A Phase 2, Efficacy, Safety, and Tolerability Study of ALKS 3831 in Schizophrenia with Alcohol Use Disorder

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CLINICAL STUDY PROTOCOL

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CONFIDENTIAL

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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 2 Efficacy, Safety, and Tolerability Study of ALKS 3831 in Schizophrenia with Alcohol Use Disorder	
Investigator(s): Multicenter, multinational study	
Study Period: Estimated date of first subject's consent: May 2014 Estimated date of last subject's completion: CY 2017	**Phase of Development:** 2

Objectives:

Primary:

- To evaluate the efficacy of olanzapine coadministered with samidorphan (ALKS 3831) compared with olanzapine coadministered with placebo in schizophrenia with alcohol use disorder (AUD)

Secondary:

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

Methodology:

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy, safety, and tolerability of ALKS 3831 in schizophrenia with AUD. Subjects must have recently (within the last 6 months) experienced an exacerbation of disease symptoms (as defined in the protocol). ALKS 3831 is a combination of olanzapine, an approved antipsychotic treatment for schizophrenia, and samidorphan, a new chemical entity.

The clinical presentation of schizophrenia often includes AUD, as it occurs in this population more frequently than in the general population and most other psychiatric disorders. Despite the prevalence of schizophrenia with AUD and the psychosocial consequences of this disease, there is no approved treatment that has been clinically tested for treating schizophrenia in this group.

Potential subjects for this trial are adults with a diagnosis of schizophrenia (based on the Diagnostic and Statistical Manual of Mental Disorders 4th edition, text revision [DSM-IV-TR]) and AUD (based on DSM 5th edition [DSM-5]). Subjects must also have recently experienced an exacerbation of disease symptoms (eg, hospitalization) but cannot exceed a pre-defined level of symptom severity at the time of screening (as measured by assessments like the Positive and Negative Syndrome Scale [PANSS] and Clinical Global Impression-Severity [CGI-S]).

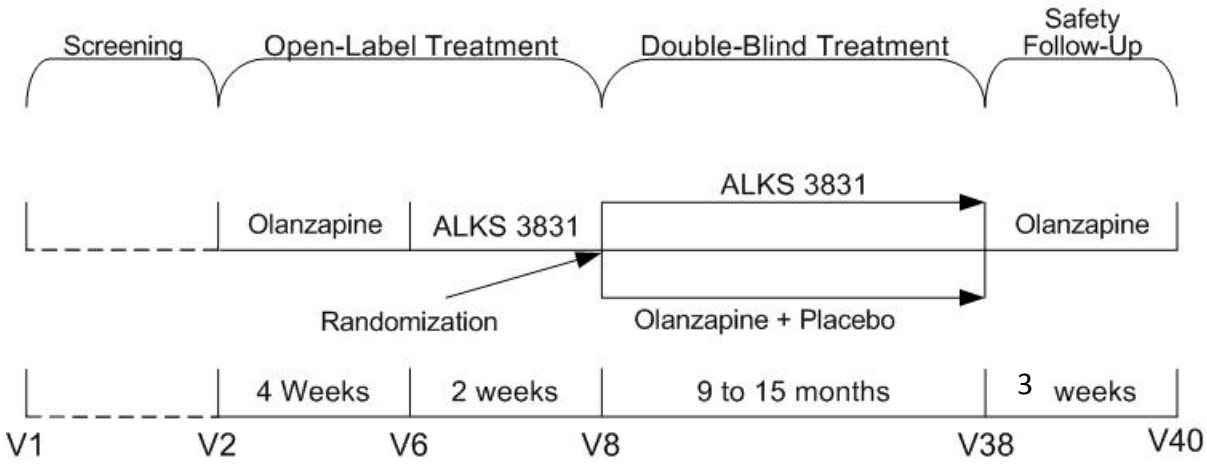
All study visits will be outpatient. After informed consent and screening, subjects will begin a 4-week open-label olanzapine dosing period followed by a 2-week open-label ALKS 3831 period (see study schematic below). Once-daily, open-label olanzapine dosing will begin at Visit 2 with the dose level determined by the principal investigator (PI). Olanzapine dose adjustments may be made during the first 3 weeks of treatment but should be fixed beginning with Visit 5. Once daily open-label ALKS 3831 dosing (olanzapine coadministered with 10 mg samidorphan using separate tablets) will begin at Visit 6 and last until Visit 8 (randomization). ALKS 3831 treatment will consist of a once-daily dose of

olanzapine (with dose level determined by the PI) plus samidorphan 10 mg to be taken at the same time (ie, coadministered) using separate tablets.

At Visit 8, subjects will be randomized in a 1:1 fashion to 1 of 2 treatment groups and will begin a double-blind treatment period. The two treatment groups are as follows:

- ALKS 3831: (ie, olanzapine [dose determined by the PI] plus samidorphan [10 mg])
- Olanzapine (dose determined by the PI) plus placebo

Subjects randomized to double-blind treatment will be followed for a minimum of 9 months and a maximum of 15 months. Visits during the double-blind period will be every 2 weeks. Each visit will consist of clinical assessments plus drug dispensing or drug dispensing only. After the end of the double-blind treatment period, subjects will complete a 3-week safety follow-up period.



Abbreviation: V = Study Visit; ALKS 3831=olanzapine + samidorphan

Number of Subjects Planned:

Approximately 450 subjects will enter the open-label olanzapine period at Visit 2. Of those, approximately 270 are expected to be randomized at Visit 8.

Main Criteria for Inclusion:

Men and women 18 through 65 years of age (inclusive) with a DSM-IV-TR diagnosis of schizophrenia and a DSM-5 diagnosis of AUD who meet pre-specified symptom severity criteria may be eligible for this study. At a minimum, subjects must also meet sponsor criteria for a recent (within 6 months) exacerbation of schizophrenia symptoms and have experienced at least 10 drinking days in the 30 days prior to screening (as measured by the Timeline Follow-Back [TLFB] method), with at least 2 of these drinking days meeting criteria for a heavy drinking day (4 drinks in a day for women and 5 drinks in a day for men), to be eligible for this study.

Investigational Product Dosage, Duration, and Mode of Administration:

ALKS 3831 refers to the combination of olanzapine and samidorphan. In this study, olanzapine and samidorphan will be coadministered orally using separate tablets for olanzapine and samidorphan to be taken once daily. Commercially available olanzapine for oral administration will be dispensed by the investigative site. All subjects will take olanzapine for the entire duration of the study.

Alkermes will provide samidorphan as 10 mg tablets. All subjects will take open-label ALKS 3831 for 2 weeks prior to randomization. Subjects randomized to the double-blind treatment period will take ALKS 3831 (olanzapine plus samidorphan) or olanzapine plus placebo for the duration of the double-blind period.

Whether or not samidorphan is classified as a controlled substance varies from country to country; some

countries have classified samidorphan as a controlled substance, but others have not. Sites will be given handling and storage instructions applicable to their country to ensure compliance with local regulations for controlled substances.

Reference Therapy Dosage, Duration, and Mode of Administration:

Placebo consists of tablets identical in size and appearance to the samidorphan tablets but without active samidorphan. Subjects who are randomized to olanzapine plus placebo will take these study drugs orally, once daily at the same time for 9 to 15 months.

Duration of Study:

The duration of the study period for a given subject will be approximately 12 to 18 months which includes up to 30 days for screening, a total of 6 weeks of open-label treatment, a 9 to 15 month double-blind treatment period, and 3 weeks for safety follow-up.

Primary Efficacy Measure:

The primary efficacy measure will be an event of exacerbation of disease symptoms (EEDS) based on the occurrence of pre-specified events indicative of exacerbation of disease symptoms, as confirmed by an independent adjudication committee (IAC). These events are pre-specified in the body of the protocol.

Other Efficacy Measures:

In addition to the primary efficacy measure, efficacy will be evaluated with the following measures:

- Pre-specified psychosocial events indicative of exacerbation of disease symptoms
- PANSS
- CGI-S
- CGI-Improvement (CGI-I)
- TLFB assessment of alcohol drinking
- Visual Analog Scale (VAS) for perception of desire for alcohol

Safety Assessments:

Safety will be evaluated with the following measures:

- Adverse events (AEs)
- Columbia-Suicidal Severity Rating Scale (C-SSRS) results
- Vital signs
- Clinical biochemistry, hematology, and urinalysis
- Electrocardiograms (ECGs)
- Weight
- Abnormal movement rating scales results [Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), Simpson-Angus Scale (SAS)]

Statistical Methods

Efficacy:

The efficacy analyses will be carried out using the intent-to-treat (ITT) population defined as all randomized subjects who receive at least 1 dose of study drug post-randomization. The primary efficacy endpoint is defined as the time from randomization to first occurrence of an EEDS, as defined in the protocol and confirmed by an IAC. The analysis comparing the 2 treatment groups will be carried out using a log-rank test. A Cox proportional hazard model will be used to further examine the treatment difference adjusting for various covariates.

Pharmacokinetics:

Pharmacokinetic data may be used in a subsequent population pharmacokinetic evaluation conducted separately. By-subject listings of plasma concentrations of olanzapine, samidorphan, and RDC-9986 (metabolite of samidorphan) will be provided.

Safety:

All subjects who receive at least 1 dose of study drug (olanzapine, samidorphan, or placebo) will be included in the safety analysis. Safety will be evaluated based on the incidence of treatment emergent adverse events (TEAEs), laboratory test results, vital signs, ECG findings, C-SSRS results, change in weight, abnormal movement scale results, and concomitant medications. Descriptive summary statistics and by-subject listings will be provided for safety measures.

Sample Size Considerations:

The sample size calculation is based on the detection of log-hazard ratio for the first EEDS during the double-blind treatment period.

Based on the previous clinical studies with olanzapine and clinical judgment, the cumulative proportion of EEDS by the end of a 9-month double-blind treatment period (the minimum duration for subjects in this study) is estimated to be 15% and 30% for the ALKS 3831 group and the olanzapine plus placebo group, respectively. Assuming an exponential distribution of survival time, and a 2-sided test at $\alpha=0.05$, a total of 70 recurrent events will be required for approximately 90% power to detect a hazard ratio of 0.45 between ALKS 3831 and olanzapine plus placebo with a randomization allocation ratio of 1:1 (ALKS 3831:olanzapine plus placebo). An estimated 270 subjects (135 subjects per treatment group) will need to be randomized at Visit 8 to observe 70 total EEDS.

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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
ALK-P	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical [classification system]
AUC	area under the curve
AUC_{∞}	area under the curve extrapolated to infinity
AUD	alcohol use disorder
BARS	Barnes Akathisia Rating Scale
BUN	blood urea nitrogen
C-SSRS	Columbia Suicide Severity Rating Scale
C-VISA™	Clinical Validation Inventory for Study Admission
CDT	carbohydrate deficient transferrin
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
CPK	creatine phosphokinase
CSA	Clinical Study Agreement
DEA	Drug Enforcement Agency
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders (4th edition, text revision)
DSM-5	Diagnostic and Statistical Manual of Mental Disorders (5th edition)
ECG	electrocardiogram
eCRF	electronic case report form
EDC	Electronic Data Capture
EEDS	event of exacerbation of disease symptoms
ET	early termination
FAS	Full Analysis Set
GCP	Good Clinical Practice

Abbreviation or Term	Explanation or Definition
GGT	gamma glutamyl transferase
HbA_{1c}	hemoglobin A_{1c}
HDL	high-density lipoprotein
IAC	Independent Adjudication Committee
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
ITT	Intent to Treat
IWRS	Interactive Web Response System
LDH	lactic dehydrogenase
LDL	low-density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini-International Neuropsychiatric Interview
PANSS	Positive and Negative Syndrome Scale
PI	principal investigator
PK	pharmacokinetics
PSP	Personal and Social Performance Scale
QTcF	QT interval corrected using the Fridericia formula
QTcB	QT interval corrected using the Bazett formula
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Simpson-Angus Scale
SCI-PANSS	Structured Clinical Interview for the Positive and Negative Syndrome Scale
SIGGI	Structured Interview Guide for Global Impressions
TEAE	treatment-emergent adverse event
TLFB	Timeline Follow-Back
TSH	thyroid stimulating hormone
US	United States
VAS	visual analog scale
WHO	World Health Organization

5. INTRODUCTION

ALKS 3831 is a combination of olanzapine and samidorphan (previously referred to as ALKS 33 or RDC-0313) being developed for the treatment of schizophrenia. Olanzapine has been available in the United States (US) and Europe since 1996 and was originally approved for the treatment of schizophrenia [EMEA 2013;Lilly USA 2013]. Olanzapine is regarded as one of the most effective antipsychotics with well-recognized efficacy and other advantages such as decreased incidence of extrapyramidal symptoms [Lieberman, 2005]. However, its efficacy and safety have not been fully evaluated in patients with schizophrenia and alcohol use disorder (AUD). Furthermore, the use of olanzapine in treatment has been limited by adverse events (AEs) related to weight gain and unintended metabolic effects.

Samidorphan is a μ-opioid receptor antagonist being developed on its own for treatment of reward disorders and in combination with olanzapine (ALKS 3831) for treatment of schizophrenia. In ALKS 3831, samidorphan has a range of potential benefits for patients with schizophrenia, such as reducing alcohol consumption and attenuating weight gain. Both of these benefits have the potential to improve long-term outcomes, such as reducing schizophrenia symptom severity and decreasing the frequency of events of exacerbation of disease symptoms (EEDS). ALK3831-401 is designed to assess efficacy of ALKS 3831 on time to EEDS after randomization to ALKS 3831 or olanzapine plus placebo following a recent exacerbation (within 6 months prior to screening) in schizophrenia with AUD. A separate study (ALK3831-302) is ongoing to assess other potential benefits of ALKS 3831 in schizophrenia.

5.1. Study Population

The clinical presentation of schizophrenia quite often includes AUD as it occurs in this patient population much more frequently than in most other psychiatric disorders or the general population. In an epidemiological study of psychiatric disorders and AUD, approximately 1 out of every 3 people with schizophrenia (33.7%) were found to meet or have met criteria for AUD, which is nearly triple the lifetime prevalence found in the general population (13.5%) [Regier, 1990]. Conversely, schizophrenia is seen more than 3 times as often in people with AUD as in the general population (odds ratio=3.3).

An increased risk for AUD in people with schizophrenia may be a part of a more general reward disorder that is part of the pathogenesis of schizophrenia and one of the core features of the disease. Evidence for a reward disorder includes the fact that most substance use disorders occur in schizophrenia more often than in the general population and often occur simultaneously [Regier, 1990]. In substance use disorders, the rewarding effects of a substance result in abnormally high levels of craving and drug-seeking with abnormally low consideration of the risks and negative effects of substance use. In AUD, this skewed risk/reward perception and alcohol drinking leads to physical and psychological effects that motivate use even when negative physical and psychosocial outcomes are frequently experienced (or are predictable) [Ahmed 2004]. Patients with schizophrenia are known to have difficulty with reward processing and this underlying neurobiological deficit, a pharmacologic predisposition for poor control of self-initiated activity, and the relative ease of access to alcohol, may explain why this population is particularly prone to AUD [Chambers, 2001]. Although the association between schizophrenia

and AUD is the strongest of nearly all psychiatric disorders, there are a substantial number of people with schizophrenia who may not be receiving treatment that specifically addresses their AUD [Drake, 1998].

In schizophrenia, AUD is a significant barrier to treatment and typically results in a poor disease course punctuated by frequent visits to "crisis settings" like jails, emergency rooms, and homeless shelters [Drake, 1998]. Ineffective treatments for schizophrenia with AUD directly contribute to the higher frequency of crisis outcomes in these patients [Dickey, 2000]. Schizophrenia with AUD is more strongly associated with violent behavior and incarceration; depression and suicide; family problems; and housing instability, all of which greatly complicate treatment. Poor outcomes are often the end of a long period of stable but deteriorating mental health as patients face the daily challenges associated with managing schizophrenia with AUD. Schizophrenia is a chronic condition that requires long-term coordinated care and management, and AUD introduces specific challenges to treating schizophrenia by affecting factors such as a patient's ability to maintain stable housing and depend on caregivers. As a result, a patient's functional status, stress level, and symptoms may worsen until he/she experiences a crisis situation and/or requires acute treatment (eg, inpatient hospitalization).

For this study, the target population will be identified using standard diagnostic criteria for schizophrenia (the Diagnostic and Statistical Manual of Mental Disorders 4th edition, text revision; DSM-IV-TR [American Psychiatric Association 2000]) and AUD (DSM-5 [American Psychiatric Association 2013]) as confirmed by the structured diagnostic interview, the Mini-International Neuropsychiatric Interview (MINI) [Sheehan, 1998], as well as other inclusion/exclusion criteria as confirmed by the Clinical Validation Inventory for Study Admission (C-VISA™). Subjects will have recently experienced an exacerbation of disease symptoms, and the primary efficacy endpoint will be time to EEDS (after randomization) using the pre-specified events defined in the protocol (Section 11.1) and confirmed by an independent adjudication committee (IAC).

5.2. Clinical and Nonclinical Experience

ALKS 3831 is being developed as a combination product containing olanzapine and samidorphan. In this study, olanzapine and samidorphan will be coadministered as separate tablets. Details of the studies summarized below are available in the ALKS 3831 Investigator's Brochure.

Samidorphan is a potent μ-opioid receptor antagonist with mixed agonist/antagonist activity at κ and δ receptors. To date there has not been any observed abuse potential in clinical or nonclinical studies. Other than binding at these human receptors, samidorphan (at 10 μM) has exhibited no significant receptor, transporter, or enzyme-ligand binding in [^{35}S]GTPγS assays of functional activity.

5.2.1. Clinical Studies

In the clinical studies of samidorphan to date, 469 subjects have received samidorphan orally (1-55.7 mg) or sublingually (1–16 mg) for up to 12 weeks. Commonly reported AEs observed across all studies included nausea, fatigue, and somnolence. Other AEs observed in these studies included dry mouth, vomiting, constipation, decreased appetite, headache, dizziness, and anorexia. Overall, no trends or clinically meaningful changes have been observed in clinical

laboratory analytes, vital sign parameters, or electrocardiogram (ECG) data. No deaths have occurred in these studies.

Samidorphan has been shown to block opioid agonist effects in opioid-experienced adults and decrease alcohol consumption in alcohol-dependent adults. In opioid-experienced adults, samidorphan blocked both the subjective (eg, Drug Liking measured with a visual analog scale [VAS]) and physiological effects (eg, pupil constriction measured with pupillometry) of the opioid agonists remifentanil (Study ALK33-004) and buprenorphine (Study ALK33-008). In adults with alcohol dependence (N=410), samidorphan (1, 2.5, or 10 mg) was associated with a reduction in drinking behavior (Study ALK33-005) compared with placebo; the largest reduction was seen with the highest samidorphan dose administered in this study (10 mg).

In addition to the reduction of alcohol drinking, samidorphan may attenuate weight gain associated with olanzapine. A Phase 1 proof-of-concept study has been conducted in healthy adults (ALK33-301) to determine the safety, tolerability, and efficacy of samidorphan when taken with olanzapine to mitigate olanzapine-related weight gain. In this study, significantly less weight gain was seen in the ALKS 3831 treatment arm than in the olanzapine plus placebo arm. A Phase 2 study, ALK3831-302, is currently underway to evaluate (as a secondary outcome) attenuation of weight gain by ALKS 3831 compared with olanzapine plus placebo in subjects with schizophrenia.

Samidorphan is a μ-opioid antagonist. Consistent with this mechanism, there has been no evidence of withdrawal upon discontinuation or addiction potential with samidorphan to date. In all studies, subjects are asked to complete a follow-up safety visit approximately 2 weeks after drug discontinuation, and no evidence of withdrawal has been reported after this abrupt discontinuation of samidorphan. The most common AEs seen with samidorphan are similar to those seen with naltrexone (an approved medication for addiction that is also a μ-opioid antagonist) and do not include AEs suggestive of addiction potential [Duramed Pharmaceuticals, Inc 2013].

Although samidorphan is a μ-opioid antagonist, agencies responsible for substance control may not consider a drug's mechanism of action when determining whether an unapproved drug should be handled as a controlled substance. For example, the US Drug Enforcement Agency (DEA) has classified samidorphan as a Schedule II substance because it is derived from opium alkaloids. In countries where samidorphan has been designated a controlled substance, samidorphan (and blinded study drug) will require handling consistent with local regulations for drugs of this class.

Olanzapine is regarded as one of the most effective antipsychotics with well-recognized efficacy and other advantages such as decreased incidence of extrapyramidal symptoms [Lieberman, 2005]. The safety and tolerability profile of olanzapine is well documented, and AE labeling is supported by an extensive safety database that includes over 8,500 adult patients.

5.2.2. Nonclinical Studies

Nonclinical data to date provide supporting (secondary pharmacology) evidence of samidorphan as a μ-opioid antagonist and a benefit in reduced alcohol consumption. In vivo nonclinical pharmacology studies have been conducted to demonstrate that samidorphan, at doses that result in exposure similar to therapeutically relevant doses in humans, blocks μ-opioid agonist effects

and reduces ethanol self-administration in rodents. In addition, these studies have demonstrated that, when administered alone, samidorphan is devoid of μ-opioid agonist-like properties.

The nonclinical safety assessment program for samidorphan and ALKS 3831 is based on recommendations for nonclinical drug toxicity and abuse liability testing in International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and US Food and Drug Administration (FDA) guidelines. A summary of completed GLP studies with samidorphan and ALKS 3831 can be found in the ALKS 3831 Investigator's Brochure.

Nonclinical abuse liability studies examining self-administration, drug discrimination, and drug dependence in rats indicate that samidorphan itself has no rewarding properties and carries no abuse potential. Furthermore, general toxicology studies of samidorphan (exposure up to 39 weeks: 2-week and 13-week rat/dog, 25-week rat, and 39-week dog studies) and ALKS 3831 (39-week dog study) have included non-dosing recovery periods during which clinical observations were made following abrupt samidorphan or ALKS 3831 discontinuation (ie, without a taper period). In these studies, there have been no clinical observations noted suggestive of withdrawal effects following samidorphan or ALKS 3831 administration.

Samidorphan has not been found to be genotoxic in vitro or in vivo at exposures (measured as area under the plasma concentration curve [AUC]) well above the ALK3831-401 samidorphan dose level (10 mg). General toxicology studies (referenced above) have identified findings only at systemic AUC_{∞} (AUC extrapolated to infinity) exposures far above the samidorphan dose level of this study. In developmental and reproductive toxicology studies conducted with samidorphan, dose-related effects were observed at systemic AUC_{∞} exposures far above the proposed samidorphan dose.

Overall, nonclinical findings to date do not suggest a human safety risk as findings occurred at exposures significantly above dose levels used in this study and were associated with increases in serum transaminases that can be readily monitored in the clinic. Moreover, exclusionary criteria and study procedures are designed to further mitigate any potential risk.

5.3. Dose Selection

Clinical and nonclinical safety and efficacy data support the selection of a once-daily 10 mg dose for the samidorphan component of ALKS 3831 in this study. In a prior study in alcohol-dependent subjects, samidorphan 10 mg showed the largest reduction in drinking behavior. Furthermore, clinical trial experience to date has shown samidorphan 10 mg to be well-tolerated.

This study includes a 2-week open label ALKS 3831 period. This open-label ALKS 3831 period is included because previous clinical studies have shown that the majority of AEs associated with samidorphan occur within the first 2 weeks of treatment. Starting all subjects on samidorphan not only establishes similar pharmacological states in the 2 groups prior to randomization but also mitigates the risk of functional unblinding because of subjects not tolerating study drug during samidorphan initiation. Both open-label periods (olanzapine and ALKS 3831) will allow investigators to address tolerability issues prior to randomization.

For all subjects, the once-daily olanzapine dose level throughout the study will be determined individually by the principal investigator (PI) or designee according to current clinical practice.

6. OBJECTIVES

6.1. Primary Objective

To evaluate the efficacy of olanzapine coadministered with samidorphan (ALKS 3831) compared with olanzapine coadministered with placebo in schizophrenia with alcohol use disorder (AUD)

6.2. Secondary Objective

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

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Subject Inclusion Criteria

Each subject must meet all of the following inclusion criteria at screening, unless otherwise specified, to be qualified to participate in this study:

1. Is between 18 and 65 years of age, inclusive
2. Is willing and able to provide informed consent
3. Is willing and able to follow the study procedures as outlined in the protocol
4. Is fluent in the language (oral and written) in which assessments will be made and can be reliably rated
5. Has a body-mass index between 18.0 and 40.0 kg/m^2, inclusive, at screening and Visit 2
6. Meets criteria for schizophrenia according to DSM-IV-TR as confirmed by the MINI administered by qualified site staff
7. Meets criteria for AUD according to DSM-5 as confirmed by the C-VISA and the MINI 7.0 AUD module administered by qualified site staff
8. Has experienced an acute exacerbation of schizophrenia within the past 6 months prior to screening that meets at least 1 of the following criteria:
   a. Was hospitalized (involuntarily or voluntarily) for symptoms of schizophrenia
      – If applicable, the total duration of any hospitalization(s) within the 30 days prior to Visit 2 must be ≤7 days.
   b. Committed deliberate self-injury, engaged in aggressive behavior, or displayed signs of suicidal or homicidal ideation deemed clinically significant by the PI
   c. Was prescribed 1 of the following changes in antipsychotic medication:
      – An increase in antipsychotic dose level due to symptom worsening
      – Change in antipsychotic due to symptom worsening
   d. Visited the emergency room or an outpatient healthcare facility (involuntarily or voluntarily) due to worsening of psychotic symptoms
9. Meets the following clinical criteria at screening* and Visit 2:
   a. Has a total Positive and Negative Syndrome Scale (PANSS) score between 50 and 90, inclusive
   b. Has a score of ≤4 for all of the following PANSS Positive (P) Scale or General Psychopathology (G) items:
      – P1 (delusions)
      – P2 (conceptual disorganization)
      – P3 (hallucinatory behavior)

- P6 (suspiciousness/persecution)
- P7 (hostility)
- G8 (uncooperativeness)

c. Has a Clinical Global Impression-Severity (CGI-S) score ≤4

* A subject who initiated olanzapine treatment during a recent hospitalization for an acute exacerbation (discharged within 2 weeks prior to screening) is not required to meet these criteria at screening, but is required to meet them at Visit 2.

10. In the opinion of the PI or designee, the subject is not a danger to himself/herself or others and has no elevated suicidal ideation or behavior at the time of screening and the subject answers "No" to items #4 and #5 of the Columbia Suicide Severity Scale (C-SSRS) for ideation and behavior in the 30 days prior to screening and Visit 2.

    - Although a recent exacerbation of symptoms is needed for inclusion in the study and suicidal behavior may qualify as an exacerbation, a subject who still represents a danger to him/herself at the time of screening is not eligible for this study.

11. Has experienced at least 10 drinking days (a day in which the subject had at least 1 standard alcoholic drink) within the 30 days prior to screening (as assessed by Timeline Follow-Back [TLFB] self-report using the TLFB definition for a standard drink)

    - At least 2 of these drinking days must be heavy drinking days, defined as 4 drinks in 1 day for women or 5 drinks in 1 day for men.

12. In accordance with the locally approved informed consent form (ICF), subjects at some sites may be required to have an informant or caregiver who meets some or all of the following criteria:

    a. Informant or caregiver will be in contact with the subject several times per week.
    b. If necessary, the informant or caregiver will accompany the subject to visits.
    c. Informant or caregiver will help ensure maximum subject adherence to study procedures.
    d. The informant or caregiver must be willing and able to provide informed consent by signing the caregiver ICF.

    In Bulgaria, subjects are required to have an informant or caregiver who meets criteria 12a, 12b, 12c and 12d.

13. Agrees to use an acceptable method of contraception for the duration of the study unless surgically sterile or postmenopausal

7.2. Subject Exclusion Criteria

A subject meeting any of the following criteria at screening, unless otherwise specified, will not qualify for participation in this study:

1. Is pregnant (as indicated by self-report or a positive pregnancy test), planning to become pregnant during the study, or breastfeeding at screening or Visit 2

2. Is investigator-site personnel or is employed by Alkermes, PPD (permanent, temporary contract worker, or designee responsible for the conduct of the study), or other third-party agents of this study or is immediate family of investigator-site personnel or an Alkermes, PPD or other third-party agents at screening or Visit 2
   - Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted
3. Had his/her first lifetime psychotic episode less than 1 year before screening or has experienced only a single lifetime psychotic episode
4. Has a known or suspected intolerance, allergy, or hypersensitivity to olanzapine at screening or Visit 2
5. Has current or pending legal charges with the potential for incarceration that could interfere with study scheduling at screening or Visit 2
6. Has had significant blood loss (>500 mL) or has donated blood or blood components within 2 months prior to screening or Visit 2
7. Is currently participating in or has participated in a clinical trial of an investigational product (drug, device, or biologic) within the 12 months prior to screening, has participated in more than 2 clinical trials within the 4 years prior to screening, or has ever participated in a samidorphan clinical trial
8. Has a history or current evidence at screening or Visit 2 of a clinically significant condition or abnormality that in the PI's (or designee's) opinion could interfere with subject safety or complicate treatment, such as (but not limited to) the following:
   - Clinically significant renal insufficiency
   - Human immunodeficiency virus (HIV)
   - Hepatitis B
   - Hepatitis C
   - Severe alcohol withdrawal, as indicated by abrupt cessation of alcohol intake followed by seizures, delirium tremens, or other severe withdrawal symptoms per investigator judgment
   - Narrow-angle glaucoma (diagnosis or risk), or any other disease or condition described as a contraindication in the local Zyprexa® label
9. Has or has had a malignant tumor within the 5 years prior to screening excluding dermal squamous cell carcinoma, basal cell carcinoma, and cervical carcinoma in situ
10. Has clinically significant hypotension or hypertension not stabilized by medical therapy; a clinically significant cardiac arrhythmia, cardiomyopathy, or cardiac conduction defect; or has a clinically significant ECG abnormality at screening or Visit 2, including (but not limited to) the following:
    - For men, QT interval (corrected using the Fridericia formula; QTcF) >450 milliseconds

- For women, QTcF >470 milliseconds

11. Has a history of a myocardial infarction or unstable angina, including a silent myocardial infarction discovered on ECG
12. Has a positive drug screen at screening for opiates (including buprenorphine, norbuprenorphine, codeine, hydrocodone, hydromorphone, methadone, morphine, oxycodone, and oxymorphone) or meets criteria for any of the following medication restrictions:
    - Has taken opioid agonists (eg, codeine, oxycodone, tramadol, or morphine) within 14 days prior to screening or anticipates needing to take opioid medication during the study period (eg, planned surgery)
    - Has taken opioid antagonists within 60 days before screening
    - Has received a long-acting formulation of any antipsychotic medication by intramuscular injection within 2 months prior to screening
        - Long-acting formulations of antipsychotics are also prohibited medications; therefore, administration should not occur or be planned to occur during screening (see Section 8.4.2)
    - Has received clozapine for more than 1 week during the past year
    - Has used naltrexone (including ReVia®/Depade® and Vivitrol®) within 2 months prior to screening; naloxone, acamprosate (Campral®), disulfiram (Antabuse®), or other medication for alcohol dependence within 14 days prior to screening; or has been admitted to an alcohol detoxification program within the past 3 months (including current treatment at screening)
    - Is currently taking an antidepressant unless the subject has been on a stable dose for at least 30 days prior to screening and it is anticipated that the dose will not change during the subject's participation in the study. The medical monitor should be contacted with any questions about the appropriateness of including a subject taking an antidepressant medication. Antipsychotic use for depression is exclusionary.
    - Is currently receiving treatment with a hypoglycemic agent (eg, metformin, insulin, sulfonylurea, etc)
    - Has used an inducer or moderate to strong inhibitor of CYP3A4 (prescription medications, over-the-counter medications, or dietary supplements) within 30 days before screening. See Appendix L for a partial list of prohibited CYP3A4 inducers and moderate to strong inhibitors.
    - Is currently using or anticipates needing to use a prohibited medication or substance anytime during the study period (see Section 8.4.2 and Section 8.4.3)

13. Have any of the following psychiatric conditions per DSM-IV-TR criteria, unless otherwise specified, as assessed by the MINI (if possible). Conditions not assessable by the MINI should be assessed by clinical judgment or the C-VISA (if applicable):
    a. Clinically significant cognitive difficulties including dementia, delirium, or amnestic syndromes, or any other cognitive disorder present within the past 2 years that, in the opinion of the PI or designee, could interfere with participation in the study (ie, could potentially compromise subject safety or adversely affect the evaluation of efficacy)
    b. Substance use disorders other than AUD within the past 1 year as defined by DSM-5 criteria for the following:
        – Hallucinogen-related disorder
        – Inhalant-related disorder
        – Opioid-related disorder
        – Sedative-, hypnotic-, or anxiolytic-related disorder
        – Stimulant-related disorder
    c. Any other psychiatric condition within the past 1 year that could, in the PI's or designee's opinion, interfere with participation in the study, especially Axis I (according to DSM-IV-TR criteria) disorders; established or confirmed diagnosis of schizoaffective disorder or bipolar disorder; or current, untreated, or unstable major depressive disorder
        – Subjects with current but stable depression, depressive symptoms, or major depressive disorder may be eligible provided schizoaffective disorder has been ruled out.
14. Is planning a significant change in caffeine use or is planning to enter a smoking cessation program
15. Has a 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
16. Has unstable thyroid dysfunction within the 6 months prior to screening (eg, hypothyroidism, hyperthyroidism, or thyroiditis that was untreated or was discovered and resulted in treatment within the 6 months prior to screening) or a thyroid stimulating hormone (TSH) level higher than 10% above the upper limit of the normal range at screening.
17. Has a neurologic condition, including (but not limited to) the following:
    - History of seizure disorder or a condition associated with seizures (excluding febrile seizures but including seizures associated with substance use or withdrawal) within the past 6 months
    - History of brain tumor, subdural hematoma, or other clinically significant neurological condition within the 1 year prior to screening
    - Head trauma with a loss of consciousness within 30 days prior to screening

- An active acute or chronic central nervous system infection
- History of stroke or cerebrovascular infarction

18. Has dyslipidemia (total cholesterol >280 mg/dL or triglycerides >500 mg/dL at screening)
19. Has diabetes or meets any of the following criteria at screening:
    - Hemoglobin A1c (HbA_{1c}) ≥6.5%
    - A random plasma glucose ≥200 mg/dL (11.1 mmol/L)
20. Has a laboratory abnormality at screening, including (but not limited to) the following (clinical laboratory assessments may be repeated if the PI feels the test may be in error):
    - Aspartate aminotransferase or alanine aminotransferase value ≥3 times the upper limit of the laboratory normal reference range
    - Absolute neutrophil count $\leq 1.5 \times 10^3$ per μL
    - Platelet count $\leq 75 \times 10^3$ per μL
    - Serum creatinine >2.5 mg/dL
21. Has no living arrangements available at screening or Visit 2, consistently lacks or loses housing (such that maintaining contact with the subject will be difficult), or has plans to leave the study site area during the study period
    - A temporary loss of living arrangements due to loss of caregiver support or other circumstances (eg, recent symptom exacerbation) is allowed if housing is typically available when schizophrenia and AUD symptoms are stable and not exacerbated.

7.3. Subject Randomization Criteria

Subjects must meet all of the following randomization inclusion criteria to be qualified to be randomized in this study:

1. Meets the following PANSS criteria at Visit 6 and Visit 8:
    a. Has a total PANSS score between 50 and 80, inclusive
    b. Has a score of ≤4 for all of the following PANSS Positive (P) Scale or General Psychopathology (G) items:
        – P1 (delusions)
        – P2 (conceptual disorganization)
        – P3 (hallucinatory behavior)
        – P6 (suspiciousness/ persecution)
        – P7 (hostility)
        – G8 (uncooperativeness)
2. Has a CGI-S score ≤4 at Visit 6 and Visit 8

Subjects must not meet any of the following randomization exclusion criteria to be qualified to be randomized in this study:

1. Has a positive drug screen for opiates (including buprenorphine, norbuprenorphine, codeine, hydrocodone, hydromorphone, methadone, morphine, oxycodone, and oxymorphone) at Visit 6

7.4. Subject Withdrawal

A completer is defined as any subject who completes the double-blind treatment period. A subject may be discontinued from the study at any time if the subject, PI, or Alkermes determines that it is not in the best interest of the subject to continue participation. Reasons for discontinuation include the following:

- AE
  - Note: An absolute neutrophil count $\leq 1.0 \times 10^3$ per µL anytime while on olanzapine should be cause for discontinuing a subject.
- Lack of efficacy
- Lost to follow-up
- Protocol violation (non-compliance with study drug or study procedures)
- Withdrawal by subject (eg, withdrawn consent)
- Pregnancy
- Study terminated by sponsor
- Other

If a subject withdraws from the study at any time for any reason, any ongoing AEs will be followed until resolution, until deemed stable by the PI, or until the subject is deemed by the investigator to be lost to follow-up. If, in the opinion of the PI or designee, 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, Alkermes and the PI will agree to an acceptable follow-up schedule.

In the event that a subject chooses to withdraw from the study, the PI should make a reasonable effort to ascertain the reason(s) for withdrawal, while fully respecting the subject's rights. The subject should be encouraged to return to the study center for an early termination (ET) visit, which will match the procedures at Visit 38 (see Section 8), and to complete a subsequent safety follow-up period. The safety follow-up period for subjects who discontinue early should mirror the safety follow-up visits displayed in Table 3. 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 subjects' status or receives more information about a subject's disposition, this information will be documented.

7.5. Replacement of Subjects

Subjects who are discontinued or lost to follow-up after randomization will not be replaced.

7.6. 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] or independent ethics committee [IEC]). As per inclusion/exclusion criteria, subjects in Bulgaria are required to have an informant or caregiver who meets the following criteria:

a. Informant or caregiver will be in contact with the subject several times per week.
b. If necessary, the informant or caregiver will accompany the subject to visits.
c. Informant or caregiver will help ensure maximum subject adherence to study procedures.

In all other cases, an informant or caregiver (hereafter, caregiver) should be identified whenever possible. This person should be in contact with the subject and be able to help with adherence to study procedures (including attending study visits when needed).

7.7. Withdrawal and Replacement of Informant or 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. In Bulgaria, the caregiver must be replaced in order for the subject to continue in the study. If the subject must also withdraw from the study (eg, the subject is in Bulgaria, and no alternative caregiver is available or 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.

8. STUDY DESIGN

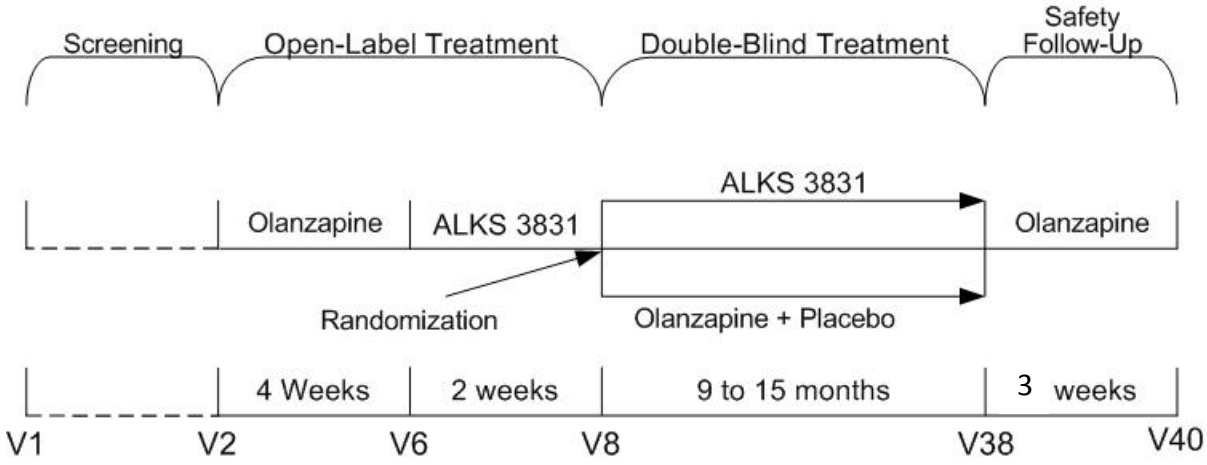
This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy, safety, and tolerability of ALKS 3831 in schizophrenia with AUD. Subjects experiencing disease symptom exacerbation (eg, inpatient hospitalization) within the past 6 months will be considered for screening. Assessment of eligibility is based on DSM-IV-TR diagnosis of schizophrenia and DSM-5 diagnosis of AUD (supported by the subject's medical history, subject self-report, and caregiver or informant report of medical history and/or drinking behavior and confirmed via the MINI and C-VISA). Subjects must also meet certain clinical criteria at screening and prior to randomization. These criteria include (but are not limited to) having a PANSS score between 50 and 90 (inclusive) at screening and Visit 2 and between 50 and 80 (inclusive) at Visit 6 and Visit 8; a PANSS item score of ≤4 on Positive (P) Scale and General Psychopathology (G) items P1, P2, P3, P6, P7, and G8; and a CGI-S score ≤4 at screening, Visit 2, Visit 6, and Visit 8. Subjects who do not meet PANSS or CGI-S criteria at screening but were prescribed olanzapine during a recent hospitalization (discharged within the 2 weeks prior to screening) may be eligible for the study if they meet symptom severity criteria at Visit 2, Visit 6, and Visit 8. Other eligibility criteria assessed between screening and randomization are ECG (Visit 2) and drug screening (Visit 6) criteria. Complete eligibility criteria are given in Section 7.1 and Section 7.2, and randomization criteria are given in Section 7.3.

All study visits will be outpatient visits. The olanzapine dose level throughout the study will be determined individually by the PI according to current clinical practice.

Subjects who are taking an antipsychotic other than olanzapine or no antipsychotic medication at Visit 2 will be tapered off of current medication (if applicable) and titrated onto olanzapine beginning at Visit 2 (see Figure 1) according to a schedule determined by the investigator in accordance with current clinical practice. Subjects who are already taking olanzapine will take their medication as currently prescribed at Visit 2 and for a period of 4 weeks (Visits 3–5) prior to initiation of ALKS 3831 (Visit 6). After Visit 2, all subjects will return to the clinic weekly for dose adjustment, as necessary (permitted at Visits 3 and 4 only), and safety monitoring (Visits 3−5). A cross-taper period of up to 3 weeks is expected when switching to olanzapine and optimizing olanzapine dose.

Unless a change in olanzapine dose is medically indicated, it will remain fixed for the remainder of the study after Visit 5. An increase in dose between Visit 5 and randomization may be a reason for withdrawal from the study, and an increase in dose after randomization is considered an EEDS (see Section 11.1). A decrease in dose is always allowed when medically indicated. If a dose reduction occurs after randomization, any subsequent dose must be greater than the dose at randomization for this increase to be considered an EEDS.

Figure 1: ALK3831-401 Study Schematic



Abbreviation: V = Study Visit; ALKS 3831=olanzapine plus samidorphan

At Visit 6, subjects will begin a 2-week open-label ALKS 3831 (olanzapine [fixed-dose] coadministered with samidorphan [10 mg]) treatment period. Subjects who do not tolerate ALKS 3831 during this open-label period may be discontinued from the study prior to randomization.

At Visit 8, subjects will be randomized in a 1:1 fashion to 1 of 2 treatment groups and will begin a double-blind treatment period. The 2 treatment groups are as follows:

- ALKS 3831: (ie, olanzapine [dose determined by the PI] plus samidorphan [10 mg])
- Olanzapine (dose determined by the PI) plus placebo

During the double-blind treatment period, subjects will complete an outpatient visit every 2 weeks. As indicated in the schedule of assessments (see Table 1, Table 2, and Table 3), at some of these visits, subjects will complete a number of clinical assessments, receive a 15-minute counseling intervention (see Section 8.3.26), and will receive a 2-week study drug supply (including extra medication in case the subject does not return to the study site on the scheduled day; see Section 10). Other visits will be only drug dispensing visits during which subjects will only receive a 2-week study drug supply. No clinical assessments will be completed at drug dispensing visits.

Subjects randomized to double-blind treatment will be followed for a minimum of 9 months and a maximum of 15 months. After the end of the double-blind treatment period, subjects will complete a 3-week safety follow-up period. The study will be stopped when the last subject randomized is scheduled to complete Visit 26. When the last subject is randomized, all subjects currently participating in the study will be informed of the target completion date of the study period. After the last double-blind treatment period visit, subjects will proceed to the safety follow-up period.

The duration of the double-blind period will be between 9 and 15 months, depending on when the study is stopped. The target completion date will be based on the number of subjects randomized with enrollment ending when approximately 270 subjects have been randomized. After the last subject is randomized, the end date of the study will be set to occur approximately 9 months later and subjects will be informed of the target completion date. Final

samidorphan/placebo dosing for these subjects will take place the night before their final visit of the double-blind treatment period. A subject who is prematurely discontinued from the study will proceed as described in Section 7.4.

After a subject completes an ET Visit and/or the safety-follow-up period, follow-up clinical care may be provided for up to 3 months if the PI determines that it is medically indicated. This care may include payments for medication and up to 3 clinic (outpatient) visits.

8.1. Overall Study Design and Plan

ALK3831-401 will be conducted in compliance with the protocol, ICH Good Clinical Practice (GCP), and applicable regulatory requirements.

8.2. Schedule of Visits and Assessments

Psychiatric symptoms, AUD, and psychosocial functioning will be assessed during study visits using the measures described below.

The schedule of visits and assessments for before randomization (Visit 8) is shown in Table 1 and the schedule after randomization is shown in Table 2 and Table 3.

For a missed visit, the site should attempt to contact the subject to reschedule (see Section 7.4).

Table 1: Schedule of Visits and Assessments for Screening and Open-label Treatment Periods (Visit 1-Visit 7)

	Screening	Open-label Treatment					
		Olanzapine				ALKS 3831	
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Study Day (Visit window is ±2 days)	**-59 to -29**	**-28**	**-21**	**-14**	**-7**	**1**	**8**
Informed Consent[1]	X						
Qualification/ Diagnostic Assessments							
Eligibility Criteria Review	X	X[2]				X[2]	
Demographics and Medical/ Psychiatric History	X						
Pregnancy Test	X					X	
Drug Screening	X					X	
Physical Exam[3]	X	X				X	
Clinical Validation Inventory for Study Admission (C-VISA™)	X						
Mini International Neuropsychiatric Interview (MINI)	X						
Readiness to Change Questionnaire	X						
Qualification/ Efficacy Measures							
Positive and Negative Syndrome Scale (PANSS)[4]	X	X				X	
Clinical Global Impression- Severity/Improvement (CGI-S and CGI-I)	X[5]	X[5]				X	
Timeline Follow-Back (TLFB)[6]	X	X				X	
Cigarette Use Question		X				X	
Visual Analog Scale (VAS) Desire for Alcohol	X		X		X		X
Personal and Social Performance Scale (PSP)	X	X					
Abnormal Involuntary Movement Scale (AIMS)		X		X		X	
Simpson-Angus Scale (SAS)		X		X		X	
Barnes Akathisia Rating Scale (BARS)		X		X		X	
Qualification/ Safety Assessments							
Adverse Event (AE) monitoring	X	X	X	X	X	X	X
Columbia Suicide Severity Rating Scale (C-SSRS)[7]	X	X	X	X	X	X	X

Table 1: Schedule of Visits and Assessments for Screening and Open-label Treatment Periods (Visit 1-Visit 7) (Continued)

	Screening	Open-label Treatment					
		Olanzapine				ALKS 3831	
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Study Day (Visit window is ±2 days)	**-59 to -29**	**-28**	**-21**	**-14**	**-7**	**1**	**8**
Qualification/ Safety Assessments (continued)							
Concomitant Medications	X	X	X	X	X	X	X
Vital Signs (including orthostatic measures)[8]	X	X	X	X	X	X	X
Clinical labs[9]	X	X				X	
Blood Samples for PK	X	X		X		X	
Body Weight, Waist Circumference, and Height[10]	X	X	X	X	X	X	X
Electrocardiogram (ECG)	X	X				X	
Other Study Procedures							
Open-label Olanzapine Dispensing[11]		X	X	X	X	X	X
Open-label Samidorphan Dispensing[11]						X	X
Dispense Emergency Treatment Card						X	
Confirm Subject's Possession of Emergency Treatment Card							X

[1] Subject and informant/caregiver informed consent (when the latter is required)
[2] The criteria assessed at these visits are limited to PANSS, CGI-S, and drug screen; see Section 7.3.
[3] Full physical examination at screening; brief physical examination at all other scheduled time points
[4] At each visit, PANSS should be administered before any other clinical assessment
[5] CGI-S only at this visit, as administered using the Structured Interview Guide for Global Impressions
[6] The subject should be assisted by the same person each time he or she is asked to complete the TLFB and this person should not conduct the subject's supportive counseling sessions.
[7] At screening, the "Baseline/Screening" version will be administered for assessing lifetime ideation and behavior, as well as ideation and behavior in the past 30 days. At all other visits, the "Since Last Visit" version will be administered.
[8] Orthostatic measures should not be completed at screening.
[9] Thyroid stimulating hormone and carbohydrate deficient transferrin are assessed at screening only; Hemoglobin A1c (HbA_{1c}) is assessed at screening and Visit 2 only.
[10] Height at screening only
[11] The recommended time of dosing for subjects is in the evening or at bedtime.

Table 2: Schedule of Visits and Assessments for Double-blind Treatment Period (Visit 8-Visit 26)

	Double-blind Placebo-controlled Treatment																		
Study Visit	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**[1]
Study Week	**3**	**5**	**7**	**9**	**11**	**13**	**15**	**17**	**19**	**21**	**23**	**25**	**27**	**29**	**31**	**33**	**35**	**37**	**39**
Qualification/Diagnostic Assessments																			
Eligibility Criteria Review[2]	X																		
Qualification/Efficacy Measures																			
PANSS[3]	X	X	X		X		X		X		X		X		X		X		X
CGI-S and CGI-I	X		X		X		X		X		X		X		X		X		X
TLFB[4]	X	X	X		X		X		X		X		X		X		X		X
Cigarette Use Question	X	X	X				X						X						X
VAS Desire for Alcohol	X		X		X		X		X		X		X		X		X		X
PSP	X						X						X						X
Exacerbation of Disease Criteria Review		X	X		X		X		X		X		X		X		X		X
AIMS	X		X		X		X		X		X		X		X		X		X
SAS	X		X		X		X		X		X		X		X		X		X
BARS	X		X		X		X		X		X		X		X		X		X
Safety Assessments																			
AE Monitoring	X	X	X		X		X		X		X		X		X		X		X
C-SSRS[5]	X	X	X		X		X		X		X		X		X		X		X
Concomitant Medications	X	X	X		X		X		X		X		X		X		X		X
Medical History[6]	X	X	X		X		X		X		X		X		X		X		X
Body Weight and Waist Circumference	X	X	X		X		X		X		X		X		X		X		X

Table 2: Schedule of Visits and Assessments for Double-blind Treatment Period (Visit 8-Visit 26) (Continued)

	Double-blind Placebo-controlled Treatment																		
Study Visit	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**
Study Week	**3**	**5**	**7**	**9**	**11**	**13**	**15**	**17**	**19**	**21**	**23**	**25**	**27**	**29**	**31**	**33**	**35**	**37**	**39**
Brief Physical Exam	X						X						X						X
Vital Signs (including orthostatic measures)	X	X	X		X		X		X		X		X		X		X		X
Clinical labs[7]	X		X				X						X						X
Electrocardiogram	X						X						X						X
Other Study Procedures																			
Randomization	X																		
Supportive Counseling	X	X	X		X		X		X		X		X		X		X		X
Confirm Emergency Treatment Card	X	X	X		X		X		X		X		X		X		X		X
Blood Samples for PK	X						X						X						X
Urine Drug Panel	X						X						X						X
OL OLZ Dispensing	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DB S/P Dispensing	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE=Adverse Event; AIMS=Abnormal Involuntary Movement Scale; BARS=Barnes Akathisia Rating Scale; CDT=Carbohydrate deficient transferrin; CGI-I=Clinical Global Impression – Improvement; CGI-S=Clinical Global Impression - Severity; C-SSRS=Columbia Suicide Severity Rating Scale; DB=double-blind; HbA_{1c}=Hemoglobin A1c; OL=open-label; OLZ=olanzapine; PANSS=Positive and Negative Syndrome Scale; PK=pharmacokinetics; PSP=Personal and Social Performance Scale; S/P=samidorphan/placebo; SAS=Simpson-Angus Scale; TLFB=Timeline Follow-Back; VAS=Visual Analog Scale

Shaded columns represent visits where only drug dispensing should occur.

[1] This is the end of the 9-month double-blind treatment period. Subjects who are only scheduled to complete 9 months of double-blind treatment should complete safety follow-up visits for Visit 39 and Visit 40 as per Table 3.

[2] PANSS and CGI-S criteria only; see Section 7.3

[3] At each visit, PANSS should be administered before any other clinical assessment.

[4] The subject should be assisted by the same person each time he or she is asked to complete the TLFB and this person should not conduct the subject's supportive counseling sessions.

[5] "Since Last Visit" version using the last administration of the C-SSRS as the "last visit"
[6] Change since last medical history assessment
[7] Except TSH; CDT should be collected at Visit 8 and 26. HbA_{1c} should not be collected at Visit 10.

Table 3: Schedule of Visits and Assessments for Continuation of Double-blind Treatment and Safety Follow-up Period (Visit 27-Visit 40)

	Double-blind Placebo-controlled Treatment												Safety Follow-up	
Study Visit	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38/ ET**	**39**	**40**
Study Week	**41**	**43**	**45**	**47**	**49**	**51**	**53**	**55**	**57**	**59**	**61**	**63**	**41/ 65**	**42/ 66**
Efficacy Measures														
PANSS[1]		X		X		X		X		X		X		X
CGI-S and CGI-I		X		X		X		X		X		X		X
TLFB[2]		X		X		X		X		X		X		X
Cigarette Use Question						X						X		
VAS Desire for Alcohol		X		X		X		X		X		X		X
PSP		X						X				X		X
Exacerbation of Disease Criteria Review		X		X		X		X		X		X		
AIMS		X		X		X		X		X		X		X
SAS		X		X		X		X		X		X		X
BARS		X		X		X		X		X		X		X
Safety Assessments														
AE Monitoring		X		X		X		X		X		X	X	X
C-SSRS[3]		X		X		X		X		X		X	X	X
Concomitant Medications		X		X		X		X		X		X	X	X
Medical History[4]		X		X		X		X		X		X	X	X
Body Weight and Waist Circumference		X		X		X		X		X		X	X	X

Table 3: Schedule of Visits and Assessments for Continuation of Double-blind Treatment and Safety Follow-up Period (Visit 27-Visit 40) (Continued)

	Double-blind Placebo-controlled Treatment												Safety Follow-up	
Study Visit	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38/ ET**	**39**	**40**
Study Week	**41**	**43**	**45**	**47**	**49**	**51**	**53**	**55**	**57**	**59**	**61**	**63**	**41/ 65**	**42/ 66**
Brief Physical Exam		X						X						X
Vital Signs (including orthostatic measures)		X		X		X		X		X		X	X	X
Clinical labs[5]		X						X				X		X
Electrocardiogram		X						X				X		X
Other Procedures														
Supportive Counseling		X		X		X		X		X		X		
Confirm Emergency Treatment Card		X		X		X		X		X		X	X	
Blood Samples for PK		X						X				X		X
Urine Drug Panel		X						X				X		
OL OLZ Dispensing	X	X	X	X	X	X	X	X	X	X	X	X	X	
DB S/P Dispensing	X	X	X	X	X	X	X	X	X	X	X			
Collect Emergency Treatment Card														X

Abbreviations: AE=Adverse Event; AIMS=Abnormal Involuntary Movement Scale; BARS=Barnes Akathisia Rating Scale; CDT=Carbohydrate deficient transferrin; CGI-I=Clinical Global Impression–Improvement; CGI-S=Clinical Global Impression-Severity; C-SSRS=Columbia Suicide Severity Rating Scale; DB=double-blind; ET=early termination; HbA_{1c}=Hemoglobin A1c; OL=open-label; OLZ=olanzapine; PANSS=Positive and Negative Syndrome Scale; PK=pharmacokinetics; PSP=Personal and Social Performance Scale; S/P=samidorphan/placebo; SAS=Simpson-Angus Scale; TLFB=Timeline Follow-Back; VAS=Visual Analog Scale

Shaded columns represent visits where only drug dispensing should occur.

[1] At each visit, PANSS should be administered before any other clinical assessment

[2] The subject should be assisted by the same person each time he or she is asked to complete the TLFB and this person should not conduct the subject's supportive counseling sessions.

[3] "Since Last Visit" version using the last administration of the C-SSRS as the "last visit"

[4] Change since last medical history assessment
[5] Except TSH; CDT and HbA_{1c} are assessed at Visit 38/ET only.

8.3. Study Procedures Descriptions

All study procedures should be administered as consistently as possible. Specifically, the subject should be assisted by the same person (whenever possible) each time he or she is asked to complete the TLFB and this person should not conduct the subject's supportive counseling sessions. The TLFB and supportive counseling sessions should not be conducted by the same person.

8.3.1. Informed Consent

The nature of the study and its risks and benefits will be explained to the subject and caregiver (in Bulgaria, and other locations where required) by the investigator or designated study personnel as outlined in Section 17.3. When a caregiver is required (eg, in Bulgaria), the caregiver ICF will also be completed. 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 Criteria Review

Eligibility for participation in the study will be confirmed as specified in Table 1 and Table 2. Complete inclusion and exclusion criteria are provided in Section 7.1 and Section 7.2. Additional criteria that must be met in order for a subject to be randomized are provided in Section 7.3.

8.3.3. Demographics and Medical History

A subject's demographic data and medical history will be reviewed and documented at the time points specified in the Table 1, Table 2, and Table 3.

At later visits, each subject's medical and psychiatric history since the prior visit will be reviewed and any identified significant change will be recorded in the source documents and eCRF, as appropriate.

8.3.4. Pregnancy Testing

A serum or urine 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 7.4, a positive pregnancy test result at any time will necessitate the subject's immediate withdrawal from the study. Additional follow-up may be required as detailed in Section 8.4.1.

8.3.5. Drug Testing

All subjects will undergo urine drug testing via a dipstick for a panel of substances at the time points specified in Table 1, Table 2, and Table 3. Results will be analyzed by the local laboratory. Urine drug screening may be repeated based on PI judgment. Urine drug screening may also be conducted at any time during the study, should the investigator feel it is warranted.

The drug testing panel will include benzodiazepines, opiates (including buprenorphine, norbuprenorphine, codeine, hydrocodone, hydromorphone, methadone, morphine, oxycodone, and oxymorphone), amphetamine/methamphetamine, tetrahydrocannabinol, phencyclidine and cocaine (and its metabolite).

A subject is not eligible for this trial if he/she has a positive test for opiates at screening or Visit 6 (see Section 7.2 and 7.3). Drug testing that is not being done to determine eligibility will be used to collect data on substance use across the trial in support of study objectives.

8.3.6. Physical Examination

A physical examination will be performed at the time points specified in Table 1, Table 2, and Table 3. A full examination will occur at screening only. After screening, a brief physical exam will be conducted.

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

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

8.3.8. Mini International Neuropsychiatric Interview

The MINI is a short, clinician-administered, structured diagnostic interview, with an administration time of approximately 15 minutes [Sheehan, 1998]. The MINI has been validated against the much longer Structured Clinical Interview for DSM Diagnoses (SCID). A sample of the MINI can be found in Appendix A. The MINI will be administered by qualified staff.

8.3.9. Readiness to Change Questionnaire

The Readiness to Change Questionnaire (Appendix B) [Rollnick, 1992] is a self-report measure that will be administered at screening.

The Readiness to Change Questionnaire is included as an exploratory measure that may be useful as a potential predictor of efficacy or stratification factor for assessing efficacy in sub-groups.

8.3.10. Positive and Negative Syndrome Scale

The PI or designee will complete the PANSS [Kay, 1987] according to the schedule in Table 1, Table 2, and Table 3 using the Structured Clinical Interview for the PANSS (SCI-PANSS; [Opler, 1999]). A sample SCI-PANSS is given in Appendix C.

8.3.11. Clinical Global Impression

The PI or designee will complete the CGI-S and Clinical Global Impression-Improvement (CGI-I) (Appendix D) scales at the time points specified in Table 1, Table 2, and Table 3. The Structured Interview Guide for Global Impressions (SIGGI; see Appendix E) will be used for administration of CGI-S. The CGI-S measures mental illness severity and the CGI-I measures

total improvement compared to the first assessment [Guy 2000]. For illness severity, clinicians are asked to rate subjects relative to their past experience with patients in the same population as the individual being rated.

8.3.12. Timeline Follow-Back

Alcohol use will be recorded using the TLFB method [Sobell and Sobell 1992] at the time points specified in Table 1, Table 2, and Table 3. At the screening visit, alcohol use data will be collected for the prior 30-day period as per TLFB instructions for administration. At all other visits, data will be collected for the period between the last completed TLFB assessment and the current visit, not to exceed 30 days. The subject should be assisted by the same person each time he or she is asked to complete the TLFB and this person should not conduct the subject's supportive counseling sessions.

8.3.13. Cigarette Use

Data on cigarette use will be collected by using the question, "How many packs of cigarettes did you smoke over the past 7 days?", at the time points specified in Table 1, Table 2, and Table 3.

8.3.14. Visual Analog Scale for Perception of Desire for Alcohol

A pen and paper 1-item VAS will be presented at the timepoints specified in Table 1, Table 2, and Table 3. The VAS is a horizontal line with a unipolar scale, anchored on the right side with "No desire at all for alcohol" (marked with a "0") and on the left side with "Strongest imaginable desire for alcohol" (marked with a "100" with a line connecting the two ends; see Appendix F). Subjects will mark the appropriate point to indicate where their "desire for alcohol" falls on this line.

8.3.15. Exacerbation of Disease Criteria Review

The criteria for an EEDS (see Section 11.1) should be reviewed by the PI or designee as indicated in Table 2 and Table 3.

8.3.16. Personal and Social Performance Scale

The PI or designee will complete the 5-point Personal and Social Performance (PSP) scale (Appendix G) [Morosini, 2000] according to the schedule in Table 1, Table 2, and Table 3.

8.3.17. Abnormal Movement Rating Scales

The PI or designee will complete the following abnormal movement rating scales: The Abnormal Involuntary Movement Scale (AIMS; see Appendix H) [Guy 1976], Barnes Akathisia Rating Scale (BARS; see Appendix I) [Barnes 1989], and Simpson-Angus Scale (SAS; see Appendix J) [Simpson and Angus 1970] at the timepoints specified in Table 1, Table 2, and Table 3.

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

8.3.18. Adverse Event Monitoring

Adverse events will be monitored continuously from the time a subject signs the informed consent document until the completion of the final study visit (see Table 1, Table 2, and Table 3). Adverse events and serious adverse events (SAEs) are defined in Section 13.1 and 13.2, respectively. Section 13.4 provides guidance on the monitoring and recording requirements for AEs. Section 13.5 provides guidance on the reporting requirements for SAEs.

8.3.19. Columbia Suicide Severity Rating Scale

The PI or designee will complete the C-SSRS (Appendix K) according to the schedule in Table 1, Table 2, and Table 3. At screening, the "Baseline/Screening" version will be administered [Posner, 2009a], and at all other visits, the "Since Last Visit" version will be administered [Posner, 2009b]. For "Since Last Visit" versions, subjects should be asked to report on ideation and behavior since the last scheduled C-SSRS assessment. The C-SSRS should be administered by a clinician trained to assess and manage suicidal ideation and behavior.

8.3.20. Concomitant Medication Review

At the time points specified in Table 1, Table 2, and Table 3, prospective subjects will be asked about the medications they have taken since the last visit and are currently taking, including prescription and nonprescription medications, vitamins, and supplements.

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

8.3.21. Vital Signs

Vital signs (ie, blood pressure, pulse, respiratory rate, and oral body temperature) will be assessed at the time points specified in Table 1, Table 2, and Table 3.

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

Orthostatic blood pressure, pulse, and respiration rate will be collected each time vital signs are measured (except at screening) in the following manner:

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

Vital signs may be collected at any time during a visit where it is scheduled.

8.3.22. Hematology, Biochemistry, and Urinalysis

Blood and urine samples for laboratory assessments will be collected at the time points specified in Table 1, Table 2, and Table 3. Specific hematology, biochemistry, and urinalysis assessments are listed in Table 4. Samples will be collected in accordance with the site's usual procedures

and analyzed by a central laboratory. Follow-up samples may be obtained for repeat testing as clinically indicated.

An absolute neutrophil count $\leq 1.0 \times 10^3$ per μL anytime while on olanzapine should be cause for discontinuing a subject. A second test can be performed within 24 hours of availability of the laboratory result to confirm the finding if the investigator feels the result may be in error. Otherwise, the subject should be discontinued.

For all timepoints (except screening) where samples will be collected, fasting assessments (fasting for at least 10 hours prior to collecting samples) should be attempted as per standard of care [Lilly USA 2013]. However, fasting may present challenges, including an increased frequency of missed visits and re-scheduling, that could negatively impact the subject's treatment. Therefore, failure to fast should not be considered a protocol deviation.

Whether or not a subject fasts and the number of hours since the subject's last meal will be entered onto the appropriate eCRF.

TSH will only be measured at screening.

Table 4: Clinical Laboratory Assessments

Hematology	Biochemistry	Urinalysis
• Hematocrit • Hemoglobin • Platelets • Red blood cell count • Total and differential (absolute) white blood cell count • Glycosylated hemoglobin (HbA_{1c})[1]	• Alanine transferase (ALT) • Albumin • Albumin/globulin ratio • Alkaline phosphatase (ALK-P) • Aspartate transferase (AST) • Bicarbonate • Blood urea nitrogen (BUN) • Carbohydrate deficient transferrin (CDT)[2] • Creatine phosphokinase (CPK) • Creatinine • Gamma-glutamyl transferase (GGT) • Glucose[3] • Insulin • Lactic dehydrogenase (LDH) • Potassium • Prolactin • Sodium • Thyroid stimulating hormone (TSH)[4] • Total bilirubin • Total, HDL and LDL cholesterol • Total protein • Triglyceride	• Color • pH • Specific gravity • Ketones • Protein • Glucose • Bilirubin • Nitrite • Urobilinogen • Occult blood • Cotinine • Microscopic examination of sediment, *only if urinalysis dipstick results are abnormal*

[1] Assessed at Visit 2, 8, 14, 20, 26, and 38
[2] Assessed at screening, Visit 8, 26, and 38
[3] Fasting assessments should be attempted at all visits where laboratory assessments are scheduled (except screening) with the time of the last meal documented on the appropriate eCRF.
[4] Assessed at screening only

8.3.23. Pharmacokinetic Assessments

Samidorphan, RDC-9986 (primary metabolite of samidorphan), and olanzapine concentrations will be determined from plasma samples collected according to Table 1, Table 2, and Table 3. The time of last study drug administration (when applicable) and the associated pharmacokinetic (PK) blood draw must both be recorded in a subject's source documents. Samples for PK

analysis will be stored at -20°C ± 10°C. These PK data may be included in a subsequent population PK analysis or other post-hoc analyses conducted outside of this study.

8.3.24. Body Height, Body Weight, and Waist Circumference

Body weight (in kilograms) will be measured 3 times whenever weight is being assessed. The median weight will be entered into an electronic data capture system. The median is the middle number when the 3 measures are put in numerical order (eg, in the sequence 1, 2, 3; the median number is 2). Subjects should be asked to void immediately prior to the body weight measurement. Subjects should be weighed on the same scale for each measurement under the same conditions. Conditions should be as consistent across visits as possible. Subjects should remove all personal items, such as watches and jewelry, prior to body weight measurement. Subjects should be weighed in hospital gowns with a consistent amount of undergarments for each measurement.

At each time that body weight is measured, waist circumference (in cm) will also be measured. These measurements will be made where indicated in Table 1, Table 2, and Table 3.

Height (in cm) will be collected at screening only (see Table 1).

8.3.25. 12-Lead Electrocardiogram

A 12-lead ECG will be recorded as specified in Table 1, Table 2, and Table 3. All scheduled ECGs must be performed after the subject has rested quietly for at least 5 minutes in the supine position.

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

ECGs will also be evaluated by a central reader.

8.3.26. Supportive Counseling

Supportive counseling will be provided as per investigator's judgment as specified in Table 2, and Table 3. Counseling will focus on the following:

1. Disease education
2. Encouragement of treatment adherence
3. Crisis intervention

The person who conducts supportive counseling sessions should not assist the subject with TLFB.

8.3.27. Drug Dispensation and Reconciliation

Section 9 provides information related to drug dispensing procedures. Study drug will be dispensed at the time points specified in Table 1, Table 2, and Table 3. The study drug use and storage information will be explained to and 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, but others have not. Sites will be given handling, storage, and reconciliation instructions applicable to their country to ensure compliance with local regulations for controlled substances.

Olanzapine will be dispensed by the site.

Samidorphan/placebo and olanzapine will be provided in separate containers (eg, blister cards and bottles). Subjects will be instructed to keep all unused tablets in their original containers and not combine pills into a single container. Subjects will also be instructed to return the original containers and any remaining study drug(s) (both olanzapine and samidorphan/placebo, as applicable) at each visit following dispensation. Study drug should not be re-dispensed to the subject after the containers have been returned. Study drug accountability will be documented as the number of tablets dispensed, dosed, lost/missing, or remaining. If applicable, the site will discuss noncompliance with the subject.

8.3.28. Emergency Treatment Card

An emergency treatment card will be distributed to each subject and collected from each subject at the timepoints specified in Table 1 and Table 3. The card will indicate that the subject may be receiving an opioid antagonist and/or olanzapine and will include the PI's contact information, a suggested pain management plan, and information regarding opiate blockade. Subjects will be instructed to keep the emergency treatment card with them at all times. Study personnel will confirm that the subjects have the card in their possession at each study visit indicated on Table 1, Table 2, and Table 3.

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. At a minimum subjects must agree to use one of the following. Additional restrictions, if required, will be clarified in the locally-approved ICF or are clarified below.

- Double-barrier protection (eg, a condom with spermicide or a diaphragm with spermicide)
- Intrauterine device
- Oral contraceptive pills and other hormonal methods (eg, a vaginal ring, contraceptive patch, contraceptive implant); oral contraceptives must have been initiated at least 30 days prior to screening

Subjects must agree to use one of the following acceptable methods of contraception for the duration of the study:

- Condom (barrier method) plus
  - Intrauterine device

    or

- Hormonal contraceptive (such as birth control pills or patches, a vaginal ring, or a contraceptive implant); oral contraceptives must have been initiated at least 30 days prior to screening

Subjects who are abstinent are eligible to be in this study, 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 any female subject becomes or is found to be pregnant while participating in the study, she will be discontinued from study drug immediately. 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 a SAE the investigator should follow the procedure of reporting SAEs (see Section 13.2).

8.4.2. Prohibited and Restricted Medications

The following medications are prohibited or restricted during the study period (unless otherwise noted) except when subjects are tapering off of the medication as described in Section 8. Trade names may be different outside of the US:

- Monoamine oxidase inhibitors (eg, phenelzine, tranylcypromine, selegiline, or moclobemide) are prohibited.
- Mood stabilizers (eg, lamotrigine, lithium, valproic acid, carbarmazepine) are prohibited (except prior to Visit 8 when medically indicated)
- Long-acting formulations of any antipsychotic and any form of clozapine are prohibited during the screening and study period.
- Benzodiazepines (except prior to Visit 8 when medically indicated) are prohibited
- Antidepressants are prohibited if it is anticipated that the dose will change during the subject's participation in the study. The medical monitor should be contacted with any questions about the appropriateness of including a subject taking an antidepressant medication. Antipsychotic use for depression is prohibited

- Varenicline (Chantix®) is prohibited. Other nicotine replacement therapy (eg, nicotine replacement patch or oral nicotine gum) is permitted if the subject regularly used the therapy prior to screening.
- Alcohol-treatment-related medications including, but not limited to, the following: naltrexone (ReVia®/Depade®), Vivitrol®, naloxone, acamprosate (Campral®) and disulfiram (Antabuse®) are prohibited throughout the study period.
- In general, the use of psychotropic medications other than study drug is discouraged during the study period, with the exception of the following:
  - Beta-blockers (eg, propranolol or pindolol), antihistamines, and anticholinergics may be used for treatment-emergent akathisia.
  - Anticholinergics may be used for extrapyramidal symptoms.
  - Non-benzodiazepine medication may be used to treat insomnia.
- Topiramate (Topamax®) and combination products containing topiramate are prohibited.
- Opioid agonists should be avoided (see Section 8.4.4 for details on pain management).
- Opioid antagonists are prohibited through the follow-up period.
- Inducers or moderate to strong inhibitors of CYP3A4 (prescription medications, over-the-counter medications, or dietary supplements) are prohibited through the follow-up period. See Appendix L for a partial list of prohibited CYP3A4 inducers and moderate to strong inhibitors.
- Medications that are contraindicated with olanzapine use or exhibit drug-interaction potential with olanzapine will be defined and prohibited at the discretion of the PI.

8.4.3. Other Prohibited Substances

Prohibited substances during the study period include amphetamines (including methamphetamine), cocaine, barbiturates, methadone, opiates (including morphine, oxycodone, methadone, and buprenorphine), and phencyclidine. Screening procedures for these substances are described in Section 8.3.5. Except as noted in Section 8.3.5, the PI will exercise his/her medical judgment as to whether or not subjects using any prohibited substances should be deemed ineligible or withdrawn.

Tobacco and/or caffeine use is allowed if the daily amount used is anticipated to remain relatively stable throughout the study period.

8.4.4. Pain Management

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

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

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

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

8.4.5. Rescue Medication

The PI is responsible for all trial-related medical decisions for subjects enrolled at his/her site and can always administer rescue medication without consulting the medical monitor. Administering rescue medication is considered an EEDS for this trial (see Section 11.1). The PI or designee should document the reason(s) for the rescue medication and the designated treatment(s). Examples of rescue medication include (but are not limited to):

- An increase in olanzapine dose
- Use of a prohibited medication, such as an antipsychotic or other psychotropic medication (see Section 8.4.2), for psychiatric treatment

8.5. Ad Hoc Study Visits

When a subject meets a criterion for an EEDS that requires a second assessment (see Section 11.1), an ad hoc study visit should be scheduled for 3 days after the first assessment when it is possible and does not compromise subject safety. Otherwise, the ad hoc visit should be scheduled within 7 days of the first assessment.

If, despite all reasonable efforts by the site, a second assessment cannot be completed within 7 days, the event will be considered an EEDS.

Assessments completed at the ad hoc study visit should include AE monitoring, concomitant medication review, C-SSRS (“Since Last Visit”), CGI-S, CGI-I, PANSS, and EEDS criteria review. Any assessment that needs to be confirmed from the first assessment should be completed before any other assessments.

9. TREATMENT OF SUBJECTS

9.1. Study Drug Dose and Administration

Study drugs include samidorphan and matching placebo tablets, and olanzapine tablets, all for oral administration.

For all subjects, open-label samidorphan 10 mg will be taken once daily for 2 weeks prior to randomization. For subjects in the double-blind treatment period, samidorphan 10 mg (or placebo) will be taken once daily for up to 15 months.

For all subjects, the dose of olanzapine will be taken once daily (to be taken at the same time as samidorphan/placebo) at an individualized dose level. Olanzapine initiation, including transition from another antipsychotic (as applicable), is a highly individualized process. Formalizing the potential clinical scenarios may pose undue burden and/or risk to subjects. Clinical judgment is essential, and for this reason, the details of this process are left to the discretion of the treating physician, who will follow current clinical practice.

All subjects will be administered olanzapine for 11 to 17 months as part of this clinical trial.

ALKS 3831 should be taken as close to bedtime as possible. Subjects should not drive or operate heavy machinery until they know how ALKS 3831 will affect them.

After Visit 5, the dose level of olanzapine will be fixed, and an increase in dose level above the dose set at Visit 5 prior to randomization may cause the subject to be discontinued. The olanzapine dose level may be decreased at any time if the PI considers it medically beneficial to the subject, such as when a subject has stable psychiatric symptoms with side effects that may be reduced if the olanzapine dose level is decreased. If the PI decreases the dose level after randomization, only an increase above the dose level at randomization will be considered an EEDS.

At study drug dispensation visits, all subjects will receive blister cards containing samidorphan or placebo for self-administration; subjects will also receive olanzapine in separate packaging. Subjects will be instructed to take 1 tablet per day from the blister card in addition to their olanzapine tablet(s) once daily in the evening or at bedtime. The subject will take the final samidorphan/placebo dose the night before the final visit of the double-blind treatment period. Olanzapine dosing will continue uninterrupted through the end of the study. Any subject who prematurely discontinues from the study will be asked to return to the clinic for an ET visit and 2 safety follow-up visits.

9.2. Treatment Adherence

Subjects who, in the opinion of the PI or designee, have demonstrated treatment adherence during the open-label olanzapine and ALKS 3831 treatment period will be randomized to double-blind treatment (samidorphan or placebo). Study personnel may be able to identify non-adherence during study visits (eg, based on responses during clinical assessments) and may also ask the subject or caregiver (if applicable) directly about adherence. Additional measures of adherence may be used at the sponsor's and PI's discretion. During the double-blind treatment

period, supportive counseling sessions will be used to encourage treatment adherence. Study staff will address non-adherence with the subject as needed.

9.3. Randomization to Treatment

At Visit 8, subjects will be randomized to receive one of the following regimens in a 1:1 ratio:

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

Randomization will be performed centrally through an Interactive Web Response System (IWRS). A unique randomization number will be assigned by an 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 a third-party biostatistician who is not otherwise involved in this study.

9.4. Blinding

All Alkermes staff, clinical staff, subjects, and caregivers will remain blinded to treatment assignment until the final database lock. All PPD staff will remain blinded except when their study function requires unblinding (eg, drug supply management, IWRS operation, etc). These unblinded staff will follow standard operating procedures to ensure that they do not bias the study.

The PI is responsible for all trial-related medical decisions. Emergency unblinding may be done without contacting a medical monitor. Any premature unblinding should be promptly documented and explained to the medical monitor within 24 hours following disclosure of study drug assignment.

If the PI is unsure whether unblinding is needed, he or she may contact the PPD or Alkermes medical monitor before the blind is broken.

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

Commercially available olanzapine will be supplied by the investigative site.

Samidorphan will be provided by Alkermes in 10 mg tablets.

Placebo consists of tablets, identical in size and appearance to the samidorphan tablets.

Subjects will take 1 tablet per day orally (either samidorphan or placebo) at the same time as their olanzapine.

10.2. Packaging and Labeling

Samidorphan and placebo will be packaged in blister packs. Blister cards will be provided in biweekly configurations. The biweekly blister card will contain 16 tablets, which provides 2 weeks of dosing with sufficient overage to allow for 2 additional daily doses.

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

10.3. Storage

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

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 8.3.27 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. Alkermes may arrange for destruction with a third party agent operating in accordance with GCP.

11. ASSESSMENT OF EFFICACY

11.1. Primary Efficacy Measure

The primary efficacy measure is an EEDS, defined as any of the following occurring during the double-blind period and is related to worsening of disease symptoms, as confirmed by the IAC:

1. Subject requires hospitalization due to worsening of disease symptoms including a psychiatric hospitalization or a hospitalization due to or for acute treatment of alcohol intoxication or withdrawal
2. Subject has a ≥25% or ≥15-point increase from randomization in PANSS total score that is confirmed at a second, ad hoc visit shortly after the first assessment (see Section 8.5)
3. Subject has a PANSS item score of P1, P2, P3, P6, P7, or G8 that meets one of the following criteria:
   - For subjects with a score ≤3 at randomization, a score ≥5 that is confirmed at a second, ad hoc visit shortly after the first assessment (see Section 8.5)
   - For subjects with a score of 4 at randomization, a score ≥6 that is confirmed at a second, ad hoc visit shortly after the first assessment (see Section 8.5)
4. Subject commits deliberate self-injury, engages in aggressive behavior, or displays signs of suicidal or homicidal ideation that is clinically significant as judged by the PI
5. Subject requires initiation of rescue medication (see Section 8.4.5), including an increase in prescribed olanzapine dose level, due to worsening of disease symptoms
   - For this study, the increase in olanzapine dose must be above the randomization dose level even if the dose level was previously decreased at some point after randomization.
6. Subject requires an emergency room visit due to worsening of disease symptoms
7. Subject withdraws or PI discontinues the subject from the study for one of the following reasons:
   a. Lack of efficacy
   b. Lost to follow-up
   c. Withdrawal by subject
8. Subject is involved in an incident leading to arrest or incarceration during the study period that is related to the subject's underlying disease

For criterion requiring a consecutive assessment, the second assessment should be scheduled within 3-7 days of the first occurrence and conducted as per Section 8.5. All EEDS cases will be reviewed by the IAC in a blinded manner. Only events confirmed by the IAC will be used for efficacy analyses. Further details on the functioning of the IAC will be included in the IAC charter.

If no withdrawal criteria have been met, subjects experiencing an EEDS (except event #7) may continue in the study at the discretion of the PI.

11.2. Other Efficacy Measures

Other efficacy measures include the following:

- Psychosocial events indicative of exacerbation of disease include any of the EEDS criteria listed above in Section 11.1 and/or any of the following additional criteria*:
  1. Subject has a change in locus of care due to a worsening in disease symptoms
  2. Subject loses employment because of a worsening in disease symptoms
  3. Subject has a change in living situation because of a worsening in symptoms

  *To constitute a psychosocial event, any of the EEDS criteria must be confirmed (in a blinded manner) by the IAC to be related to worsening of disease symptoms.
- PANSS
- CGI-S
- CGI-I
- TLFB
- VAS Perception of Desire for Alcohol

11.3. Exploratory Efficacy Measures

Exploratory efficacy measures for this study include the following:

- CDT
- PSP
- Cigarette use
- Other

12. ASSESSMENT OF PHARMACOKINETICS AND PHARMACODYNAMICS

For all subjects, samidorphan, RDC-9986 (primary metabolite of samidorphan) and olanzapine concentrations will be determined from plasma samples collected according to the Table 1, Table 2, and Table 3. Pharmacokinetic data may be used in a subsequent population PK evaluation 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:

- Treatment-emergent adverse events (TEAEs)
- Vital signs (ie, blood pressure, pulse, respiratory rate, and body temperature)
- Laboratory findings (ie, hematology, chemistry, and urinalysis)
- ECG results
- Weight
- C-SSRS
- AIMS
- BARS
- SAS

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 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, meaning the subject is at immediate risk of death from the reaction as it occurs. This definition of life-threatening does not include a reaction that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongation of existing hospitalization.

- Results in disability/ incapacity (eg, a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/ birth defect

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

Some outcomes of pregnancy may meet the criteria as an SAE. All neonatal deaths that occur within 1 month of birth should be reported as an SAE, without regard to causality. In addition, any infant death occurring more than 1 month after birth that the investigator assesses as possibly related to the in utero exposure to the study drug should be reported. See Section 8.4.1 for details on reporting pregnancies.

13.3. Relationship to Study Drug

The assessment of study drug relationship to each AE will be reported on the appropriate source document (and SAE form, in the event of an SAE) by the investigator (or designated sub investigator) according to his/her best clinical judgment. The criteria listed in Table 5 should be used to guide this assessment. Please note that not all criteria must be present to be indicative of a particular drug relationship. All study drugs are considered "test drugs" for the purposes of the definitions listed in the table. However, relationship and action taken will be assessed separately in the EDC (electronic data capture) system for olanzapine and samidorphan/placebo. It is possible that a PI may assess that a given AE is related to both study drugs (eg, possibly related to olanzapine and possibly related to samidorphan).

Table 5: Adverse Event Causality Guidelines

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

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

13.4. Monitoring and Recording of Adverse Events

Adverse event data collection will begin after a subject signs the ICF and will continue until completion of the safety follow-up visit. Any AE or SAE having an onset after the safety follow-up visit will not be collected or reported unless the 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 regardless of 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 ALKS 3831 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 **Drug Safety within 24 hours of discovery, by faxing the report to the following:**

Attention: Drug Safety

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. This assessment will be done twice as follows: once for olanzapine and once for samidorphan/placebo. The report submitted will include both assessments.

14. STATISTICS

14.1. Sample Size Considerations

The sample size calculation is based on the detection of log-hazard ratio for the first EEDS during the double-blind treatment period.

Based on the previous clinical studies with olanzapine and clinical judgment, the 9-month cumulative proportion of subjects experiencing an EEDS will be 15% and 30% for the ALKS 3831 group and olanzapine plus placebo group, respectively. Assuming an exponential distribution of survival time, and a 2-sided test at α=0.05, a total of 70 EEDS will be required for approximately 90% power to detect a hazard ratio of 0.45 between ALKS 3831 and olanzapine plus placebo with a randomization allocation ratio of 1:1 (ALKS 3831:olanzapine plus placebo). Approximately 270 subjects (135 subjects per treatment group) will need to be randomized at Visit 8 to observe 70 total EEDS.

14.2. General Statistical Methodology

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

In general, summary statistics (n, mean, standard deviation, median, minimum, and maximum for continuous variables and number and percent 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

The open-label olanzapine population is defined as all enrolled subjects who received at least 1 dose of olanzapine during the open-label olanzapine treatment period.

The open-label ALKS 3831 population is defined as all enrolled subjects who received at least 1 dose of olanzapine or samidorphan during the open label ALKS 3831 treatment period.

The primary safety population is defined as all randomized subjects who receive at least 1 dose of study drug (olanzapine, samidorphan, or placebo) during the double-blind placebo-controlled treatment period. The intent-to-treat (ITT) population is the same as the primary safety population.

14.2.2. Demographics and Baseline Data

Demographics and baseline characteristics, including but not limited to gender, age, race, weight and BMI will be summarized with descriptive statistics. Medical history will be summarized using the number and percent of subjects reporting each category.

14.3. Efficacy Analyses

14.3.1. Primary Efficacy Measure

The efficacy analyses will be carried out using the ITT population and EEDS that the IAC has confirmed as meeting the pre-specified criteria. The primary efficacy endpoint is defined as the time from randomization to an EEDS. The analysis comparing the 2 treatment groups will be carried out using a log-rank test. A Cox proportional hazard model will be used to further examine the treatment difference adjusting for various covariates. The relationship between the primary efficacy endpoint and alcohol intake during the double-blind placebo-controlled treatment period may be explored by (but not limited to) a Cox proportional hazard model.

Additional details will be described in the SAP.

14.3.2. Other Efficacy Endpoints

Other efficacy endpoints will include (but are not limited to) the following:

- The rate and number of EEDS
- The proportion of subjects with psychosocial events indicative of exacerbation of symptoms during the double-blind treatment period
- The rate and number of psychosocial events indicative of exacerbation of symptoms during the double-blind treatment period
- Change from baseline in PANSS total and sub-scale score during the double-blind treatment period
- Change from baseline in CGI-S score during the double-blind treatment period
- CGI-I score during the double-blind treatment period
- Complete response profile of drinking during the double-blind treatment period
- Change from baseline in VAS score for perception of desire for alcohol during the double-blind treatment period

The statistical methods include, but are not limited to, the following: Negative binomial regression will be used to compare treatment difference in the number and rate of EEDS and the number and rate of psychosocial events indicative of exacerbation symptoms during the double-blind treatment period. Logistic regression will be used to compare treatment difference in the proportion of subjects with psychosocial events during the double-blind treatment period. An ANCOVA model with LOCF (last observation carried forward) approach will be used to compare treatment difference in change from baseline during the double-blind treatment period in PANSS total and sub-scale score, CGI-S and VAS score for perception of desire for alcohol. Wilcoxon rank sum test will be used to compare treatment difference in CGI-I score. Drinking profile will be analyzed by an Anderson-Gill model.

Additional efficacy endpoints and analysis methods may be defined in the Statistical Analysis Plan.

14.4. Pharmacokinetic Analyses

Concentrations of olanzapine, samidorphan and its metabolite (RDC-9986) will be listed. Pharmacokinetic concentrations may be used to assess adherence and/or as part of a subsequent population PK analysis to be conducted separately from this study.

14.5. Safety Analyses

Safety will be evaluated based on the incidence of TEAEs, laboratory test results, vital signs, ECG findings, C-SSRS results, abnormal movement rating scales results, as well as concomitant medications. Reported AE terms will be coded using the MedDRA (Medical Dictionary for Regulatory Activities) preferred terms and system organ classes.

The incidence of TEAEs will be summarized for each study period, treatment group, and overall by severity and by relationship to study drug. The summary tables will include the number and percent of subjects with TEAEs overall, by system organ class, and by preferred terms within each system organ class. Additional AE summary tables will be defined in the SAP.

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

Potentially clinically significant (PCS) values for each relevant parameter will be defined in the SAP.

QT, QTcB, and QTcF intervals will be calculated at each ECG assessment. Interval data will be summarized by study period and treatment group at each time point for the absolute value and for changes from baseline. In addition, the number and percentages of subjects with post-baseline results QTcB and QTcF values >450, 480, or 500 milliseconds and an increase from baseline of >30 or 60 milliseconds from baseline will be summarized. Other ECG variables that are collected will be summarized as well.

C-SSRS will be summarized by number and percent of subjects with any abnormal findings at post-baseline visits by study period and treatment group. AIMS, BARS, and SAS will be summarized by study period and treatment group for the absolute value and for changes from baseline at each visit.

Concomitant medications will be coded using World Health Organization Drug Dictionary Anatomical Therapeutic Chemical (WHO-ATC) class. The number and percentage of subjects using concomitant medications will be summarized by study period and treatment group.

15. DIRECT ACCESS TO SOURCE DATA/ DOCUMENTS

15.1. Study Monitoring

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

15.2. Audits and Inspections

By signing the protocol, the investigator agrees that, within local regulatory restrictions and institutional and ethical considerations, authorized representatives of Alkermes, a regulatory authority, and/or an 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, 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 PI must obtain IRB/IEC approval for the investigation. Initial IRB/IEC approval as well as all materials approved by the IRB/IEC for this study, including the subject and caregiver consent forms 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 compliance, Alkermes may conduct a quality assurance audit. Please see Section 15.2 for details regarding the audit process.

16.1. Case Report Forms

This study will use eCRFs. All eCRFs will be completed by the clinic staff prior to review by the Alkermes monitor or designated representative.

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/she will maintain in confidence information furnished to him or her by Alkermes and will divulge such information to his/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 PI or designee 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 Alkermes 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. Alkermes is committed to complying with GCP standards; GCP is an international ethical and scientific quality standard used for designing, conducting, recording, and reporting studies involving the participation of human subjects. Complying with these standards provide assurance that the rights, safety, and well-being of study subjects will be protected, consistent with the principles having their origin in the Declaration of Helsinki.

17.3. Written Informed Consent

The PI (or authorized designee) at each center will ensure that the subject and caregiver (in Bulgaria, and anywhere a caregiver is required) are given full and adequate oral and written information about the nature, purpose, potential and possible risks and benefits of the study. Each prospective subject and caregiver will receive the required, IRB/IEC-approved ICF(s) that summarizes all pertinent study information. The subject and caregiver will be given ample time to read the forms and ask questions about the study. All information is to be provided in a language understandable to the subject and must not include any language that waives the subject's legal rights. Prospective subjects must also be informed of their right to withdraw consent without prejudice at any time during the study. If the subject chooses to participate, he/she must sign the main ICF and when required, the caregiver must sign the caregiver ICF.

All subjects will be informed of their rights to privacy and will be made aware that the study data will be submitted to Alkermes, the IRB/IEC, the 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 ICFs, which must be reviewed and signed by all applicable study participants.

The time that informed consent is obtained must be documented. The PI must maintain the original, signed ICFs in the subject's source documents. A copy of the signed ICF(s) 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. Principal investigators are responsible for handling data in a manner consistent with local and international regulations on personal data (including health information) collection and protection.

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.

If available, a paper copy of all laboratory reports will remain with the source documents at the study site. All out of range laboratory values will be deemed as clinically significant or not clinically significant by the investigator. Clinically significant values will be considered AEs and recorded as such on the eCRFs.

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

18.2. Inspection of Records

Alkermes or its representative will be allowed to conduct site visits to the investigational facilities for the purpose of monitoring any aspect of the study. The 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 essential clinical study documents (eg, worksheets, drug accountability forms, and other administrative documentation) shall be governed by the terms and conditions of the site's CSA. If the CSA does not state specific document retention terms, then the site shall keep essential clinical study documentation for the longer of:

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

Subjects' medical files should be retained in accordance with the applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution, or private practice.

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 Alkermes.

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

19. REFERENCES

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20. APPENDICES

Appendix A. Sample Mini-International Neuropsychiatric Interview

Appendix B. Sample Readiness to Change Questionnaire

Appendix C. Sample Positive and Negative Syndrome Scale

Appendix D. Sample Clinical Global Impression-Improvement

Appendix E. Sample Structured Interview Guide for Global Impressions

Appendix F. Sample Visual Analog Scale

Appendix G. Sample Personal and Social Performance Scale

Appendix H. Sample Abnormal Involuntary Movement Scale

Appendix I. Sample Barnes Akathisia Scale

Appendix J Sample Simpson-Angus Scale

Appendix K. Sample Columbia Suicide Severity Rating Scale

- "Baseline/ Screening" Version
- "Since Last Visit" Version

Appendix L Partial List of Prohibited Cytochrome P450 3A4 (CYP3A4) Inducers and Moderate-to-Strong Inhibitors

APPENDIX A. SAMPLE MINI-INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW

M.I.N.I.

MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW

English Version 6.0.0

DSM-IV

USA: **D. Sheehan[1], J. Janavs, K. Harnett-Sheehan, M. Sheehan, C. Gray.**
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DISCLAIMER

Our aim is to assist in the assessment and tracking of patients with greater efficiency and accuracy. Before action is taken on any data collected and processed by this program, it should be reviewed and interpreted by a licensed clinician.

This program is not designed or intended to be used in the place of a full medical and psychiatric evaluation by a qualified licensed physician – psychiatrist. It is intended only as a tool to facilitate accurate data collection and processing of symptoms elicited by trained personnel.

M.I.N.I. 6.0.0 (October 10, 2010) (10/10/10)

Patient Name:		***Patient Number:***	
Date of Birth:		***Time Interview Began:***	
Interviewer's Name:		***Time Interview Ended:***	
Date of Interview:		***Total Time:***	

	MODULES	TIME FRAME	MEETS CRITERIA	DSM-IV-TR	ICD-10	PRIMARY DIAGNOSIS
A	MAJOR DEPRESSIVE EPISODE	Current (2 weeks)	❒			
		Past	❒			
		Recurrent	❒			
	MAJOR DEPRESSIVE DISORDER	Current (2 weeks)	❒	296.20-296.26 Single	F32.x	❒
		Past	❒	296.20-296.26 Single	F32.x	❒
		Recurrent	❒	296.30-296.36 Recurrent	F33.x	❒
B	SUICIDALITY	Current (Past Month) ❒ Low ❒ Moderate ❒ High	❒			
C	MANIC EPISODE	Current	❒			
		Past	❒			
	HYPOMANIC EPISODE	Current	❒			
		Past	❒	❒ Not Explored		
	BIPOLAR I DISORDER	Current	❒	296.0x-296.6x	30.x- F31.9	❒
		Past	❒	296.0x-296.6x	F30.x- F31.9	❒
	BIPOLAR II DISORDER	Current	❒	296.89	F31.8	❒
		Past	❒	6.89	F31.8	❒
	BIPOLAR DISORDER NOS	Current	❒	2 0	F31.9	❒
		Past	❒	296.	F31.9	❒
D	PANIC DISORDER	Current (Past M h)	❒	300.01/300.21	F40.01-F41.0	❒
		Lifetime	❒			
E	AGORAPHOBIA	Curren	❒	300.22	F40.00	❒
F	SOCIAL PHOBIA (Social Anxiety Disorder)	Current (P M				
		Generalized	❒	300.23	F40.1	❒
		on-Generali	❒	300.23	F40.1	❒
G	OBSESSIVE-COMPULSIVE DISORDER	urren t M h)	❒	300.3	F42.8	❒
H	POSTTRAUMATIC STRESS DISORDE	Cu t (Past Month)	❒	309.81	F43.1	❒
I	ALCOHOL DEPENDENCE	Past 12 M ths	❒	303.9	F10.2x	❒
	ALCOHOL ABUSE	Months	❒	305.00	F10.1	❒
J	SUBSTANCE DEPENDENCE (Non-alcoh	Past 12 Months	❒	304.00-.90/305.20-.90	F11.2X-F19.2X	❒
	SUBSTANCE ABUSE (hol)	Past 12 Months	❒	304.00-.90/305.20-.90	F11.1-F19.1	❒
K	PSYCHOTIC DIS DERS	Lifetime	❒	295.10-295.90/297.1/	F20.xx-F29	❒
		Current	❒	297.3/293.81/293.82/ 293.89/298.8/298.9	F20.xx-F29	
	MOOD DISORDER WITH	Lifetime	❒	296.24/296.04-296.94	F32.3/F33.3/	❒
	PSYCHOTIC FEATURES	Current	❒	296.24/296.04-296.94	F30.2/F31.2/F31.5 F31.8/F31.9/F39	❒
L	ANOREXIA NERVOSA	Current (Past 3 Months)	❒	307.1	F50.0	❒
M	BULIMIA NERVOSA	Current (Past 3 Months)	❒	307.51	F50.2	❒
	ANOREXIA NERVOSA, BINGE EATING/PURGING TYPE	Current	❒	307.1	F50.0	❒
N	GENERALIZED ANXIETY DISORDER	Current (Past 6 Months)	❒	300.02	F41.1	❒
O	MEDICAL, ORGANIC, DRUG CAUSE RULED OUT		❒ No	❒ Yes	❒ Uncertain	
P	ANTISOCIAL PERSONALITY DISORDER	Lifetime	❒	301.7	F60.2	❒

IDENTIFY THE PRIMARY DIAGNOSIS BY CHECKING THE APPROPRIATE CHECK BOX.
(Which problem troubles you the most or dominates the others or came first in the natural history?)

The translation from DSM-IV-TR to ICD-10 coding is not always exact. For more information on this topic see Schulte-Markwort. Crosswalks ICD-10/DSM-IV-TR. Hogrefe & Huber Publishers 2006.

GENERAL INSTRUCTIONS

The M.I.N.I. was designed as a brief structured interview for the major Axis I psychiatric disorders in DSM-IV and ICD-10. Validation and reliability studies have been done comparing the M.I.N.I. to the SCID-P for DSM-III-R and the CIDI (a structured interview developed by the World Health Organization). The results of these studies show that the M.I.N.I. has similar reliability and validity properties, but can be administered in a much shorter period of time (mean 18.7 ± 11.6 minutes, median 15 minutes) than the above referenced instruments. It can be used by clinicians, after a brief training session. Lay interviewers require more extensive training.

INTERVIEW:

In order to keep the interview as brief as possible, inform the patient that you will conduct a clinical interview that is more structured than usual, with very precise questions about psychological problems which require a yes or no answer.

GENERAL FORMAT:

The M.I.N.I. is divided into **modules** identified by letters, each corresponding to a diagnostic category.

•At the beginning of each diagnostic module (except for psychotic disorders module), screening question(s) corresponding to the main criteria of the disorder are presented in a **gray box**.

•At the end of each module, diagnostic box(es) permit the clinician to indicate whether diagnostic criteria are met.

CONVENTIONS:

Sentences written in « normal font » should be read exactly as written to the patient in order to standardize the assessment of diagnostic criteria.

Sentences written in « CAPITALS » should not be read to the patient. They are instructions for the interviewer to assist in the scoring of the diagnostic algorithms.

Sentences written in « **bold** » indicate the time frame being investigated. The interviewer should read them as often as necessary. Only symptoms occurring during the time frame indicated should be considered in scoring the responses.

Answers with an arrow above them (➡) indicate that one of the criteria necessary for the diagnosis(es) is not met. In this case, the interviewer should go to the end of the module, circle « **NO** » in all the diagnostic boxes and move to the next module.

When terms are separated by a *slash (/)* the interviewer should read only those symptoms known to be present in the patient (for example, question G6).

Phrases in (parentheses) are clinical examples of the symptom. These may be read to the patient to clarify the question.

RATING INSTRUCTIONS:

All questions must be rated. The rating is done at the right of each question by circling either Yes or No. Clinical judgment by the rater should be used in coding the responses. Interviewers need to be sensitive to the diversity of cultural beliefs in their administration of questions and rating of responses. The rater should ask for examples when necessary, to ensure accurate coding. The patient should be encouraged to ask for clarification on any question that is not absolutely clear.

The clinician should be sure that each dimension of the question is taken into account by the patient (for example, time frame, frequency, severity, and/or alternatives).

Symptoms better accounted for by an organic cause or by the use of alcohol or drugs should not be coded positive in the M.I.N.I. The M.I.N.I. Plus has questions that investigate these issues.

For any questions, suggestions, need for a training session or information about updates of the M.I.N.I., please contact:

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A. MAJOR DEPRESSIVE EPISODE

(➡ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE **NO** IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

A1	a	Were you ever depressed or down, most of the day, nearly every day, for two weeks?	NO	YES
		IF NO, CODE NO TO **A1b**: IF **YES** ASK:		
	b	For the past two weeks, were you depressed or down, most of the day, nearly every day?	NO	YES
A2	a	Were you ever much less interested in most things or much less able to enjoy the things you used to enjoy most of the time, for two weeks?	NO	YES
		IF NO, CODE NO TO **A2b**: IF **YES** ASK:		
	b	In the past two weeks, were you much less interested in most things or much less able to enjoy the things you used to enjoy, most of the time?	NO	YES
		➡ IS **A1a** OR **A2a** CODED **YES**?	NO	YES

A3 IF **A1b** OR **A2b** = **YES**: EXPLORE THE **CURRENT** AND THE MOST SYMPTOMATIC **PAST** EPISODE, OTHERWISE
IF **A1b** AND **A2b** = **NO**: EXPLORE ONLY THE MOST SYMPTOMATIC **PAST** EPISODE

Over that two week period, when you felt depressed or uninterested:

		Past 2 Weeks		Past Episode	
a	Was your appetite decreased or increased nearly every day? Did your weight decrease or increase without trying intentionally (i.e., by ±5% of body weight or ±8 lb or ± 3.5 kg, for a 160 lb/70 kg person in a month)? IF **YES** TO EITHER, CODE **YES**.	NO	YES	NO	YES
b	Did you have trouble sleeping nearly every night (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively)?	NO	YES	NO	YES
c	Did you talk or move more slowly than normal or were you fidgety, restless or having trouble sitting still almost every day?	NO	YES	NO	YES
d	Did you feel tired or without energy almost every day?	NO	YES	NO	YES
e	Did you feel worthless or guilty almost every day?	NO	YES	NO	YES
	IF **YES**, ASK FOR EXAMPLES. THE EXAMPLES ARE CONSISTENT WITH A DELUSIONAL IDEA. Current Episode ❒ No ❒ Yes; Past Episode ❒ No ❒ Yes				
f	Did you have difficulty concentrating or making decisions almost every day?	NO	YES	NO	YES
g	Did you repeatedly consider hurting yourself, feel suicidal, or wish that you were dead? Did you attempt suicide or plan a suicide? IF **YES TO EITHER, CODE YES.**	NO	YES	NO	YES
A4	Did these symptoms cause significant problems at home, at work, socially, at school or in some other important way?	NO	YES	NO	YES
A5	In between 2 episodes of depression, did you ever have an interval of at least 2 months, without any significant depression or any significant loss of interest?			NO	YES

ARE **5** OR MORE ANSWERS (**A1-A3**) CODED **YES** AND IS **A4** CODED YES FOR THAT TIME FRAME?

SPECIFY IF THE EPISODE IS CURRENT AND / OR PAST.

IF **A5** IS CODED **YES,** CODE **YES** FOR RECURRENT.

NO	**YES**
MAJOR DEPRESSIVE EPISODE	
CURRENT	❒
PAST	❒
RECURRENT	❒

A6 a How many episodes of depression did you have in your lifetime? _____

Between each episode there must be at least 2 months without any significant depression.

B. SUICIDALITY

				Points
	In the past month did you:			
B1	Have any accident? This includes taking too much of your medication accidentally. IF NO TO B1, SKIP TO B2; IF YES, ASK B1a:	NO	YES	0
B1a	Plan or intend to hurt yourself in any accident either actively or passively (e.g. by not avoiding a risk)? IF NO TO B1a, SKIP TO B2: IF YES, ASK B1b:	NO	YES	0
B1b	Intend to die as a result of any accident?	NO	YES	0
B2	Feel hopeless?	NO	YES	1
B3	Think that you would be better off dead or wish you were dead?	NO	YES	1
B4	Think about hurting or injuring yourself or have mental images of harming yourself, with at least some intent or awareness that you might die as a result?	NO	YES	4
B5	Think about suicide (killing yourself)?	NO	YES	6

IF NO TO B5, SKIP TO B7. OTHERWISE ASK:

Frequency		Intensity	
Occasionally	❒	Mild	❒
Often	❒	Moderate	❒
Very often	❒	Severe	❒

B6	Have difficulty restraining yourself from acting on these impulses?	NO	YES	8
B7	Have a suicide method in mind (e.g. how)?	NO	YES	8
B8	Have a suicide plan in mind (e.g. when or where)?	NO	YES	8
B9	Intend to act on thoughts of killing yourself?	NO	YES	8
B10	Intend to die as a result of a suicidal act?	NO	YES	8
B11	Take any active steps to prepare to injure yourself or to prepare for a suicide attempt in which you expected or intended to die? This includes times when you were going to kill yourself, but were interrupted or stopped yourself, before harming yourself. IF NO TO B11, SKIP TO B12.	NO	YES	9
B11a	Take active steps to prepare to kill yourself, but you did not start the suicide attempt?	NO	YES	
B11b	Start a suicide attempt, but then **you stopped yourself** before harming yourself (aborted attempt)?	NO	YES	
B11c	Start a suicide attempt, but then **someone or something stopped you** before harming yourself (interrupted attempt)?	NO	YES	
B12	Injure yourself on purpose without intending to kill yourself?	NO	YES	4
B13	Attempt suicide (to kill yourself)?	NO	YES	10

A suicide attempt means you did something where you could possibly be injured, with at least a slight intent to die.

IF NO, SKIP TO B14:

Hope to be rescued / survive ❒
Expected / intended to die ❒

In your lifetime:

B14 Did you ever make a suicide attempt (try to kill yourself)? NO YES 4

"A suicide attempt is any self injurious behavior, with at least some intent (> 0) to die as a result or if intent can be inferred, e.g. if it is clearly not an accident or the individual thinks the act could be lethal, even though denying intent."
(C-CASA definition). Posner K et al. Am J Psychiatry 164:7, July 2007.

IS AT LEAST **1** OF THE ABOVE (EXCEPT B1) CODED **YES**?

NO **YES**

IF YES, ADD THE TOTAL POINTS FOR THE ANSWERS (B1-B14)
CHECKED 'YES' AND SPECIFY THE SUICIDALITY SCORE AS INDICATED IN THE DIAGNOSTIC BOX:

SUICIDALITY CURRENT

1-8 points Low ❒
9-16 points Moderate ❒
≥ 17 points High ❒

MAKE ANY ADDITIONAL COMMENTS ABOUT YOUR ASSESSMENT OF THIS PATIENT'S CURRENT AND NEAR FUTURE SUICIDALITY IN THE SPACE BELOW:

C. MANIC AND HYPOMANIC EPISODES

(➡ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN MANIC AND HYPOMANIC DIAGNOSTIC BOXES, AND MOVE TO NEXT MODULE)

Do you have any family history of manic-depressive illness or bipolar disorder, or any family member who had mood swings treated with a medication like lithium, sodium valproate (Depakote) or lamotrigine (Lamictal)? NO YES

THIS QUESTION IS NOT A CRITERION FOR BIPOLAR DISORDER, BUT IS ASKED TO INCREASE THE CLINICIAN'S VIGILANCE ABOUT THE RISK FOR BIPOLAR DISORDER.

IF YES, PLEASE SPECIFY WHO:_____

C1 a Have you **ever** had a period of time when you were feeling 'up' or 'high' or 'hyper' or so full of energy or full of yourself that you got into trouble, - or that other people thought you were not your usual self? (Do not consider times when you were intoxicated on drugs or alcohol.) NO YES

IF PATIENT IS PUZZLED OR UNCLEAR ABOUT WHAT YOU MEAN BY 'UP' OR 'HIGH' OR 'HYPER', CLARIFY AS FOLLOWS: By 'up' or 'high' or 'hyper' I mean: having elated mood; increased energy; needing less sleep; having rapid thoughts; being full of ideas; having an increase in productivity, motivation, creativity, or impulsive behavior; phoning or working excessively or spending more money.

IF NO, CODE NO TO **C1b**: IF **YES** ASK:

b Are you currently feeling 'up' or 'high' or 'hyper' or full of energy? NO YES

C2 a Have you **ever** been persistently irritable, for several days, so that you had arguments or verbal or physical fights, or shouted at people outside your family? Have you or others noticed that you have been more irritable or over reacted, compared to other people, even in situations that you felt were justified? NO YES

IF NO, CODE NO TO **C2b**: IF **YES** ASK:

b Are you currently feeling persistently irritable? NO YES

➡

IS **C1a** OR **C2a** CODED **YES**? NO YES

C3 IF **C1b** OR **C2b** = **YES**: EXPLORE THE **CURRENT** AND THE MOST SYMPTOMATIC **PAST** EPISODE, OTHERWISE
IF **C1b** AND **C2b** = **NO**: EXPLORE ONLY THE MOST SYMPTOMATIC **PAST** EPISODE

During the times when you felt high, full of energy, or irritable did you:

		Current Episode		Past Episode	
a	Feel that you could do things others couldn't do, or that you were an especially important person? IF **YES**, ASK FOR EXAMPLES. THE EXAMPLES ARE CONSISTENT WITH A DELUSIONAL IDEA. Current Episode ❒ No ❒ Yes; Past Episode ❒ No ❒ Yes	NO	YES	NO	YES
b	Need less sleep (for example, feel rested after only a few hours sleep)?	NO	YES	NO	YES
c	Talk too much without stopping, or so fast that people had difficulty understanding?	NO	YES	NO	YES
d	Have racing thoughts?	NO	YES	NO	YES

		Current Episode		Past Episode	
e	Become easily distracted so that any little interruption could distract you?	NO	YES	NO	YES
f	Have a significant increase in your activity or drive, at work, at school, socially or sexually or did you become physically or mentally restless?	NO	YES	NO	YES
g	Want so much to engage in pleasurable activities that you ignored the risks or consequences (for example, spending sprees, reckless driving, or sexual indiscretions)?	NO	YES	NO	YES

C3 SUMMARY: WHEN RATING CURRENT EPISODE: NO YES NO YES

IF C1b IS NO, ARE 4 OR MORE C3 ANSWERS CODED YES?
IF C1b IS YES, ARE 3 OR MORE C3 ANSWERS CODED YES?

WHEN RATING PAST EPISODE:
IF C1a IS NO, ARE 4 OR MORE C3 ANSWERS CODED YES?
IF C1a IS YES, ARE 3 OR MORE C3 ANSWERS CODED YES?

CODE YES ONLY IF THE ABOVE 3 OR 4 SYMPTOMS OCCURRED DURING THE SAME TIME PERIOD.

RULE: ELATION/EXPANSIVENESS REQUIRES ONLY THREE C3 SYMPTOMS, WHILE IRRITABLE MOOD ALONE REQUIRES 4 OF THE C3 SYMPTOMS.

C4 What is the longest time these symptoms lasted?

a)	3 days or less	❒		❒
b)	4 to 6 days	❒		❒
c)	7 days or more	❒		❒

C5 Were you hospitalized for these problems? NO YES NO YES

IF YES, CIRCLE YES IN MANIC EPISODE FOR [illegible] FRAME AND GO TO C7.

C6 Did these symptoms cause significant prob[illegible]s at ho[illegible] work, socially in your relationships with [illegible], at school or [illegible]ome other important way? NO YES NO YES

ARE **C3** SUMMARY AND **C5** AND **C6** [illegible]ES?

OR

ARE **C3** SUM[illegible]RY A[illegible]**4C** AND **C[illegible]** CODED **YES** AND IS **C5** CODED **NO**?

SPECIFY IF THE EPISODE[illegible]T AND / OR PAST.

NO	**YES**
MANIC EPISODE	
CURRENT	❒
PAST	❒

Is C3 SUMMARY **CODED YES** AND ARE **C5** AND **C6** CODED **NO** AND IS EITHER **C4b** OR **C4c** CODED **YES**?

OR

ARE **C3** SUMMARY AND **C4b** AND **C6** CODED **YES** AND IS **C5** CODED **NO?**

SPECIFY IF THE EPISODE IS CURRENT AND / OR PAST.

IF **YES** TO CURRENT MANIC EPISODE, THEN CODE CURRENT HYPOMANIC EPISODE AS **NO.**

IF **YES** TO PAST MANIC EPISODE, THEN CODE PAST HYPOMANIC EPISODE AS **NOT EXPLORED.**

HYPOMANIC EPISODE

CURRENT ❒ **NO**
❒ **YES**

PAST ❒ **NO**
❒ **YES**
❒ **NOT EXPLORED**

ARE **C3** SUMMARY AND **C4a** CODED **YES** AND IS **C5** CODED **NO**?

HYPOMANIC SYMPTOMS

SPECIFY IF THE EPISODE IS CURRENT AND / OR PAST.

IF **YES** TO CURRENT MANIC EPISODE OR HYPOMANIC EPISODE,
THEN CODE CURRENT HYPOMANIC SYMPTOMS AS **NO.**

IF **YES** TO PAST MANIC EPISODE OR YES TO PAST HYPOMANIC EPISOD
THEN CODE PAST HYPOMANIC SYMPTOMS AS **NOT EXPLORED.**

CURRE ❒ **NO**
❒ **YES**

PAST ❒ **NO**
❒ **YES**
❒ **NOT EXPLORED**

C7 a) IF MANIC EPISODE IS POSITIVE FO CURRE OR PAS ASK:
Did you have 2 or more of these (ma epis lasting 7 days or more (**C4c**) in your lifetime (including the current episode esent)? NO YES

b) IF MANIC OR HYPOMAN EPIS IS POSITIV OR EITHER CURRENT OR PAST ASK:
Did you have 2 or more these (h ic) episodes lasting just 4 to 6 days (**C4b**) in your lifetime (including e cu nt episode)? NO YES

c) IF THE ST "HYPOM SYM OMS" CATEGORY IS CODED POSITIVE ASK:
Did yo have hypo nic symptoms lasting only 1 to 3 days (**C4a**) 2 or more times in your li e, (includin e current episode if present)? NO YES

D. PANIC DISORDER

(➡ MEANS : CIRCLE NO IN D5, D6 AND D7 AND SKIP TO E1)

D1	a	Have you, on more than one occasion, had spells or attacks when you **suddenly** felt anxious, frightened, uncomfortable or uneasy, even in situations where most people would not feel that way?	➡ NO	YES
	b	Did the spells surge to a peak within 10 minutes of starting?	➡ NO	YES
D2		At any time in the past, did any of those spells or attacks come on unexpectedly or occur in an unpredictable or unprovoked manner?	➡ NO	YES
D3		Have you ever had one such attack followed by a month or more of persistent concern about having another attack, or worries about the consequences of the attack - or did you make a significant change in your behavior because of the attacks (e.g., shopping only with a companion, not wanting to leave your house, visiting the emergency room repeatedly, or seeing your doctor more frequently because of the symptoms)?	NO	YES
D4		**During the worst attack that you can remember:**		
	a	Did you have skipping, racing or pounding of your heart?	NO	YES
	b	Did you have sweating or clammy hands?	NO	YES
	c	Were you trembling or shaking?	NO	YES
	d	Did you have shortness of breath or difficulty breathing?	NO	YES
	e	Did you have a choking sensation or a lump in your throat?	NO	YES
	f	Did you have chest pain, pressure or discomfort?	NO	YES
	g	Did you have nausea, stomach problems or sudden diarrhea?	NO	YES
	h	Did you feel dizzy, unsteady, lightheaded or faint?	NO	YES
	i	Did things around you feel strange, unreal, detached or unfamiliar, or did you feel outside of or detached from part or all of your body?	NO	YES
	j	Did you fear that you were losing control or going crazy?	NO	YES
	k	Did you fear that you were dying?	NO	YES
	l	Did you have tingling or numbness in parts of your body?	NO	YES
	m	Did you have hot flushes or chills?	NO	YES
D5		ARE BOTH **D3,** AND **4** OR MORE **D4** ANSWERS, CODED **YES**? IF YES TO D5, SKIP TO D7.	NO	YES *PANIC DISORDER LIFETIME*
D6		IF **D5** = **NO,** ARE ANY D4 ANSWERS CODED **YES**? THEN SKIP TO **E1.**	NO	YES *LIMITED SYMPTOM ATTACKS LIFETIME*

D7 In the past month, did you have such attacks repeatedly (2 or more), and did you have persistent concern about having another attack, or worry about the consequences of the attacks, or did you change your behavior in any way because of the attacks? NO YES

PANIC DISORDER CURRENT

E. AGORAPHOBIA

E1 Do you feel anxious or uneasy in places or situations where help might not be available or escape might be difficult, like being in a crowd, standing in a line (queue), when you are alone away from home or alone at home, or when crossing a bridge, or traveling in a bus, train or car or where you might have a panic attack or the panic-like symptoms we just spoke about? NO YES

IF **E1** = **NO**, CIRCLE **NO** IN **E2**.

E2 Do you fear these situations so much that you avoid them, or suffer through them, or need a companion to face them? NO YES

AGORAPHOBIA CURRENT

IS **E2** (CURRENT AGORAPHOBIA) CODED **YES**

and

IS **D7** (CURRENT PANIC DISORDER) CODED **YES**?

NO **YES**

PANIC DISORDER with Agoraphobia CURRENT

IS **E2** (CURRENT AGORAPHOBIA) CODED **NO**

and

IS **D7** (CURRENT PANIC DISORDER) CODED **YES**?

NO **YES**

PANIC DISORDER without Agoraphobia CURRENT

IS **E2** (CURRENT AGORAPHOBIA) CODED **YES**

and

IS **D5** (PANIC DISORDER LIFETIME) CODED **NO**?

NO **YES**

AGORAPHOBIA, CURRENT without history of Panic Disorder

F. SOCIAL PHOBIA (Social Anxiety Disorder)

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO AND MOVE TO THE NEXT MODULE)

F1	In the past month, did you have persistent fear and significant anxiety at being watched, being the focus of attention, or of being humiliated or embarrassed? This includes things like speaking in public, eating in public or with others, writing while someone watches, or being in social situations.	➡ NO	YES
F2	Is this social fear excessive or unreasonable and does it almost always make you anxious?	➡ NO	YES
F3	Do you fear these social situations so much that you avoid them or suffer through them most of the time?	➡ NO	YES
F4	Do these social fears disrupt your normal work, school or social functioning or cause you significant distress?		

SUBTYPES

Do you fear and avoid 4 or more social situations?

If YES Generalized social phobia (social anxiety disorder)

If NO Non-generalized social phobia (social anxiety disorder)

EXAMPLES OF SUCH SOCIAL SITUATIONS TYPICALLY INCLUDE

- INITIATING OR MAINTAINING A CONVERSATION,
- PARTICIPATING IN SMALL GROUPS,
- DATING,
- SPEAKING TO AUTHORITY FIGURES,
- ATTENDING PARTIES,
- PUBLIC SPEAKING,
- EATING IN FRONT OF OTHERS,
- URINATING IN A PUBLIC WASHROOM, ETC.

NOTE TO INTERVIEWER: PLEASE ASSESS WHETHER THE SUBJECT'S FEARS ARE RESTRICTED TO NON-GENERALIZED ("ONLY 1 OR SEVERAL") SOCIAL SITUATIONS OR EXTEND TO GENERALIZED ("MOST") SOCIAL SITUATIONS. "MOST" SOCIAL SITUATIONS IS USUALLY OPERATIONALIZED TO MEAN 4 OR MORE SOCIAL SITUATIONS, ALTHOUGH THE DSM-IV DOES NOT EXPLICITLY STATE THIS.

NO **YES**

SOCIAL PHOBIA
(Social Anxiety Disorder)
CURRENT

GENERALIZED ❒

NON-GENERALIZED ❒

G. OBSESSIVE-COMPULSIVE DISORDER

(➡ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE NO AND MOVE TO THE NEXT MODULE)

G1	In the past month, have you been bothered by recurrent thoughts, impulses, or images that were unwanted, distasteful, inappropriate, intrusive, or distressing? - (For example, the idea that you were dirty, contaminated or had germs, **or** fear of contaminating others, **or** fear of harming someone even though it disturbs or distresses you, or fear you would act on some impulse, **or** fear or superstitions that you would be responsible for things going wrong, **or** obsessions with sexual thoughts, images or impulses, **or** hoarding, collecting, **or** religious obsessions.) (DO NOT INCLUDE SIMPLY EXCESSIVE WORRIES ABOUT REAL LIFE PROBLEMS. DO NOT INCLUDE OBSESSIONS DIRECTLY RELATED TO EATING DISORDERS, SEXUAL DEVIATIONS, PATHOLOGICAL GAMBLING, OR ALCOHOL OR DRUG ABUSE BECAUSE THE PATIENT MAY DERIVE PLEASURE FROM THE ACTIVITY AND MAY WANT TO RESIST IT ONLY BECAUSE OF ITS NEGATIVE CONSEQUENCES.)	NO YES ↓ SKIP TO **G4**
G2	Did they keep coming back into your mind even when you tried to ignore or get rid of them?	NO YES ↓ SKIP TO **G4**
G3	Do you think that these obsessions are the product of your own mind and that they are not imposed from the outside?	NO YES **obsessions**
G4	In the past month, did you do something repeatedly without being able to resist doing it, like washing or cleaning excessively, counting or checking things over and over, or repeating, collecting, arranging things, or other superstitious rituals?	NO YES **compulsions**
	IS **G3** OR **G4** CODED **YES**?	➡ NO YES
G5	At any point, did you recognize that either these obsessive thoughts or these compulsive behaviors were excessive or unreasonable?	➡ NO YES
G6	In the past month, did these obsessive thoughts and/or compulsive behaviors significantly interfere with your normal routine, your work or school, your usual social activities, or relationships, or did they take more than one hour a day?	**NO** **YES** ***O.C.D. CURRENT***

H. POSTTRAUMATIC STRESS DISORDER

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE **NO**, AND MOVE TO THE NEXT MODULE)

H1	Have you ever experienced or witnessed or had to deal with an extremely traumatic event that included actual or threatened death or serious injury to you or someone else? EXAMPLES OF TRAUMATIC EVENTS INCLUDE: SERIOUS ACCIDENTS, SEXUAL OR PHYSICAL ASSAULT, A TERRORIST ATTACK, BEING HELD HOSTAGE, KIDNAPPING, FIRE, DISCOVERING A BODY, WAR, OR NATURAL DISASTER, WITNESSING THE VIOLENT OR SUDDEN DEATH OF SOMEONE CLOSE TO YOU, OR A LIFE THREATENING ILLNESS.	➡ NO	YES
H2	Did you respond with intense fear, helplessness or horror?	➡ NO	YES
H3	During the past month, have you re-experienced the event in a distressing way (such as in dreams, intense recollections, flashbacks or physical reactions) or did you have intense distress when you were reminded about the event or exposed to a similar event?	➡ NO	YES

H4	**In the past month:**			
	a	Have you avoided thinking about or talking about the event ?	NO	YES
	b	Have you avoided activities, places or people that remind you of the event?	NO	YES
	c	Have you had trouble recalling some important part of what happened?	NO	YES
	d	Have you become much less interested in hobbies or social activities?	NO	YES
	e	Have you felt detached or estranged from others?	NO	YES
	f	Have you noticed that your feelings are numbed?	NO	YES
	g	Have you felt that your life will be shortened or that you will die sooner than other people?	NO	YES
		ARE **3** OR MORE **H4** ANSWERS CODED **YES**?	➡ NO	YES
H5	**In the past month:**			
	a	Have you had difficulty sleeping?	NO	YES
	b	Were you especially irritable or did you have outbursts of anger?	NO	YES
	c	Have you had difficulty concentrating?	NO	YES
	d	Were you nervous or constantly on your guard?	NO	YES
	e	Were you easily startled?	NO	YES
		ARE **2** OR MORE **H5** ANSWERS CODED **YES**?	➡ NO	YES

H6	During the past month, have these problems significantly interfered with your work, school or social activities, or caused significant distress?	**NO** **YES** ***POSTTRAUMATIC STRESS DISORDER CURRENT***

I. ALCOHOL DEPENDENCE / ABUSE

(➡ MEANS: GO TO DIAGNOSTIC BOXES, CIRCLE **NO** IN BOTH AND MOVE TO THE NEXT MODULE)

			➡	
I1	**In the past 12 months**, have you had 3 or more alcoholic drinks, - within a 3 hour period, - on 3 or more occasions?		NO	YES
I2	**In the past 12 months**:			
	a	Did you need to drink a lot more in order to get the same effect that you got when you first started drinking or did you get much less effect with continued use of the same amount?	NO	YES
	b	When you cut down on drinking did your hands shake, did you sweat or feel agitated? Did you drink to avoid these symptoms (for example, "the shakes", sweating or agitation) or to avoid being hungover? IF **YES** TO ANY, CODE **YES**.	NO	YES
	c	During the times when you drank alcohol, did you end up drinking more than you planned when you started?	NO	YES
	d	Have you tried to reduce or stop drinking alcohol but failed?	NO	YES
	e	On the days that you drank, did you spend substantial time obtaining alcohol, drinking, or recovering from the effects of alcohol?	NO	YES
	f	Did you spend less time working, enjoying hobbies, or being with others because of your drinking?	NO	YES
	g	If your drinking caused you health or mental problems, did you still keep on drinking?	NO	YES

ARE **3** OR MORE **I2** ANSWERS CODED **YES**?

* IF YES, SKIP I3 QUESTIONS AND GO TO NEXT MODULE. "DEPENDENCE PREEMPTS ABUSE" IN DSM IV TR.

NO	YES*
	ALCOHOL DEPENDENCE **CURRENT**

I3	**In the past 12 months:**			
	a	Have you been intoxicated, high, or hungover more than once when you had other responsibilities at school, at work, or at home? Did this cause any problems? (CODE **YES** ONLY IF THIS CAUSED PROBLEMS.)	NO	YES
	b	Were you intoxicated more than once in any situation where you were physically at risk, for example, driving a car, riding a motorbike, using machinery, boating, etc.?	NO	YES
	c	Did you have legal problems more than once because of your drinking, for example, an arrest or disorderly conduct?	NO	YES
	d	If your drinking caused problems with your family or other people, did you still keep on drinking?	NO	YES

ARE **1** OR MORE **I3** ANSWERS CODED **YES**?

NO	YES
	ALCOHOL ABUSE **CURRENT**

J. SUBSTANCE DEPENDENCE / ABUSE (NON-ALCOHOL)

(➡ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

Now I am going to show you / read to you a list of street drugs or medicines.

			➡	
J1	a	**In the past 12 months**, did you take any of these drugs more than once, to get high, to feel elated, to get "a buzz" or to change your mood?	NO	YES

CIRCLE EACH DRUG TAKEN:

Stimulants: amphetamines, "speed", crystal meth, "crank", "rush", Dexedrine, Ritalin, diet pills.

Cocaine: snorting, IV, freebase, crack, "speedball".

Narcotics: heroin, morphine, Dilaudid, opium, Demerol, methadone, Darvon, codeine, Percodan, Vicodin, OxyContin.

Hallucinogens: LSD ("acid"), mescaline, peyote, psilocybin, STP, "mushrooms", "ecstasy", MDA, MDMA.

Phencyclidine: PCP ("Angel Dust", "Peace Pill", "Tranq", "Hog"), or ketamine ("Special K").

Inhalants: "glue", ethyl chloride, "rush", nitrous oxide ("laughing gas"), amyl or butyl nitrate ("poppers").

Cannabis: marijuana, hashish ("hash"), THC, "pot", "grass", "weed", "reefer".

Tranquilizers: Quaalude, Seconal ("reds"), Valium, Xanax, Librium, Ativan, Dalmane, Halcion, barbiturates, Miltown, GHB, Roofinol, "Roofies".

Miscellaneous: steroids, nonprescription sleep or diet pills. Cough Medicine? Any others?

SPECIFY THE MOST USED DRUG(S): _____

WHICH DRUG(S) CAUSE THE BIGGEST PROBLEMS?: _____

FIRST EXPLORE THE DRUG CAUSING THE BIGGEST PROBLEMS AND MOST LIKELY TO MEET DEPENDENCE / ABUSE CRITERIA.

IF MEETS CRITERIA FOR ABUSE OR DEPENDENCE, SKIP TO THE NEXT MODULE. OTHERWISE, EXPLORE THE NEXT MOST PROBLEMATIC DRUG.

J2 **Considering your use of (NAME OF DRUG / DRUG CLASS SELECTED), in the past 12 months:**

	a	Have you found that you needed to use much more (NAME OF DRUG / DRUG CLASS SELECTED) to get the same effect that you did when you first started taking it?	NO	YES
	b	When you reduced or stopped using (NAME OF DRUG / DRUG CLASS SELECTED), did you have withdrawal symptoms (aches, shaking, fever, weakness, diarrhea, nausea, sweating, heart pounding, difficulty sleeping, or feeling agitated, anxious, irritable, or depressed)? Did you use any drug(s) to keep yourself from getting sick (withdrawal symptoms) or so that you would feel better?	NO	YES
		IF **YES** TO EITHER, CODE **YES**.		
	c	Have you often found that when you used (NAME OF DRUG / DRUG CLASS SELECTED), you ended up taking more than you thought you would?	NO	YES
	d	Have you tried to reduce or stop taking (NAME OF DRUG / DRUG CLASS SELECTED) but failed?	NO	YES
	e	On the days that you used (NAME OF DRUG / DRUG CLASS SELECTED), did you spend substantial time (>2 HOURS), obtaining, using or recovering from the drug, or thinking about the drug?	NO	YES
	f	Did you spend less time working, enjoying hobbies, or being with family or friends because of your drug use?	NO	YES
	g	If (NAME OF DRUG / DRUG CLASS SELECTED) caused you health or mental problems, did you still keep on using it?	NO	YES

ARE **3** OR MORE **J2** ANSWERS CODED **YES**?

SPECIFY DRUG(S): _____

***** IF YES, SKIP J3 QUESTIONS, MOVE TO NEXT DISORDER.
"DEPENDENCE PREEMPTS ABUSE" IN DSM IV TR.

NO	YES *

SUBSTANCE DEPENDENCE
CURRENT

Considering your use of (NAME THE DRUG CLASS SELECTED), in the past 12 months:

J3 a Have you been intoxicated, high, or hungover from (NAME OF DRUG / DRUG CLASS SELECTED) more than once, when you had other responsibilities at school, at work, or at home? Did this cause any problem? NO YES

(CODE **YES** ONLY IF THIS CAUSED PROBLEMS.)

b Have you been high or intoxicated from (NAME OF DRUG / DRUG CLASS SELECTED) more than once in any situation where you were physically at risk (for example, driving a car, riding a motorbike, using machinery, boating, etc.)? NO YES

c Did you have legal problems more than once because of your drug use, for example, an arrest or disorderly conduct? NO YES

d If (NAME OF DRUG / DRUG CLASS SELECTED) caused problems with your family or other people, did you still keep on using it? NO YES

ARE **1** OR MORE **J3** ANSWERS CODED **YES**?

SPECIFY DRUG(S): _____

NO	YES

SUBSTANCE ABUSE
CURRENT

K. PSYCHOTIC DISORDERS AND MOOD DISORDER WITH PSYCHOTIC FEATURES

ASK FOR AN EXAMPLE OF EACH QUESTION ANSWERED POSITIVELY. CODE **YES** ONLY IF THE EXAMPLES CLEARLY SHOW A DISTORTION OF THOUGHT OR OF PERCEPTION OR IF THEY ARE NOT CULTURALLY APPROPRIATE. BEFORE CODING, INVESTIGATE WHETHER DELUSIONS QUALIFY AS "BIZARRE".

DELUSIONS ARE "BIZARRE" IF: CLEARLY IMPLAUSIBLE, ABSURD, NOT UNDERSTANDABLE, AND CANNOT DERIVE FROM ORDINARY LIFE EXPERIENCE.
HALLUCINATIONS ARE SCORED "BIZARRE" IF: A VOICE COMMENTS ON THE PERSON'S THOUGHTS OR BEHAVIOR, OR WHEN TWO OR MORE VOICES ARE CONVERSING WITH EACH OTHER.
THE PURPOSE OF THIS MODULE IS TO EXCLUDE PATIENTS WITH PSYCHOTIC DISORDERS. THIS MODULE NEEDS EXPERIENCE.

					BIZARRE
		Now I am going to ask you about unusual experiences that some people have.			
K1	a	Have you ever believed that people were spying on you, or that someone was plotting against you, or trying to hurt you? **NOTE**: ASK FOR EXAMPLES TO RULE OUT ACTUAL STALKING.	NO	YES	YES
	b	**IF YES OR YES BIZARRE:** do you currently believe these things?	NO	YES	YES ↳**K6**
K2	a	Have you ever believed that someone was reading your mind or could hear your thoughts, or that you could actually read someone's mind or hear what another person was thinking?	NO	YES	YES
	b	**IF YES OR YES BIZARRE:** do you currently believe these things?	NO	YES	YES ↳**K6**
K3	a	Have you ever believed that someone or some force outside of yourself put thoughts in your mind that were not your own, or made you act in a way that was not your usual self? Have you ever felt that you were possessed? CLINICIAN: ASK FOR EXAMPLES AND DISCOUNT ANY THAT ARE NOT PSYCHOTIC.	NO	YES	YES
	b	**IF YES OR YES BIZARRE:** do you currently believe these things?	NO	YES	YES ↳**K6**
K4	a	Have you ever believed that you were being sent special messages through the TV, radio, internet, newspapers, books, or magazines or that a person you did not personally know was particularly interested in you?	NO	YES	YES
	b	**IF YES OR YES BIZARRE:** do you currently believe these things?	NO	YES	YES ↳**K6**
K5	a	Have your relatives or friends ever considered any of your beliefs odd or unusual? INTERVIEWER: ASK FOR EXAMPLES. ONLY CODE **YES** IF THE EXAMPLES ARE **CLEARLY** DELUSIONAL IDEAS NOT EXPLORED IN QUESTIONS K1 TO K4, FOR EXAMPLE, SOMATIC OR RELIGIOUS DELUSIONS OR DELUSIONS OF GRANDIOSITY, JEALOUSY, GUILT, RUIN OR DESTITUTION, ETC.	NO	YES	YES
	b	**IF YES OR YES BIZARRE:** do they currently consider your beliefs strange?	NO	YES	YES
K6	a	Have you ever heard things other people couldn't hear, such as voices?	NO	YES	
		IF YES TO VOICE HALLUCINATION: Was the voice commenting on your thoughts or behavior or did you hear two or more voices talking to each other?	NO		YES
	b	**IF YES OR YES BIZARRE TO K6a:** have you heard sounds / voices in the past month?	NO	YES	
		IF YES TO VOICE HALLUCINATION: Was the voice commenting on your thoughts or behavior or did you hear two or more voices talking to each other?	NO		YES ↳**K8b**

K7 a Have you ever had visions when you were awake or have you ever seen things other people couldn't see? NO YES

CLINICIAN: CHECK TO SEE IF THESE ARE CULTURALLY INAPPROPRIATE.

b **IF YES:** have you seen these things in the past month? NO YES

CLINICIAN'S JUDGMENT

K8 b IS THE PATIENT CURRENTLY EXHIBITING INCOHERENCE, DISORGANIZED SPEECH, OR MARKED LOOSENING OF ASSOCIATIONS? NO YES

K9 b IS THE PATIENT CURRENTLY EXHIBITING DISORGANIZED OR CATATONIC BEHAVIOR? NO YES

K10 b ARE NEGATIVE SYMPTOMS OF SCHIZOPHRENIA, E.G. SIGNIFICANT AFFECTIVE FLATTENING, POVERTY OF SPEECH (ALOGIA) OR AN INABILITY TO INITIATE OR PERSIST IN GOAL-DIRECTED ACTIVITIES (AVOLITION), PROMINENT DURING THE INTERVIEW? NO YES

K11 a ARE 1 OR MORE « a » QUESTIONS FROM K1a TO K7a CODED **YES OR YES BIZARRE** AND IS EITHER:

MAJOR DEPRESSIVE EPISODE, (CURRENT, RECURRENT OR PA
OR
MANIC OR HYPOMANIC EPISODE, (CURRENT OR PAST) COD **YES**? NO YES
↳ **K13**

IF NO TO K11 a, CIRCLE NO IN BOTH 'MOOD DISORDER WIT OTIC FEATURES' DIAGNOSTIC BOXES AND MOVE TO K13.

b You told me earlier that you had period(s) when you felt (depressed/high/persistently irritable).

Were the beliefs and experien es you just describe SYMPTOMS CODED **YES** FROM **K1a** TO **K7**a) restricted exclusively to times when you were feeling depressed/high/irritable?

IF THE PATIENT EVER H PERIOD OF A 2 WEEKS OF HAVING THESE BELIEFS OR EXPERIENCES (PSYCHOTIC SYM OMS) WHEN THEY WE NOT DEPRESSED/HIGH/IRRITABLE, CODE NO TO THIS DISORDER.

IF THE ANSWER NO TO TH ORDE ALSO CIRCLE NO TO K12 AND MOVE TO K13

NO	YES
MOOD DISORDER WITH *PSYCHOTIC FEATURES*	
LIFETIME	

K12 a ARE 1 OR MORE « b » QUESTIONS FROM K1b TO K7b CODED **YES OR YES BIZARRE** AND IS EITHER:

MAJOR DEPRESSIVE EPISODE, (CURRENT)
OR
MANIC OR HYPOMANIC EPISODE, (CURRENT) CODED **YES**?

IF THE ANSWER IS YES TO THIS DISORDER (LIFETIME OR CURRENT), CIRCLE NO TO K13 AND K14 AND MOVE TO THE NEXT MODULE.

NO	YES
MOOD DISORDER WITH *PSYCHOTIC FEATURES*	
CURRENT	

K13 ARE 1 OR MORE « b » QUESTIONS FROM K1b TO K6b, CODED **YES BIZARRE**?

OR

ARE 2 OR MORE « b » QUESTIONS FROM K1b TO K10b, CODED **YES** (RATHER THAN **YES BIZARRE**)?

AND DID AT LEAST TWO OF THE PSYCHOTIC SYMPTOMS OCCUR DURING THE SAME 1 MONTH PERIOD?

NO **YES**

PSYCHOTIC DISORDER
CURRENT

K14 IS **K13** CODED **YES**

OR

ARE 1 OR MORE « a » QUESTIONS FROM K1a TO K6a, CODED **YES BIZARRE**?

OR

ARE 2 OR MORE « a » QUESTIONS FROM K1a TO K7a, CODED **YES** (RATHER THAN **YES BIZARRE**)

AND DID AT LEAST TWO OF THE PSYCHOTIC SYMPTOMS OCCUR DURING THE SAME 1 MONTH PERIOD?

NO **YES**

PSYCHOTIC DISORDER
LIFETIME

L. ANOREXIA NERVOSA

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE **NO**, AND MOVE TO THE NEXT MODULE)

L1	a	How tall are you?	❑❑ft ❑❑in. ❑❑❑cm	
	b.	What was your lowest weight in the past 3 months?	❑❑❑lb ❑❑❑kg	
	c	IS PATIENT'S WEIGHT EQUAL TO OR BELOW THE THRESHOLD CORRESPONDING TO HIS / HER HEIGHT? (SEE TABLE BELOW)	➡ NO	YES

In the past 3 months:

L2		In spite of this low weight, have you tried not to gain weight?	➡ NO	YES
L3		Have you intensely feared gaining weight or becoming fat, even though you were underweight?	➡ NO	YES
L4	a	Have you considered yourself too big / fat or that part of your body was too big / fat?	NO	YES
	b	Has your body weight or shape greatly influenced how you felt about yourself?	NO	YES
	c	Have you thought that your current low body weight was normal or excessive?	NO	YES
L5		ARE 1 OR MORE ITEMS FROM **L4** CODED **YES**?	➡ NO	YES
L6		FOR WOMEN ONLY: During the last 3 months, did you miss all your menstrual periods when they were expected to occur (when you were not pregnant)?	➡ NO	YES

FOR WOMEN: ARE **L5 AND L6** CODED **YES**?

FOR MEN: IS **L5** CODED **YES**?

NO **YES**

ANOREXIA NERVOSA
CURRENT

HEIGHT / WEIGHT TABLE CORRESPONDING TO A BMI THRESHOLD OF 17.5 KG/M^2

Height/Weight														
ft/in	4'9	4'10	4'11	5'0	5'1	5'2	5'3	5'4	5'5	5'6	5'7	5'8	5'9	5'10
lb	81	84	87	89	92	96	99	102	105	108	112	115	118	122
cm	145	147	150	152	155	158	160	163	165	168	170	173	175	178
kg	37	38	39	41	42	43	45	46	48	49	51	52	54	55

Height/Weight					
ft/in	5'11	6'0	6'1	6'2	6'3
lb	125	129	132	136	140
cm	180	183	185	188	191
kg	57	59	60	62	64

The weight thresholds above are calculated using a body mass index (BMI) equal to or below 17.5 kg/m^2 for the patient's height. This is the threshold guideline below which a person is deemed underweight by the DSM-IV and the ICD-10 Diagnostic Criteria for Research for Anorexia Nervosa.

M. BULIMIA NERVOSA

(➡ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE **NO** IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

M1	In the past three months, did you have eating binges or times when you ate a very large amount of food within a 2-hour period?	NO ➡	YES
M2	In the last 3 months, did you have eating binges as often as twice a week?	NO ➡	YES
M3	During these binges, did you feel that your eating was out of control?	NO ➡	YES
M4	Did you do anything to compensate for, or to prevent a weight gain from these binges, like vomiting, fasting, exercising or taking laxatives, enemas, diuretics (fluid pills), or other medications?	NO ➡	YES
M5	Does your body weight or shape greatly influence how you feel about yourself?	NO ➡	YES
M6	DO THE PATIENT'S SYMPTOMS MEET CRITERIA FOR ANOREXIA NERVOSA?	NO ↓ Skip to M8	YES
M7	Do these binges occur only when you are under (____lb/kg)? INTERVIEWER: WRITE IN THE ABOVE PARENTHESIS THE THRESHOLD WEIGHT FOR THIS PATIENT'S HEIGHT FROM THE HEIGHT / WEIGHT TABLE IN THE ANOREXIA NERVOSA MODULE.	NO	YES

M8 IS **M5** CODED **YES** AND IS EITHER **M6** OR **M7** CODED **NO**?

NO **YES**

BULIMIA NERVOSA
CURRENT

IS **M7** CODED **YES**?

NO **YES**

ANOREXIA NERVOSA
Binge Eating/Purging Type
CURRENT

N. GENERALIZED ANXIETY DISORDER

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE **NO**, AND MOVE TO THE NEXT MODULE)

N1	a	Were you excessively anxious or worried about several routine things, over the past 6 months? IN ENGLISH, IF THE PATIENT IS UNCLEAR ABOUT WHAT YOU MEAN, PROBE BY ASKING (Do others think that you are a "worry wart"?) AND GET EXAMPLES.	➡ NO	YES
	b	Are these anxieties and worries present most days?	➡ NO	YES
		ARE THE PATIENT'S ANXIETY AND WORRIES RESTRICTED EXCLUSIVELY TO, OR BETTER EXPLAINED BY, ANY DISORDER PRIOR TO THIS POINT?	➡ NO	YES
N2		Do you find it difficult to control the worries?	➡ NO	YES
N3		FOR THE FOLLOWING, CODE **NO** IF THE SYMPTOMS ARE CONFINED TO FEATURES OF ANY DISORDER EXPLORED PRIOR TO THIS POINT**.**		
		When you were anxious over the past 6 months, did you, most of the time:		
	a	Feel restless, keyed up or on edge?	NO	YES
	b	Have muscle tension?	NO	YES
	c	Feel tired, weak or exhausted easily?	NO	YES
	d	Have difficulty concentrating or find your mind going blank?	NO	YES
	e	Feel irritable?	NO	YES
	f	Have difficulty sleeping (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively)?	NO	YES
		ARE **3** OR MORE **N3** ANSWERS CODED **YES?**	➡ NO	YES
N4		Do these anxieties and worries disrupt your normal work, school or social functioning or cause you significant distress?	**NO**	**YES**

GENERALIZED ANXIETY DISORDER
CURRENT

O. RULE OUT MEDICAL, ORGANIC OR DRUG CAUSES FOR ALL DISORDERS

IF THE PATIENT CODES POSITIVE FOR ANY CURRENT DISORDER ASK:

Just before these symptoms began:

O1a	Were you taking any drugs or medicines?	❒ No	❒ Yes	❒ Uncertain
O1b	Did you have any medical illness?	❒ No	❒ Yes	❒ Uncertain

IN THE CLINICIAN'S JUDGMENT: ARE EITHER OF THESE LIKELY TO BE DIRECT CAUSES OF THE PATIENT'S DISORDER?
IF NECESSARY ASK ADDITIONAL OPEN-ENDED QUESTIONS.

O2	**SUMMARY**: HAS AN ORGANIC CAUSE BEEN RULED OUT?	❒ No	❒ Yes	❒ Uncertain

P. ANTISOCIAL PERSONALITY DISORDER

(➡ MEANS : GO TO THE DIAGNOSTIC BOX AND CIRCLE NO)

P1 **Before you were 15 years old, did you:**

a	repeatedly skip school or run away from home overnight?	NO	YES
b	repeatedly lie, cheat, "con" others, or steal?	NO	YES
c	start fights or bully, threaten, or intimidate others?	NO	YES
d	deliberately destroy things or start fires?	NO	YES
e	deliberately hurt animals or people?	NO	YES
f	force someone to have sex with you?	NO	YES

➡

ARE **2** OR MORE **P1** ANSWERS CODED **YES**? NO YES

DO NOT CODE **YES** TO THE BEHAVIORS BELOW IF THEY ARE EXCLUSIVELY POLITICALLY OR RELIGIOUSLY MOTIVATED**.**

P2 **Since you were 15 years old, have you:**

a	repeatedly behaved in a way that others would consider irresponsible, like failing to pay for things you owed, deliberately being impulsive or deliberately not working to support yourself?	NO	YES
b	done things that are illegal even if you didn't get caught (for example, destroying property, shoplifting, stealing, selling drugs, or committing a felony)?	NO	YES
c	been in physical fights repeatedly (including physical fights with your spouse or children)?	NO	YES
d	often lied or "conned" other people to get money or pleasure, or lied just for fun?	NO	YES
e	exposed others to danger without caring?	NO	YES
f	felt no guilt after hurting, mistreating, lying to, or stealing from others, or after damaging property?	NO	YES

ARE **3** OR MORE **P2** QUESTIONS CODED **YES**?

NO **YES**

ANTISOCIAL PERSONALITY DISORDER
LIFETIME

THIS CONCLUDES THE INTERVIEW

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Translations	M.I.N.I. 4.4 or earlier versions	M.I.N.I. 4.6/5.0, M.I.N.I. Plus 4.6/5.0 and M.I.N.I. Screen 5.0:
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Finnish	M. Heikkinen, M. Lijeström, O. Tuominen	M. Heikkinen, M. Lijeström, O. Tuominen
French	Y. Lecrubier, E. Weiller, I. Bonora, P. Amorim, J.P. Lepine	Y. Lecrubier, E. Weiller, P. Amorim, T. Hergueta
German	I. v. Denffer, M. Ackenheil, R. Dietz-Bauer	G. Stotz, R. Dietz-Bauer, M. Ackenheil
Greek	S. Beratis	T. Calligas, S. Beratis, GN Papidimitriou, T Matsoukas CR Soldatos
Gujarati		M. Patel, B. Patel, Organon
Hebrew	J. Zohar, Y. Sasson	R. Barda, I. Levinson, A. Aviv
Hindi		C. Mittal, K. Batra, S. Gambhir, Organon
Hungarian	I. Bitter, J. Balazs	I. Bitter, J. Balazs
Icelandic		J.G. Stefansson
Italian	I. Bonora, L. Conti, M. Piccinelli, M. Tansella, G. Cassano, Y. Lecrubier, P. Donda, E. Weiller	L. Conti, A. Rossi, P. Donda
Japanese		T. Otsubo, H. Watanabe, H. Miyaoka, K. Kamijima, J.Shinoda, K.Tanaka, Y. Okajima

Kannada		Organon
Korean		K.S. Oh and Korean Academy of Anxiety Disorders
Latvian	V. Janavs, J. Janavs, I. Nagobads	V. Janavs, J. Janavs
Lithuanian		A. Bacevicius
Luganda		WW. Muhweziosal, H. Agren
Malayalam		Organon
Marathi		Organon
Norwegian	G. Pedersen, S. Blomhoff	K.A. Leiknes , U. Malt, E. Malt, S. Leganger
Polish	M. Masiak, E. Jasiak	M. Masiak, E. Jasiak
Portuguese	P. Amorim	P. Amorim, T. Guterres
Punjabi		A. Gahunia, S. Gambhir
Romanian		O. Driga
Russian		A. Bystritsky, E. Selivra, M. Bystritsky, L. Shumyak, M. Klisinska.
Serbian	I. Timotijevic	I. Timotijevic
Setswana	K. Ketlogetswe	
Slovenian	M. Kocmur	
Spanish	L. Ferrando, J. Bobes-Garcia, J. Gilbert-Rahola, Y. Lecrubier	L. Ferrando, L. Franco-Alfonso, M. Soto, J. Bobes-Garcia, O. Soto, L. Franco, G. Heinze, C. Santana, R. Hidalgo
Swedish	M. Waern, S. Andersch, M. Humble	C. Allgulander, H. Agren M. Waern, A. Brimse, M. Humble.
Tamil		Organon
Telugu		Organon
Thai		P. Kittirattanapaiboon, S. Mahatnirunkul, P. Udomrat, P. Silpakit,, M. Khamwongpin, S. Srikosai.
Turkish	T. Örnek, A. Keskiner, I. Vahip	T. Örnek, A. Keskiner, A.Engeler
Urdu		S. Gambhir
Yiddish		J. Goldman, Chana Pollack, Myrna Mniewski

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MOOD DISORDERS: DIAGNOSTIC ALGORITHM

Consult Modules:

A	Major Depressive Episode
C	(Hypo)manic Episode
K	Psychotic Disorders

MODULE K:

1a	IS **K11b** CODED YES?	NO	YES
1b	IS **K12a** CODED YES?	NO	YES

MODULES A and C:		Current	Past
2	a CIRCLE YES IF A DELUSIONAL IDEA IS IDENTIFIED IN **A3e**	YES	YES
	b CIRCLE YES IF A DELUSIONAL IDEA IS IDENTIFIED IN **C3a**	YES	YES

c Is a Major Depressive Episode coded YES (current or pa
and
is Manic Episode coded NO (current and past)?
and
is Hypomanic Episode coded NO (current and past)
and
is "Hypomanic Symptoms" coded NO nt and pas ?

Specify:

- If the depressive episode is **current** or t or both
- **With Psychotic Featu** Curre 1b or 2a urrent) = YES
  With Psychotic Feature ast: If or st) = YES

MAJOR DEPRESSIVE DISORDER		
	current	past
MDD	❑	❑
With Psychotic Features		
Current	❑	
Past		❑

d Is a Manic Episode coded YES (current or past)?

Specify:

- If the Bipolar I Disorder is **current** or **past** or both
- With **Single Manic Episode**: If Manic episode (current or past) = YES and MDE (current and past) = NO
- **With Psychotic Features** Current: If 1b or 2a (current) or 2b (current) = YES
  With Psychotic Features Past: If 1a or 2a (past) or 2b (past) = YES
- If the **most recent episode** is manic, depressed, mixed or hypomanic or unspecified (all mutually exclusive)
- **Unspecified** if the Past Manic Episode is coded YES AND Current (C3 Summary AND C4a AND C6 AND O2) are coded YES

BIPOLAR I DISORDER

	current	past
Bipolar I Disorder	❑	❑
Single Manic Episode	❑	❑

With Psychotic Features

Current	❑
Past	❑

Most Recent Episode

Manic	❑
Depressed	❑
Mixed	❑
Hypomanic	❑
Unspecified	❑

e Is Major Depressive Episode coded YES (current or past)
and
Is Hypomanic Episode coded YES (current or past)
and
Is Manic Episode coded NO (current and past)?

Specify:

- If the Bipolar Disorder is **current** or **past** or both
- If the most recent mood episode is **hypomanic** or **depressed** (mutually exclusive)

BIPOLAR II DISORDER

	current	past
Bipolar II Disorder	❑	❑

Most Recent Episode

Hypomanic	❑
Depressed	❑

f Is MDE coded NO (current and past)
and
Is Manic Episode coded NO (current and past
and
Is C4b coded YES for the appropriate time frame
and
Is C7b coded YES?

---

or

Is Manic Episode coded NO (current and past)
and
Is Hypomanic Episode coded NO (current and past)
and
Is C4a coded YES for the appropriate time frame
and
Is C7c coded YES?

Specify if the Bipolar Disorder NOS is **current** or **past** or both.

BIPOLAR DISORDER NOS

	current	past
Bipolar Disorder NOS	❑	❑

M.I.N.I. PLUS

The shaded modules below are additional modules available in the MINI PLUS beyond what is available in the standard MINI. The un-shaded modules below are in the standard MINI.

These MINI PLUS modules can be inserted into or used in place of the standard MINI modules, as dictated by the specific needs of any study.

	MODULES	TIME FRAME
A	MAJOR DEPRESSIVE EPISODE	Current (2 weeks) Past Recurrent
	MAJOR DEPRESSIVE DISORDER	Current (2 weeks) Past Recurrent
	MDE WITH MELANCHOLIC FEATURES	Current (2 weeks)
	MDE WITH CATATONIC FEATURES	Current (2 weeks)
	MDE WITH ATYPICAL FEATURES	Current (2 weeks)
	MAJOR DEPRESSIVE DISORDER WITH PSYCHOTIC FEATURES	Current Past
	MINOR DEPRESSIVE DISORDER (DEPRESSIVE DISORDER NOS)	Current (2 weeks) Past Recurrent
	MOOD DISORDER DUE TO A GENERAL MEDICAL CONDITION	Current (2 weeks) Past
	SUBSTANCE INDUCED MOOD DISORDER	Current (2 weeks) Past
AY	DYSTHYMIA	Current
B	SUICIDALITY	Current (Past Month) ❑ Low ❑ Moderate ❑ High
C	MANIC EPISODE	Current Past
	HYPOMANIC EPISODE	Current Past
	BIPOLAR I DISORDER	Current Past
	BIPOLAR II DISORDER	Current Past
	BIPOLAR DISORDER NOS	Current Past
	BIPOLAR I DISORDER WITH PSYCHOTIC FEATURES	Current Past
	MANIC EPISODE DUE TO A GENERAL MEDICAL CONDITION	Current (2 weeks) Past
	HYPOMANIC EPISODE DUE TO A GENERAL MEDICAL CONDITION	Current (2 weeks) Past
	SUBSTANCE INDUCED MANIC EPISODE	Current (2 weeks) Past

	SUBSTANCE INDUCED HYPOMANIC EPISODE	Current (2 weeks) Past
	MOOD DISORDER NOS	Lifetime
D	PANIC DISORDER	Current (Past Month) Lifetime
	ANXIETY DISORDER WIITH PANIC ATTACKS DUE TO A GENERAL MEDICAL CONDITION	Current
	SUBSTANCE INDUCED ANXIETY DISORDER WITH PANIC ATTACKS	Current
E	AGORAPHOBIA	Current
F	SOCIAL PHOBIA (Social Anxiety Disorder)	Current (Past Month) Generalized Non-Generalized
FA	SPECIFIC PHOBIA	Current
G	OBSESSIVE-COMPULSIVE DISORDER (OCD)	Current (Past Month)
	OCD DUE TO A GENERAL MEDICAL CONDITION	Current
	SUBSTANCE INDUCED OCD	Current
H	POSTTRAUMATIC STRESS DISORDER	Current (Past Month)
HL	POSTTRAUMATIC STRESS DISORDER	Lifetime
I	ALCOHOL DEPENDENCE ALCOHOL ABUSE	Past 12 Months Past 12 Months
IL	ALCOHOL DEPENDENCE ALCOHOL ABUSE	Lifetime Lifetime
J	SUBSTANCE DEPENDENCE (Non-alcohol) SUBSTANCE ABUSE (Non-alcohol)	Past 12 Months Past 12 Months
JL	SUBSTANCE DEPENDENCE (Non-alcohol) SUBSTANCE ABUSE (Non-alcohol)	Lifetime Lifetime
K	PSYCHOTIC DISORDERS	Lifetime Current
	MOOD DISORDER WITH PSYCHOTIC FEATURES	Current
	MOOD DISORDER WITH PSYCHOTIC FEATURES	Lifetime
	SCHIZOPHRENIA	Current Lifetime
	SCHIZOAFFECTIVE DISORDER	Current Lifetime
	SCHIZOPHRENIFORM DISORDER	Current Lifetime
	BRIEF PSYCHOTIC DISORDER	Current Lifetime
	DELUSIONAL DISORDER	Current Lifetime
	PSYCHOTIC DISORDER DUE TO A GENERAL MEDICAL CONDITION	Current Lifetime

	SUBSTANCE INDUCED PSYCHOTIC DISORDER	Current Lifetime
	PSYCHOTIC DISORDER NOS	Current Lifetime
L	ANOREXIA NERVOSA	Current (Past 3 Months)
M	BULIMIA NERVOSA	Current (Past 3 Months)
	BULMIA NERVOSA, PURGING TYPE	Current
	BULMIA NERVOSA, NON-PURGING TYPE	Current
	ANOREXIA NERVOSA, BINGE EATING/PURGING TYPE	Current
	ANOREXIA NERVOSA, RESTRICTING TYPE	Current
N	GENERALIZED ANXIETY DISORDER (GAD)	Current (Past 6 Months)
	GAD DUE TO A GENERAL MEDICAL CONDITION	Current
	SUBSTANCE INDUCED GAD	Current
O	SOMATIZATION DISORDER	Current Lifetime
P	HYPOCHONDRIASIS	Current
Q	BODY DYSMORPHIC DISORDER	Current
R	PAIN DISORDER	Current
S	CONDUCT DISORDER	Current (past 12 months)
T	ATTENTION DEFICIT/ HYPERACTIVITY DISORDER	Current (Past 6 months) (Children /Adolescents)
	ADHD COMBINED	
	ADHD INATTENTIVE	
	ADHD HYPERACTIVE / IMPULSIVE	
TA	ATTENTION DEFICIT/ HYPERACTIVITY DISORDER	Current (Past 6 months) (Adults)
	ADHD COMBINED	
	ADHD INATTENTIVE	
	ADHD HYPERACTIVE / IMPULSIVE	
U	PREMENSTRUAL DYSPHORIC DISORDER	Current
V	MIXED ANXIETY DEPRESSIVE DISORDER	Current
W	ADJUSTMENT DISORDERS	Current
X	MEDICAL, ORGANIC, DRUG CAUSE RULED OUT	
Y	ANTISOCIAL PERSONALITY DISORDER	Lifetime

APPENDIX B. SAMPLE READINESS TO CHANGE QUESTIONNAIRE

SAMPLE READINESS TO CHANGE QUESTIONNAIRE

0=strongly agree; 1=agree; 2=unsure; 3=disagree; 4=strongly disagree

1.	I don't think I drink too much	0	1	2	3	4
2.	I am trying to drink less than I used to	0	1	2	3	4
3.	I enjoy my drinking, but sometimes I drink too much	0	1	2	3	4
4.	Sometimes I think I should cut down on my drinking	0	1	2	3	4
5.	It's a waste of time thinking about my drinking	0	1	2	3	4
6.	I have just recently changed my drinking habits	0	1	2	3	4
7.	Anyone can talk about wanting to do something about drinking, but I am actually doing something about it	0	1	2	3	4
8.	I am at the stage where I should think about drinking alcohol less	0	1	2	3	4
9.	My drinking is a problem sometimes	0	1	2	3	4
10.	There is no need for me to think about changing my drinking	0	1	2	3	4
11.	I am actually changing my drinking habits right now	0	1	2	3	4
12.	Drinking less alcohol would be pointless for me	0	1	2	3	4

APPENDIX C. SAMPLE 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 D. SAMPLE CLINICAL GLOBAL IMPRESSION - IMPROVEMENT

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

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

APPENDIX E. SAMPLE STRUCTURED INTERVIEW GUIDE FOR GLOBAL IMPRESSIONS

Structured Interview Guide for Global Impressions (SIGGI)

PPD 2014

ALK3831-401

Instructions for Raters

This interview guide explores the *global impact* of identified "**targeted**" symptoms of interest on behavior and function within the PAST SEVEN DAYS. To be eligible for this study (**ALK3831-401**), subjects must meet DSM-IV-TR or DSM-5 criteria for Schizophrenia AND DSM-5 criteria for Alcohol Use Disorder (AUD). In this study, subjects may have mild to moderate symptoms of schizophrenia and symptoms of AUD that overall cause minimal, mild, or moderate impact on behavior or function.

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 presence of relevant symptoms of schizophrenia and AUD 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 *(includes BOTH Schizophrenia and Alcohol Use Disorder)*

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)? SYMPTOM LISTING (Identify SYMPTOM and DURATION)

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? _____ **% of time**

4. SCORE AND DOCUMENT
CGI SEVERITY ASSESSMENT: _____ (1-7) (use scoring guide/anchors provided for specific study/evaluation) **DOCUMENT JUSTIFICATION FOR DERIVED SCORE FROM ALL AVAILABLE CLINICAL DATA:**

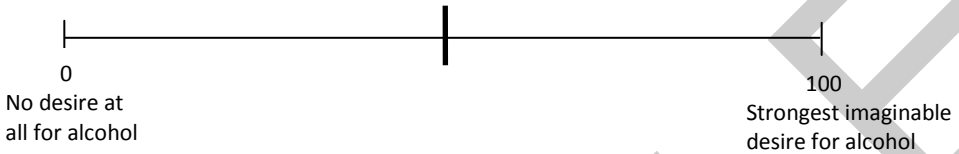
CGI-S SCORING GUIDELINES		
1	Normal, not at all ill	Symptoms of disorder have not been present in the past seven days
2	Borderline mentally ill	Subtle or suspected pathology present within the past seven days
3	Mildly ill	Clearly established symptoms causing minimal, if any, distress for the subject or difficulty in social and occupational function
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 F. SAMPLE VISUAL ANALOG SCALE

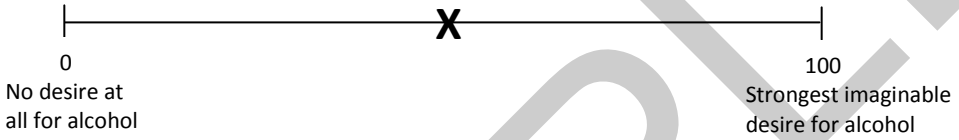
VISUAL ANALOG SCALE – Desire for Alcohol

Instructions: Below is a question regarding your desire for alcohol. We would like to know how strong your desire for alcohol has been during this past week. Please indicate your answer by placing a vertical mark (**I**) somewhere on the line between **0** and **100** to indicate how strong your desire for alcohol has been this past week.

Correct:

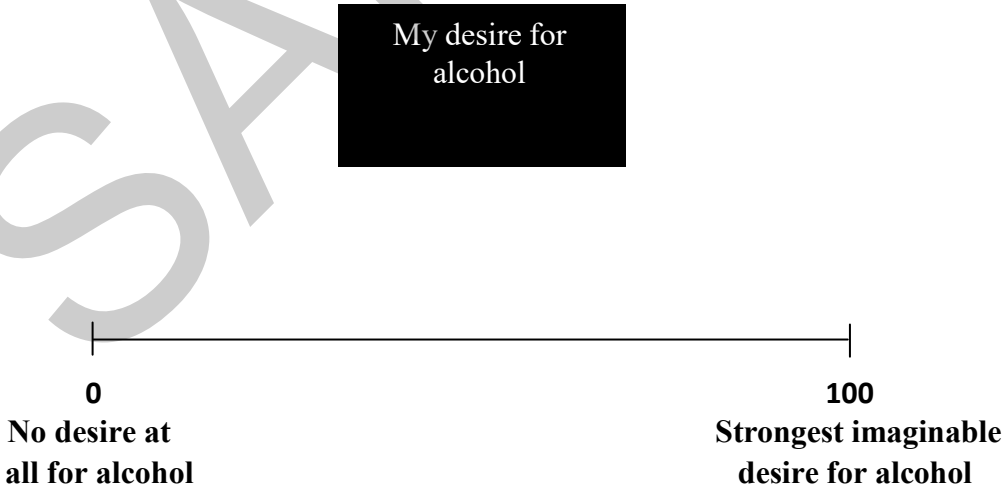


Incorrect:



If you make a mistake, cross out your answer, initial and date it, and place a new vertical mark on the line.

Please indicate how strong your desire for alcohol has been during this past week below:



APPENDIX G. SAMPLE PERSONAL AND SOCIAL PERFORMANCE SCALE

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

(1) Make note of the patient's level of dysfunction during the *past month* for the 4 main areas below. The *functioning criteria* below must be used to determine the level of dysfunction. Note that there are some common criteria for areas a-c and other criteria specifically for area d.

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

Level of severity: areas a-c

(i) Absent
(ii) Mild: only recognised by someone who is very close to the person
(iii) Manifest: difficulties that are clearly visible to anybody, although they do not substantially interfere with the person's ability to perform a role in this area, taking into account his/her socio-cultural context, age, sex and level of education.
(iv) Marked: difficulties considerably hinder the person from performing his/her role in this area. The person is still capable of performing some tasks, although insufficiently and occasionally, without professional or social help. If the person is helped by someone, s/he may qualify for the previous level of functioning.
(v) Severe: difficulties that make the person unable to perform any role in this area if not helped by a professional, or the person has a destructive role, however, there are no survival risks
(vi) Very severe: deterioration and extreme difficulties which may put the person's survival at risk

Levels of severity: area d

(i) Absent
(ii) Mild: being rude, unsociable or slight complaints
(iii) Manifest: speaking too loudly or speaking to others in a too familiar manner, or eating in a socially unacceptable way
(iv) Marked: insulting other people in public, breaking or throwing objects, frequently behaving in a socially unacceptable way, but not dangerous way (e.g. undressing or urinating in public)
(v) Severe: frequent verbal threats or physical attacks without intention or possible serious injuries
(vi) Very severe: frequent aggressive acts, aimed to cause serious injuries

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

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

(3) Adjustment within the 10-point range

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

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

APPENDIX H. SAMPLE 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

PPD Version 1.6 June, 2011

APPENDIX I. SAMPLE 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.

PPD Version 1.6 June, 2011

APPENDIX J. SAMPLE 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

PPD 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

PPD Version 1.6 June, 2011

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 K. SAMPLE COLUMBIA SUICIDE SEVERITY RATING SCALE

- "Baseline/ Screening" Version
- "Since Last Visit" Version

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

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

Disclaimer:

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

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

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

SUICIDAL IDEATION

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

	Lifetime: Time He/She Felt Most Suicidal	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g. *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…..and I would never go through with it".* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). For prior to study entry, ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation*** Past X Months - ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	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.

Disclaimer:

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

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

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

SUICIDAL IDEATION

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

Since Last Visit

1. Wish to be Dead — Yes ☐ No ☐

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

If yes, describe:

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

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

If yes, describe:

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

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

If yes, describe:

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

Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".*
Have you had these thoughts and had some intention of acting on them?

If yes, describe:

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

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

If yes, describe:

INTENSITY OF IDEATION

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

Most Severe

Most Severe Ideation: _____ _____

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

Frequency ____

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

Duration ____

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

Controllability ____

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

Deterrents ____

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

Reasons for Ideation ____

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

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

APPENDIX L. PARTIAL LIST OF PROHIBITED CYTOCHROME P450 3A4 (CYP3A4) 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