication of health status based on self-rating in the following five categories: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Additionally, it asks subjects to rank their health status on a visual analogue scale (VAS) from "worst imaginable health state" to "best imaginable health state."

8.3.10. Rater Review

Rater (ie, study staff) accuracy at screening on pre-specified study measures (ie, PANSS) will be reviewed by central raters.

Later reviews will take place according to a pre-specified schedule (subject to change based on rater accuracy) after the measure has been administered using an audio recording of the screening interview. Rater review is necessary for mitigating inaccurate inclusion/exclusion assessments and inaccurate efficacy assessments.

Rater assessments require subject interviews to be audio recorded. The audio recording will be disclosed and explained to the subject by study staff and will be disclosed in the ICF during the informed consent process. No subject will be recorded without the knowledge that a recording is being made.

8.3.11. Laboratory Assessments

8.3.11.1. Drug Testing

A drug screen for opioids (including codeine, hydrocodone, hydromorphone, methadone, morphine, oxycodone, and oxymorphone) and drugs of abuse (including amphetamine/ methamphetamine, phencyclidine, and cocaine) will be performed at the timepoints specified in Table 3. Urine drug screens may be repeated based on investigator judgment. The test may also be repeated at any time during the study, should the investigator feel it is warranted. Subjects are not eligible for participation if the results are positive at screening. If a subject is determined to be using any of these substances during the treatment period, the investigator should contact the medical monitor to discuss the course of action.

8.3.11.2. Hematology, Biochemistry, and Urinalysis

Fasting blood and urine samples will be collected at the timepoints specified in Table 3 for specific hematology, biochemistry, and urinalysis assessments listed in Table 4. Subjects will be instructed not to eat or drink anything (except water) for 8 hours before each visit where blood samples for biochemistry and hematology assessments will be collected. Samples will be collected in accordance with the site's standard procedures and analyzed by a central laboratory. Laboratory assessments may be repeated at the investigator's discretion.

Table 4: Clinical Laboratory Assessments

Hematology	Biochemistry	Urinalysis
Hematocrit	**General Chemistry**	Bilirubin
Hemoglobin	Albumin	Color and appearance
Platelet count	Bicarbonate	Glucose
Red blood cell count	Calcium	Ketones
Total and differential (absolute) white blood cell count	Chloride	Leukocytes
	Creatine phosphokinase	Nitrite
	Glucose	Occult blood
	Lactic dehydrogenase	pH
	Potassium	Protein
	Sodium	Specific gravity
	Total protein	Urobilinogen
	Uric acid	Cotinine
	Endocrine Function Test	
	Thyroid-stimulating hormone[a]	Microscopic examination of sediment, *only if urinalysis dipstick results are abnormal*
	HbA1c	
	Prolactin	
	Insulin	
	Liver Function Tests	
	Alanine aminotransferase	
	Alkaline phosphatase	
	Aspartate aminotransferase	
	Gamma-glutamyl transferase	
	Total bilirubin	
	Renal Function Tests	
	Blood urea nitrogen	
	Creatinine	
	Lipid Panel	
	High-density lipoprotein	
	Low-density lipoprotein	
	Total cholesterol	
	Triglycerides	

[a] At screening only

8.3.11.3. Pregnancy Testing

A urine/serum pregnancy test will be administered to all women at the timepoints specified in Table 3. At the screening visit, results must be negative for the subject to be eligible for the study. As highlighted in Section 7.3 a positive pregnancy test result at any time will necessitate the subject's immediate withdrawal from the study. Additional follow-up may be necessary as indicated in Section 8.4.1

8.3.11.4. Serology Testing

A blood sample for a serology panel testing for hepatitis B surface antigen, anti-hepatitis C antibodies, and human immunodeficiency virus (HIV) will be performed at screening only (Table 3). A positive hepatitis C antibody test must be confirmed by RNA testing to be exclusionary.

8.3.12. Pharmacokinetic Assessments

Concentrations of olanzapine, samidorphan, and metabolites of interest will be determined from plasma samples collected according to the schedule in Table 3. The time of last study drug administration (when applicable) and the time of each PK blood draw must be documented in the subject's source documents. Samples for PK analysis will be stored at -20°C ±10°C. The PK data from these samples may be included in a subsequent population PK analysis or other post-hoc analyses conducted outside of this study.

8.3.13. Genotype Sampling

A blood sample may be collected (at the timepoint indicated in Table 3) for evaluation of genotypes that are potentially related to response and to explore potential genetic associations with efficacy, adverse effects, symptoms, or outcomes. No other tests will be performed with these samples.

8.3.14. Randomization

At the timepoint specified in Table 3, subjects will be randomized as outlined in Section 9.3.

8.3.15. Drug Dispensation and Reconciliation

Section 9 provides information related to drug dispensing procedures. Study drug will be dispensed at the timepoints specified in Table 3. The study drug use and storage information will be explained to/reviewed with the subject.

Whether or not samidorphan is classified as a controlled substance varies from country to country; some countries have classified samidorphan as a controlled substance, while others have not. Sites will be given storage, handling, and reconciliation instructions applicable to their country to ensure compliance with local regulations for controlled substances.

8.3.16. Emergency Treatment Card

An emergency treatment card will be distributed to each subject and collected from each subject at the timepoints indicated in Table 3. 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 card with them at all times. Study personnel will confirm that subjects have the card in their possession at each study visit as indicated in Table 3.

8.3.17. Adverse Event Monitoring

Adverse events will be monitored continuously from the time a subject signs the informed consent document until the completion of the final study visit (see Table 3). Adverse events and serious adverse events (SAEs) are defined in Section 13.1 and 13.2, respectively. Section 13.4 provides guidance on the monitoring and recording requirements for AEs. Section 13.5 provides guidance on the reporting requirements for SAEs.

8.4. Study Requirements and Restrictions

8.4.1. Contraception and Pregnancy

All male and female subjects must agree to use an acceptable method of contraception for the duration of the study unless they are surgically sterile or post-menopausal (see below). The following are considered acceptable methods of contraception:

1. Double-barrier protection (eg, a condom with spermicide or a diaphragm with spermicide)
2. Intrauterine device (IUD)
3. Oral contraceptive pills and other hormonal methods (eg, a vaginal ring, contraceptive patch, contraceptive implant)

Subjects who are abstinent are eligible, provided they agree to use an acceptable contraceptive method should they become sexually active.

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. Partner vasectomy is not considered an approved acceptable method of contraception for a female subject.

Women who are postmenopausal are also exempt from the requirement to use contraception. For the purpose of this study, postmenopausal is defined as the permanent cessation of menstruation for at least 12 months prior to screening in women who are 45 years of age or older.

If a subject becomes pregnant while participating in the study, she will be discontinued from study drug immediately. Pregnancies in female subjects and female partners of male subjects should be handled in the same manner. The investigator must fill out a Pregnancy Report Form and submit the information to the sponsor within 24 hours of awareness of the pregnancy, irrespective of whether an adverse event has occurred. The early termination and safety follow-up visits will be scheduled. The investigator will follow the pregnancy until completion or until pregnancy termination and notify the outcome to the sponsor. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE the investigator should follow the procedure of reporting SAEs (see Section 13.5). Additional follow-up may be required.

8.4.2. Prohibited Medications

The use of any antipsychotic other than study drug is prohibited except when subjects are tapering off of current medication (see Section 8.1). Prohibited medications include the following:

- Monoamine oxidase inhibitors (eg, phenelzine, tranylcypromine, selegiline, or moclobemide)
- Long-acting formulations of any antipsychotic agent
- Antipsychotic agents (with the exception of cross-tapering of previous antipsychotic during first 2-weeks post randomization)
- Use of antipsychotic sleep aids (eg, Seroquel®) is prohibited. However, use of benzodiazepines to treat some symptoms is permissible (see Section 8.4.3)
- In general, the use of psychotropic medications other than study drug is prohibited with the exception of the following (these medications should only be administered after all assessments have been completed for that visit):
  - Beta-blockers (eg, propranolol or pinodolol), antihistamines, and anticholinergics may be used for treatment-emergent akathisia
  - Anticholinergics may be used for extrapyramidal symptoms
- Chantix® (varenicline) is prohibited. However, nicotine replacement therapy including nicotine replacement patch and oral nicotine gum is permitted
- All prescription or over-the-counter (OTC) agents taken for the purpose of weight reduction
- Systemic steroids administered by oral, intravenous, or intramuscular route
- Topiramate (Topamax®) and combination products containing topiramate; Calcitonin (eg, Miacalcin®)
- Diabetes treatments and hypoglycemic agents including Metformin and Insulin
- Antidepressants that have been started within 30 days of screening are prohibited. An antidepressant should not be started during a subject's participation in the study. Subjects who have been on a stable dose of an antidepressant for at least 30 days before screening may be allowed to participate in the study if it is anticipated that the dose will not change during the subject's participation in the study

Medications that are contraindicated with olanzapine use or exhibit drug-interaction potential with olanzapine are prohibited.

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. Refer to Appendix A for a list of CYP3A4 inhibitors and inducers.

The CRO medical monitor should be consulted for any questions about use of any psychotropic medications during a subject's participation in this study.

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 and throughout the study period is prohibited. **Note**: during the study period, opioid agonists should be avoided as they may be rendered ineffective by samidorphan.

8.4.3. Permitted Therapy

Permissible potential medications to treat extrapyramidal symptoms may include benzodiazepines, antihistamines, and anticholinergics. Benzodiazepines should be utilized for treatment-emergent akathisia. While insomnia may be treated with a variety of agents, short half-life benzodiazepines should be utilized to avoid the potential for lingering effects on daytime functioning and study assessments (eg, triazolam). Non-benzodiazepine medication may be used to treat insomnia (eg, zolpidem, eszopiclone). Treatment of agitation and/or anxiety with benzodiazepines is permissible. However, doses should be restricted to no more than a 2 mg lorazepam equivalent per day and should be kept as stable as possible throughout study so as not to interfere with daytime functioning and study assessments.

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.

8.4.5. Other Restrictions and Requirements

Additional restrictions and requirements include:

- Prohibited substances include amphetamines (including methamphetamine), cocaine, barbiturates, methadone, opioids (including morphine, oxycodone, methadone, and buprenorphine), and phencyclidine

- Subjects will be required to abstain from blood or blood product donation during the study and for 30 days following the follow-up visit
- Subjects will be instructed to maintain their normal caffeine intake and/or tobacco use as well as normal activity/exercise throughout the study. Subjects will be asked to abstain from strenuous physical activity for 48 hours prior to each study visit
- Subjects are prohibited from participating in a weight management program (including weight loss surgery) or from entering a smoking cessation program for the duration of the study

Subjects will be asked to refrain from driving, operating machinery, or engaging in hazardous activities until they and the investigator are sure the study drug is not impairing their judgment and/or ability to perform skilled tasks.

See Section 8.3.4 for details regarding the concomitant medication review.

9. TREATMENT OF SUBJECTS

9.1. Study Drug Dose and Administration

Study drugs include:

- ALKS 3831 10/10 (10 mg olanzapine/10 mg samidorphan) or 20/10 (20 mg olanzapine/10 mg samidorphan) administered as a coated bilayer tablet
- Olanzapine 10 mg or 20 mg administered as a coated bilayer tablet

At Visit 2 and all subsequent visits until Visit 17 (EOT), subjects will be given blister cards containing study drug to take at home. Subjects will be instructed to take one tablet by mouth each day, preferably at bedtime. Dosing may be switched to another time at the investigator's discretion if there are tolerability problems; however, frequent switching is discouraged.

Subjects will be instructed to keep all unused tablets in their blister card and to return unused tablets to the study site at their next visit. If dosing is to occur at that visit, the dose should be taken from the subject's next blister card, not from the card they are returning.

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

9.2. Study Drug Return and Adherence Review

Subjects will undergo a study drug adherence review at the timepoints indicated in Table 3. Subjects will be instructed to keep all unused tablets in their original containers and to return the original containers with any unused study drug at each visit following dispensation. Study drug accountability will be documented as the number of tablets dispensed, dosed, lost/missing, or remaining. If applicable, the site will discuss non-adherence with the subject

9.3. Randomization/Method of Assigning Subjects to Treatment

Subjects meeting eligibility criteria at baseline (Day 1) will be randomized in a 1:1 ratio to ALKS 3831 or olanzapine.

Randomization will be performed centrally through an Interactive Web Response System (IWRS). A unique randomization number will be assigned by the IWRS once eligibility has been determined. Once a randomization number has been assigned, that number must not be used again if, for example, a subject is withdrawn from the study. Codes will be prepared by an independent biostatistician who is not otherwise involved in this study.

9.4. Blinding

All Alkermes staff, clinical staff, and subjects will be blinded to treatment assignment until database lock.

The principal investigator is responsible for all trial-related medical decisions. If the investigator deems it necessary to break the study blind in the interest of a subject's medical safety, he or she must make every effort to contact the CRO/sponsor medical monitor before the blind is broken.

If the site is unable to contact the medical monitor prior to breaking the blind, the medical monitor must be contacted within 24 hours following disclosure of study drug assignment. Any premature unblinding should be promptly documented.

Breaking the blind for a single subject will not affect the blind for the remaining subjects.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

The ALKS 3831 drug product will be supplied as a coated bilayer tablet in two fixed-dose combinations:

- ALKS 3831 10/10 (10 mg olanzapine/10 mg samidorphan)
- ALKS 3831 20/10 (20 mg olanzapine/10 mg samidorphan)

Samidorphan is a Schedule II controlled substance. Thus, ALKS 3831 should be treated as a Schedule II controlled substance in the US and any other country in which it is controlled.

Matching olanzapine-only drug will be manufactured by Alkermes, Inc and will be supplied as a coated bilayer tablet in two dose strengths:

- OLZ 10 (10 mg olanzapine)
- OLZ 20 (20 mg olanzapine)

10.2. Packaging and Labeling

ALKS 3831 and olanzapine will be supplied in blister packs. Blister cards will be in weekly and biweekly configurations. Weekly blister cards will contain 9 tablets, enough for 1 week of dosing plus sufficient overage for 2 additional once daily doses. Biweekly blister cards will contain 16 tablets, enough for 2 weeks of dosing plus sufficient overage for 2 additional once daily doses.

10.3. Storage

Product should be stored at not more than 25°C.

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 investigator will be responsible for the oversight of recording the receipt and administration of study drug, and for insuring the supervision of the storage and allocation of these supplies. The investigator is required to maintain current drug dispensing and accountability logs throughout the study. The investigator may delegate accountability duties to an appropriate and qualified pharmacist or staff member who is under the supervision of the investigator. The investigator or designee must allow the Clinical Research Associate or equivalent to perform drug reconciliation during each study monitoring visit. All unused supplies will be checked against the study drug movement records before investigational drug is returned or destroyed.

Refer to Section 8.3.15 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. Packages may be destroyed on site according to Good Clinical Practice (GCP) and site practice. Alternatively, the sponsor may arrange for destruction with a third party vendor operating in accordance with GCP and/or Good Manufacturing Practice (GMP), as applicable.

11. ASSESSMENT OF EFFICACY

The following assessments will be used to collect efficacy throughout the study:

- Weight (Primary Endpoint)

Antipsychotic efficacy measures include the following:

- Positive and Negative Symptom Scale (PANSS)
- Clinical Global Impression – Severity (CGI-S)
- Clinical Global Impression – Improvement (CGI-I)

See Section 8.3.7 and Section 8.3.9.2 for more details on weight measurement and antipsychotic efficacy assessments.

Other Assessments

- Cigarette Use Questionnaire
- Impact of Weight on Quality of Life – Lite (IWQOL-Lite) Questionnaire
- EuroQol-5D (EQ-5D)
- Substudy: an exploratory substudy will measure body composition (using Bioelectrical Impedance Analysis [BIA]) in subjects at a subset of sites participating in the main ALK3831-A303 study

See Section 8.3.9.4 for more details on the questionnaires and quality of life assessments. See Addendum A for substudy details.

12. ASSESSMENT OF PHARMACOKINETICS AND PHARMACODYNAMICS

Concentrations of olanzapine, samidorphan, and metabolites of interest will be determined from plasma samples collected according to the schedule in Table 3. Pharmacokinetic (PK) data from these samples may be included in a subsequent population PK analysis conducted outside of this study. By-subject listings of plasma concentrations will be provided.

13. ASSESSMENT OF SAFETY

The following assessments will be collected to measure safety and tolerability throughout the study:

- Adverse events (AEs)
- Waist Circumference
- Clinical laboratory parameters including chemistry, hematology, and urinalysis
- Vital signs (oral temperature, respiratory rate, orthostatic blood pressure, and heart rate)
- Electrocardiogram parameters (Uncorrected QT, QTcF, QTcB, PR, RR, and QRS intervals)
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Abnormal Involuntary Movement Scale (AIMS)
- Simpson-Angus Scale (SAS)
- Barnes Akathisia Rating Scale (BARS)

See Section 8.3.9.3 for more details regarding safety assessment questionnaires.

13.1. 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 informed consent form (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 investigator. Clinically significant values will be considered AEs and recorded as such on the eCRFs.

Pregnancy is not considered an AE, although a subject will be withdrawn from the study if a pregnancy occurs. As described in Section 8.4.1, the pregnancy must be reported to Alkermes and additional follow-up may be required.

13.2. Definition of Serious Adverse Event

An 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 to be 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.

13.3. 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 investigator (or designated sub-investigator) according to his/her best clinical judgment. The criteria listed in Table 5 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.

Table 5: Adverse Event Causality Guidelines

Relationship	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.

13.4. Monitoring and Recording of Adverse Events

Adverse event data collection will begin after a subject signs the ICF and will continue until completion of the final study visit (Visit 19 for subjects completing the study or the final monthly visit for subjects discontinuing study drug, but returning for monthly visits). Any AE or SAE having an onset after the final study visit will not be reported unless the investigator feels that the event may be related to the study drug.

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

The investigator will assess all AEs regarding any causal relationship to the study drug (see Section 13.3), 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 investigator, or until the subject is deemed by the investigator to be lost to follow-up.

For clinical study safety reporting purposes, the most recent version of the Investigator's Brochure 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 investigator. If a subject withdraws from the study for any reason, any ongoing AEs will be followed until resolution, until deemed stable by the investigator, or until the subject is deemed by the investigator to be lost to follow-up.

13.5. Reporting of Serious Adverse Events

All SAEs must be reported to PPD within 1 business day of discovery, by emailing: PPD or 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 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.

14. STATISTICS

14.1. Sample Size Considerations

The initial target sample size is 200 randomized subjects per treatment group (400 in total). This sample size will provide at least 90% power to detect a significant difference in mean percent change in body weight at Week 24 of 4% or more (3.0% on ALKS 3831 vs 7% on olanzapine group with standard deviation of 9%) and a 13% difference in proportion of subjects with ≥10% weight gain at Week 24 (14% on ALKS 3831 vs 27% on olanzapine group).

An unblinded interim analysis is planned to be conducted to determine if the final sample size will be increased to 540 (270 subjects per treatment group Section 14.7).

14.2. General Statistical Methodology

The statistical analysis methods are described below. Additional details will be provided in the Statistical Analysis Plan (SAP).

In general, summary statistics (n, mean, standard deviation [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 confidence intervals, unless stated otherwise, will be 2-sided and will be set at α=0.05.

14.2.1. Study Populations

14.2.1.1. Safety Population

The safety population includes all randomized subjects who receive at least one dose of study drug (ALKS 3831 or olanzapine).

14.2.1.2. Efficacy Population

The efficacy population includes:

- Full analysis set (FAS) population: all subjects in the safety population who have at least one postbaseline weight assessment
- Early weight gain population: all subjects in the FAS population who gain weight (>0 kg) at Week 1

14.3. Demographics and Baseline Data

Demographics and baseline characteristics such as gender, age, race, weight, BMI, and psychiatric history will be summarized by treatment group. If there are heterogeneities between study 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 made in the efficacy and safety analyses.

Medical history will be summarized for the safety population using the number of observations and percentage of subjects reporting each category.

14.4. Efficacy Analyses

Efficacy analyses will be based on the relevant efficacy population. Baseline for the primary efficacy analysis is defined as the last non-missing assessment before the first dose of the double-blind study drug. All statistical tests will be two-sided hypothesis tests performed at the 5% significance level. All confidence intervals will be two-sided 95% confidence intervals, unless specified otherwise.

Primary Endpoints

The primary endpoints are:

- Percent change from baseline in body weight at Week 24 in the FAS population
- Proportion of subjects with ≥10% weight gain at Week 24 in the FAS population

For percent change from baseline in body weight at Week 24, the primary analysis will be carried out using an analysis of covariance (ANCOVA) method. The ANCOVA model will include treatment group, race (Black or African American, non-Black or African American), and age (<30, ≥30) as factors, and baseline weight as a covariate. Missing values will be addressed using a multiple imputation (MI) approach, as described in the SAP. The variables in the MI model will at least include the same variables as used in the ANCOVA model. Additional sensitivity analyses will be carried out to explore the impact of missing data.

For proportion of subjects with ≥10% weight gain at Week 24, the primary analyses will be carried out using a logistic regression model. The model will include treatment group, race (Black or African American, non-Black or African American), and age (<30, ≥30) as factors, and baseline weight as a covariate. Missing values will be addressed using the MI approach, as described above.

Key Secondary Endpoint

The key secondary endpoint is:

- Proportion of subjects with ≥7% weight gain at Week 24

The key secondary endpoint will be analyzed using the same approach as the analysis for the proportion of subjects with ≥10% weight gain at Week 24 in the FAS population.

A fixed sequence approach will be used to control overall Type I error rate. First, both primary endpoints will be tested at an alpha level of 0.05. If both primary endpoints are statistically significant, the key secondary endpoint will be tested at an alpha level of 0.05.

Other Endpoints

Other endpoints are:

- Percent change from baseline in body weight at Week 24 in the early weight gain population
- Proportion of subjects with ≥10% weight gain at Week 24 in the early weight gain population
- Change from baseline in fasting lipids (fasting triglycerides, low-density lipoprotein [LDL], high-density lipoprotein [HDL], total cholesterol), fasting glucose, fasting insulin, and HbA1c by visit
- Absolute change in body weight by visit
- Change from baseline in waist circumference by visit
- Change from baseline in PANSS total score and subscales by visit
- Change from baseline in CGI-S by visit
- CGI-I score by visit
- Change from baseline in IWQOL-Lite total score and subscales by visit
- Change from baseline in EQ-5D score by visit

The body weight- and waist circumference-related endpoints will be analyzed in the same manner as the co-primary endpoints. An ANCOVA model will be used for continuous endpoints. The model will include treatment group, race (Black or African American, non-Black or African American), and age (<30, ≥30) as factors, and baseline value as a covariate. A logistic regression model will be used for categorical endpoint, adjusting for the same covariates. Missing values will be addressed by an MI approach.

Change from baseline in fasting lipids (fasting triglycerides, LDL, HDL, total cholesterol) and fasting glucose, fasting insulin, and HbA1c will be analyzed by a mixed model with repeated measurements (MMRM) model. The model will include treatment, visit, treatment-by-visit interaction term, race (Black or African American, non-Black or African American) and age (<30, ≥30) as categorical fixed effects; the baseline value will be included as a covariate.

Change from baseline in PANSS, CGI-S, IWQOL-Lite and EQ-5D will be analyzed by MMRM model. The model will include treatment, visit, and treatment-by-visit interaction term as categorical fixed effects; the baseline value will be included as a covariate.

PANSS responder status (<20%, ≥20% improvement over baseline PANSS), CGI-I score, and CGI-I responder status (≤2 vs >2) will be presented by summary statistics.

14.5. Pharmacokinetic/Pharmacodynamic Analyses

Listings will be provided for concentrations of olanzapine, samidorphan, and metabolites of interest.

14.6. Safety and Tolerability Analyses

The safety analysis will be carried out using the Safety Population. For each safety parameter, the last assessment of the parameter before the first dose of randomized study drug will be used as the baseline for all analyses of that safety parameter. All safety analyses will be based on observed data only, and no missing values will be imputed.

Reported adverse event terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by preferred term and system organ class categories.

The number and percentage of treatment emergent adverse events (TEAEs) will be summarized by treatment group by system organ class, and preferred terms within each system organ class. Subjects with SAEs, and AEs contributing to discontinuation will also be summarized.

Observed values and change from baseline in BMI, waist circumference, laboratory parameters, vital signs, and ECG parameters will be summarized by treatment group and study visit.

The number and percentage of subjects who have met potentially clinically significant (PCS) criteria at any postbaseline visit will be summarized by treatment group for laboratory, vital signs, weight, and ECG parameters. Supporting listings will be provided.

The number and percentage of subjects with shifts in laboratory and extra pyramidal symptoms (EPS) parameters (AIMS, BARS, and SAS) will also be summarized by treatment group. Supporting listings will be provided.

The number and percentage of subjects with C-SSRS assessments of suicidal ideation and behavior will also be summarized.

Prior and concomitant medication use will be summarized by World Health Organization (WHO) Drug Dictionary Anatomical Therapeutic Class (ATC) code and by treatment group. Listings will be provided for all safety endpoints.

14.7. Interim Analysis

One unblinded interim analysis will be conducted by an independent statistical center (ISC) when 50% of subjects (N=200) have completed the double-blind treatment period or have discontinued from the study. The details regarding the conduct of the unblinded interim analysis will be specified in the interim analysis operational plan and the statistical testing methodology will be specified in the interim analysis plan (IAP).

The conditional power (CP) will be computed for both primary endpoints. Based on the conditional power, it will be assigned into one of 3 zones: favorable (CP ≥90%), promising (30% ≤ CP <90%), or unfavorable (CP <30%). The target sample size of 200 per arm will be increased to 270 subjects per arm when the conditional power for either primary endpoint is in the promising zone and neither of the primary endpoints is in the unfavorable zone. Otherwise, the target sample size will be maintained at 200 subjects per arm. Overall Type 1 error rate for the final analysis are maintained using CHW method (Cui et al, 1999) by combining the Z test statistics from two independent stages (before and after the interim analysis) with a fixed weight based on the original sample size. There will be no early stopping for efficacy or futility. The sponsor will not be informed with any unblinded interim analysis results except for a

recommendation to either increase the sample size to 540 subjects (270 per arm) or to leave the sample size unchanged.

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.

15.2. Audits and Inspections

By signing the protocol, the investigator agrees that, within local regulatory restrictions and institutional and ethical considerations, authorized representatives of Alkermes, a regulatory authority, and/or an institutional review board (IRB)/independent ethics committee (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, x-rays, 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 investigator should contact Alkermes immediately if contacted by a regulatory agency regarding an inspection.

15.3. Institutional Review Board/Independent Ethics Committee

The investigator 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 form and recruitment materials, must be maintained by the investigator 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 data accuracy, completeness and compliance, the study site should have processes in place for data review and quality control. Alkermes may also 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 eCRF data must be based on source documents or approved to be the original data (ie, data directly reported on the eCRF). All eCRFs will be completed by the clinic staff prior to review by the Alkermes monitor or designated representative.

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

16.2. Confidentiality of Data

By signing this protocol, the investigator 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 Study Agreement (CSA) 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 ICF 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 investigator. The protocol must be re-approved by the IRB/IEC upon receipt of amendments and annually, as local regulatory requirements require.

The investigator 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.

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 investigator (or authorized designee) at each center will ensure that the subject (or the subject's legal representative) 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 informed consent form (ICF) that summarizes the pertinent study information and will be given ample time to read the form 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/she must sign the ICF before any study-specific procedures are conducted.

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 contract research organization (CRO) 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 ICF, which must be reviewed and approved by the IRB, and then signed by all applicable study participants.

The time that informed consent is obtained must be documented. The investigator must maintain the original, signed ICF in the subject's source documents. A copy of the signed ICF 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 CSA for further details.

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 investigator or other authorized study personnel. All data entries will be verified for accuracy and correctness by independent monitors. The electronic data capture system maintains a full audit trail.

All electronic source data collected outside of the eCRF such as central laboratory data will be transferred directly to Alkermes for incorporation into the final datasets. 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 investigator. Clinically significant values will be considered AEs and recorded as such on the eCRFs.

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 investigator 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 all essential clinical study documents shall be governed by the terms and conditions of the site's CSA and in accordance with ICH guidelines/local regulatory requirements as follows:

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by the terms of the CSA. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

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.

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 investigators and the sponsor. Please refer to the CSA for details on the procedures for publishing and presenting data.

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20. LIST OF APPENDICES

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

Partial List of CYP3A4 Inhibitors and Inducers (This is not an all-inclusive 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

APPENDIX B. CLINICAL GLOBAL IMPRESSION

- Severity
- Improvement

Clinical Global Impression – Severity of Illness and Improvement of Illness (CGI-S and CGI-I)

Severity of Illness (CGI-S) 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
Global Improvement (CGI-I) Rate total improvement whether or not in your judgment it is due entirely to drug treatment. Compared to his/her condition at admission, how much has he/she 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

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

APPENDIX C. POSITIVE AND NEGATIVE SYNDROME SCALE

PANSS

Positive and Negative Syndrome Scale

Stanley R. Kay, Ph.D.
Lewis A. Opler, M.D., Ph.D.
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 rating*: 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. ABNORMAL INVOLUNTARY MOVEMENT SCALE

Abnormal Involuntary Movement Scale (AIMS)

Movement ratings: Rate highest severity observed. Rate movements that occur upon activation one ***less*** than those observed spontaneously.

Code:
0 = None
1 = Minimal, may be extreme normal
2 = Mild
3 = Moderate
4 = Severe

		(Circle One)				
FACIAL AND ORAL MOVEMENTS:	**1. MUSCLES OF FACIAL EXPRESSION** e.g movements of forehead, eyebrows, periorbital area, cheeks, including frowning, blinking, smiling, grimacing	**0**	**1**	**2**	**3**	**4**
	2. LIPS AND PERIORAL AREA e.g. puckering, pouting, smacking	**0**	**1**	**2**	**3**	**4**
	3. JAW e.g. biting, clenching, chewing, mouth opening, lateral movement	**0**	**1**	**2**	**3**	**4**
	4. TONGUE Rate only increases in movement both in and out of mouth. NOT inability to sustain movement	**0**	**1**	**2**	**3**	**4**
EXTREMITY MOVEMENTS:	**5. UPPER (ARMS, WRISTS, HANDS, FINGERS)** Include choreic movements (i.e. rapid, objectively purposeless, irregular, spontaneous), athetoid movements (i.e. slow, irregular, complex, serpentine). Do NOT include tremor (i.e. repetitive, regular, rhythmic)	**0**	**1**	**2**	**3**	**4**
	6. LOWER (LEGS, KNEES, ANKLES, TOES) e.g. lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot	**0**	**1**	**2**	**3**	**4**
TRUNK MOVEMENTS:	**7. NECK, SHOULDERS, HIPS** e.g.rocking, twisting, squirming, pelvic gyrations	**0**	**1**	**2**	**3**	**4**
GLOBAL JUDGMENT:	**8. SEVERITY OF ABNORMAL MOVEMENTS**	None, normal **0** Minimal **1** Mild **2** Moderate **3** Severe **4**				
	9. INCAPACITATION DUE TO ABNORMAL MOVEMENTS	None, normal **0** Minimal **1** Mild **2** Moderate **3** Severe **4**				
	10. PATIENT'S AWARENESS OF ABNORMAL MOVEMENTS. RATE ONLY PATIENT'S REPORT	No awareness **0** Aware, no distress **1** Aware, mild distress **2** Aware, moderate distress **3** Aware, severe distress **4**				
DENTAL STATUS:	**11. Current problems with teeth and/or dentures?**	No **0** Yes **1**				
	12. Does patient usually wear dentures?	No **0** Yes **1**				

Rater Signature: _____ **Date: _____**

Guy, W. ed. ECDEU Assessment Manual for Psychopharmacology. US Dept of HEW, Publication No. (Adm): 76-338, 1976

APPENDIX E. BARNES AKATHISIA SCALE

Barnes Akathisia Rating Scale (BARS)

Instructions: Patient should be observed while they are seated, and then standing while engaged in neutral conversation (for a minimum of two minutes in each position). Symptoms observed in other situations, for example, while engaged in activity on the ward, may also be rated. Subsequently, the subjective phenomena should be elicited by direct questioning.
Please circle the appropriate scores.

Objective

0 Normal, occasional fidgety movements of the limbs
1 Presence of characteristic restless movements: shuffling or tramping movements of the legs/feet, or swinging of one leg while sitting, *and/or* rocking from foot to foot or "walking on the spot" when standing, *but* movements present for less than half the time observed
2 Observed phenomena, as described in (1) above, which are present for at least half the observation period
3 Patient is constantly engaged in characteristic restless movements, *and/or* has the inability to remain seated or standing without walking or pacing, during the time observed

Subjective

Awareness of restlessness
0 Absence of inner restlessness
1 Non-specific sense of inner restlessness
2 The patient is aware of an inability to keep the legs still, or a desire to move the legs, *and/or* complains of inner restlessness aggravated specifically by being required to stand still
3 Awareness of an intense compulsion to move most of the time *and/or* reports strong desire to walk or pace most of the time

Distress related to restlessness
0 No distress
1 Mild
2 Moderate
3 Severe

Global Clinical Assessment of Akathisia
0 ***Absent.*** No evidence of awareness of restlessness. Observation of characteristic movements of akathisia in the absence of a subjective report of inner restlessness or compulsive desire to move the legs should be classified as pseudoakathisia
1 ***Questionable.*** Non-specific inner tension and fidgety movements
2 ***Mild akathisia.*** Awareness of restlessness in the legs *and/or* inner restlessness worse when required to stand still. Fidgety movements present, but characteristic restless movements of akathisia not necessarily observed. Condition causes little or no distress
3 ***Moderate akathisia.*** Awareness of restlessness as described for mild akathisia above, combined with characteristic restless movements such as rocking from foot to foot when standing. Patient finds the condition distressing
4 ***Marked akathisia.*** Subjective experience of restlessness includes a compulsive desire to walk or pace. However, the patient is able to remain seated for at least five minutes. The condition is obviously distressing.
5 ***Severe akathisia.*** The patient reports a strong compulsion to pace up and down most of the time. Unable to sit or lie down for more than a few minutes. Constant restlessness which is associated with intense distress and insomnia.

Rater Signature: _____ **Date: _____**

Scoring the Barnes Akathisia Rating Scale (BARS)

The Barnes Akathisia Rating Scale is scored as follows:
Objective Akathisia, Subjective Awareness of Restlessness and Subjective Distress Related to Restlessness are rated on a 4-point scale from 0 – 3 and are summed yielding a total score ranging from 0 to 9.

The Global Clinical Assessment of Akathisia uses a 5-point scale ranging from 0 – 4.

Reproduced from: Barnes TR: A Rating Scale for Drug-Induced Akathisia. British Journal of Psychiatry 154:672-676, 1989.

Clintara Version 1.6 June, 2011

APPENDIX F. SIMPSON-ANGUS SCALE

SIMPSON ANGUS RATING SCALE

Circle the appropriate score for each item:

1.		**GAIT** The patient is examined as he walks into the examining room: his gait, the swing of arms, his general posture; all form the basis for an overall score for this item. This is rated as follows:
	0	Normal
	1	Mild diminution in swing while the patient is walking
	2	Obvious diminution in swing suggesting shoulder rigidity
	3	Stiff gait with little or no arm swing noticeable
	4	Rigid gait with arms slightly pronated; or stopped-shuffling gait with propulsion and retropulsion
2.		**ARM DROPPING** The patient and the examiner both raise their arms to shoulder height and let them fall to their sides. In a normal subject a stout slap is heard as the arms hit the sides. In the patient with extreme Parkinson's syndrome, the arms fall very slowly.
	0	Normal, free fall with loud slap and rebound
	1	Fall slowed slightly with less audible contact and little rebound
	2	Fall slowed, no rebound
	3	Marked slowing, no slap at all
	4	Arms fall as though against resistance; as though through glue
3.		**SHOULDER SHAKING** The subject's arms are bent at a right angle at the elbow and are taken one at a time by the examiner who grabs one hand and also clasps the other around the patient's elbow. The subject's upper arm is pushed to and fro and the humerus is externally rotated. The degree of resistance from normal to extreme rigidity is scored as follows:
	0	Normal
	1	Slight stiffness and resistance
	2	Moderate stiffness and resistance
	3	Marked rigidity with difficulty in passive movement
	4	Extreme stiffness and rigidity with almost a frozen joint

Modified from: Simpson GM, Angus JWS: A rating scale for extrapyramidal side effects. Acta Psychiatrica Scandinavica 212:11-19, 1970. Revised

Clintara Version 1.5 June, 2011

4.		**ELBOW RIGIDITY** The elbow joints are separately bent at right angles and passively extended and flexed, with the subject's biceps observed and simultaneously palpated. The resistance to this procedure is rated. (The presence of cogwheel rigidity is noted separately.)
	0	Normal
	1	Slight stiffness and resistance
	2	Moderate stiffness and resistance
	3	Marked rigidity with difficulty in passive movement
	4	Extreme stiffness and rigidity with almost a frozen joint
5.		**WRIST RIGIDITY OR FIXATION OF POSITION** The wrist is held in one hand and then the fingers held by the examiner's other hand with the wrist moved to extension, and both ulnar and radial deviation. The resistance to this procedure is rated:
	0	Normal
	1	Slight stiffness and resistance
	2	Moderate stiffness and resistance
	3	Marked rigidity with difficulty in passive movement
	4	Extreme stiffness and rigidity with almost a frozen joint
6.		**LEG PENDULOUSNESS** The patient sits on a table with his legs hanging down and swinging free. The ankle is grasped by the examiner and raised until the knee is partially extended. It is then allowed to fall. The resistance to falling and the lack of swinging form the basis for the score on this item:
	0	The legs swing freely
	1	Slight diminution in the swing of the legs
	2	Moderate resistance to swing
	3	Marked resistance and damping of swing
	4	Complete absence of swing
7.		**HEAD ROTATION** The patient sits or stands and is told that you are going to move his head side to side, that it will not hurt and that he should try and relax. (Questions about pain in the cervical area or difficulty in moving his head should be obtained to avoid causing any pain.) Clasp the patient's head between the two hands with fingers on back of the neck. Gently rotate the head in a circular motion 3 times and evaluate the muscular resistance to the movement.
	0	Loose, no resistance
	1	Slight resistance to movement although the time to rotate may be normal
	2	Resistance is apparent and time of rotation is slowed
	3	Resistance is obvious and rotation is slowed
	4	Head appears stiff and rotation is difficult to carry out

Subject ID No._____ Visit No._____

Modified from: Simpson GM, Angus JWS: A rating scale for extrapyramidal side effects. Acta Psychiatrica Scandinavica 212:11-19, 1970. Revised

8.		**GLABELLA TAP** Subject is told to open his eyes and not to blink. The glabella region is tapped at a steady, rapid speed. The number of times patient blinks in succession is noted:
	0	0-5 blinks
	1	6-10 blinks
	2	11-15 blinks
	3	16-20 blinks
	4	21 and more blinks
9.		**TREMOR** Patient is observed walking into examining room and then is examined for this item:
	0	Normal
	1	Mild finger tremor, obvious to sight and touch
	2	Tremor of hand or arm occurring spasmodically
	3	Persistent tremor of one or more limbs
	4	Whole body tremor
10.		**SALIVATION** Patient is observed while talking and then asked to open his mouth and elevate his tongue. The following ratings are given:
	0	Normal
	1	Excess salivation so that pooling takes place if the mouth is open and the tongue raised
	2	Excess salivation is present and might occasionally result in difficulty in speaking
	3	Speaking with difficulty because of excess salivation
	4	Frank drooling

Rater Signature: _____ Date: _____

Subject ID No._____ Visit No._____

Modified from: Simpson GM, Angus JWS: A rating scale for extrapyramidal side effects. Acta Psychiatrica Scandinavica 212:11-19, 1970. Revised

APPENDIX G. COLUMBIA-SUICIDE SEVERITY RATING SCALE

- Baseline/Screening Version
- Since Last Visit Version

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

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	**Past __ Months**
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** ☐	**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 during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐	**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** ☐	**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** ☐	**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** ☐	**Yes** ☐ **No** ☐

INTENSITY OF IDEATION

	Most Severe	Most Severe
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). For prior to study entry, ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation*** Past X Months - ***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)*	**Lifetime**	**Past __ Years**
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** ☐ ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes No** ☐ ☐	**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 _____	**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 _____	**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** ☐ ☐	**Yes No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No** ☐ ☐	**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 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:

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 H. IMPACT OF WEIGHT ON QUALITY OF LIFE-LITE

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

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 I. EUROQOL-5D

Health Questionnaire

English version for the USA

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

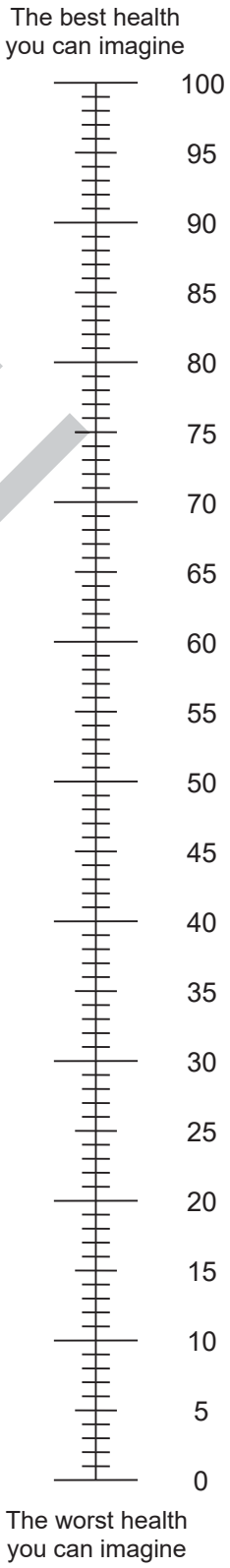
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



21. ADDENDUM

Addendum A Substudy

ADDENDUM A. SUBSTUDY TO PROTOCOL ALK3831-A303 (FOR SELECTED SITES ONLY)

Introduction and Rationale

Weight gain is a well-documented side effect associated with olanzapine use (Eli Lilly and Company 2016) and thus is the primary efficacy measure in ALK3831-A303 (see Section 5.1 of the protocol). In addition to weight gain, changes to body composition (ie, increases in total fat mass and in visceral fat accumulation) have also been observed with olanzapine use in subjects with schizophrenia (Ader et al, 2008; Graham et al, 2005).

Bioelectrical Impedance Analysis (BIA) is a method of measuring body composition in which an electrical current is passed through the body and an impedance value is generated based on body height and the measured electrical conductance. Because fat mass and lean mass conduct electricity differently, the relative proportion of each tissue type can be derived from the impedance value (Ellis 2000).

Advancements in bioelectrical impedance technology allow for body composition measurements that can be collected uniformly across clinical trial sites without additional burden to the subjects in contrast to other methods such as dual-energy X-ray absorptiometry (DEXA) and magnetic resonance imaging (MRI). Using BIA, this substudy will evaluate body composition in a subset of subjects at a select number of sites participating in ALK3831-A303. As this is an exploratory substudy, body composition will be measured at two timepoints to provide data which may inform future studies.

Objective

The objective of this exploratory substudy is to determine body composition during Visit 2 and at the end of treatment (Visit 17/ early termination [ET]) of subjects who are participating in study ALK3831-A303.

Selection of Subjects

Eligible subjects who are at an ALK3831-A303 site participating in the substudy and who sign a separate consent will have these additional assessments collected if they meet the inclusion and exclusion criteria below.

Subject Inclusion Criteria

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

1. Enrolled in study ALK3831-A303 at a site equipped with a body composition analyzer
2. Consented to have body composition analysis conducted on or prior to Visit 2

Subject Exclusion Criteria

Each subject must not meet the following criteria to be qualified to participate in this substudy.

1. Subjects with an electronic implant or devices of any kind (eg, pacemaker, infusion pump) or any active or powered prostheses.

Subject Withdrawal

Subjects may withdraw consent from participation in this substudy at any time. If they do so, they may continue full participation in the main ALK3831-A303 study.

Substudy Design

The substudy will be conducted in up to 200 subjects participating in the main ALK3831-A303 study. The substudy will be completed in conjunction with the main study protocol. Subjects who enroll in the substudy will complete all the study procedures described in the main study protocol (see Table 1). Additionally, subjects in the substudy will have a body composition assessment done prior to dosing at Visit 2 (confirmation of eligibility and randomization visit) and then again upon completion of the study at Visit 17/ET (see Table 1).

Table 1: Substudy Schedule of Assessments

	Screening	24-Week Double-Blind Treatment															Safety Follow-up		Monthly Visits
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17/ ET**	**18**	**19**	**20 to 24**
Study Week (Visit Window of ±2 Days for Visits 3-24)			**1**	**2**	**3**	**4**	**5**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	
Consent for Substudy	X	X[a]																		
Body Composition Assessment		X															X			

Abbreviation: ET=early termination

[a] If not consented at Visit 1, subjects may be consented at Visit 2 prior to any assessments.

Body Impedance Analysis Procedure

Body composition will be assessed using the Seca Medical Body Composition Analyzer (mBCA 514). For the body composition measurements, subjects should be asked to void immediately prior to measurement and should be dressed in a hospital gown with consistent under-attire for each measurement. Subjects should remove all personal items (including shoes, watches, and jewelry) and they should be standing on the same scale for each measurement under the same condition. At timepoints when body composition is measured, subjects will be asked to stand on the two separate study-supplied scales. The body composition analysis should not be performed when the subject is attached to any portable electronic equipment (eg, a portable electrocardiogram machine).

Substudy Exploratory Endpoints

This substudy will assess the following exploratory endpoints:

- Absolute change from baseline in lean mass
- Absolute change from baseline in fat mass
- Change from baseline in percent body fat

Statistical Analysis

The analysis will be carried out using ANCOVA (analysis of covariance) model with treatment group, race (Black or African American, Non-Black or African American), and baseline age (<30, ≥30 years) as factors, and the baseline value as the covariate. Please refer to the statistical analysis plan (SAP) for analysis details. Results from the substudy will be provided in an addendum, which will be included as an appendix of the main ALK3831-A303 clinical study report.

Safety Reporting

Adverse events and serious adverse events will be captured and reported in accordance with the main ALK3831-A303 study (Section 13 of the protocol).

Informed Consent

A separate informed consent will be obtained from subjects who voluntarily agree to participate in the BIA substudy. The Informed Consent Form reflecting this substudy will be submitted for review and approval to the responsible Institutional Review Board (IRB).

Institutional Review Board

The Informed Consent Form for this substudy will be submitted for review and approval to the IRB charged with this responsibility.

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