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

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CLINICAL STUDY PROTOCOL

ALK3831-A305

Study Title	A Phase 3 Study to Determine the Antipsychotic Efficacy and Safety of ALKS 3831 in Adult Subjects with Acute Exacerbation of Schizophrenia
Document Date	Amendment 1.0: 22 September 2016 Original Protocol: 05 August 2015
Sponsor	Alkermes, Inc. 852 Winter Street Waltham, MA 02451 USA

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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 Determine the Antipsychotic Efficacy and Safety of ALKS 3831 in Adult Subjects with Acute Exacerbation of Schizophrenia	
Investigator(s): This is a multinational multicenter study	
Study Period: Estimated date of first subject's consent: Q4 2015 Estimated date of last subject's last visit: Q1 2018	**Phase of Development:** 3

Objectives:

Primary:

- To evaluate the antipsychotic efficacy of ALKS 3831 (a fixed-dose combination of olanzapine and samidorphan) in adult subjects with acute exacerbation of schizophrenia.

Secondary:

- To evaluate the safety and tolerability of ALKS 3831 in adult subjects with acute exacerbation of schizophrenia

Methodology: This is a Phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled study in subjects experiencing an acute exacerbation of schizophrenia. Subjects will be screened up to 10 days prior to randomization. Upon completion of screening assessments, subjects meeting eligibility criteria will be admitted to an inpatient unit on Day -1, if they are not already inpatient. Currently prescribed antipsychotics will be discontinued at screening.

On Day 1 (Visit 2), subjects meeting eligibility criteria will be randomized in a 1:1:1 fashion to one of the following 3 treatment groups: ALKS 3831, olanzapine, or placebo, and will receive double-blind treatment for up to 4 weeks.

On Days 1 and 2, subjects randomized to ALKS 3831 will receive 10/10 [10 mg olanzapine/10 mg samidorphan] and subjects randomized to olanzapine will receive 10 mg. On Day 3, the dose will be increased to 20/10 [20 mg olanzapine/10 mg samidorphan] for subjects randomized to ALKS 3831 or 20 mg for subjects randomized to olanzapine. Following the increase on Day 3, the dose may be decreased to 10/10 (ALKS 3831) or 10 mg (olanzapine) at end of week 1 (Day 7) or week 2 (Day 15) if there are tolerability problems based on judgment of the investigator. No further dose adjustments will be allowed Day 15 onward for the remaining 2 weeks of the treatment period. All subjects will receive 1 tablet daily in a blinded manner.

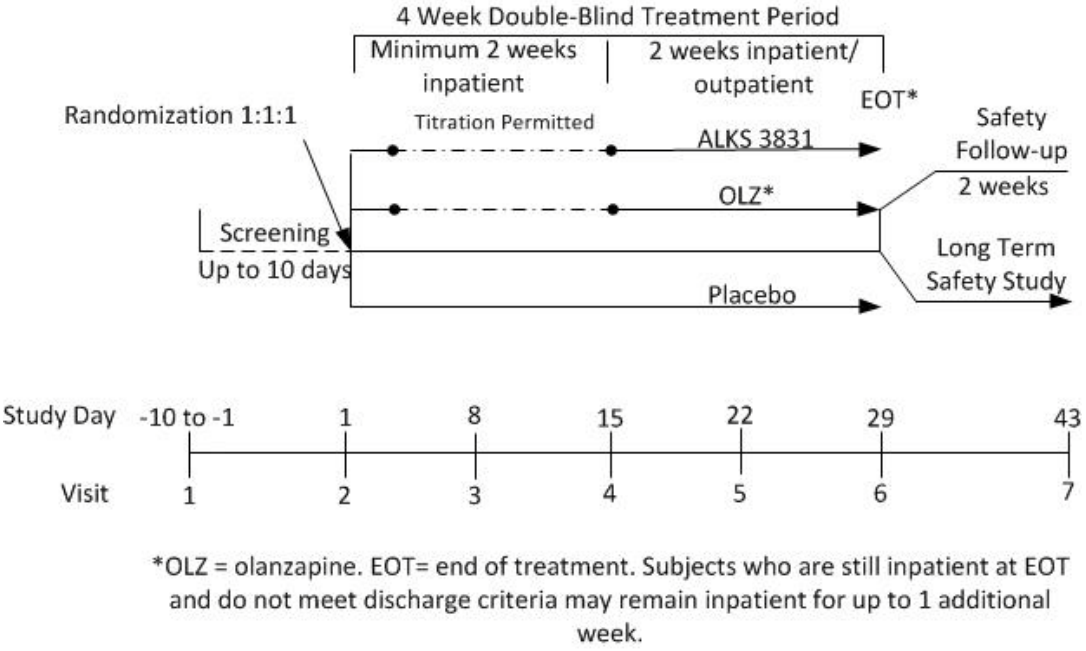
Subjects are required to be inpatient for the first 2 weeks of the treatment period (until Day 15). Following the mandatory 2-week inpatient stay, subjects can either continue the study as inpatients for the full 4-week treatment period or be discharged at the end of Week 2 or end of Week 3 if they meet the discharge criteria specified in Section 8.1.1.

Subjects completing 4 weeks of treatment with study drug will be eligible to continue in the open-label, long-term safety study (ALK3831-A306) and continue to receive ALKS 3831 for up to 52 weeks. Subjects not continuing in the long term safety study will enter a 2-week safety follow-up period. During

this follow-up period subjects may be treated with any antipsychotic medication according to physician recommendations.

Subjects who are inpatient at the end of the 4-week treatment period and are not continuing in the extension study (ALK3831-A306) may continue as inpatients for up to 1 additional week of the 2-week safety follow-up period. These subjects may be discharged from the inpatient unit at any time during this week based on investigator's judgment. For subjects continuing in the safety extension study (ALK3831-A306), details regarding the additional inpatient week will be provided in the ALK3831-A306 protocol.

Study Design Schematic



*OLZ = olanzapine. EOT= end of treatment. Subjects who are still inpatient at EOT and do not meet discharge criteria may remain inpatient for up to 1 additional week.

Number of Subjects Planned: Approximately 390 subjects will be randomized in a 1:1:1 ratio to each of the following 3 treatment groups: ALKS 3831, Olanzapine, and Placebo

Main Criteria for Inclusion:

Men and women 18 through 70 years of age (inclusive) with DSM-5 diagnosis of schizophrenia who meet pre-specified symptom severity criteria, meet sponsor criteria for an acute exacerbation of schizophrenia symptoms, and have a stable living environment (when not hospitalized) as well as a designated caregiver or informant in countries where a caregiver is required.

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 containing either 10 mg or 20 mg of olanzapine only and no additional active ingredients. Placebo will be supplied as a bilayer tablet identical to the ALKS 3831 and olanzapine tablets

but with no active ingredients. Olanzapine or placebo tablets will be taken by mouth once daily, preferably at bedtime.

Duration of Study: The total duration of this study is approximately 7.5 weeks, including a 10-day screening period (Days -10 to -1), a 4-week treatment period (Days 1-29), and 1 follow-up visit 2 weeks after EOT (Day 43).

Criteria for Evaluation:

Efficacy: Evaluation of efficacy will be based on the following measures:

- Positive and Negative Syndrome Scale (PANSS)
- Modified Overt Aggression Scale (MOAS)
- Clinical Global Impressions-Severity (CGI-S)
- Clinical Global Impressions-Improvement (CGI-I)

Pharmacokinetics/ pharmacodynamics: Concentrations of olanzapine, samidorphan, and metabolites of interest will be determined from plasma samples collected according to the schedule in Table 1. PK data from these samples may be included in a subsequent population PK analysis or other post-hoc analyses conducted outside of this study.

Safety: Evaluation of safety will be based on the following measures:

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

Efficacy Endpoints:

Primary Endpoint

The primary efficacy endpoint is change from baseline in PANSS total score at Week 4.

Key Secondary Endpoint

Change from baseline in CGI-S score at Week 4

Other Secondary Endpoints

- Change from baseline in PANSS total score and PANSS subscales (positive, negative, general psychopathology) by visit
- Change from baseline in MOAS score by visit
- Change from baseline in CGI-S by visit
- CGI-I at each postbaseline visit

- PANSS responders (≥ 30% improvement from baseline in PANSS total score) by visit
- CGI-I responders (CGI-I score of 2 [much improved] or 1 [very much improved]) by visit
- Overall Response defined as: PANSS total score ≥ 30% improvement from baseline or CGI-I score of 1 or 2 by visit
- Change from baseline in PANSS-Excited Component (EC) score (comprised of 5 items, excitement, tension, hostility, uncooperativeness, and poor impulse control) by visit

Statistical Methods:

Efficacy: Efficacy analyses will be based on the full analysis set (FAS) population defined as all randomized subjects who receive at least one dose of study drug and at least one postbaseline PANSS assessment. All statistical tests will be 2-sided hypothesis tests performed at the 5% significance level. All confidence intervals will be 2-sided 95% confidence intervals, unless otherwise specified.

Pharmacokinetics/ pharmacodynamics: PK data may be included in a subsequent population PK analysis or other post-hoc analyses conducted outside of this study. Concentrations of olanzapine, samidorphan, and metabolites of interest will be provided as by-subject listings.

Safety: The safety analysis will be carried out using the Safety Population, defined as all randomized subjects who receive at least one dose of study drug. 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 laboratory parameters, weight, BMI, waist circumferences, 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.

Sample Size Considerations: The planned sample size is 390 subjects in total, 130 subjects per treatment group. This sample size will provide at least 90% power to show superiority for ALKS 3831 group when compared to placebo at the 2-sided alpha level of 0.05, assuming a 10-point improvement of PANSS total score at week 4, a standard deviation (SD) of 20, and a dropout rate of 30%.

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4. LIST OF ABBREVIATIONS

The following abbreviations are used in this study protocol.

Abbreviation or Term	Explanation or Definition
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical [classification system]
BARS	Barnes Akathisia Rating Scale
BMI	body mass index
CGI-I	Clinical Global Impressions - Improvement
CGI-S	Clinical Global Impressions - Severity
CNS	central nervous system
CSA	Clinical Study Agreement
C-SSRS	Columbia-Suicide Severity Rating Scale
C-VISA	Clinical Validation Inventory for Study Admission
DSM-5	Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition
EC	Ethics Committee
ECG	Electrocardiogram
ECT	electroconvulsive therapy
eCRF	electronic case report form
EOT	end of treatment
EPS	extra pyramidal symptom
ET	early termination
FAS	full analysis set
GCP	Good Clinical Practice
GI	gastrointestinal
GMP	Good Manufacturing Practice
HbA1c	Hemoglobin A1c
HDPE	high density polyethylene
HIV	human immunodeficiency virus

Abbreviation or Term	Explanation or Definition
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IUD	intrauterine device
IWRS	interactive web response system
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Neuropsychiatric Interview
MMRM	mixed model with repeated measures
MOAS	Modified Overt Aggression Scale
OLZ	Olanzapine
OTC	over-the-counter
PANSS	Positive and Negative Syndrome Scale
PCS	Potentially Clinically Significant
PK	pharmacokinetic
QTcB	QT interval corrected using the Bazett formula
QTcF	QT interval corrected using the Fridericia formula
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Simpson-Angus Scale
SCID	Structured Clinical Interview for DSM Diagnoses
SD	Standard Deviation
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
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, Tiihonen, Lonnqvist et al. 2009, Lambert, Conus et al. 2010). The decreased life expectancy is due to a combination of direct effects of the disease, eg increased rates of suicide and violence (Kuo, Tsai et al. 2005, Hodgins 2008), as well as indirect causes including increased incidence of obesity and cardiovascular disease (Nasrallah, Meyer et al. 2006, Saha, Chant 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, Stroup 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 lbs 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 (a μ-opioid antagonist) under investigation for the treatment of schizophrenia. Phase 1 and Phase 2 studies demonstrated that coadministration of samidorphan with olanzapine mitigates the weight gain experienced with olanzapine alone. 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. 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.

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, Farmer 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, van et al. 2006). Samidorphan (also referred to as ALKS 33 or RDC-0313), is structurally derived from naltrexone and is a potent μ-opioid antagonist. In clinical studies, it 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 has the potential as an improved 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 versus 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 chemical entity in clinical development by Alkermes. Samidorphan is a μ-opioid receptor antagonist. 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). 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). Overall, approximately 600 subjects have been exposed to samidorphan. Commonly reported adverse events (AEs) observed across all studies included nausea, fatigue, and somnolence. Overall, no trends or clinically meaningful changes have been observed in clinical laboratory analytes, vital sign parameters, or electrocardiogram (ECG) data.

5.2.2. Olanzapine

Olanzapine has been available in the US since 1996 and was originally approved for the treatment of schizophrenia, but has since been approved for other indications including the treatment of schizophrenia in adolescents and bipolar disorder. The safety and tolerability profile

of olanzapine is well documented, and adverse event labeling is supported by an extensive safety database that includes over 8,500 adult patients (Eli Lilly and Company 2015). Commonly reported AEs consistent across all or most dosage forms in short-term, placebo controlled trials include somnolence, constipation, dry mouth, accidental injury, weight gain, postural hypotension, dizziness, asthenia, fever and abnormal gait.

5.3. Study Rationale

Schizophrenia is a lifelong illness with evolving symptoms that can fluctuate in severity over time and with changes in treatment regimen. A major goal in designing treatments for schizophrenia is to effectively stabilize symptoms, keep them stable over the long term, and minimize side effects. In a Phase 2 study, ALK3831-302, ALKS 3831 exhibited similar antipsychotic efficacy to olanzapine as well as a significant attenuation of olanzapine-induced weight gain. ALK3831-302 was conducted in subjects with schizophrenia that were classified as psychiatrically stable. The present study is designed to assess the ability of ALKS 3831 to stabilize symptoms in a subject population with unstable symptomology experiencing an acute exacerbation of schizophrenia. The study will evaluate the efficacy of ALKS 3831 on psychiatric symptoms, including aggression, relative to placebo. It will also assess the safety and tolerability of ALKS 3831 in subjects with an acute exacerbation of schizophrenia.

5.4. Dose Rationale

The selected doses of ALKS 3831 (20/10 and 10/10) are within the approved olanzapine therapeutic dose range for the treatment of schizophrenia (Eli Lilly and Company 2015). 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, 10–20 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 the antipsychotic efficacy of ALKS 3831 (a fixed-dose combination of olanzapine and samidorphan) in adult subjects with an acute exacerbation of schizophrenia.

6.2. Secondary Objective

The secondary objective of this study is to evaluate the safety and tolerability of ALKS 3831 in adult subjects with an acute exacerbation of 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. Is willing and able to provide written informed consent
2. Is age 18–70 years, inclusive, at screening
3. Has a body mass index (BMI) of 18.0–40.0 kg/m^2, inclusive at screening
4. Agrees to abide by the contraception requirements specified in the protocol
5. Meets criteria for the DSM-5 diagnosis of schizophrenia, confirmed with the Mini International Neuropsychiatric Interview (MINI):
   - Is currently experiencing an acute exacerbation or relapse
   - If inpatient at screening, has been hospitalized for less than two weeks for the current exacerbation
6. Total PANSS Score ≥80 at screening and baseline (Visits 1 and 2)
7. A score ≥4 on at least three of the following PANSS Positive Scale (P) Items at Visits 1 and 2:
   - Item 1 (P1; delusions)
   - Item 2 (P2; conceptual disorganization)
   - Item 3 (P3; hallucinatory behavior)
   - Item 6 (P6; suspiciousness/persecution)
8. CGI-S Score ≥4 at screening and Visits 1 and 2
9. Resides in a stable living situation when not hospitalized
10. Subjects at some sites may be required to have an informant or caregiver who meets some or all of the following criteria in accordance with the locally approved informed consent form (ICF):
    a. Informant or caregiver will be in contact with the subject several times per week
    b. If necessary, the informant or caregiver will accompany the subject to visits
    c. Informant or caregiver will help ensure maximum subject adherence to study procedures
    d. The informant or caregiver must be willing and able to provide informed consent by signing the caregiver ICF.
11. 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 Exclusion Criteria

1. Subject has had a psychiatric hospitalization for more than 30 days during the 90 days before screening
2. Subject initiated first antipsychotic treatment within the past 12 months, or <1 year has elapsed since the initial onset of active-phase of schizophrenia symptoms.
3. 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
4. Subject poses a current suicide risk in the opinion of the investigator or as confirmed by the following:
   - Answers "Yes" on items 4 or 5 (C-SSRS-ideation) with the most recent episode occurring within the past 2 months, or answers "Yes" to any of the 5 items (C-SSRS-behavior) with an episode occurring within the last year
5. Subject's PANSS score improves ≥30% from Visit 1 to Visit 2

7.2.2. Exclusion Criteria Based on Treatment History

6. Subject has a history of treatment resistance, defined as failure to respond to 2 adequate trials of different antipsychotic medications (a minimum of 4 weeks at the subject's maximum tolerated dose)
7. Subject has used clozapine within 6 months prior to screening or has a history of clozapine use for treatment-resistant schizophrenia
8. Subject has a history of poor or inadequate response to treatment with olanzapine
9. Subject received olanzapine, mesoridazine, chlorpromazine, or thioridazine at any time during the past 6 months 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
10. Subject requires or has had electroconvulsive therapy (ECT) treatment in the 2-month period prior to screening

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

11. Subject has a diagnosis (based on DSM-5 criteria) of moderate or severe alcohol or drug use disorder currently or at any time during the 3 months prior to screening.
12. Subject has a positive urine drug screen for opioids, amphetamine/ methamphetamine, phencyclidine, or cocaine at screening
13. Subject has taken opioid agonists (eg, codeine, oxycodone, tramadol, or morphine) within the 14 days prior to screening and/or anticipates a need to take opioid medication during the study period (eg, planned surgery) or has taken opioid antagonists within 60 days prior to screening
14. Subject is taking any weight loss agents or hypoglycemic agents at screening
15. 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 screening

7.2.4. Exclusion Criteria Based on Medical Conditions/Medical History

16. Subject has known risk of narrow-angle glaucoma
17. 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 or tardive dystonia within 30 days of screening
    - Inflammatory bowel disease or any other gastrointestinal (GI) disorder associated with weight loss, anorexia nervosa, bulimia nervosa, or binge eating disorder
    - Neurologic conditions including the following:
      - History of seizure disorder or a condition associated with seizures (exception: history of febrile seizures)
      - History of brain tumor, subdural hematoma or other clinically significant neurological condition within the 12 months prior to screening
      - Head trauma with loss of consciousness within the 12 months prior to screening
      - Active acute or chronic central nervous system (CNS) infection
      - Stroke within the 6 months prior to screening

- 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 3 months prior to screening

18. Subject has a history of diabetes
19. Subject has undergone a significant blood loss (>500 mL) or blood product donation (including platelets or plasma) within 60 days of screening or anticipates blood or blood product donation at any time during the trial

7.2.5. Exclusion Criteria Based on Laboratory Assessments at Screening

20. Subject has any of the following lab results at screening:
    - Hemoglobin A1c (HbA1c) ≥ 6.0%
    - Dyslipidemia, defined for this study as total fasting cholesterol >280 mg/dL or fasting triglycerides >500 mg/dL
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) value ≥2 times the upper limit of the laboratory normal reference range
    - Absolute neutrophil count $\leq 1.5 \times 10^3$ μL
    - Platelet count $\leq 75 \times 10^3$ μL
    - Serum creatinine >2.5 mg/dL
    - Positive pregnancy test result
21. Positive serology test for hepatitis B surface antigen, hepatitis C antibody (confirmed by RNA testing), or human immunodeficiency virus (HIV) antibody at screening
22. Clinically significant ECG abnormality at Visit 1 or baseline Visit 2
23. QT interval >450 msec for men and >470 msec for women, as corrected by the Fridericia formula (QTcF), observed at Visit 1 or baseline Visit 2

7.2.6. General Exclusion Criteria

24. Subject is currently pregnant or breastfeeding, or is planning to become pregnant during the study period.
25. 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
26. Subject is currently under involuntary hospitalization or incarceration
27. Subject has participated in another clinical trial in which the subject received an experimental or investigational drug or agent within 6 months before screening by self-report or through confirmation using an clinical trial subject registry
28. Subject has participated in a clinical study with ALKS 3831 or samidorphan at any time

29. Subject is employed by Alkermes, PPD or study site (permanent, temporary contract worker, or designee responsible for the conduct of the study) or is immediate family* of an Alkermes, PPD or study site employee

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

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. 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

Additionally, if a subject has an ANC<1.0×10^3µL or HbA1c ≥6.5% at any time from Visit 2 to Visit 6, the PI (or designee) should discontinue the subject from participation immediately.

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. 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.

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. Randomized subjects are to be asked to return to the clinic for an early termination (ET) visit and to complete a subsequent safety follow-up period. 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 Visit 6. 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 made on the appropriate electronic case report form (eCRF).

A subject will be deemed lost to follow-up after 3 attempts at contact have been made and it has been at least 1 month since the last subject contact. The 3rd attempt at contact must be a certified letter accompanied by a survey inquiring the reason for study discontinuation. All attempts at contact will be documented. The reason for discontinuation will be documented. If the PI becomes aware of a change in the subject's status or receives more information about a subject's disposition, this information will be documented.

7.4. Replacement of Subjects

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

7.5. Identification of Informant or Caregiver

In some cases a caregiver may be required for a subject to join the study (eg, by a local institutional review board [IRB]). This person should be in contact with the subject, able to help with adherence to study procedures (including attending study visits when needed), and able to report on the subject's safety and behavior.

7.6. Withdrawal and Replacement of Caregiver

Some sites may require the caregiver to sign a caregiver ICF (separate from a subject ICF). A caregiver who is required to sign a caregiver ICF may withdraw consent at any time, in which case he/she can no longer fill the caregiver role for this study. Any other caregiver may decide to stop cooperating with study staff or be lost to follow-up, in which case he/she can no longer fill the caregiver role for this study. If a caregiver can no longer fill the caregiver role, he/ she should be replaced if possible. If the caregiver cannot be replaced, most subjects will be able to continue in the study. If the subject must also withdraw from the study (eg, the caregiver provided transportation to the site and no other travel arrangements can be made for the subject), the PI should make a reasonable effort to ascertain the reason(s) for the caregiver's withdrawal, while fully respecting the caregiver's and subject's rights. A full explanation about the caregiver's withdrawal should be included with explanation of the subject's discontinuation in the appropriate eCRF.

8. STUDY DESIGN

8.1. Overall Study Design and Plan

This is a Phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled study in subjects experiencing an acute exacerbation of schizophrenia. Subjects will be screened up to 10 days prior to randomization. Upon completion of screening assessments, subjects meeting eligibility criteria will be admitted to an inpatient unit on Day -1, if they are not already inpatient. Currently prescribed antipsychotics will be discontinued at screening.

Study design and timeline are summarized in the schematic shown in Figure 1.

On Day 1 (Visit 2), subjects meeting eligibility criteria will be randomized in a 1:1:1 fashion to one of the following 3 treatment groups: ALKS 3831, olanzapine, or placebo, and will receive double-blind treatment for up to 4 weeks.

On Days 1 and 2, subjects randomized to ALKS 3831 will receive 10/10 [10 mg olanzapine/ 10 mg samidorphan] and subjects randomized to olanzapine will receive 10 mg. On Day 3, the dose will be increased to 20/10 [20 mg olanzapine/10 mg samidorphan] for subjects randomized to ALKS 3831 or 20 mg for subjects randomized to olanzapine. Following the increase on Day 3, the dose may be decreased to 10/10 (ALKS 3831) or 10 mg (olanzapine) at end of week 1(Day 7) or week 2 (Day 15) if there are tolerability problems based on judgment of the investigator. No further dose adjustments will be allowed Day 15 onward for the remaining 2-weeks of the treatment period. All subjects will receive 1 capsule daily in a blinded manner.

Subjects are required to be inpatient for the first 2 weeks of the treatment period (until Day 15). Following the mandatory 2-week inpatient stay, subjects can either continue the study as inpatients for the full 4-week treatment period or be discharged at the end of Week 2 or end of Week 3 if they meet the discharge criteria specified in Section 8.1.1.

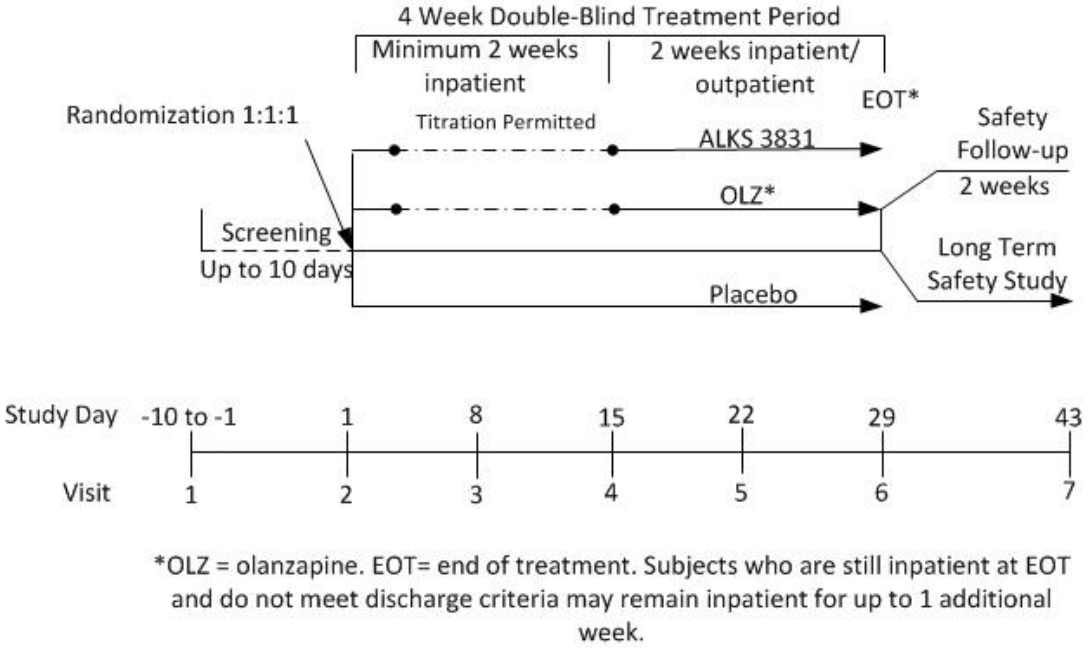
Following discharge, subjects will be contacted by study staff at least once between their weekly site visits to monitor their status and determine if there are any safety concerns that would precipitate re-admission to the inpatient facility. If subjects are re-admitted to the inpatient facility due to safety concerns, it will be recorded as an SAE.

Subjects completing 4 weeks of treatment with study drug will be eligible to continue in the open-label, long-term safety study (ALK3831-A306) and receive ALKS 3831 for up to 52 weeks. Subjects not continuing in the long term safety study will enter a 2-week safety follow-up period. During this follow-up period subjects may be treated with any antipsychotic medication according to physician recommendations.

Subjects who are inpatient at the end of the 4-week treatment period and are not continuing in the extension study (ALK3831-A306) may continue as inpatients for up to 1 additional week of the 2-week safety follow-up period. These subjects may be discharged from the inpatient unit at any time during this week based on investigator's judgment. For subjects continuing in the safety extension study (ALK3831-A306), details regarding the additional inpatient week will be provided in the ALK3831-A306 protocol.

The total duration of this study is approximately 7.5 weeks, including a 10-day screening period (Days -10 to -1), a 4-week treatment period (Days 1-29), and 1 follow-up visit 2 weeks after EOT (Day 43).

Figure 1: Study Design Schematic



*OLZ = olanzapine. EOT= end of treatment. Subjects who are still inpatient at EOT and do not meet discharge criteria may remain inpatient for up to 1 additional week.

8.1.1. Discharge Criteria

Subjects are eligible to be discharged at end of Week 2, Week 3, or Week 4 if they meet ALL of the following criteria:

1. Subjects are judged clinically suitable for discharge by the investigator:
   a. Subjects have shown a sustained pattern of improvement relative to their condition on Day 1 within the past week.
   b. Subjects are not a danger to themselves or others
   c. Subjects can be discharged into a supervised living environment deemed suitable by the investigator.
2. Subjects show stabilization of symptoms as confirmed by PANSS:
   a. PANSS total score <70
   b. Score <4 on selected PANSS positive items (Item 1 [P1; delusions], item 2 [P2; conceptual disorganization], item 3 [P3; hallucinatory behavior], and item 6 [P6; suspiciousness/persecution])
3. Subjects answer "No" on items 4 or 5 of the Columbia-Suicide Severity Rating Scale (C -SSRS-ideation), and "No" to all 5 items of (C-SSRS-behavior)

Subjects not meeting the discharge criteria will continue as inpatients for the remainder of the study and for up to 1 additional week if they do not meet discharge criteria at EOT.

8.2. Schedule of Visits and Assessments

The schedule of visits and assessments is shown in Table 1.

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

Premature discontinuation procedures are provided in Section 7.3.

Table 1: Schedule of Visits and Assessments

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

Table 1: Schedule of Visits and Assessments (Continued)

Period	Screening	Double-Blind Treatment Period					Follow-Up[1]
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Study Day	**-10 to -1**	**1**	**8**	**15**	**22[2]**	**29/ET[2]**	**43[2]**
Concomitant Medication Review	X	X	X	X	X	X	X
Columbia-Suicide Severity Rating Scale (C-SSRS)[11]	X	X[3]	X	X	X	X	X
Abnormal Movement Scales[12]		X[3]	X	X	X	X	X
Positive and Negative Syndrome Scale (PANSS)[13]	X	X[3]	X	X	X	X	
Modified Overt Aggression Scale[14]		X	X	X	X[15]	X[15]	
Clinical Global Impression – Severity (CGI-S)	X[16]	X	X	X	X	X	
Clinical Global Impression – Improvement (CGI-I)			X	X	X	X	
Informed Consent for ALK3831-A306						X[17]	
Emergency treatment card[18]		X				X	
Admission to Inpatient Unit[19]	X						
Discharge from Inpatient Unit[20]				X	X	X	
Study Drug Dispensation[21]		X	X	X	X		
Study Drug Return and Adherence Review			X	X	X	X	

[1] Follow-up Visit (V7) is not required for subjects who enroll in ALK3831-A306
[2] A visit window of ±2 days (anchored to Day 1) is allowed
[3] Predose
[4] Full physical exam at screening; brief physical exam at all subsequent time points.

[5] Urine drug screen via dipstick at screening and prior to randomization on Day 1. Drug screen at Visits 5 and 6 applies to outpatient subjects only. Urine drug screen includes opiates, phencyclidine (PCP), amphetamine/methamphetamine, and cocaine.
[6] For outpatient subjects only
[7] Serology testing includes anti-human immunodeficiency virus (HIV) antibody, hepatitis B surface antigen, and anti-hepatitis C antibody.
[8] Subjects must fast (no food or drink except water) for at least 8 hours before lab draws. Lab draws are to be conducted in the morning for all specified visits.
[9] One PK sample will be collected at the specified visits to measure plasma levels of olanzapine, samidorphan, and metabolites of interest
[10] 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.
[11] The "Baseline/Screening" version of the C-SSRS will be used at screening; the "Since Last Visit" version to be used at all other scheduled visits.
[12] Abnormal movement scales include the following: Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and Simpson-Angus Scale (SAS).
[13] With the exception of the screening visit, the PANSS should be administered before other psychiatric assessments at each specified study visit.
[14] The MOAS will be performed on all subjects at Visits 2, 3 and 4 and only on inpatient subjects at Visits 5 and 6.
[15] Only for inpatient subjects
[16] CGI-S will be administered at the Screening Visit using the structured interview guide for global impressions (SIGGI)
[17] The informed consent form for the open-label extension, ALK3831-A306, must be distributed to subjects by the end of treatment. However, the form may be distributed to subjects earlier at the investigator's discretion.
[18] Emergency treatment card to be dispensed at randomization (Visit 2), confirmed at subsequent time points, and collected at Visit 6, EOT.
[19] Subjects will be admitted to the inpatient unit on the same day as their screening assessments if they are not already inpatient.
[20] Subjects may be discharged at Day 15, Day 22, or Day 29 if they meet discharge criteria. Subjects not meeting discharge criteria at Day 29 may remain inpatient for up to 1 additional week and may be discharged from the inpatient unit at any point during this week at the investigator's discretion.
[21] During the inpatient stay, study drug will be administered daily by study staff, preferably at bedtime. Upon discharge, subjects will be given study drug to take daily, preferably at bedtime though dose timing may be adjusted at the investigator's discretion based on tolerability.

8.3. Study Procedures Descriptions

Details of the study procedures are described below. The overall schedule of assessments is provided in Table 1.

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 1 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 time point(s) specified in Table 1.

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 1), 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.

8.3.5. Vital Signs

Vital signs (ie, blood pressure, heart rate, respiratory rate, and oral body temperature) will be assessed at the time point(s) specified in Table 1. 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 time points specified in Table 1. 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 time points specified in Table 1.

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 time points specified in Table 1. 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).

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 1 provides information on the time points 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. Structured Interview Guide for Global Impression (SIGGI, Appendix B) will be used to administer the CGI-S.

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, Lecrubier 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 1.

8.3.9.2. Efficacy Assessments

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 time points specified in Table 1. 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). For the Screening Visit, the Structured Interview Guide for Global Impression (SIGGI, Appendix B) will be used to administer the CGI-S.

8.3.9.2.2. Clinical Global Impression-Improvement

The PI or designee will complete the CGI-Improvement (CGI-I, Appendix B) at the time points specified in Table 1. The CGI-I measures improvement from the first assessment(Guy 1976).

8.3.9.2.3. Modified Overt Aggression Scale

The PI or designee will complete the MOAS (Appendix C) (Kay, Wolkenfeld et al. 1988). The MOAS provides a weighted measure of aggression based on four primary components (verbal aggression, aggression against property, auto-aggression, and physical aggression). It is a recall assessment based on behavior observed over a defined period of time, for the purposes of this study, the past week, and therefore, to maintain consistency in observation and rating, the assessment will be performed only on subjects that are inpatient according to the schedule indicated in Table 1.

8.3.9.2.4. Positive and Negative Syndrome Scale

The PI or designee will complete the PANSS (Appendix D) (Kay, Fiszbein et al. 1987) according to the schedule in Table 1. 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 E) (Guy 1976), the Barnes Akathisia Rating Scale (BARS, Appendix F) (Barnes 1989), and the Simpson-Angus Scale (SAS, Appendix G) (Simpson and Angus 1970) at the time points specified in Table 1.

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 H) according to the schedule in Table 1. The “Baseline/Screening” version (Posner, Brent et al. 2009) is to be completed at Visit 1 and the “Since Last Visit” version (Posner, Brent et al. 2009) is to be completed at all subsequent scheduled time points. The C-SSRS should be administered by a qualified clinician trained in assessing and managing suicidal ideation and behavior.

8.3.10. Clinical Validation Inventory for Study Admission and Ongoing Rater Review

Rater (ie, study staff) accuracy at screening on pre-specified study measures (ie, PANSS) will be reviewed by central raters employed by Clintara, LLC using the C-VISA™.

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 urine drug screen for opiates (including codeine, hydrocodone, hydromorphone, methadone, morphine, oxycodone, and oxymorphone) and drugs of abuse (including amphetamine/ methamphetamine, phencyclidine and cocaine) will be performed at the time points specified in Table 1. 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 time points specified in Table 1 for specific hematology, biochemistry, and urinalysis assessments listed in Table 2. 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 2: Clinical Laboratory Assessments

Hematology	Biochemistry	Urinalysis
Hematocrit	General Chemistry	Bilirubin
Hemoglobin	Albumin	Color and appearance
Platelets	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	
	HbgA1c[1]	Microscopic examination of sediment, *only if urinalysis dipstick results are abnormal*
	Insulin	
	Thyroid Stimulating Hormone[2]	
	Prolactin	
	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	

[1] At screening, predose on Day 1, and EOT

[2] At screening only; if the TSH results indicate the value is outside of normal limits, the central lab will automatically test the same screening visit sample and provide a free T4 and T3 analysis

8.3.11.3. Pregnancy Testing

As described in Section 8.4.1, a urine/ serum pregnancy test will be administered to all women at the time points specified in Table 1. 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.

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 1. 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. 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 time point indicated in Table 1) 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 time point specified in Table 1, subjects will be randomized as outlined in Section 9.3.

8.3.15. Drug Dispensation and Reconciliation

Section 9.1 provides information related to drug dispensing procedures. Study drug will be dispensed/ administered at the time points specified in Table 1. 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.

Study drug will be supplied as oral, bilayer tablets for once daily dosing in high-density polyethylene (HDPE) bottles with desiccant.

While subjects are inpatient, study drug will be administered by study staff daily, preferably at bedtime. If/when subjects are discharged from the inpatient facility, they will be given study drug to take at home. 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-compliance with the subject.

8.3.16. Emergency Treatment Card

An emergency treatment card will be distributed to each subject and collected from each subject at the time points indicated in Table 1. 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 indicated in Table 1.

8.3.17. Adverse Event Monitoring

AEs will be monitored continuously from the time a subject signs the informed consent document until the completion of the final study visit (see Table 1). AEs and serious adverse events (SAEs) are defined in Section 13.1 and 13.2, respectively. Section 13.4 provides guidance on the monitoring and reporting 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. Prior antipsychotic medication should be discontinued at screening (at Visit 1). All subjects should be in an inpatient setting when discontinuing prior antipsychotic medication, at the investigator's discretion. Allowable washout period is 2-5 days starting at Visit 1. If administration of an antipsychotic during a subject's participation in the study is being considered (eg, as rescue treatment), the investigator should contact the medical monitor to discuss the appropriate course of action.

Prohibited medications include the following:

- Monoamine oxidase inhibitors (eg, phenelzine, tranylcypromine, selegiline, or moclobemide)
- Long-acting formulations of any antipsychotic agent
- Antipsychotic agents
  - Use of antipsychotic sleep aids (eg, Seroquel) is prohibited. However, use of benzodiazepines to treat some symptoms is permissible (see Section 8.4.3 for permitted therapy)
- In general, the use of psychotropic medications other than study drug is prohibited with the exception of the following:
  - Beta-blockers (eg, propranolol or pinodolol), antihistamines, and anticholinergics may be used for treatment-emergent akathisia
  - Anticholinergics may be used for extrapyramidal symptoms
- Nicotine replacement therapy including nicotine replacement patch and oral nicotine gum is permitted. However, Chantix® (varenicline) is not 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®), Exenatide (Byetta®); Sulfonylureas (eg, Diamicron®, Amaryl®, Glucotrol®, Micronase®); Meglitinides (eg, Starlix®, Prandin®); Metformin or other hypoglycemic agent
- 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. See Appendix A for a list of P450 (CYP) 3A4 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 duration is prohibited. **Note**: during the study period, opioid agonists should be avoided as they may be rendered ineffective by samidorphan.

See Section 8.3.4 for details regarding the concomitant medication review.

8.4.3. Permitted Therapy

Permissible medications to treat extrapyramidal symptoms may include benzodiazepines, antihistamines, and anticholinergics. Continuous use of these medications should be avoided if possible and they should only be given to the patient after all study assessments have been performed. While insomnia may be treated with a variety of agents, short half-life benzodiazepines should be utilized due to 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. Non-medication Therapy

Psychotherapy should not be started or changed during a subject's participation in the study. It is acceptable for a subject already receiving psychotherapy to participate in the study. While on the inpatient study unit during participation in the study, initiation of augmenting psychotherapies (ie, group therapy) deemed by the clinical investigator to be of clinical benefit while on the inpatient study unit is discouraged, though standard milieu-related activities are acceptable.

8.4.5. 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.

8.4.6. Fasting

Subjects are required to fast for at least 8 hours (no food or drink except water) prior to lab blood draws.

8.4.7. Inpatient Stay

Eligible subjects must be admitted to the inpatient study facility on the same day as their screening assessments and are required to remain inpatient for the first 2 weeks of the treatment period (until Day 15). Subjects may be discharged on Day 15, Day 22, or Day 29 if they meet discharge criteria (See Section 8.1.1). Subjects who are inpatient at the end of the 4-week treatment period and are not continuing in the extension study (ALK3831-A306) may continue as inpatients for up to 1 additional week of the 2-week safety follow-up period. These subjects may be discharged from the inpatient unit at any time during this week based on investigator's judgment. For subjects continuing in the safety extension study (ALK3831-A306), details regarding the additional inpatient week will be provided in the ALK3831-A306 protocol.

8.4.8. Other Restrictions and Requirements

Additional restrictions and requirements include:

- Prohibited substances include amphetamines (including methamphetamine), cocaine, barbiturates, methadone, opiates (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 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
- Subjects will be required to follow the clinic's in-house rules

9. TREATMENT OF SUBJECTS

9.1. Study Drug Dose and Administration

Study drugs include:

- ALKS 3831 10/10 or 20/10 (10 mg olanzapine/10 mg samidorphan or 20 mg olanzapine/10 mg samidorphan respectively) administered as a coated bilayer tablet
- Olanzapine 10 mg or 20 mg administered as a coated bilayer tablet
- Placebo matching 10 mg and 20 mg tablets.

During the inpatient period, subjects will be administered study drug orally, once daily preferably at bedtime. Following discharge on Day 15 or later, subjects will be given study drug to take home and instructed to take one tablet orally preferably at bedtime. If there are tolerability problems, dosing may be switched to another time based on the judgment of the investigator; frequent switching is discouraged.

9.2. Treatment Adherence

Subjects will undergo a study drug adherence review at the time points indicated in Table 1. In addition to these scheduled adherence reviews, for subjects discharged on Day 15 or 22, study staff will check in with them or a caregiver (if applicable) between assessment visits to monitor treatment adherence.

9.3. Randomization/ Method of Assigning Subjects to Treatment

Subjects meeting eligibility criteria at baseline (Day 1) will be randomized in a 1:1:1 ratio to one of the following treatment groups:

- ALKS 3831
- Olanzapine
- Placebo

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, subjects and caregivers 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

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)

Matching olanzapine-only drug will be supplied as a coated bilayer tablet in two dose strengths:

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

Matching placebo will be supplied in two dose strengths:

- Placebo to match 10/10 ALKS 3831 and 10 mg olanzapine comparator
- Placebo to match 20/10 ALKS 3831 and 20 mg olanzapine comparator

10.2. Packaging and Labeling

All tablets will be packaged in HDPE bottles with desiccant. Bottle labels will meet all applicable local and regulatory requirements.

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

Refer to Section 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

11.1. Efficacy Measures

- Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein et al. 1987)
- Modified Overt Aggression Scale (MOAS) (Kay, Wolkenfeld et al. 1988)
- Clinical Global Impression of Severity (CGI-S) (Guy 1976)
- Clinical Global Impression of Improvement (CGI-I) (Guy 1976)

See Section 8.3.9.2 for details regarding efficacy assessments.

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 1. 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

Safety will be assessed on the basis of:

- Adverse events
- Abnormal Involuntary Movement Scale (AIMS)
- Barnes Akathisia Rating Scale (BARS)
- Simpson-Angus Scale (SAS)
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Vital signs (oral temperature, respiratory rate, pulse, systolic and diastolic blood pressure)
- Electrocardiogram parameters (heart rate, RR, PR, QRS, and QT)
- Clinical laboratory parameters (chemistry, hematology, and urinalysis; see Table 2)
- Weight/BMI and Waist Circumference

See Section 8.3.9.3 for more details on the AIMS, BARS, SAS and C-SSRS.

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 3 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 3: 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

AE data collection will begin after a subject signs the ICF and will continue until completion of the safety follow-up visit (Visit 7). Any AE or SAE having an onset after the safety follow-up visit will not be collected or 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 planned sample size is 390 subjects in total, randomized 1:1:1to ALKS 3831, olanzapine and placebo arms. This sample size will provide at least 90% power to show superiority for ALKS 3831 group when compared to placebo at the 2-sided alpha level of 0.05, assuming a 10-point improvement of PANSS total score at week 4, a standard deviation (SD) of 20, and a dropout rate of 30%.

14.2. General Statistical Methodology

The statistical analysis methods are described below. Additional details will be provided in the Statistical Analysis Plan to be finalized before database lock and unblinding.

In general, summary statistics (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 $\alpha = 0.05$.

14.2.1. Study Populations

14.2.1.1. Safety Population

The safety population includes all randomized subjects who receive at least 1 dose of study drug during the double-blind treatment period.

14.2.1.2. Efficacy Population

The full analysis set (FAS) population will be used for efficacy analysis and includes all subjects in the safety population who have at least one post-baseline PANSS assessment.

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 FAS population. Baseline for efficacy analysis is defined as the last non-missing efficacy assessment before the first dose of study drug in the double-blind treatment period. All statistical tests will be 2-sided hypothesis tests performed at the 5% significance level. All confidence intervals will be 2-sided 95% confidence intervals, unless specified otherwise.

14.4.1. Primary Endpoint

The primary efficacy endpoint is change from baseline in PANSS total score at Week 4.

For the primary efficacy endpoint, change from baseline in PANSS total score at week 4, analysis will be carried out using a mixed model with repeated measurements (MMRM) with an unstructured variance-covariance matrix based on the observed data. The model will include visit, treatment, and interaction term of visit and treatment as categorical variables, and baseline PANSS total score as a covariate. The statistical test will be carried out as follows:

The change from baseline in PANSS total score at Week 4 in ALKS 3831 group will be compared to that in the placebo group using superiority testing at two-sided alpha level of 0.05.

14.4.2. Key Secondary Endpoint

The key secondary endpoint is change from baseline in CGI-S score at Week 4.

The analysis will be carried out using MMRM as described for the primary endpoint.

14.4.3. Other Endpoints

- Change from baseline in PANSS total score and PANSS subscales (positive, negative, general psychopathology) by visit
- Change from baseline in MOAS score by visit
- Change from baseline in CGI-S by visit
- CGI-I at each postbaseline visit
- PANSS responders (≥ 30% improvement from baseline in PANSS total score) by visit
- CGI-I responders (CGI-I score of 2 [much improved] or 1 [very much improved]) by visit
- Overall Response defined as: PANSS total score ≥ 30% improvement from baseline or CGI-I score of 1 or 2 by visit
- Change from baseline in PANSS-Excited Component (EC) score (comprised of 5 items, excitement, tension, hostility, uncooperativeness, and poor impulse control) by visit

For proportion of subjects exhibiting improvement on CGI-I assessment, a logistic regression based on last observation carried forward (LOCF) imputation for missing data will be used to

compare ALKS 3831 with placebo. The model will include treatment group, and baseline PANSS total score as covariates.

For all other endpoints, each point will be summarized by treatment groups for all visits. Each active group (ALKS 3831 or olanzapine) will be compared to placebo. For continuous outcome, a similar approach to that for PANSS total score will be used. For dichotomous outcome, a similar approach to that used for CGI-I improvement scores will be used. More details will be provided in the statistical analysis plan (SAP).

14.5. Pharmacokinetic Analyses

Listings will be provided for concentrations of olanzapine, samidorphan, and metabolites of interest. PK concentrations may be used in a subsequent population PK analysis conducted outside of this study.

14.6. Safety 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. Safety endpoint will include adverse events (AEs), clinical laboratory parameters, vital signs, electrocardiographic (ECG) parameters, Columbia–Suicide Severity Rating Scale (C-SSRS) scores, body weight, BMI, waist circumference, AIMS, BARS, and SAS. 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.

Safety assessments will be summarized using descriptive statistics along with supportive listings.

The number and percentage of TEAEs will be summarized by treatment group and overall by system organ class, and preferred terms within each system organ class. SAEs and AEs resulting in treatment discontinuation will also be summarized.

Observed values and change from baseline in laboratory parameters, weight, BMI, waist circumference, 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 post-baseline visit will be summarized by treatment group labs, vitals, weight, and ECG parameters. Supporting listings will be provided.

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

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

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

Listings will be provided for all safety endpoints.

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. APPENDICES

Appendix A Partial list of prohibited cytochrome P450 (CYP) 3A4 inducers and moderate-to-strong inhibitors

Appendix B Clinical Global Impression

- Severity
  - Structured Interview Guide for Global Impression (SIGGI)
- Improvement

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- Baseline/ Screening
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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
  - Structured Interview Guide for Global Impression (SIGGI)
- 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

Structured Interview Guide for Global Impression (SIGGI)

ALK3831-A305

Clintara LLC, 2015

<u>Instructions for Raters</u>

This interview guide applies the clinical global impression of severity (CGI-S) to explore the *global impact* of identified **"targeted" symptoms of schizophrenia** on behavior and function within the PAST SEVEN DAYS. In this study, subjects must meet DSM-5 criteria for Schizophrenia <u>and</u> have moderate symptoms of schizophrenia that have at least a moderate impact on behavior and/or function overall.

Generally, the SIGGI interview *follows* a review of the psychiatric history, the administration of a symptomatic questionnaire that identifies *current clinically relevant symptoms,* and collection of any collateral information from reliable informants. ***USE ALL AVAILABLE CLINICAL INFORMATION TO COMPLETE THIS FORM.***

The interview proceeds as follows:

1. EXPLANATION: Explain the purpose of the interview and obtain the subjects consent to participate.
2. SYMPTOM IDENTIFICATION: Inquire about (and/or confirm) the <u>presence of relevant symptoms of Schizophrenia</u> that have been present within the past week (PAST 7 DAYS).
3. IMPACT ASSESSMENT: Inquire about the amount of current distress (if any) or interference that the specific "targeted" symptoms have caused for the subject in the past week (PAST 7 DAYS).
4. SCORE *AND* DOCUMENT: Using the scoring anchors provided, determine the most appropriate global score and provide **written documentation** to support the derived score.

1. EXPLANATION AND CONSENT
I'd like to ask you some questions about some of the symptoms that you have experienced within the past week. Some of these questions may have already been asked and others will be new questions. ***I'm interested in how much the symptoms that you've experienced in the past week have affected you at home, at work, at school, in your relationships with others, or while you pursue your usual interests or activities (such as hobbies).*** ***Is that okay with you?***
2. SYMPTOM IDENTIFICATION (<u>**focus on symptoms of schizophrenia**</u>)
Let's begin by listing the most troubling symptoms that you have experienced within the past week (7 days). Can you describe them? How long have you had these symptoms (describe each specific symptom)? <u>SYMPTOM LISTING (Identify SYMPTOM and DURATION)</u> **1.** ________________ **Duration:** ________________ **2.** ________________ **Duration:** ________________ **3.** ________________ **Duration:** ________________ **4.** ________________ **Duration:** ________________ **5.** ________________ **Duration:** ________________ NOTE TO RATER: Please include any relevant symptoms identified from any other sources beyond this interview that may be present within the PAST SEVEN days. Summarize and confirm each symptom and its duration before proceeding

3. IMPACT ASSESSMENT

A. Have any of these symptoms interfered with your ability to function? ☐ **YES** ☐ **NO**

INQUIRE ABOUT RELEVANT ACTIVITIES: work, study, pursuit of hobbies or interests, participation in social events, or attending school.

IF SUBJECT RESPONDS YES, ASK***: In what way have the symptoms interfered?***
DOCUMENT RESPONSES IN THE SUBJECT'S OWN WORDS (with examples):

B. Have any of these symptoms interfered with your relationships? ☐ **YES** ☐ **NO**

INQUIRE ABOUT: friendships, social or work relationships, and interactions with family members.

IF SUBJECT RESPONDS YES, ASK***: In what way have the symptoms interfered with your relationships in the past week?***
DOCUMENT RESPONSES IN THE SUBJECT'S OWN WORDS (with examples):

IF THE SUBJECT RESPONDS ***YES*** TO *EITHER* OF THE ABOVE IMPACT QUERIES (A or B), ASK THE FOLLOWING QUESTIONS:

Regarding these symptoms, how troubling or distressing have these symptoms been for you?
Can you give me an example? DOCUMENT RESPONSES IN THE SUBJECT'S OWN WORDS (with examples):

QUANTIFICATION (RATER: refer to queries A or B above)

How many DAYS in the past week have these symptoms disturbed you or interfered with your behavior or function? **_____days**

How much of the time during the day (or night) have these symptoms disturbed you or interfered with your behavior or function? **_____ %**

4. SCORE AND DOCUMENT

CGI SEVERITY ASSESSMENT: _____(1-7)

(use scoring guide/anchors provided for specific study/evaluation)

PLEASE DOCUMENT BELOW THE JUSTIFICATION FOR DERIVED SCORE FROM ALL AVAILABLE CLINICAL DATA:

CGI-S Scoring Guidelines

1	Normal, not at all ill	Symptoms of disorder have *not* been present in the past seven days
2	Borderline mentally ill	Subtle or suspected pathology present within the past seven days
3	Mildly ill	Clearly established symptoms causing minimal, if any, distress for the subject or difficulty in social and occupational function can be documented within the past seven days
4	Moderately ill	Overt symptoms causing ***noticeable, but modest, functional impairment or distress*** for the subject; Some symptoms may warrant adjustment of medication
5	Markedly ill	Intrusive symptoms that ***distinctly impair social/occupational function*** or ***cause intrusive levels of distress for the subject;*** There is overt behavioral or social dysfunction that is obvious to others
6	Severely ill	Disruptive pathology; behavior and function are frequently influenced by symptoms; Extent of overt dysfunction may require intervention from others
7	Among the most extremely ill patients	Pathology drastically interferes in many life functions; patient may be hospitalized

APPENDIX C. MODIFIED OVERT AGGRESSION SCALE

Taken from: Kay SR, Wolkenfeld F, Murrill LM (1988) Profiles of aggression among psychiatric patients. I. Nature and prevalence. J Nerv Ment Dis 176:539-546

Association (p. 69–70). Washington, DC: American Psychiatric Press.
Tardiff K, Sweillam A (1980) Assault, suicide, and mental illness. *Arch Gen Psychiatry* 37:164–169.
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Yudofsky SC, Silver JM, Jackson W, et al (1986) The Overt Aggression Scale for the objective rating of verbal and physical aggression. *Am J Psychiatry* 143:35–39.

Appendix: Modified Overt Aggression Scale

Patient's name _____ Rater _____
Ward ____ Shift ____ Date _____
Hospital no. ___ Sex ___ Period of observation ____

Directions: For each category of aggressive behavior, check the *highest* applicable rating point to describe the most serious act of aggression committed by the patient during the specified observation period.

Verbal aggression. Verbal hostility, such as statements or invectives that seek to inflict psychological harm on another through devaluation/degradation, and threats of physical attack.

____ 0. No verbal aggression
____ 1. Shouts angrily, curses mildly, or makes personal insults
____ 2. Curses viciously, is severely insulting, has temper outbursts
____ 3. Impulsively threatens violence toward others or self
____ 4. Threatens violence toward others or self repeatedly or deliberately (*e.g.*, to gain money or sex)

Aggression against property. Wanton and reckless destruction of ward paraphernalia or others' possessions.

____ 0. No aggression against property
____ 1. Slams door angrily, rips clothing, urinates on floor
____ 2. Throws objects down, kicks furniture, defaces walls
____ 3. Breaks objects, smashes windows
____ 4. Sets fires, throws objects dangerously

Autoaggression. Physical injury toward oneself, such as self-mutilation or suicide attempt.

____ 0. No autoaggression
____ 1. Picks or scratches skin, pulls out hair, hits self (without injury)
____ 2. Bangs head, hits fists into walls, throws self on floor
____ 3. Inflicts minor cuts, bruises, burns, or welts on self
____ 4. Inflicts major injury on self or makes a suicide attempt

Physical aggression. Violent action intended to inflict pain, bodily harm, or death upon another.

____ 0. No physical aggression
____ 1. Makes menacing gestures, swings at people, grabs at clothing
____ 2. Strikes, kicks, pushes, scratches, pulls hair of others (without injury)
____ 3. Attacks others, causing mild injury (bruises, sprains, welts, etc.)
____ 4. Attacks others, causing serious injury (fracture, loss of teeth, deep cuts, loss of consciousness, etc.)

Rating summary

Scale	*Scaled score*	*Weighted score*
Verbal aggression	____	×1 = ____
Aggression against property	____	×2 = ____
Autoaggression	____	×3 = ____
Physical aggression	____	×4 = ____
Total weighted score		____

APPENDIX D. POSITIVE AND NEGATIVE SYNDROME SCALE

SCI-PANSS

SCI–PANSS

Structured Clinical Interview – Positive and Negative Syndrome Scale

Lewis A. Opler, M.D., Ph.D.
Stanley R. Kay, Ph.D.
J.P. Lindenmayer, M.D., &
Abraham Fiszbein, M.D.

MHS

Structured Clinical Interview for the Positive and Negative Syndrome Scale

SCI-PANSS

L. A. Opler, M.D., Ph.D. S. R. Kay, Ph.D. J. P. Lindenmayer, M.D. A. Fiszbein, M.D.

Patient Name or ID: _____

Interviewer: _____ Date: _____ / _____ / _____

Data on "Lack of Spontaneity and Flow of Conversation" (N6), "Poor Rapport" (N3), and "Conceptual Disorganization" (P2)

Hi, I'm ... We're going to be spending the next 30 to 40 minutes talking about you and your reasons for being here. Maybe you can start out by telling me something about yourself and your background?

(Instruction to interviewer: Allow at least 5 minutes for a non-directive phase serving to establish rapport in the context of an overview before proceeding to the specific questions listed below.)

Data on "Anxiety" (G2)

1. Have you been feeling worried or nervous in the past week? _____

   IF YES, skip to question 3. IF NO, continue.

2. Would you say that you're usually calm and relaxed? _____

   IF YES, skip to question 8. IF NO, continue.

3. What's been making you feel nervous (worried, not calm, not relaxed)? _____

4. Just how nervous (worried, etc.) have you been feeling? _____

5. Have you been shaking at times, or has your heart been racing? _____

6. Do you get into a state of panic? _____

7. Has your sleep, eating, or participation in activities been affected? _____

Data on "Delusions (General)" (P1) and "Unusual Thought Content" (G9)

8. Have things been going well for you? _____

9. Has anything been bothering you lately? _____

10. Can you tell me something about your thoughts on life and its purpose? _____

11. Do you follow a particular philosophy (any special rules, teachings, or religious doctrine)? _____

12. Some people tell me they believe in the Devil; what do you think? _____

IF NO (i.e., he/she doesn't believe in the Devil), skip to question 14.
IF YES (i.e., he/she does believe), continue.

13. Can you tell me more about this? _____

14. Can you read other people's minds? _____

IF NO, skip to question 16. IF YES, continue.

15. How does that work? _____

16. Can others read your mind? _____

IF NO, skip to question 19. IF YES, continue.

17. How can they do that? _____

18. Is there any reason that someone would want to read your mind? _____

19. Who controls your thoughts? _____

Data on "Suspiciousness/Persecution" (P6) and "Poor Impulse Control" (GI4)

20. How do you spend your time these days? _____

21. Do you prefer to be alone? _____

22. Do you join in activities with others? _____

IF YES, skip to question 25. IF NO, continue.

23. Why not? ... Are you afraid of people, or do you dislike them? _____

IF NO, skip to question 26. IF YES, continue.

24. Can you explain? _____

Skip to question 26.

25. Tell me about it. _____

26. Do you have many friends? _____

IF YES, skip to question 30. IF NO, continue.

27. Just a few? _____

IF YES, skip to question 29. IF NO, continue.

28. Any? .... Why? _____

Skip to question 32.

29. Why just a few friends? _____

30. Close friends? _____

IF YES, skip to question 32. IF NO, continue.

31. Why not? _____

32. Do you feel that you can trust most people? _____

IF YES, skip to question 34. IF NO, continue.

33. Why not? _____

34. Are there some people in particular who you don't trust? _____

IF NO to question 34 and YES to question 32, skip to question 41.

IF NO to question 34 and NO to question 32, skip to question 36.

IF YES to question 34, continue.

35. Can you tell me who they are? _____

36. Why don't you trust people (or name specific person)? _____

IF "DON'T KNOW" OR "DON'T WANT TO SAY," continue. Otherwise, skip to question 41.

37. Do you have a good reason not to trust ...?

_____

38. Is there something that .... did to you? _____

39. Perhaps something that ... might do to you now? _____

IF NO, skip to question 41. IF YES, continue.

40. Can you explain to me? _____

41. Do you get along well with others? _____

IF YES, skip to question 43. IF NO, continue.

42. What's the problem? _____

43. Do you have a quick temper? _____

44. Do you get into fights? _____

IF NO, skip to question 48. IF YES, continue.

45. How do these fights start? _____

46. Tell me about these fights. _____

47. How often does this happen? _____

48. Do you sometimes lose control of yourself? _____

IF NO, skip to question 50. IF YES, continue.

49. What happens when you lose control of yourself? _____

50. Do you like most people? _____

IF YES, skip to question 52. IF NO, continue.

51. Why not? _____

52. Are there perhaps some people who don't like you? _____

IF NO, skip to question 54. IF YES, continue.

53. For what reason? _____

54. Do others talk about you behind your back? _____

IF NO, skip to question 57. IF YES, continue.

55. What do they say about you? _____

56. Why? _____

57. Does anyone ever spy on you or plot against you? _____

58. Do you sometimes feel in danger? _____

IF NO, skip to question 64. IF YES, continue.

59. Would you say that your life is in danger? _____

60. Is someone thinking of harming you or even perhaps thinking of killing you? _____

61. Have you gone to the police for help? _____

62. Do you sometimes take matters into your own hands or take action against those who might harm you?

_____

IF NO, skip to question 64. IF YES, continue.

63. What have you done? _____

Data on "Hallucinatory Behavior" (P3) and associated delusions

64. Do you once in a while have strange or unusual experiences? _____

65. Sometimes people tell me that they can hear noises or voices inside their head that others can't hear. What about you? _____

IF YES, skip to question 68. IF NO, continue.

66. Do you sometimes receive personal communications from the radio or TV? _____

IF YES, skip to question 68. IF NO, continue.

67. From God or the Devil?: _____

IF NO, skip to question 83. IF YES, continue.

68. What do you hear? _____

69. Are these as clear and loud as my voice? _____

70. How often do you hear these voices, noises, messages, etc.? _____

71. Does this happen at a particular time of day or all the time? _____

IF HEARING NOISES ONLY, skip to question 80. IF HEARING VOICES, continue.

72. Can you recognize whose voices these are? _____

73. What do the voices say? _____

74. Are the voices good or bad? _____

75. Pleasant or unpleasant? _____

76. Do the voices interrupt your thinking or your activities? _____

77. Do they sometimes give you orders or instructions? _____

IF NO, skip to question 80. IF YES, continue.

78. For example? _____

79. Do you usually obey these orders (instructions)? _____

80. What do you make of these voices (or noises); where do they really come from? _____

81. Why do you have these experiences? _____

82. Are these normal experiences? _____

83. Do ordinary things sometimes look strange or distorted to you? _____

84. Do you sometimes have "visions" or see things that others can't see? _____

IF NO, skip to question 88. IF YES, continue.

85. For example? _____

86. Do these visions seem very real or life-like? _____

87. How often do you have these experiences? _____

88. Do you sometimes smell things that are unusual or that others don't smell? _____

IF NO, skip to question 90. IF YES, continue.

89. Please explain. _____

90. Do you get any strange or unusual sensations from your body? _____

IF NO, skip to question 92. IF YES, continue.

91. Tell me about this. _____

Data on "Somatic Concern" (GI)

92. How have you been feeling in terms of your health? _____

IF OTHER THAN "GOOD," skip to question 94. IF "GOOD," continue.

93. Do you consider yourself to be in top health? _____

IF YES, skip to question 95. IF NO, continue.

94. What has been troubling you? _____

95. Do you have any medical illness or disease? _____

96. Has any part of your body been troubling you? _____

IF YES, skip to question 98. IF NO, continue.

97. How is your head? Your heart? Stomach? The rest of your body? _____

98. Could you explain? _____

99. Has your head or body changed in shape or size? _____

IF NO, skip to question 102. IF YES, continue.

100. Please explain. _____

101. What is causing these changes? _____

Data on "Depression" (G6)

102. How has your mood been in the past week: mostly good, mostly bad? _____

IF "MOSTLY BAD," skip to question 104. IF "MOSTLY GOOD," continue.

103. Have there been times in the past week when you were feeling sad or unhappy? _____

IF NO, skip to question 114. IF YES, continue.

104. Is there something in particular that is making you sad? _____

105. How often do you feel sad? _____

106. Just how sad have you been feeling? _____

107. Have you been crying lately? _____

108. Has your mood in any way affected your sleep? _____

109. Has it affected your appetite? _____

110. Do you participate less in activities on account of your mood? _____

111. Have you had any thoughts of harming yourself? _____

IF NO, skip to question 114. IF YES, continue.

112. Any thoughts about ending your life? _____

IF NO, skip to question 114. IF YES, continue.

113. Have you attempted suicide? _____

Data on "Guilt Feelings" (G3) and "Grandiosity" (P5)

114. If you were to compare yourself to the average person, how would you come out: a little better, maybe a little worse, or about the same? _____

IF "BETTER," skip to question 117.
IF "ABOUT THE SAME," skip to question 118.
IF "WORSE," continue.

115. Worse in what ways? _____

116. Just how do you feel about yourself? _____

Skip to question 120.

117. Better in what ways? _____

Skip to question 120.

118. Are you special in some ways? _____

IF NO, skip to question 120. IF YES, continue.

119. In what ways? _____

120. Would you consider yourself gifted? _____

121. Do you have talents or abilities that most people don't have? _____

IF NO, skip to question 123. IF YES, continue.

122. Please explain. _____

123. Do you have any special powers? _____

IF NO, skip to question 126. IF YES, continue.

124. What are these? _____

125. Where do these powers come from? _____

126. Do you have extrasensory perception (ESP), or can you read other people's minds? _____

127. Are you very wealthy? _____

IF NO, skip to question 129. IF YES, continue.

128. Explain please. _____

129. Can you be considered to be very bright? _____

IF NO, skip to question 131. IF YES, continue.

130. Why would you say so? _____

131. Would you describe yourself as famous? _____

132. Would some people recognize you from TV, radio, or the newspaper? _____

IF NO, skip to question 134. IF YES, continue.

133. Can you tell me about it? _____

134. Are you a religious person? _____

IF NO, skip to question 140. IF YES, continue.

135. Are you close to God? _____

IF NO, skip to question 140. IF YES, continue.

136. Did God assign you some special role or purpose? _____

137. Can you be one of God's messengers or angels? _____

IF NO, skip to question 139. IF YES, continue.

138. What special powers do you have as God's messenger (angel)? _____

139. Do you perhaps consider yourself to be God? _____

140. Do you have some special mission in life? _____

IF NO, skip to question 143. IF YES, continue.

141. What is your mission? _____

142. Who assigned you to that mission? _____

143. Did you ever do something wrong — something you feel bad or guilty about? _____

IF NO, skip to question 149. IF YES, continue.

144. Just how much does that bother you now? _____

145. Do you feel that you deserve punishment for that? _____

IF NO, skip to question 149. IF YES, continue.

146. What kind of punishment would you deserve? _____

147. Have you at times thought of punishing yourself? _____

IF NO, skip to question 149. IF YES, continue.

148. Have you ever acted on those thoughts of punishing yourself? _____

Data on "Disorientation" (GIO)

149. Can you tell me today's date (i.e., the day, month, and year)? _____

IF YES, skip to question 151. IF NO, continue.

150. Can you tell me what day of the week it is? _____

151. What is the name of the place that you are in now? _____

IF NOT HOSPITALIZED, skip to question 154. IF HOSPITALIZED, continue.

152. What ward are you on? _____

153. What is the address of where you're now staying? _____

IF ABLE TO TELL, skip to question 155. IF NOT ABLE TO TELL, continue.

154. Can you tell me your home address? _____

IF NOT HOSPITALIZED, skip to question 156. IF HOSPITALIZED, continue.

155. If someone had to reach you by phone, what number would that person call? _____

156. If someone had to reach you at home, what number would that person call? _____

157. What is the name of the doctor who is treating you? _____

IF NOT HOSPITALIZED, skip to question 159. IF HOSPITALIZED, continue.

158. Can you tell me who else is on the staff and what they do? _____

159. Do you know who is currently the president (prime minister, etc.)? _____

160. Who is our governor (premier, etc.)? _____

161. Who is the mayor (town supervisor, etc.) of this city (town, etc.)? _____

Data on "Difficulty in Abstract Thinking" (N5)

I'm going to now say a pair of words, and I'd like you to tell me in what important way they're alike. Let's start, for example, with the words "apple" and "banana." How are they alike — what do they have in common? **IF THE RESPONSE IS THAT "THEY'RE BOTH FRUIT", THEN SAY:** Good. Now what about ...? *(Select three other items from the Similarities list at varying levels of difficulty from Appendix A.)*

IF AN ANSWER IS GIVEN THAT IS CONCRETE, TANGENTIAL, OR IDIOSYNCRATIC (E.G., "THEY BOTH HAVE SKINS," "YOU CAN EAT THEM," "THEY'RE SMALL," OR "MONKEYS LIKE THEM"), THEN SAY: OK, but they're both fruit. Now how about ... and ... : how are these alike? *(Select three other items from the Similarities list at varying levels of difficulty from Appendix A.)*

APPENDIX A
Items for Similarities in the evaluation of "Difficulty in Abstract Thinking"

Circle the Similarities Used

1. How are a ball and an orange alike?
2. Apple and banana ?
3. Pencil and pen?
4. Nickel and dime?

5. Table and chair?
6. Tiger and elephant?
7. Hat and shirt?
8. Bus and train?

9. Arm and leg?
10. Rose and tulip?
11. Uncle and cousin?
12. The sun and the moon?

13. Painting and poem?
14. Hilltop and valley?
15. Air and water?
16. Peace and prosperity?

Note on Appendix A: Similarities are generally assessed by sampling four items at different levels of difficulty (i.e., one item selected from each quarter of the full set). When using the PANSS longitudinally, items should be systematically altered with successive interviews so as to provide different selections from the various levels of difficulty and thus minimize repetition.

Notes on Similarities responses:

You've probably heard the expression, "Carrying a chip on the shoulder." What does that really mean? There's a very old saying, "Don't judge a book by its cover." What is the deeper meaning of this proverb? *(Select two other proverbs from the list in Appendix B at varying levels of difficulty.)*

APPENDIX B
Items for assessing PROVERB INTERPRETATION in the evaluation of "Difficulty in Abstract Thinking"

Circle the Proverbs Used

What does the saying mean:
1. "Plain as the nose on your face"
2. "Carrying a chip on your shoulder"
3. "Two heads are better than one"
4. "Too many cooks spoil the broth"

5. "Don't judge a book by its cover"
6. "One man's food is another man's poison"
7. "All that glitters is not gold"
8. "Don't cross the bridge until you come to it"

9. "What's good for the goose is good for the gander"
10. "The grass always looks greener on the other side"
11. "Don't keep all your eggs in one basket"
12. "One swallow does not make a summer"

13. "A stitch in time saves nine"
14. "A rolling stone gathers no moss"
15. "The acorn never falls far from the tree"
16. "People who live in glass houses should not throw stones at others"

Note on Appendix B: Proverb interpretation is generally assessed by sampling four items at different levels of difficulty (i.e., one item selected from each quarter of the full set). When using the PANSS longitudinally, items should be systematically altered with successive interviews so as to provide different selections from the various levels of difficulty and thus minimize repetition.

Notes on Proverb responses:

Data on "Lack of Judgment and Insight" (G12)

162. How long have you been in the hospital (clinic, etc.)? _____

163. Why did you come to the hospital (clinic, etc.)? _____

164. Did you need to be in a hospital (clinic, etc.)? _____

IF YES, skip to question 167. IF NO, continue.

165. Did you have a problem that needed treatment? _____

IF NO, skip to question 169. IF YES, continue.

166. Would you say that you had a psychiatric or mental problem? _____

IF NO, skip to question 169. IF YES, continue.

167. Why?....would you say that you had a psychiatric or mental problem? _____

IF NO, skip to question 169. IF YES, continue.

168. Can you tell me about it and what it consisted of? _____

169. In your own opinion, do you need to be taking medicine? _____

IF YES, skip to question 171.
IF NO and <u>unmedicated</u>, skip to question 172.
IF NO and <u>medicated</u>, continue.

170. Why then are you taking medicines? _____

Skip to question 172.

171. Why?... Does the medicine help you in any way? _____

172. Do you at this time have any psychiatric or mental problems? _____

IF YES, skip to question 174. IF NO, continue.

173. For what reason are you at the hospital (clinic, etc.)? _____

Skip to question 175.

174. Please explain _____

175. Just how serious are these problems? _____

IF UNHOSPITALIZED, skip to question 178.
IF HOSPITALIZED, continue.

176. Are you ready yet for discharge from the hospital? _____

177. Do you think you'll be taking medicine for your problems after discharge? _____

178. What are your future plans? _____

179. What about your longer-range goals? _____

Well, that's about all I have to ask of you now. Are there any questions that you might like to ask of me? Thank you for your cooperation.

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APPENDIX E. 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 F. 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.

APPENDIX G. 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 H. COLUMBIA-SUICIDE SEVERITY RATING SCALE

- Baseline/Screening
- Since Last Visit

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 <u>some intent to act on such thoughts</u>, as opposed to *"I have the thoughts but I definitely will not do anything about them".* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**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

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. <u>Lifetime</u> - ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation*** <u>Past X Months</u> - ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could /can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others. (2) Mostly to get attention, revenge or a reaction from others. (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain. (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (0) Does not apply	____	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**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.

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

If yes, describe:

Yes ☐ **No** ☐

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

If yes, describe:

Yes ☐ **No** ☐

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

If yes, describe:

Yes ☐ **No** ☐

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

If yes, describe:

Yes ☐ **No** ☐

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

If yes, describe:

Yes ☐ **No** ☐

INTENSITY OF IDEATION

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

Most Severe Ideation: _____ _____

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

Most Severe

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

____

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

____

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

____

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

____

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

____

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