A Phase 3 Multicenter Study of the Long-term Safety and Tolerability of ALKS 5461 for the Adjunctive Treatment of Major Depressive Disorder in Adults who Have an Inadequate Response to Antidepressant Therapy (the FORWARD-2 Study)

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CLINICAL STUDY PROTOCOL

ALK5461-208

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Sponsor	Alkermes, Inc. 852 Winter Street Waltham, MA 02451 USA

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2. SYNOPSIS

Name of Sponsor/ Company:
Alkermes, Inc

Name of Study Drug:
ALKS 5461

Name of Active Ingredients:
buprenorphine (BUP) and samidorphan

Title of Study:
A Phase 3 Multicenter Study of the Long-term Safety and Tolerability of ALKS 5461 for the Adjunctive Treatment of Major Depressive Disorder in Adults who Have an Inadequate Response to Antidepressant Therapy (the FORWARD-2 Study)

Investigators:
This will be a multicenter, multinational study.

Study Period:	**Phase of development:**
First subject consented: Q2 2014 Last subject completed: 2017	3

Objective:

- To assess the long-term safety and tolerability of ALKS 5461 for use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD)

Methodology:

ALKS 5461 is a fixed-dose combination product consisting of BUP and samidorphan in a 1:1 (weight/weight) ratio. Throughout this protocol ALKS 5461 dose levels will be referred to as dose of BUP/samidorphan expressed as weight in mg (eg, a 2 mg BUP:2 mg samidorphan dose will be expressed as ALKS 5461 2/2).

This study will evaluate the safety and tolerability, and explore the treatment effect of ALKS 5461 administered for 52 weeks as an adjunctive therapy to antidepressants for the treatment of MDD in subjects who have had 1 to 2 inadequate responses to an approved antidepressant therapy (ADT).

Subjects will have been treated with an adequate dose of an approved ADT for at least 8 weeks, with a stable dose over the last 4 weeks prior to study entry. An adequate dose is defined as a dose that is greater than or equal to the minimum effective dose on the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (ATRQ), inclusive of up to 3 weeks for titration into the adequate dose range.

Subjects will enter into the study in one of the following 3 ways, based on their previous experience with ALKS 5461:

1. New Subjects: those who have not been randomized in a prior study of ALKS 5461 within 2 years
2. Continuing Subjects: those who have completed the treatment period of study ALK5461-205, ALK5461-206, ALK5461-207, or ALK5461-210 within the past 10 days
3. Lead-in Subjects: those who participated in study ALK5461-205, ALK5461-206, or ALK5461-207 within the past 10 days, and met the criteria for response to ADT during the prospective lead-in (PLI) period of that antecedent study, but did not meet the criteria for

remission

All New Subjects will be initially evaluated for eligibility at screening (Visit 1), to occur up to 28 days prior to Visit 2. Continuing Subjects and Lead-in Subjects will not have a separate screening visit and will begin participation in this study at Visit 2.

At Visit 2, all eligible, consenting subjects will begin the treatment period. Subjects who are not receiving ALKS 5461 at study entry will require a 1-week titration period. Subjects entering the study already receiving ALKS 5461 will not require a titration period. To maintain the blinded dosing scheme in ALK5461-206 and ALK5461-207, Continuing Subjects from those studies will be blinded to whether or not they receive a 1-week titration.

Starting on Day 8 (Visit 3), the target dose for the remaining 51 weeks for all participating subjects will be ALKS 5461 2/2. Attempts should be made to achieve and maintain the ALKS 5461 2/2 dose throughout that period, if it is tolerated. However, flexible down-titration to ALKS 5461 1/1 or 0.5/0.5 is permitted at the investigator's discretion, if tolerability issues persist. Once a subject has stabilized after down-titration, attempts should again be made to achieve and maintain the target dose of ALKS 5461 2/2 over the course of treatment, dependent on the individual subject's experience with study drug tolerability.

Dose adjustment of ADT during the treatment period is permitted for optimal therapeutic effect within the recommended dose range, however ADT dose adjustment should not be made within the same week as ALKS 5461 dose adjustment. Furthermore, subjects are not permitted to change ADTs during the course of the study period.

During the 52-week treatment period, subjects will return to the clinic for periodic scheduled visits (Visits 2-14) at which safety, tolerability, and treatment effect over time will be assessed.

A 4-week safety follow-up period will occur following the ALKS 5461 treatment period. During the 4-week follow-up period, there are a total of 4 clinic visits (Visits 15-18), as well as 7 safety assessments by phone. The clinic visits will occur 1 day, 1 week, 2 weeks, and 4 weeks following the end of treatment visit (Visit 14). The phone assessments will occur daily for the first week between visits, and weekly during the second and third week.

If any adverse events (AEs) are reported that relate to opioid withdrawal (eg, nausea, vomiting, restlessness, hyperhidrosis) during a phone assessment in the follow-up period, the subject will be asked to come into the clinic as soon as possible to receive a Clinical Opiate Withdrawal Scale (COWS) assessment.

Number of Subjects (planned):

It is estimated that approximately 1,500 subjects will be enrolled in this study.

Main Criteria for Inclusion:

The main criteria for study eligibility are as follows:

- New Subjects must have a Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) MDD diagnosis and an inadequate response to current approved ADT. They will not have participated in a prior trial of ALKS 5461 within 2 years.
- Continuing Subjects must have completed the treatment period of ALK5461-205, ALK5461-206, ALK5461-207, or ALK5461-210 within 10 days of the baseline visit for this study.
- Lead-in Subjects must have completed the PLI period of ALK5461-205, ALK5461-206, or ALK5461-207 within 10 days of the baseline visit for this study and met the criteria for response to ADT during the PLI, but not for remission.

Study Drug, Dosage, Duration, and Mode of Administration:

ALKS 5461 consists of buprenorphine (BUP), a United States Drug Enforcement Administration (US DEA) Schedule III narcotic, and samidorphan, a US DEA Schedule II controlled substance.

The following doses will be used in the study:

- ALKS 5461 0.5/0.5 (0.5 mg BUP:0.5 mg samidorphan)
- ALKS 5461 1/1 (1 mg BUP:1 mg samidorphan)
- ALKS 5461 2/2 (2 mg BUP:2 mg samidorphan)

Tablets will be administered sublingually, daily for up to 52 weeks.

Reference Therapy, Dosage, Duration and Mode of Administration:

This safety study has no reference therapy.

Study and Treatment Duration:

For New Subjects, the study duration will be up to 60 weeks, which includes up to 4 weeks for the screening period, 52 weeks for the dosing period, and 4 weeks for the follow-up period.

For Continuing Subjects and Lead-in Subjects, the study duration will be up to 56 weeks, which includes 52 weeks for the dosing period, and 4 weeks for the follow-up period.

Criteria for Evaluation:

Safety and Tolerability:

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

- AEs
- clinical laboratory tests (chemistry, hematology, and urinalysis)
- vital signs
- body weight
- electrocardiogram (ECG)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- COWS

Efficacy: The following assessments will be made for exploratory evaluation of treatment effect over time:

- Montgomery-Åsberg Depression Rating Scale (MADRS)
- Hamilton Rating Scale for Anxiety (HAM-A)
- Clinical Global Impression – Severity (CGI-S)

Pharmacokinetics:

Plasma samples will be collected at specified time points from consenting subjects enrolled in the US only. These samples will be used to quantify concentrations of BUP, samidorphan, and relevant metabolites. Concentrations of background ADTs that subjects report taking during the study may be quantified, as appropriate.

Statistical Methods:

Safety: Safety and tolerability analyses will be performed using data from the safety population, defined as all subjects who receive at least 1 dose of ALKS 5461. Reported AE terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) preferred terms and system organ class categories.

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

Efficacy: Exploratory evaluation of treatment effect over time will be performed using data from the full analysis set (FAS), defined as all subjects who receive at least 1 dose of ALKS 5461 and complete at least 1 post-baseline efficacy assessment (MADRS).

Pharmacokinetics:

Plasma concentration data for BUP, samidorphan, and relevant metabolites as well as background ADTs will be listed and summarized. Additionally, concentration data obtained from this study may be combined with data from other studies for population PK analysis, which will be reported separately.

Sample Size Considerations:

It is estimated that approximately 1,500 subjects will be enrolled in order to ensure that a minimum of 100 subjects achieve 12 months of exposure to ALKS 5461 and a minimum of 300 subjects achieve 6 months of exposure.

3. TABLE OF CONTENTS

LIST OF TABLES

LIST OF APPENDICES

4. LIST OF ABBREVIATIONS

The following abbreviations are used in this study protocol.

Abbreviation or specialist term	Explanation
ADT	antidepressant therapy
AE	adverse event
ATRQ	Massachusetts General Hospital Antidepressant Treatment Response Questionnaire
BMI	body mass index
BUP	buprenorphine
CGI-S	Clinical Global Impression–Severity
COWS	Clinical Opiate Withdrawal Scale
CRO	contract research organization
C-SSRS	Columbia Suicide Severity Rating Scale
CSA	Clinical Study Agreement
CST	Clinical Surveillance Team
CYP	cytochrome P450
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision
ECG	electrocardiogram
eCRF	electronic case report form
FAS	full analysis set
GCP	Good Clinical Practice
HAM-A	Hamilton Rating Scale for Anxiety
HAM-D	17-item Hamilton Rating Scale for Depression
HbA1c	glycosylated hemoglobin
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
IRT	interactive response technology

Abbreviation or specialist term	Explanation
IUD	intrauterine device
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	major depressive disorder
MDE	major depressive episode
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Neuropsychiatric Interview
OTC	over-the-counter
PCS	potentially clinically significant
PK	pharmacokinetic(s)
PLI	prospective lead-in
QTcB	corrected QT interval – Bazett's formula
QTcF	corrected QT interval – Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SL	sublingual
SIGH-A	Structured Interview Guide for the Hamilton Rating Scale for Anxiety
SIGH-D	Structured Interview Guide for the Hamilton Rating Scale for Depression
SIGMA	Structured Interview Guide for the Montgomery-Åsberg Depression Rating Scale
SNRI	serotonin-norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TEAE	treatment-emergent adverse event
WHO-ATC	World Health Organization Anatomical Therapeutic Chemical

5. INTRODUCTION

Alkermes is developing ALKS 5461, a fixed-dose combination tablet consisting of buprenorphine (BUP) and samidorphan in a 1:1 (weight/weight) ratio for once-daily sublingual administration for use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD).

MDD is a serious, and in some cases life-threatening, condition. Current therapy is limited and insufficient. Selective serotonin reuptake inhibitors (SSRI) or serotonin-norepinephrine reuptake inhibitors (SNRI) are recommended as first-line therapy; however, the large majority of patients do not experience an adequate response [Rush, 2006]. For patients with MDD who have an inadequate response to approved first-line antidepressant therapy (ADT) the only currently approved agents for adjunctive treatment are atypical antipsychotics. However, this class of medicines is associated with serious toxicity, including tardive dyskinesia, which may be irreversible, as well as neuroleptic malignant syndrome and agranulocytosis, both of which are potentially fatal. These conditions and other side effects of the atypical antipsychotics commonly lead to discontinuation of treatment [Spielmans, 2013].

The development of an adjunctive treatment that avoids the toxicity associated with atypical antipsychotics is an important step toward addressing the suboptimal treatment of MDD and the related public health consequences. ALKS 5461 offers a unique mechanism of action for the treatment of MDD, modulation of the opioid system. From 1982 to the present, there have been at least 8 published studies of BUP in depressed patients [Spielmans, 2013]. These studies demonstrated striking antidepressant effects with BUP treatment, particularly in patients with MDD who have had multiple prior inadequate responses to therapy. Despite this evidence of efficacy with BUP, the risk of diversion, abuse, and dependence have precluded routine clinical use of BUP, and opioids in general, in the treatment of depression.

ALKS 5461 is a fixed-dose combination of BUP (a μ-opioid receptor partial agonist) and samidorphan (a μ-opioid receptor antagonist). Samidorphan is a new chemical entity optimized for high potency and high sublingual (SL) bioavailability to facilitate co-formulation with BUP for SL administration. ALKS 5461 was specifically designed to confer therapeutic benefits in the treatment of MDD through modulation of the opioid system. The inclusion of samidorphan in the ALKS 5461 combination is intended to counteract the subjective, rewarding and addictive properties of BUP and thus address the risk of abuse and dependence.

Subjects treated with ALKS 5461 in Phase 1 and the Phase 2 studies showed substantial and clinically important improvements in depressive symptoms compared with those treated with placebo. Safety and tolerability data from these studies showed that ALKS 5461 was safe and generally well tolerated, and further no evidence has been found that ALKS 5461 is associated with motor disorders or metabolic dysregulation, the important toxicities associated with atypical antipsychotics. All together these findings indicate that ALKS 5461 has the potential to address an unmet medical need in this serious and in some cases life-threatening, condition.

Full summaries of nonclinical and clinical results available to date on the pharmacokinetics (PK), safety, and efficacy of ALKS 5461, as well as of samidorphan and buprenorphine as individual and co-administered therapeutic agents are summarized in the Investigator's Brochure (IB).

5.1. Study Rationale

Subjects with MDD and an inadequate response to concomitant ADT who were treated with ALKS 5461 in both a Phase 1 study (ALK33BUP-201) and a Phase 2 study (ALK5461-202) showed substantial and clinically important improvements in depressive symptoms compared with those who received placebo. Safety and tolerability data from these studies showed that ALKS 5461 was safe and generally well tolerated, and further showed no evidence that ALKS 5461 is associated with motor disorders or metabolic dysregulation, the important toxicities associated with atypical antipsychotics.

In the clinical trials of ALKS 5461 to date, however, only data on the short-term safety and tolerability of ALKS 5461 have been collected. This study is designed to assess long-term safety and tolerability of ALKS 5461, as well as to explore treatment effect over time.

5.2. Dose Selection

Note: Throughout this protocol ALKS 5461 dose levels will be referred to as dose of BUP/samidorphan expressed as weight in mg (eg, a 2 mg BUP:2 mg samidorphan dose will be expressed as ALKS 5461 2/2).

Doses for the current study were identified based on completed studies of ALKS 5461 including a drug-drug interaction study of BUP with samidorphan (ALK33-008), and a Phase 2 (ALK5461-202) study in adults with MDD and inadequate response to concomitant ADT.

Study ALK33-008, the drug-drug interaction study, showed that a 1:1 ratio of BUP and samidorphan in doses up to 8/8 provided maximal blockade of objective and subjective μ opioid agonist effects of BUP. Thus doses in the current study, which use a 1:1 ratio, are expected to mitigate BUP's subjective, rewarding, and addictive effects.

Study ALK5461-202 was a Phase 2, multicenter, randomized, double-blind, placebo-controlled, sequential-parallel-comparison-design clinical trial which evaluated ALKS 5461 at doses of 2/2 and 8/8. The ALKS 5461 2/2 dose was shown to be safe, well tolerated, and efficacious. After 4 weeks of dosing, statistically significant improvements from baseline were found for the ALKS 5461 2/2 group versus the placebo group for the primary efficacy endpoint (change in the 17-item Hamilton Rating Scale for Depression [HAM-D] total score), as well as several secondary endpoints, (change in Montgomery-Åsberg Depression Rating Scale [MADRS] total score and Clinical Global Impression - Severity [CGI-S] score). Additionally, the rate of treatment response and the rate of remission as defined by MADRS scores were significantly higher in the ALKS 5461 2/2 group versus the placebo group.

The selection of the ALKS 5461 2/2 dose is further supported by its improved tolerability profile compared with results for the ALKS 5461 8/8 dose.

6. OBJECTIVE

The objective of this study is to assess the long-term safety and tolerability of ALKS 5461 for use as an adjunctive therapy to antidepressants for the treatment of MDD.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Subject Inclusion Criteria

7.1.1. All Subjects

In order to qualify for participation in this study, all subjects must meet all of the following criteria:

1. Be willing and able to provide informed consent
2. Be willing and able to follow the study procedures as outlined in the protocol, including adherence with both approved antidepressant therapy (ADT) and study drug regimen
3. Agree to use an approved method of contraception for the duration of the study unless surgically sterile or postmenopausal (See Section 8.4.1 for details)
4. Have the potential to safely benefit from the administration of ALKS 5461, in the opinion of the investigator

7.1.2. New Subjects

In order to qualify for participation in this study, in addition to meeting the criteria for all subjects presented in Section 7.1.1, New Subjects must also meet all of the following criteria:

5. Be between 18 and 70 years of age, inclusive
6. Have a body mass index (BMI) 18.0 - 40.0 kg/m^2
7. Have not been randomized in a prior study of ALKS 5461 within 2 years
8. Have a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) MDD diagnosis at screening, as assessed and confirmed by the Mini International Neuropsychiatric Interview (MINI) administered by qualified site staff. The diagnosis of MDD must be considered by the investigator as the primary source of current distress and functional impairment
9. Have a current major depressive episode (MDE) lasting 8 weeks to 24 months
10. Have been treated with an adequate dose of an approved ADT during the current MDE for at least 8 weeks, with the same, adequate dose over the last 4 weeks, which is expected to remain stable throughout the study
11. Have an inadequate response to current ADT and up to 1 prior ADT during the current MDE. An inadequate response is defined as less than a 50% reduction in depressive symptom severity during a course of treatment at least 8 weeks in duration with an adequate dose of an approved ADT, as assessed on-site using the Massachusetts General Hospital Antidepressant Treatment Questionnaire (ATRQ)

    (NOTE: If a subject had an adequate response to an ADT in the past, but now has relapsed on the same ADT at the same or lower dose and is experiencing a new MDE, this would not represent an adequate trial of an ADT for this new MDE)

12. Have a HAM-D total score of ≥14 at Visit 1 and ≥10 at Visit 2

7.1.3. Continuing Subjects

In order to qualify for participation in this study, in addition to meeting the criteria for all subjects presented in Section 7.1.1, Continuing Subjects must also meet the following criterion:

13. Have completed the treatment period of ALK5461-205, ALK5461-206, ALK5461-207, or ALK5461-210 within 10 days of Visit 2

7.1.4. Lead-in Subjects

In order to qualify for participation in this study, in addition to meeting the criteria for all subjects presented in Section 7.1.1, Lead-in Subjects must also meet all of the following criteria:

14. Have completed the prospective lead-in (PLI) of study ALK5461-205, ALK5461-206, or ALK5461-207 within the past 10 days; criteria for completion of the PLI includes 1) at least 8 weeks of ADT with at least 5 weeks at the minimally effective dose and 2) completion of Visits 1a through 1f
15. Have demonstrated a treatment response during the PLI of the antecedent study, but failed to achieve remission from MDD, as determined in an interactive voice or web response system (IxRS) using masked criteria

7.2. Subject Exclusion Criteria

7.2.1. All Subjects

No individuals may participate in this trial if they meet any of the following criteria:

1. Have any finding that in the view of the investigator or medical monitor would compromise the safety of the subject or affect their ability to fulfill the protocol visit schedule or visit requirements
2. Have a positive test for drugs of abuse at screening or Visit 2 (exception: a positive screen for benzodiazepine may not be exclusionary when such medication is medically indicated for insomnia)
3. Are pregnant, planning to become pregnant, or breastfeeding during the study

7.2.2. New Subjects

New Subjects will be excluded from participation in this trial if they meet any of the following criteria:

4. Have any current “primary” Axis I diagnosis other than MDD, where “primary” is defined by the investigator as the primary source of current distress and functional impairment
5. Have any of the following psychiatric conditions per DSM-IV-TR criteria, as assessed by the MINI. Conditions not assessable by the MINI should be assessed by clinical judgment:
    a. Lifetime history of an Axis I diagnosis of dementia, schizophrenia or other psychotic disorder (including psychotic depression), or bipolar disorder (I or II)

b. History within the past 12 months of an Axis I diagnosis of eating disorder, posttraumatic stress disorder, or acute stress disorder
c. Clinically significant current Axis II diagnosis of borderline, antisocial, paranoid, schizoid, schizotypal, or histrionic personality disorder
d. Current diagnosis or clinical evidence of any cognitive disorder at screening

6. Have experienced hallucinations, delusions, or any psychotic symptoms in the current MDE
7. Have initiated psychotherapy within 6 weeks of screening
8. Have received adjunctive therapy at an adequate dose and duration in combination with their approved ADT for the purpose of augmenting the effects of the ADT at any time during the current MDE (such adjunctive therapies include, but are not restricted to: atypical antipsychotics, monoamine oxidase inhibitors, lithium, tricyclic antidepressants, psychostimulants, bupropion, and BUP)
9. Have been hospitalized for MDD within 3 months prior to screening
10. Have used opioid agonists (eg, codeine, oxycodone, tramadol, morphine) or opioid antagonists (eg, naloxone, naltrexone) within 14 days before screening, or have an anticipated need for opioid use at any point during the study (eg, planned surgery)
11. Have used an extended-release formulation of an opioid antagonist within 2 months prior to screening
12. Have initiated a hypnotic agent for insomnia (eg, benzodiazepines, zolpidem, trazodone) within 30 days prior to screening. Have used a hypnotic agent for insomnia >3 times/week within 30 days of screening, or expect to use any of these agents at >3 times/week at any time during the study. Have used a hypnotic agent for any indication other than insomnia within 30 days prior to screening (see Section 8.4.2.2 for further details)
13. Have initiated or had dose adjustment to hormone replacement therapy (including testosterone) or an oral contraceptive within 30 days of screening
14. Have used inducers or moderate to strong inhibitors of cytochrome P450 (CYP) 3A4 (prescription medications, over-the-counter medications [OTC], or dietary supplements) within 30 days prior to screening (see Appendix A for examples of prohibited CYP3A4 modulators)
15. Have received electroconvulsive therapy treatment within the last 2 years, or received more than 1 course of electroconvulsive treatment during their lifetime
16. Pose a current suicide risk, as evidenced by any of the following:
    a. it is the opinion of the investigator that the subject may be at risk for suicide
    b. the subject responds “Yes” to Question # 4 (“Active Suicidal Ideation with Some Intent to Act, Without Specific Plan”) or Question # 5 (“Active Suicidal Ideation with Specific Plan and Intent”) on the Baseline Columbia Suicide Severity Rating Scale (C-SSRS), if the most recent episode occurred within the past 12 months
    c. the subject has attempted suicide within the past 2 years

17. Have a QT interval >450 msec for men and >470 msec for women, assessed in a relaxed state, as corrected by the Fridericia formula (QTcF) observed at Visit 1 or Visit 2
18. Have an aspartate aminotransferase or alanine transaminase measurement of >2 times the upper limit of normal at Visit 1.
19. Have current evidence of or history of any of the following:
    a. compromised respiratory function (eg, chronic obstructive pulmonary disease, respiratory depression, signs or symptoms of hypoxia at screening)
    b. thyroid pathology (unless stabilized and euthyroid for >3 months at the time of screening)
    c. seizure disorder (excluding febrile seizures)
    d. hepatitis or human immunodeficiency virus (HIV) infection
    e. myasthenia gravis
    f. any contraindicated medical condition as per the approved labeling for buprenorphine
20. Have current evidence of, or a history in the past 12 months of, alcohol or substance abuse or dependence (excluding nicotine) per DSM-IV-TR criteria as assessed by the MINI
21. Have a positive breath alcohol test at screening
22. Have a history of intolerance, allergy or hypersensitivity to BUP or opioid antagonists (eg, naltrexone, naloxone)
23. Have had a significant blood loss (>500 mL) or blood donation (including platelets or plasma) within 60 days of screening or between screening and randomization, or anticipated blood donation at any time during the trial
24. Have participated in any of the following:
    a. clinical studies of more than 2 distinct investigational products with a central nervous system indication in the past 4 years
    b. any clinical study of an investigational product given as an adjunctive treatment for MDD at any time during the current MDE
    c. any clinical study of an investigational product and/or have received an investigational drug or device within 30 days of screening
25. Are an employee of the investigator or study center, or immediate family* of such employees or the investigator
26. Are an employee or an immediate family member* of an employee (permanent, temporary contract worker, or designee responsible for the conduct of the study) of Alkermes or the contract research organization (CRO) executing this study or any prior ALKS 5461 study

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

7.3. Subject Withdrawal

Any subject who signs the informed consent form for this study but does not qualify for ALKS 5461 dosing will be considered a screen failure.

A subject may be discontinued from the study at any time if the subject, investigator, or sponsor determines that it is not in the best interest of the subject to continue participation.

Examples of reasons for subject discontinuation may include, but are not limited to, the following:

- Failure to meet eligibility criteria
- Adverse Event
- Lack of Efficacy
- Physician's decision
- Pregnancy (see Section 8.4.1)
- Protocol violation
- Non-compliance with study drug
- Withdrawal of consent
- Lost to follow-up
- Study terminated by Sponsor
- Other

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) and/or IxRS. The reason for discontinuation will be documented. If a subject is lost to follow-up, a reasonable attempt to contact the subject must be made and documented.

If a subject withdraws from the study for any reason, any ongoing adverse events (AEs) will be followed until resolution, until deemed stable by the investigator, or until the subject is deemed by the investigator to be lost to follow-up. If, in the opinion of the investigator, it is necessary to monitor a subject beyond the safety follow-up period, the follow-up period may be extended as necessary. In such instances, the sponsor and the investigator will agree to an acceptable follow-up schedule.

In the event that a subject chooses to withdraw from the study, the investigator should make a reasonable effort to ascertain the reason(s) for withdrawal, while fully respecting the subject's rights to do so. Subjects will be asked to return to the clinic for an early termination visit and follow-up visits. The early termination visit should be scheduled within 24 hours of the subject's last dose and will mirror the assessments scheduled to be collected at Visit 14. Following the early termination visit, subjects will be asked to participate in the safety follow-up period as detailed in Table 3. If the subject fails or refuses to return to the study center for clinic visits, 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.

7.4. Replacement of Subjects

Subjects who withdraw after receiving the first dose of study drug in this study will not be replaced.

8. STUDY DESIGN

8.1. Overall Study Design and Plan

This is a multicenter, multinational, study to evaluate the long-term safety and tolerability, and to explore treatment effect of 52 weeks of ALKS 5461 administration for use as an adjunctive therapy to antidepressants for the treatment of MDD in subjects who have had 1 to 2 inadequate responses to an approved ADT. All subjects in the study will have been treated with an adequate dose of an approved ADT for at least 8 weeks, at a stable dose over the last 4 weeks prior to study entry. An adequate dose is defined as the minimum effective dose or higher according to the applicable current approved label, inclusive of up to 1 week for titration into the adequate dose range.

Subjects will enter into the study in one of three ways, based on their previous experience with ALKS 5461:

1. New Subjects: those who have not randomized in a prior study of ALKS 5461 within 2 years
2. Continuing Subjects: those who have completed the treatment period of study ALK5461-205, ALK5461-206, ALK5461-207, or ALK5461-210 within the past 10 days
3. Lead-in Subjects: those who participated in study ALK5461-205, ALK5461-206, or ALK5461-207 and have completed the PLI within the past 10 days, and met the criteria for response to ADT during the PLI period of that antecedent study, but did not meet the criteria for remission. Criteria for completion of the PLI includes 1) at least 8 weeks of ADT with at least 5 weeks at the minimally effective dose and 2) completion of Visits 1a through 1f.

All New Subjects will be initially evaluated for eligibility at screening (Visit 1), to occur up to 28 days prior to Visit 2.

For Lead-in and Continuing Subjects, Visit 2 will be the first visit of this study and there will not be a separate screening visit.

While completion of Visit 2 of the antecedent study for Lead-In Subjects is not required, if a subject has completed a Visit 2 of the antecedent study, completed assessments taken at Visit 2 of the antecedent study do not need to be repeated at Visit 2 of this study unless more than 10 days elapses between these visits.

For Continuing Subjects, Visit 2 of this study must occur within 10 days of the subject's end of treatment visit in the prior study. Completed assessments taken at the end of treatment visit of the antecedent study do not need to be repeated at Visit 2 of this study. At Visit 2, all eligible, consenting subjects will begin the treatment period. Subjects entering the study already receiving ALKS 5461 will not require titration; all other subjects will require a 1-week ALKS 5461 titration period. Depending on the antecedent study, the titration may be blinded. Regardless of method of entry, all subjects will have been taking an SSRI, SNRI, or bupropion for at least 8 weeks at the beginning of the treatment period (Visit 2), and at an adequate dose for at least

5 weeks. Table 1 below shows the Week 1 titration and blinding schemes for the subjects entering by each path.

Table 1: Week 1 Titration and Blinding by Entry Dose and Antecedent Study

Dose Upon Study Entry	Antecedent Study	Week 1 Blinding	Week 1 Dosing Scheme
No study drug being given	• New Subjects • Lead-in Subjects • ALK5461-205 (after 1-week discontinuation period)	Unblinded	1-Week Titration • Days 1–3: ALKS 5461 0.5/0.5 • Days 4–7: ALKS 5461 1/1 • Days 8–364: ALKS 5461 2/2
Placebo	• ALK5461-206 • ALK5461-207	Blinded	
ALKS 5461 1/1	• ALK5461-207	Blinded	No Titration • Days 1–364: ALKS 5461 2/2
ALKS 5461 2/2	• ALK5461-206 • ALK5461-207	Blinded	
	• ALK5461-210	Unblinded	

Dosing is described in detail in Section 9.1.2. From Week 2 to 52, all participating subjects will take ALKS 5461 2/2 and an approved ADT, with allowable dose adjustments for tolerability as described in Section 9.5.

Study staff will administer the first dose of ALKS 5461 at Visit 2 (Day 1). From that point on during the treatment period, according to the schedule of visits as shown in Table 2, the staff will dispense ALKS 5461 for subjects' self-administration. Subjects will be advised to take the study drug at bedtime.

During the 52-week treatment period, subjects will return to the clinic for periodic scheduled visits (Visits 2-14) at which safety, tolerability, and treatment effect over time will be assessed.

A 4-week safety follow-up period will occur following the ALKS 5461 treatment period. During the 4-week follow-up period, there are a total of 4 clinic visits (Visits 15-18), as well as 7 safety assessments by phone. The clinic visits will occur 1 day, 1 week, 2 weeks, and 4 weeks following the end of treatment visit (Visit 14). The phone assessments will occur daily for the first week between visits, and weekly during the second and third week. See Table 3 for the schedule of assessments during the follow-up period.

If any AEs are reported that relate to opioid withdrawal (eg nausea, vomiting, restlessness, hyperhidrosis) during a phone assessment in the follow-up period, the subject will be asked to come into the clinic as soon as possible to receive a Clinical Opiate Withdrawal Scale (COWS) assessment.

After completing the study, ADT may be continued for up to 3 months, as appropriate, based on the investigator's clinical judgment.

8.2. Schedule of Visits and Assessments

The schedule of visits and assessments is shown in Table 2 for screening through the treatment period, and in Table 3 for the safety follow-up period.

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

Subjects who discontinue from the study prematurely will be encouraged to return for an early termination (ET) visit and to participate in a subsequent follow-up period. The Visit 14 assessments will serve as early termination assessments for any subject who withdraws prior to completion. The safety follow-up period for subjects who discontinue early should mirror the visits displayed in Table 3.

Table 2: Schedule of Visits and Assessments, Screening and Treatment Period

Evaluation	Screening [a]	ALKS 5461 Treatment Period												
		Base-line	Week 1	Week 2	Week 4	Week 6	Week 8	Week 14	Week 20	Week 26	Week 32	Week 38	Week 44	Week 52
Study Day:	**-28 to -1**	**1**	**8 (±1)**	**15 (±1)**	**29 (±3)**	**43 (±3)**	**57 (±3)**	**99 (±3)**	**141 (±3)**	**183 (±3)**	**225 (±3)**	**267 (±3)**	**309 (±3)**	**ET/365 [b] (±3)**
Visit Number:	**1**	**2 [c]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Informed Consent [d]	X													
Qualification/ Diagnostic Assessments														
Eligibility Criteria Review	X	X [e]												
Demographics	X													
Medical/ Psychiatric History	X	X [e]												
Serology Testing [f]	X													
ATRQ	X													
MINI	X													
Breath Alcohol Test [g]	X													
Height	X													
Full Physical Examination	X													
HAM-D	X	X [e]												
Qualification/ Safety Assessments														
Weight/ Vital Signs [h]	X	X [e]	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X [e]	X							X				X
Drug Screening [i]	X	X [e]	X					X		X		X		X
Pregnancy Testing [j]	X	X [e]						X		X		X		X
Symptom-Directed Physical Examination		X												X

Table 2: Schedule of Visits and Assessments, Screening and Treatment Period (Continued)

Evaluation	Screening[a]	ALKS 5461 Treatment Period											
		Base-line	Week 1	Week 2	Week 4	Week 6	Week 8	Week 14	Week 20	Week 26	Week 32	Week 38	Week 44	Week 52
Study Day:	**-28 to -1**	**1**	**8 (±1)**	**15 (±1)**	**29 (±3)**	**43 (±3)**	**57 (±3)**	**99 (±3)**	**141 (±3)**	**183 (±3)**	**225 (±3)**	**267 (±3)**	**309 (±3)**	**ET/365[b] (±3)**
Visit Number:	**1**	**2[c]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Blood and Urine Samples for Safety Labs	X	X[e]	X					X		X		X		X
C-SSRS[k]	X	X[e]	X	X	X	X	X	X	X	X	X	X	X	X
COWS[l]														X
Adverse Event Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication Review [m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Illicit Substances Review [n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Exploratory Efficacy Assessments														
HAM-A		X[e]			X		X	X		X		X		X
CGI-S		X[e]	X	X	X	X	X	X	X	X	X	X	X	X
MADRS[o]	X	X[e]	X	X	X	X	X	X	X	X	X	X	X	X
Additional Study Procedures														
Dispense Study Drug[p]		X	X	X	X	X	X	X	X	X	X	X	X	
Study Drug Adherence Review[q]			X	X	X	X	X	X	X	X	X	X	X	X
ADT Adherence Review [r]		X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sample – PK [s]			X	X	X	X	X	X	X	X	X	X	X	X
Emergency Treatment Card [t]		X	X	X	X	X	X	X	X	X	X	X	X	X

ADT=antidepressant therapy; ATRQ=Massachusetts General Hospital Antidepressant Treatment Questionnaire; CGI-S=Clinical Global Improvement – Severity; COWS=clinical opiate withdrawal scale; C-SSRS=Columbia Suicide Severity Rating Scale; ECG=electrocardiogram; ET=early termination; HAM-A=Hamilton Rating Scale for Anxiety; HAM-D=17-item Hamilton Rating Scale for Depression; MADRS=Montgomery-Åsberg Depression Rating Scale; MINI=Mini International Neuropsychiatric Interview; PK=pharmacokinetic.

[a] Only New Subjects will participate in the screening visit. Screening may be repeated in some cases for Potential New Subjects, but only after approval by the medical monitor

[b] Visit 14/ET should occur within 24 hours of the subject's last dose of ALKS 5461

[c] For Continuing Subjects and Lead-in Subjects, identical assessments taken at the subject's Visit 2 of the antecedent study for Lead in Subjects and last treatment visit of the antecedent study for continuing subjects do not need to be repeated at Visit 2 unless ,more than 10 days elapses between these visits. If more than 10 days elapses between visits, all assessments must be performed at Visit 2 (ie data cannot be carried forward).

[d] Eligible, consenting New Subjects will give written consent at the screening visit. Eligible, consenting Continuing Subjects and Lead-in Subjects will give written consent prior to participating in any study-specific procedures on Visit 2

[e] To be conducted predose on Visit 2

[f] For hepatitis B surface antigen, anti-hepatitis C antibodies, and human immunodeficiency virus

[g] Breath alcohol test may be repeated for any participating subject at any point during the study based on investigator's judgment

[h] Vital sign measurements include oral temperature, respiratory rate, blood pressure, and heart rate. Blood pressure, respiratory rate, and heart rate will be measured after the subject has been in a supine position for at least 5 minutes

[i] Centralized drug screen testing at screening, local drug screen testing (via dipstick) for all other time points. The urine drug screen at Visit 1 may be repeated based on investigator judgment. The test can also be repeated at any time during the study, should the investigator feel it is warranted

[j] Serum pregnancy testing at screening; urine pregnancy testing at all other visits

[k] At screening the "Baseline" version of the C-SSRS will be administered and at all other visits the "Since Last Visit" version will be administered

[l] COWS to be administered by a medical professional

[m] All medications (prescription and non-prescription, including vitamins and herbal supplements) including ADT taken within 30 days will be recorded at screening. Any changes will be recorded at subsequent visits

[n] Subject will be queried at screening on illicit substances used within 30 days, with updates made at each subsequent visit

Note: additional dispensation visits may be required based on country specific regulatory requirements. No other activities or assessments are done on these days.

[o] The MADRS should be administered prior to the HAM-D, CGI-S and HAM-A on visits when multiple assessments are scheduled

[p] First dose of ALKS 5461 (at Visit 2) to be administered on-site; ALKS 5461 to be dispensed at each indicated visit for subjects to self-administer starting on Day 2. Self-administration should be recommended to occur at bedtime

[q] Via pill count and subject query

[r] Via subject query

[s] One PK blood sample will be collected during each indicated visit from consenting subjects enrolled in the United States only. When PK and safety blood samples are scheduled to be collected on the same day, efforts should be made to collect both samples during the same draw.

[t] Dispense card on Visit 2; confirm possession of card at each subsequent visit and re-dispense if necessary

Table 3: Schedule of Assessments, Safety Follow-up Period

Evaluation	**Safety Follow-up Period**										
Days post end of treatment:	**1 (+1)**	**2 (+1)**	**3 (+1)**	**4 (+1)**	**5 (+1)**	**6 (+1)**	**7 (+1)**	**10 (+2)**	**14 (±2)**	**21 (+2)**	**28 (±2)**
Study Day:	**366**	**367**	**368**	**369**	**370**	**371**	**372**	**375 (+2)**	**379 (±2)**	**386 (+2)**	**393 (±2)**
Visit[a]	**15**	**Phone**	**Phone**	**Phone**	**Phone**	**Phone**	**16**	**Phone**	**17**	**Phone**	**18**
Adverse Event Monitoring[b]	X	X	X	X	X	X	X	X	X	X	X
Concomitant Med Review[c]	X	X	X	X	X	X	X	X	X	X	X
Illicit Substances Review[c]	X						X		X		X
Emergency Treatment Card[d]	X						X		X		X
ADT Adherence Review[e]	X						X		X		X
Brief Symptom-Directed Physical Exam	X						X		X		X
Weight/ Vital Signs[f]	X						X		X		X
C-SSRS[g]	X						X		X		X
Drug Screen[h]	X						X		X		X
COWS[i]	X						X		X		X
12-Lead ECG											X
Blood and Urine Samples for Safety Labs											X
CGI-S							X		X		X

ADT=antidepressant therapy; CGI-S=Clinical Global Impression Scale – Severity; COWS=clinical opiate withdrawal scale; C-SSRS=Columbia Suicide Severity Rating Scale; ECG=electrocardiogram.

[a] Visits labeled "Phone" should occur by telephone whenever possible. In regions where local privacy restrictions do not permit contact by telephone, alternative forms of contact are acceptable

[b] If any AEs are reported that relate to opioid withdrawal (eg, nausea, vomiting, restlessness, hyperhidrosis) during a phone assessment, the subject will be asked to come into the clinic as soon as possible to receive a COWS assessment

[c] Any changes since last visit to be recorded

[d] Possession of card to be confirmed at each clinic visit until Visit 18 when card should be collected

[e] Via subject query

[f] Vital sign measurements at all visits to include oral temperature, respiratory rate, blood pressure and heart rate. Respiratory rate, blood pressure and heart rate to be measured in the supine position

[g] "Since Last Visit" version to be administered

[h] Local drug screen via dipstick

[i] COWS to be administered by a medical professional

8.3. Study Procedures Descriptions

8.3.1. Informed Consent

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

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

8.3.2. Confirmation of Eligibility

For New Subjects, eligibility for participation in the study will be confirmed at the screening visit and reconfirmed at Visit 2 predose, on the first day of dosing.

Continuing Subjects and Lead-in Subjects will not attend a screening visit. Their eligibility will be confirmed at Visit 2. Identical assessments collected at Visit 2 for Lead-In Subjects (if performed) and the last treatment visit of the antecedent study for Continuing Subject their last visit of the antecedent ALKS 5461 study in which they participated will not be repeated at Visit 2 unless more than 10 days elapses between visits.

8.3.3. Demographics

For New Subjects only, demographic data will be reviewed and documented at screening.

For Continuing Subjects and Lead-in Subjects, demographic information will be carried over from information recorded in the antecedent ALKS 5461 study in which they participated.

8.3.4. Medical and Psychiatric History

For New Subjects, medical and psychiatric history will be reviewed and documented at screening. Information collected for psychiatric history should include duration of current MDE, number of lifetime MDEs, number of prior ADT failures and number of ADT failures within the current MDE. For all participating subjects, this information will be carried over from information recorded in the antecedent ALKS 5461 study in which they participated.

8.3.5. Physical Examination

For New Subjects, a full physical examination will be performed at screening. All participating subjects will have brief, symptom-directed physical examinations at all other time points specified in Table 2 and Table 3.

8.3.6. Height

For New Subjects only, height will be measured at the screening visit.

8.3.7. Weight

For New Subjects, weight will be measured at the screening visit. All participating subjects will be weighed at all other time points shown in Table 2 and Table 3.

Subjects should be weighed on the same scale for each measurement under the same conditions, with a consistent amount of clothing for each measurement. Subjects should remove shoes and all personal items prior to body weight measurement.

8.3.8. Vital Signs

Vital signs will be measured at each visit and include oral body temperature, respiratory rate, blood pressure, and heart rate. Blood pressure, respiratory rate and heart rate will be measured after the subject has been in a supine position for at least 5 minutes.

Effort will be made to measure all blood pressure and pulse rate from the same arm, preferably the subject's dominant arm, throughout the study.

The blood pressure cuff will be calibrated per study site standard procedures. Automated measurement is preferred, but if performed manually, heart rate will be measured in the brachial artery for at least 30 seconds.

As specified in Table 2, on the first day of dosing, vital signs are to be measured predose.

8.3.9. 12-Lead Electrocardiogram

A 12-lead ECG will be conducted at the time points specified in 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.

ECGs will be conducted using calibrated equipment and assessed by a qualified clinician. The following ECG parameters will be collected: heart rate, RR, PR, QRS, and QT. QTcB (QT interval corrected using the Bazett formula), and QTcF will be automatically calculated by the ECG machine.

ECGs will be additionally evaluated by a central reader.

8.3.10. Concomitant Medication Review

At screening all New Subjects will be asked about the medications they have taken in the last 30 days. For a potential subject to qualify for the study, those exclusions outlined in Section 8.4.2.2 must be ruled out. At each subsequent study visit, review of concomitant medications will be repeated for all participating subjects. Concomitant medications to be reviewed at each study visit include:

- prescription medications (including ADT)
- nonprescription/ over-the-counter (OTC) medications
- vitamins and supplements

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

8.3.11. Illicit Substances Review

For New Subjects, all illicit substances consumed/used within 30 days will be reviewed and recorded at the screening visit, including name, amount, frequency and start and stop dates. Changes at each subsequent study visit will be recorded for all participating subjects.

8.3.12. Emergency Treatment Cards

An emergency treatment card will be distributed to each subject prior to first dosing. The card will indicate that the subject will be receiving BUP, a partial opioid receptor agonist, and samidorphan, an opioid receptor antagonist. The card will include the investigator's contact information, a suggested pain management plan, and information regarding opioid blockade and withdrawal. Subjects will be instructed to keep the emergency treatment card with them at all times. See Table 2 and Table 3 for details on card distribution, confirmation of possession, and collection.

8.3.13. Pharmacokinetic Assessments

Plasma samples for PK will be collected according to the schedule of events (Table 2), from consenting subjects enrolled in the US only.

The date and time of last dose of study drug as well as ADT, and the date and time of the PK blood draw will be recorded. Blood samples for these analyses will be stored at -20°C±10°C.

Samples will be assayed by a central laboratory for determination of BUP and samidorphan concentrations, as well as relevant metabolites. Concentrations of background ADTs that subjects report taking during the study may be quantified, as appropriate.

8.3.14. Adverse Event Monitoring

The monitoring of adverse events will begin once informed consent is obtained and will be performed at each visit (see Section 13). Adverse events will be monitored continuously until the completion of the final study visit.

Adverse events and serious adverse events (SAEs) are defined in Section 13.1 and Section 13.2, respectively.

Section 13.4 provides guidance on the monitoring and reporting requirements for adverse events. Section 13.5 provides guidance on the reporting requirements for SAEs.

8.3.15. Laboratory Assessments

8.3.15.1. Serology Testing

New Subjects will provide a blood sample for a serology panel testing for hepatitis B surface antigen, anti-hepatitis C antibodies, and HIV at screening. Results must be negative for a subject to be eligible for the study.

8.3.15.2. Breath Alcohol Test

New subjects will undergo an alcohol test at screening via breathalyzer. A negative breath alcohol will be required for a New Subject to enter into the study. However, the test at Visit 1 may be repeated based on investigator judgment.

The breath alcohol test may be repeated for any participating subject at any time during the study, should the investigator feel it is warranted.

8.3.15.3. Urine Drug Screening

New Subjects will undergo urine drug screening for drugs of abuse at Visit 1 and laboratory analysis will be centralized. At all other time points specified in Table 2 and Table 3, all participating study subjects will have urine drug screening via dipstick; results will be analyzed by the local laboratory.

Drug screening will be performed for amphetamines, barbiturates, benzodiazepines, cocaine (metabolite), tetrahydrocannabinol, opioids, and phencyclidine. The opioid panel to be performed at screening for New Subjects (analyzed centrally) will include BUP, codeine, hydrocodone, hydromorphone, methadone, morphine, oxycodone, and oxymorphone. Drug screens administered at all other visits as specified in Table 2 and Table 3 (analyzed locally) will include all aforementioned opioids.

Negative urine drug screening at Visit 1 and Visit 2 will be required for a subject to enter in the study. However, an exception may be made for a benzodiazepine, when such medication is medically indicated for insomnia.

The urine drug test at screening may be repeated based on investigator judgment. The test can also be repeated at any time during the study, should the investigator feel it is warranted. Action taken in response to a positive urine drug screen after Visit 2 should be based on a medical evaluation in consultation with the medical monitor.

8.3.15.4. Pregnancy Testing

A serum pregnancy test will be administered to all female New Subjects at screening. Results must be negative for a female subject to be eligible for the study.

A urine pregnancy test will be administered to all participating female subjects predose, on the first day of dosing. Results must be negative prior to administration of study drug.

At all other time point(s) specified in Table 2 and Table 3, all female subjects will have urine pregnancy testing; results must be negative for a subject to continue in the study.

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.

8.3.15.5. Hematology, Biochemistry, and Urinalysis

Blood and urine samples for laboratory safety assessments will be collected at the time points specified in Table 2 and Table 3. Specific hematology, biochemistry, and urinalysis assessments are listed in Table 4.

Table 4: Clinical Laboratory Assessments

Hematology	Biochemistry	Urinalysis
• Glycosylated hemoglobin (HbA1c)[a] • Hematocrit • Hemoglobin • Platelets • Red blood cell count • Total and differential (absolute) white blood cell count	• Alanine transferase (ALT) • Albumin • Alkaline phosphatase (ALK-P) • Aspartate transferase (AST) • Bicarbonate • Blood urea nitrogen (BUN) • Calcium • Chlorine • Creatine phosphokinase (CPK) • Creatinine • Gamma-glutamyl transferase (GGT) • High-density lipoprotein (HDL) • Lactic dehydrogenase (LDH) • Low-density lipoprotein (LDL) • Magnesium • Phosphorus • Potassium • Prolactin[b] • Random Glucose • Sodium • Thyroid-stimulating hormone[c] • Total bilirubin • Total cholesterol • Total protein • Triglycerides • Uric acid	• Bilirubin • Color and appearance • Glucose • Ketones • Leukocytes • Microscopic examination of sediment, *only if urinalysis dipstick results are abnormal* • Nitrite • Occult blood • pH • Protein • Specific gravity • Urobilinogen

[a] HbA1c to be analyzed at Visits 2, 8, 10, 12, and 14/ET
[b] Prolactin to be analyzed at Visits 1, 2, 10, and 14/ET
[c] Only at Visit 1

Reference ranges for evaluated laboratory tests will be supplied by the assigned laboratory before the study starts. Procedures for sampling and processing laboratory assessments will be described in a separate laboratory manual.

In the event of a difficult blood draw or where there is a limited quantity of blood available for testing, blood collection for biochemistry should be prioritized over hematology.

If unexplained abnormal laboratory test values are observed, follow-up samples may be obtained for repeat testing as clinically indicated.

Results of clinical laboratory testing will appear on electronically produced laboratory reports submitted directly to the site from the central laboratory, if applicable.

8.3.16. Structured Interviews and Questionnaires

Brief descriptions of each of the structured interviews and questionnaires to be administered are provided below. Table 2 and Table 3 provide details on the time points during which each measure should be administered. All structured interviews and questionnaires will be administered by trained and qualified study personnel.

At screening, the medical and psychiatric history and MINI diagnostic interview must be conducted prior to the HAM-D and MADRS.

The MADRS should be administered prior to the HAM-D, CGI-S and HAM-A on visits when multiple assessments are scheduled.

8.3.16.1. Assessments for Study Eligibility

8.3.16.1.1. Massachusetts General Hospital Antidepressant Treatment Response Questionnaire

The ATRQ is a clinician-administered scale used to document history of antidepressant treatment and to determine treatment resistance in MDD. A sample of the ATRQ can be found in Appendix C.

8.3.16.1.2. Mini International Neuropsychiatric Interview

The MINI is a short, clinician-administered, structured diagnostic interview, with an administration time of approximately 15 minutes. The MINI has been validated against the much longer Structured Clinical Interview for DSM diagnoses. A sample of the MINI can be found in Appendix D.

8.3.16.1.3. Seventeen-Item Hamilton Rating Scale for Depression

The HAM-D is a clinician-administered 17-item depression scale designed to be sensitive to treatment effects [Hamilton 1960]. The Structured Interview Guide for the HAM-D (SIGH-D) will be used for administration. A sample of the SIGH-D can be found in Appendix E.

8.3.16.1.4. Clinical Surveillance Team Eligibility Review for New Subjects

The Clinical Surveillance Team (CST) is a division of PPD CNS Clinical Development. The CST eligibility review is an independent evaluation of the eligibility of the subject. Sites enrolling new subjects will complete the CST Pre-Baseline Packet at screening and forward the data to the CST so that review may be completed as soon as possible after screening and before the next study visit. The investigator may use the results of this tool at his or her discretion.

8.3.16.2. Safety Assessments

8.3.16.2.1. Columbia Suicide Severity Rating Scale

The C-SSRS is a clinician-administered instrument that assesses suicidal ideation and behavior [Posner, 2011]. The "Baseline" version of the instrument will be administered to New Subjects at the screening visit. The "Since Last Visit" version will be administered to all participating subjects at all other visits. A sample of the C-SSRS can be found in Appendix F.

8.3.16.2.2. Clinical Opiate Withdrawal Scale

The COWS is an 11-item questionnaire designed to measure an individual's level of opiate withdrawal [Wesson and Ling 2003]. The COWS should be administered by a medical professional. A sample of the COWS can be found in Appendix G.

8.3.16.3. Efficacy Assessments

8.3.16.3.1. Montgomery-Åsberg Depression Rating Scale

The MADRS is a clinician-administered, 10-item depression scale designed to be sensitive to the effects of antidepressant treatment [Montgomery and Asberg 1979]. The Structured Interview Guide for the MADRS (SIGMA) will be used for administration. A sample of the SIGMA can be found in Appendix H.

8.3.16.3.2. Hamilton Rating Scale for Anxiety

The HAM-A is a clinician-administered 14-item scale developed to measure the severity of anxiety symptoms [Hamilton 1959]. The Structured Interview Guide for the HAM-A (SIGH-A) will be used for administration. A sample of the SIGH-A can be found in Appendix I.

8.3.16.3.3. Clinical Global Impression – Severity

The CGI-S is a clinician-administered scale that measures severity of mental illness [Guy 2000]. The CGI-S asks that the clinician rates the subject relative to their past experience with patients with MDD. A sample of the CGI-S can be found in Appendix J.

8.4. Study Requirements and Restrictions

8.4.1. Contraception and Pregnancy

All male and female subjects must agree to use an acceptable method of contraception for the duration of the study unless they are surgically sterile or post-menopausal (see below). At a minimum subjects must agree to use one of the following. Additional restrictions, if required, will be clarified in the locally approved informed consent form (ICF).

- Double-barrier protection (eg, a condom with spermicide or a diaphragm with spermicide)
- Intrauterine device (IUD)

- Hormonal contraceptives (eg, birth control pills, a vaginal ring, contraceptive patch, contraceptive implant; must be initiated and at a stable dose for at least 30 days prior to screening; see Section 8.4.2.2).

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

Subjects who are surgically sterile are exempt from the requirement to use contraception. Women who have undergone a hysterectomy, bilateral tubal ligation, or bilateral salpingo-oophorectomy are considered surgically sterile. Men who have undergone a vasectomy are considered surgically sterile. Partner vasectomy is not considered an approved acceptable method of contraception for a female subject.

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

If any female subject becomes or is found to be pregnant while participating in the study, she will be discontinued 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 end-of-treatment 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. Concomitant and Prohibited Medications

8.4.2.1. Concomitant Medications

All medications taken by a given subject within 30 days of screening through follow-up will be recorded as detailed in Section 8.3.10. The concomitant medication review on each visit will include all prescription medications including ADT, OTC medications, and vitamins and dietary supplements. Concomitant medications will be reviewed at all clinic visits and all phone assessments.

Subjects will be permitted to continue taking concomitant medications during the study provided that these medications are not prohibited (see Sections 7.2 and 8.4.2.2). The investigator may discontinue or adjust the dose of any of these concomitant medications to ensure subject safety. At the investigator's discretion, new concomitant medications may be administered during the course of the study for the treatment of an AE or a change in disease state. If a prohibited medication is needed, the investigator should notify the medical monitor as soon as possible to discuss the continued participation of the subject in the study.

Dose adjustment of approved ADT during the treatment period is permitted for optimal therapeutic effect within the recommended dose range, however ADT dose adjustment should not be made within the same week as ALKS 5461 dose adjustment. Further, subjects are not permitted to change ADTs during the course of the study period.

See Section 9.5 for complete details of ALKS 5461 dose adjustments.

8.4.2.2. Prohibited Medications

The use of any kind of adjunctive therapy, other than ALKS 5461, at an adequate dose and duration in combination with an ADT at any time during the current MDE for the purpose of augmenting the effects of the ADT is prohibited. Adjunctive therapy other than ALKS 5461 is prohibited from screening through the final follow-up visit. Prohibited adjunctive therapies include, but are not restricted to the following:

- atypical antipsychotics (eg, aripiprazole, quetiapine, olanzapine)
- monoamine oxidase inhibitors (eg, phenelzine, tranylcypromine, selegiline)
- lithium
- tricyclic antidepressants (eg, amitriptyline, nortriptyline, desipramine)
- psychostimulants (eg, methylphenidate, dextroamphetamine/ amphetamine)
- bupropion
- BUP

The use of opioid agonists (eg, codeine, oxycodone, tramadol, morphine) or opioid antagonists (eg, naloxone, naltrexone) within 14 days before screening through the final follow-up visit is prohibited. Use of extended-release opioid antagonists within 2 months prior to screening through the final follow-up visit is prohibited.

The initiation or dose adjustment of hormone replacement therapy (including testosterone) or an oral contraceptive within 30 days of screening is prohibited. Such therapy is permissible if a stable dose of hormone replacement therapy or oral contraceptive is taken for at least 30 days prior to screening and the same stable dose is expected to be taken throughout the study.

Hypnotic agents for insomnia (eg, benzodiazepines, zolpidem, trazodone) are not permitted if started within 30 days of screening or if started at any time during the study. Such agents are permitted if they have been used stably for at least 30 days before screening not more than 3 times/week, and are expected to be used stably at ≤ 3 times/week throughout the study. For an insomnia indication, benzodiazepine is permissible if equivalent to ≤2 mg/day of lorazepam, trazodone up to 100 mg/day, zolpidem or zaleplon up to 10 mg/day, or Ambien CR up to 12.5 mg/day. Hypnotic agents are not permitted within 30 days prior to screening through the final follow-up visit if prescribed for an indication other than insomnia.

Use of inducers or moderate to strong inhibitors of CYP3A4 (prescription medications, OTC medications, or dietary supplements) within 30 days before screening through the final follow-up visit is prohibited. See Appendix A for a list of prohibited inducers and moderate to strong inhibitors of CYP3A4.

8.4.3. Pain Management

Because the ALKS 5461 co-formulation contains samidorphan, a μ-opioid receptor antagonist, patients may experience reduced or ineffective analgesia when taking an opioid analgesic agent concurrently with ALKS 5461, including several days after last dosing of ALKS 5461.

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

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

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

9. TREATMENT OF SUBJECTS

9.1. Study Drug Dose and Administration

9.1.1. Description of ALKS 5461

The ALKS 5461 drug product will be formulated as tablets for sublingual (SL) administration and will contain a ratio of 1:1 BUP: samidorphan as free base equivalents by weight. BUP is a Schedule III narcotic and samidorphan is a Schedule II controlled substance. Thus, ALKS 5461 should be treated as a Schedule II controlled substance in the US. Outside the US, ALKS 5461 should be handled according to local regulations. See Section 10 for information on storage and handling of controlled substances.

The study drug formulation contains common pharmaceutical excipients that are listed in the US as "GRAS" (Generally Recognized As Safe [GRAS]) and accepted for use as food additives in Europe: lactose monohydrate, microcrystalline cellulose, crospovidone, sucralose, citric acid, sodium citrate, and magnesium stearate.

9.1.2. Study Drug Dose and Dosing Regimen

Dosing begins at Visit 2, with a 1-week titration for subjects not already taking ALKS 5461 upon study entry. The 1-week titration will be blinded for Continuing Subjects entering from ALK5461-206 and ALK5461-207. See Section 8.1 and Table 1 for details on Week 1 titration and blinding.

One tablet will be taken sublingually on each dosing day. The tablet should be placed under the tongue and kept under the tongue until completely dissolved. **The tablet must not be swallowed.** Eating and drinking should be avoided for 15 minutes after dosing. At Visit 2, study site personnel will administer the tablet and visually confirm that the tablet has dissolved completely. From Day 2 on, subjects will self-administer the daily SL dose; it is recommended that subjects take ALKS 5461 at bedtime.

9.2. Treatment Adherence

According to the schedule in Table 2 and Table 3, at each specified dispensing visit, subjects will receive a supply of ALKS 5461 to last until the following visit. Subjects will be instructed to bring the bottle or blister pack (as applicable, see Section 10.1) with them to each subsequent visit. Subjects will also be instructed to bring in containers of their ADT. Drug adherence will be reviewed with subjects at each visit.

9.3. Method of Assigning Subjects to Treatment

Three different groups of subjects will be enrolled in this study, some of whom will require a 1-week ALKS 5461 titration, as described in Section 8.1. From Day 8 on, all participating subjects will receive ALKS 5461 2/2.

9.4. Blinding

Subjects who are not already taking ALKS 5461 on study entry will begin treatment with a 1-week titration period. As explained in Section 8.1 and Table 1, to maintain the blinded dosing scheme in antecedent studies ALK5461-206 and ALK5461-207, subjects entering from those studies will be blinded to whether or not they will participate in the 1-week titration. Study subjects, investigators, site staff and the sponsor will remain blinded to the treatment assignment in all applicable antecedent studies.

Beginning on Day 8, all participating subjects will receive open-label ALKS 5461 2/2, as tolerability allows.

9.5. Study Drug Dose Adjustment and Stopping Rules

Starting on Day 8 (Visit 3), attempts should be made to achieve and maintain the target dose of ALKS 5461 2/2 over the course of treatment, if tolerated. However, at any time during the study, flexible down-titration to ALKS 5461 1/1 and then to ALKS 5461 0.5/0.5 is permitted at the investigator's discretion, if tolerability issues persist. Once a subject has stabilized after down-titration, attempts should again be made to achieve and maintain the target dose of ALKS 5461 2/2 over the course of treatment, dependent on the individual subject's experience with study drug tolerability.

Dose adjustment of approved ADT during the treatment period is permitted for optimal therapeutic effect within the recommended approved dose range, however ADT dose adjustment should not be made within the same week as ALKS 5461 dose adjustment. Furthermore, subjects are not permitted to change ADTs during the course of the study period.

The study may be stopped at any time or study sites may be closed at the sponsor's discretion.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Packaging and Labeling

A subset of subjects in North America may receive ALKS 5461 in child-resistant bottles. Otherwise, study drug will be packaged in child-resistant blister packs. All packaging will be labeled in a manner that meets applicable local and regulatory requirements.

Dosing for Week 1 will be in accordance with Table 1. During this period subjects will receive either child-resistant bottles or child-resistant blister packs containing 9 tablets to cover the week from Visit 2 to Visit 3 (+2 day visit window). During Week 1, titration packaging will be either blinded or unblinded dependent on the antecedent study, as outlined in Table 1.

All subjects will receive open-label child-resistant bottles or open-label child-resistant blister packs of ALKS 5461 on Visit 3 through Visit 13, each containing 9 tablets. The number of bottles or blister packs distributed to the subject at each visit will be dependent upon the number of days between the specific scheduled visits.

Subjects should follow the dosing instructions as printed on the packaging.

10.2. Storage

ALKS 5461 contains BUP and samidorphan. Under the US Controlled Substances Act, buprenorphine is a Schedule III narcotic. Samidorphan is considered a Schedule II controlled substance, derived from opium alkaloids. Therefore, ALKS 5461 must be stored in accordance with local controlled substance requirements, and in the US, restrictions related to Schedule II controlled substances.

The investigator will take adequate precautions, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

Complete details on storage condition requirements can be found in the Investigator's Brochure.

10.3. Accountability

The investigator will be responsible for the oversight of recording the receipt and administration of ALKS 5461, and for insuring the supervision of the storage and allocation of these supplies.

The investigator is required to maintain current drug dispensing and accountability logs throughout the study. The investigator may delegate accountability duties to an appropriate and qualified pharmacist or staff member who is under the supervision of the investigator.

The investigator or designee must allow the Clinical Research Associate or equivalent to perform drug reconciliation during each study monitoring visit. All unused supplies will be checked against the study drug movement records before investigational drug is returned or destroyed.

Subject-level study drug accountability will be documented in the subjects' source documents and eCRFs. If drug cannot be accounted for, actions will be taken that are appropriate for a drug

containing controlled substances. These actions may include but are not limited to re-training subject on adherence or discontinuation of subject from the trial.

10.4. Handling and Disposal

All unused study drug, which contains the controlled substances buprenorphine and samidorphan, must be handled and disposed of in accordance with the Good Clinical Practice (GCP), Good Manufacturing Practice (GMP), and controlled substance requirements. The sponsor will provide additional instruction as to the disposition of unused investigational product. Until instructions have been provided, each study site must store unused materials on site in the manner described in Section 10.2. All study drug must be accounted for on the study drug accountability logs.

11. ASSESSMENT OF EFFICACY

ALKS 5461 treatment effect over time will be assessed in an exploratory manner based on change from baseline in MADRS total score, HAM-A score, and CGI-S score.

12. ASSESSMENT OF PHARMACOKINETICS

Concentrations of BUP, samidorphan, their relevant metabolites, and reported background ADTs will be quantified in consenting subjects enrolled in the US only. Plasma samples will be collected at time points shown in Table 2.

13. ASSESSMENT OF SAFETY

Safety and tolerability will be assessed on the basis of:

- treatment-emergent AEs (TEAEs)
- clinical laboratory parameters (ie, hematology, chemistry, and urinalysis)
- vital sign measurements (ie, oral body temperature, respiratory rate, blood pressure, and pulse)
- weight
- ECG findings
- C-SSRS results
- COWS

13.1. Definition of Adverse Event

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

Illnesses present prior to the subject signing the informed consent form (ICF) are considered to be pre-existing conditions (which may include AEs from a previous ALKS 5461 study for Continuing Subjects or Lead-in Subjects) 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:

- Results in death
- Is life-threatening. The subject is at immediate risk of death from the reaction as it occurs. This does not include reaction that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization. Hospital admission for elective surgery scheduled prior to study entry is not considered an SAE

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

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

Some outcomes of pregnancy may meet the criteria of an SAE. These include: spontaneous abortion (including miscarriage or missed abortion), stillbirth, neonatal death, or congenital anomaly (including that in an aborted fetus, stillbirth, neonatal death). 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.

Table 5: Adverse Event Causality Guidelines

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

13.4. Monitoring and Recording of Adverse Events

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

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

The investigator will assess all AEs regarding any causal relationship to the study drug (see Section 13.3), the intensity (severity) of the event, action taken, and subject outcome.

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

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

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

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

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

13.5. Reporting of Serious Adverse Events

All SAEs must be reported to PPD within 1 business day of discovery, by faxing the report to the following:

Attention: PPD Safety and Pharmacovigilance

FAX Number: PPD

In Case of fax issues, E-mail: PPD

The written report should be submitted on the SAE form provided for this purpose. The report must include the investigator's opinion as to whether the event is study drug-related. If this relationship is determined to be possibly, probably, or definitely related to study drug, evidence to support this assessment must also be provided.

14. STATISTICS

14.1. Sample Size Considerations

Approximately 1,500 subjects will be enrolled in order to achieve at least 100 subjects with 12 months and 300 subjects with 6 months of exposure to ALKS 5461.

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.

In general, summary statistics (n, mean, standard deviation, median, minimum, and maximum values for continuous variables, and number and percentage of subjects in each category for categorical variables) will be provided by treatment group for evaluated variables.

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

14.2.1. Study Population

14.2.1.1. Efficacy Population

The exploratory efficacy endpoints to assess treatment effect over time will be analyzed using data from the full analysis set (FAS), defined as all subjects who receive at least 1 dose of ALKS 5461 and receive 1 post-baseline efficacy assessment (MADRS).

14.2.1.2. Safety Population

The safety population, defined as all subjects who receive at least 1 dose of ALKS 5461, will be used in the safety analyses.

14.2.1.3. Pharmacokinetic Population

The pharmacokinetic population is defined as all subjects who have at least 1 measurable plasma concentration of any analyte during the treatment period.

14.3. Subject Disposition

The number (percentage) of subjects completing or prematurely discontinuing from the study will be tabulated for all subjects enrolled. The reasons for discontinuation will also be tabulated.

14.4. Demographics and Baseline Data

For all participating subjects, baseline is defined as Visit 2.

Demographics and baseline characteristics such as gender, age, race, weight, and baseline physical examination reports, vital signs, and clinical laboratory data will be summarized.

Psychiatric history including duration of current MDE, number of lifetime MDEs, number of prior lifetime ADT failures and number of ADT failures within the current MDE will be summarized.

14.5. Efficacy Analyses

As stated in Section 11, treatment effect over time will be assessed in an exploratory manner based on change from baseline in MADRS total score, HAM-A total score, and CGI-S score. Results will be presented as described in Section 14.2 and the SAP.

14.6. Pharmacokinetic Analyses

Plasma concentrations of BUP, samidorphan, their relevant metabolites, and reported background ADTs will be summarized by visit. Concentration data may be used in a subsequent population PK evaluation conducted outside of this study.

14.7. Safety and Tolerability Analyses

Safety and tolerability will be evaluated throughout the study with the assessments described below, at the time points presented in Table 2 and Table 3.

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

14.7.1. Adverse Events

Reported AE terms will be coded using MedDRA® preferred terms and system organ classes.

TEAEs are defined as adverse events that occur or worsen after the first dose of study drug. The incidence of TEAEs will be summarized for all TEAEs and for categories defined by preferred term and system organ class. Subjects with SAEs or AEs leading to discontinuation will also be summarized.

14.7.2. Concomitant Medications

Concomitant medications (defined as medications taken between 30 days before screening through the follow-up visit) will be coded using the World Health Organization Anatomical Therapeutic Chemical (WHO-ATC) class. The number and percentage of subjects using concomitant medications will be summarized.

14.7.3. Columbia Suicide Severity Rating Scale

Individual items and summary scores of the C-SSRS will be summarized by visit.

14.7.4. Laboratory Data

For hematology and blood chemistry assessments, baseline, value, and change from baseline will be summarized by visit. The number (percentage) of subjects with PCS values will be summarized.

14.7.5. Weight and Body Mass Index

Weight (kg) and BMI (kg/m^2) measurements will be summarized by visit for baseline, value, and change from baseline. The number (percentage) of subjects with PCS values will be summarized.

14.7.6. Vital Signs

Vital signs assessments will be summarized by visit for baseline, value, and change from baseline.

14.7.7. 12-Lead Electrocardiograms

ECG parameters will be summarized for baseline, value, and change from baseline by visit.

In addition, the number and percentages of subjects with post-baseline results QTcB and QTcF values >450, 480, or 500 msec and an increase from baseline of >30 or 60 msec from baseline will be summarized.

14.7.8. Clinical Opiate Withdrawal Scale

The number (percentage) of subjects will be summarized for COWS total score categories (mild, moderate, moderately severe, and severe opioid withdrawal) by visit.

15. DIRECT ACCESS TO SOURCE DATA/ DOCUMENTS

15.1. Study Monitoring

Monitoring of the study site (including, but not limited to, reviewing eCRFs for accuracy and completeness) will be performed by an Alkermes monitor or designee.

15.2. Audits and Inspections

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

The investigator should contact Alkermes immediately if contacted by a regulatory agency regarding an inspection.

15.3. Institutional Review Board/Independent Ethics Committee

The investigator must obtain IRB/IEC approval for the investigation. Initial IRB/IEC approval as well as all materials approved by the IRB/IEC for this study, including the subject consent form and recruitment materials, must be maintained by the investigator and made available for inspection.

16. QUALITY CONTROL AND QUALITY ASSURANCE

This study will be conducted under GCP and all applicable regulatory requirements. To ensure data accuracy, completeness and compliance, the study site should have processes in place for data review and quality control. Alkermes may also conduct a quality assurance audit. Please see Section 15.2 for details regarding the audit process.

16.1. Case Report Forms

This study will use eCRFs. All eCRF data must be based on source documents or approved to be the original data (eg, data directly reported on the eCRF). All eCRFs will be completed by the clinic staff prior to review by the Alkermes monitor or designated representative.

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

16.2. Confidentiality of Data

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

17. ETHICAL CONSIDERATIONS

17.1. Ethics Review

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

All substantial protocol changes will be submitted to the respective competent authority and the IRB/IEC according to local procedures and will be implemented only after approval. All SAE reports will be submitted immediately to the competent authority and IRB/IEC per local requirements.

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

17.2. Ethical Conduct of the Study

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

17.3. Written Informed Consent

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

All subjects will be informed of their rights to privacy and will be made aware that the study data will be submitted to Alkermes, the IRB, the 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 monitor and/or aforementioned parties may inspect their medical records to verify the accuracy and completeness of the study records and results.

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

The date that informed consent is obtained must be documented. The investigator must maintain the original, signed ICF in the subject's source documents. A copy of the signed ICF must be given to the subject.

18. DATA HANDLING AND RECORDKEEPING

An overview of study data handling and recordkeeping procedures and restrictions is provided in the subsequent sections; please refer to the CSA for further details.

18.1. Data Capture

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

All 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 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 the sponsor.

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. Prohibited Cytochrome P450 3A4 (CYP3A4) Inducers and Moderate-to-Strong Inhibitors

Appendix B. Maximum Daily Dose Table for Antidepressant Therapy Taken During the Study

Appendix C. Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (ATRQ) - Sample

Appendix D. Mini International Neuropsychiatric Interview (MINI) - Sample

Appendix E. Structured Interview Guide for the 17-Item Hamilton Rating Scale for Depression (SIGH-D) - Sample

Appendix F. Columbia Suicide Severity Rating Scale (C-SSRS) - Samples

- "Baseline" Version
- "Since Last Visit" Version

Appendix G. Clinical Opiate Withdrawal Scale (COWS) - Sample

Appendix H. Structured Interview Guide for the Montgomery-Åsberg Depression Rating Scale (SIGMA) - Sample

Appendix I. Structured Interview Guide for the Hamilton Rating Scale for Anxiety (SIGH-A) - Sample

Appendix J. Clinical Global Impression Scale - Severity (CGI-S) - Sample

APPENDIX A. 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.

Partial List of Moderate to Strong CYP3A4 inhibitors:

- Amprenavir
- Aprepitant
- Atazanavir
- Boceprevir
- Ciprofloxacin
- Clarithromycin
- Conivaptan
- Crizotinib
- Darunavir/ritonavir
- Diltiazem
- Erythromycin
- Fosamprenavir
- Fluconazole
- Imatinib
- Indinavir
- Itraconazole
- Ketoconazole
- Lopinavir/ritonavir
- Nefazodone
- Nelfinavir
- Posaconazole
- Ritonavir
- Saquinavir
- Telaprenavir
- Telithromycin
- Troleandomycin
- Verapamil
- Voriconazole

Partial List of Moderate to Strong CYP3A4 inducers:

- Bosentan
- Carbamazepine
- Efavirenz

- Etravirine
- Modafinil
- Nafcillin
- Nevirapine
- Phenobarbital
- Phenytoin
- Rifampin
- Rifabutin
- St. John’s Wort

APPENDIX B. MAXIMUM DAILY DOSE TABLE FOR ANTIDEPRESSANT THERAPY TAKEN DURING THE STUDY

Maximum Daily Dose Allowed for Antidepressant Therapy Taken During the Trial

Drug Class

Selective Serotonin Reuptake Inhibitors (SSRIs)

Brand Name	Generic Name	Maximum Daily Dose	Permitted for PIR Subjects?
Luvox	fluvoxamine	300 mg	
Paxil	paroxetine	50 mg	
Paxil CR	paroxetine	62.5 mg	
Prozac	fluoxetine	80 mg	Yes
Zoloft	sertraline	200 mg	Yes
Celexa	citalopram	40 mg	
Lexapro	escitalopram	20 mg	Yes
Viibryd	vilazodone	40 mg	
Brintellix	vortioxetine	20 mg	

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

Brand Name	Generic Name	Maximum Daily Dose	Permitted for PIR Subjects?
Effexor	venlafaxine	375 mg	Yes
Effexor XR	venlafaxine	225 mg	Yes
Cymbalta	duloxetine	120 mg	Yes
Pristiq	desvenlafaxine	400 mg	
Savella	milnacipran	200 mg	
Fetzima	levomilnacipran	120 mg	

Other Antidepressants

Brand Name	Generic Name	Maximum Daily Dose	Permitted for PIR Subjects?
Wellbutrin	bupropion	450 mg	Yes
Wellbutrin SR	bupropion	400 mg	Yes
Wellbutrin XL	bupropion	450 mg	Yes

APPENDIX C. MASSACHUSETTS GENERAL HOSPITAL ANTIDEPRESSANT TREATMENT RESPONSE QUESTIONNAIRE (ATRQ) - SAMPLE

Rater Initials	Time Performed (24 hours)	Has the rater changed from the previous assessment?	
	___ ___ : ______	Yes □ No □ N/A □ 1st administration of this instrument to this subject	
Subject Initials:	Subject ID No.	Date of Assessment (DD/MMM/YYYY)	Visit No.
		___ ___/___ ___ ___/_________ ___	

MGH ANTIDEPRESSANT TREATMENT RESPONSE QUESTIONNAIRE (ATRQ)

Please indicate the correct answer to the following questions:

1. Have you received any treatment with medications since the beginning of **THIS CURRENT** episode or period of depression? Please circle the correct answer.

YES **NO**

2. If **YES**, please review the list on pages 2-3 and put a check next to any medication(s) that you have taken for **at least 8 or 10 weeks** during THIS episode or period of depression.

3. Of those medication(s) that you have checked from the list on pages 2-3, please put a second check next to those that you have taken at a dosage **equal to or greater than** the minimum dosage listed for that medication.

4. Of those medication(s) that you have checked from the list on pages 2-3, please put a third check next to those that you have taken with another drug [e.g., buspirone (Buspar), lithium, psychostimulants such as methylphenidate (Ritalin), atypical antipsychotics such as olanzapine (Zyprexa)] added to augment or boost the antidepressant effect.

5. Of the medications that you have checked on pages 2-3, please write below the name of the one that you feel helped you the most with your depression:

____

6. If a rating of 100 is "completely improved" and 0 is "not improved at all", how close to 100 did you get on this medication? Please put a check next to the answer that best applies to you.

_____ a) less than 25% improved

_____ b) between 25% and 49% improved

_____ c) between 50% and 75% improved

_____ d) more than 75% improved

Rater Initials	Time Performed (24 hours)	Has the rater changed from the previous assessment?	
	___ ___ : _____	Yes □ No □ N/A □ 1st administration of this instrument to this subject	
Subject Initials:	Subject ID No.	Date of Assessment (DD/MMM/YYYY)	Visit No.
		___ ___/___ ___ ___/_____ ___	

List of Antidepressant Medications

INSTRUCTIONS: Please check the names of any medications that you have taken for **at least 8 or 10 weeks** since the beginning of **THIS EPISODE** or period of depression. Please also check if your daily dosage of the medication was **equal to or greater than the minimum dose** listed below. Finally, please check whether a drug [e.g., buspirone, lithium, psychostimulants such as methylphenidate, atypical antipsychotics such as olanzapine] was added to augment or boost the antidepressant effect.

Drug Class **Brand Name**	**Generic Name**	**At least 8 weeks**	or	**At least 10 weeks**	**Minimum** Dose**	**Equal to or greater than**	**Minimum** Dose**	**Equal to or greater than**	**Added to augment or boost effect?**
Tricyclic Antidepressants									
Adapin	doxepin	_____		_____	150 mg/d	_____	250 mg/d	_____	_____
Anafranil	clomipramine	_____		_____	150 mg/d	_____	250 mg/d	_____	_____
Asendin	amoxapine	_____		_____	150 mg/d	_____	250 mg/d	_____	_____
Endep/Elavil	amitriptyline	_____		_____	150 mg/d	_____	250 mg/d	_____	_____
Ludiomil	maprotiline	_____		_____	150 mg/d	_____	250 mg/d	_____	_____
Norpramin	desipramine	_____		_____	150 mg/d	_____	250 mg/d	_____	_____
Pamelor	nortriptyline	_____		_____	75 mg/d	_____	125 mg/d	_____	_____
Sinequan	doxepin	_____		_____	150 mg/d	_____	250 mg/d	_____	_____
Surmontil	trimipramine	_____		_____	150 mg/d	_____	250 mg/d	_____	_____
Tofranil	imipramine	_____		_____	150 mg/d	_____	250 mg/d	_____	_____
Vivacti	protriptyline	_____		_____	30 mg/d	_____	60 mg/d	_____	_____
Azafen	pipofezine	_____		_____	150 mg/d	_____	300 mg/d	_____	_____
Agedal/Elronon	noxiptiline	_____		_____	100 mg/d	_____	200 mg/d	_____	_____
Monoamine Oxidase Inhibitors (MAOIs)									
Marplan	isocarboxazid	_____		_____	30 mg/d	_____	60 mg/d	_____	_____
Nardil	phenelzine	_____		_____	45 mg/d	_____	90 mg/d	_____	_____
Parnat	tranylcypromine	_____		_____	30 mg/d	_____	60 mg/d	_____	_____
Emsam	selegiline patch	_____		_____	6 mg/24 hrs	_____	12 mg/24 hrs	_____	_____
Aurorix	moclobemide	_____		_____	300 mg/d	_____	600 mg/d	_____	_____
Pirazidol	pirlindole	_____		_____	200 mg/d	_____	300 mg/d	_____	_____

** **Note** = The left column (minimum dose) shows the dose that is minimally adequate; the right column (minimum dose) shows the minimal dose of the drug at an optimized level. Patients have adequate dosing as long as the dose is equal or greater than the dose on the left.

Rater Initials			Time Performed (24 hours)	Has the rater changed from the previous assessment?	
			__ __ : _____	Yes □ No □ N/A □ 1st administration of this instrument to this subject	
Subject Initials:			Subject ID No.	Date of Assessment (DD/MMM/YYYY)	Visit No.
				__ __/__ __ __/_____ __	

Selective Serotonin Reuptake Inhibitors (SSRIs)

Luvox	fluvoxamine	_____	_____	50 mg/d	_____	150 mg/d	_____	_____
Paxil	paroxetine	_____	_____	20/25 mg/d	_____	60/75 mg/d	_____	_____
Prozac	fluoxetine	_____	_____	20 mg/d	_____	60 mg/d	_____	_____
Zoloft	sertraline	_____	_____	50 mg/d	_____	150 mg/d	_____	_____
Celexa	citalopram	_____	_____	20 mg/d	_____	60 mg/d	_____	_____
Lexapro	escitalopram	_____	_____	10 mg/d	_____	30 mg/d	_____	_____
Viibryd	vilazodone	_____	_____	40 mg/d	_____	80 mg/d	_____	_____
Brintellix	vortioxetine	_____	_____	10 mg/d	_____	20 mg/d	_____	_____

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

Effexor	venlafaxine	_____	_____	150 mg/d	_____	250 mg/d	_____	_____
Cymbalta	duloxetine	_____	_____	60 mg/d	_____	120 mg/d	_____	_____
Pristiq	desvenlafaxine	_____	_____	50 mg/d	_____	100 mg/d	_____	_____
Savella	milnacipran	_____	_____	100 mg/d	_____	200 mg/d	_____	_____
Fetzima	levomilnacipran	_____	_____	40 mg/d	_____	120 mg/d	_____	_____

Other Antidepressants

Desyrel	trazodone	_____	_____	300 mg/d	_____	600 mg/d	_____	_____
Serzone	nefazodone	_____	_____	300 mg/d	_____	600 mg/d	_____	_____
Wellbutrin	bupropion	_____	_____	300 mg/d	_____	450 mg/d	_____	_____
Remeron	mirtazapine	_____	_____	15 mg/d	_____	45 mg/d	_____	_____
Valdoxan	agomelatine	_____	_____	25 mg/d	_____	50 mg/d	_____	_____
Stablon	tianeptine	_____	_____	37.5 mg/d	_____	75 mg/d	_____	_____
Edronax	reboxetine	_____	_____	4 mg/d	_____	8 mg/d	_____	_____
Bolvidon/Depnon/ Norval/Tolvon	mianserin	_____	_____	30 mg/d	_____	90 mg/d	_____	_____
Insidon	opipramol	_____	_____	150 mg/d	_____	300 mg/d	_____	_____

Did you receive electro-convulsive treatment (ECT) during **this current** episode (please circle one): **YES NO**
Did you **ever** receive vagal nerve stimulation (VNS) or deep brain stimulation (DBS) (please circle one): **YES NO**

**** Note =** The left column (minimum dose) shows the dose that is minimally adequate; the right column (minimum dose) shows the minimal dose of the drug at an optimized level. Patients have adequate dosing as long as the dose is equal or greater than the dose on the left.

APPENDIX D. MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW (MINI) - SAMPLE

M.I.N.I.

MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW

English Version 6.0.0

DSM-IV

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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)

	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	F30.x- F31.9	❒
		Past	❒	296.0x-296.6x	F30.x- F31.9	❒
	BIPOLAR II DISORDER	Current	❒	296.89	F31.8	❒
		Past	❒	296.89	F31.8	❒
	BIPOLAR DISORDER NOS	Current	❒	296.80	F31.9	❒
		Past	❒	296.80	F31.9	❒
D	PANIC DISORDER	Current (Past Month)	❒	300.01/300.21	F40.01-F41.0	❒
		Lifetime	❒			
E	AGORAPHOBIA	Current	❒	300.22	F40.00	❒
F	SOCIAL PHOBIA (Social Anxiety Disorder)	Current (Past Month)				
		Generalized	❒	300.23	F40.1	❒
		Non-Generalized	❒	300.23	F40.1	❒
G	OBSESSIVE-COMPULSIVE DISORDER	Current (Past Month)	❒	300.3	F42.8	❒
H	POSTTRAUMATIC STRESS DISORDER	Current (Past Month)	❒	309.81	F43.1	❒
I	ALCOHOL DEPENDENCE	Past 12 Months	❒	303.9	F10.2x	❒
	ALCOHOL ABUSE	Past 12 Months	❒	305.00	F10.1	❒
J	SUBSTANCE DEPENDENCE (Non-alcohol)	Past 12 Months	❒	304.00-.90/305.20-.90	F11.2X-F19.2X	❒
	SUBSTANCE ABUSE (Non-alcohol)	Past 12 Months	❒	304.00-.90/305.20-.90	F11.1-F19.1	❒
K	PSYCHOTIC DISORDERS	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 PSYCHOTIC FEATURES	Lifetime	❒	296.24/296.04-296.94	F32.3/F33.3/	❒
		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**?

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

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

NO **YES**

SUICIDALITY CURRENT

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

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?

	Current Episode	Past Episode
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 THAT TIME FRAME AND GO TO C7.

C6 Did these symptoms cause significant problems at home, at work, socially in your relationships with others, at school or in some other important way? NO YES NO YES

ARE **C3** SUMMARY AND **C5** AND **C6** CODED **YES**?

OR

ARE **C3** SUMMARY AND **C4c** AND **C6** CODED **YES** AND IS **C5** CODED **NO**?

SPECIFY IF THE EPISODE IS CURRENT 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**?

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 EPISODE,
THEN CODE PAST HYPOMANIC SYMPTOMS AS **NOT EXPLORED.**

HYPOMANIC SYMPTOMS

CURRENT ❒ **NO**
❒ **YES**

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

C7 a) IF MANIC EPISODE IS POSITIVE FOR EITHER CURRENT OR PAST ASK:
Did you have 2 or more of these (manic) episodes lasting 7 days or more (**C4c**) in your lifetime (including the current episode if present)? NO YES

b) IF MANIC OR HYPOMANIC EPISODE IS POSITIVE FOR EITHER CURRENT OR PAST ASK:
Did you have 2 or more of these (hypomanic) episodes lasting just 4 to 6 days (**C4b**) in your lifetime (including the current episode)? NO YES

c) IF THE PAST "HYPOMANIC SYMPTOMS" CATEGORY IS CODED POSITIVE ASK:
Did you have these hypomanic symptoms lasting only 1 to 3 days (**C4a**) 2 or more times in your lifetime, (including the 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?	**NO**	**YES**

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.

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

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

I. ALCOHOL DEPENDENCE / ABUSE

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

		➡ NO	YES
I1	**In the past 12 months**, have you had 3 or more alcoholic drinks, - within a 3 hour period, - on 3 or more occasions?		

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.

			➡ NO	YES
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?		

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:**

			NO	YES
	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?		
	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?		
		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?		
	d	Have you tried to reduce or stop taking (NAME OF DRUG / DRUG CLASS SELECTED) but failed?		
	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?		
	f	Did you spend less time working, enjoying hobbies, or being with family or friends because of your drug use?		
	g	If (NAME OF DRUG / DRUG CLASS SELECTED) caused you health or mental problems, did you still keep on using it?		

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.

		Now I am going to ask you about unusual experiences that some people have.			BIZARRE
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 PAST)
OR
MANIC OR HYPOMANIC EPISODE, (CURRENT OR PAST) CODED **YES**? NO YES
↳ **K13**

IF NO TO K11 a, CIRCLE NO IN BOTH 'MOOD DISORDER WITH PSYCHOTIC 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 experiences you just described (SYMPTOMS CODED **YES** FROM **K1a** TO **K7a**) restricted exclusively to times when you were feeling depressed/high/irritable?

IF THE PATIENT EVER HAD A PERIOD OF AT LEAST 2 WEEKS OF HAVING THESE BELIEFS OR EXPERIENCES (PSYCHOTIC SYMPTOMS) WHEN THEY WERE NOT DEPRESSED/HIGH/IRRITABLE, CODE NO TO THIS DISORDER.

IF THE ANSWER IS NO TO THIS DISORDER, 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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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 past)?
and
is Manic Episode coded NO (current and past)?
and
is Hypomanic Episode coded NO (current and past)?
and
is "Hypomanic Symptoms" coded NO (current and past)?

Specify:

- If the depressive episode is **current** or **past** or both
- **With Psychotic Features** Current: If 1b or 2a (current) = YES
  With Psychotic Features Past: If 1a or 2a (past) = 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 E. STRUCTURED INTERVIEW GUIDE FOR THE 17-ITEM HAMILTON RATING SCALE FOR DEPRESSION (SIGH-D) - SAMPLE

STRUCTURED INTERVIEW GUIDE
FOR THE HAMILTON DEPRESSION SCALE (SIGH-D)

Janet B.W. Williams, PhD

INTERVIEWER

The first question for each item should be asked exactly as written. Often this question will elicit enough information about the severity and frequency of a symptom for you to rate the item with confidence. Follow-up questions are provided, however, for use when further exploration or additional clarification of symptoms is necessary. The specified questions should be asked until you have enough information to rate the item confidently. In some cases, you may also have to add your own follow-up questions to obtain necessary information.

Time period. The interview questions indicate that the ratings should be based on the patient's condition in the past week.

Referent of "usual" or "normal" condition. Several of the interview questions in the HAM-D refer to the patient's usual or normal functioning. In some cases, such as when the patient has Dysthymia or Seasonal Affective Disorder, the referent should be to the last time they felt OK (i.e., not depressed or high) for at least a few weeks.

This instrument provides an interview guide for the Hamilton Depression Scale (Hamilton, Max: A rating scale for depression. J Neurol Neurosurg Psychiat 23:56-61, 1960). The anchor point descriptions, with very minor modifications, have been taken from the ECDEU Assessment Manual (Guy, William, ECDEU Assessment Manual for Psychopharmacology, Revised 1976, DHEW Publication No. (ADM) 76-338). Additional designators were added in parentheses to the depression scale anchor points by Kobak, Lipsitz and Williams to further standardize ratings. A reliability study of the SIGH-D (interview guide for the HAM-D alone) was published in the Archives of General Psychiatry (1988;45:742-747).

For further information contact PPD at PPD

Revised 21 February 2007.

Rater Initials			Time Performed (24 hours)								Has the rater changed from the previous assessment?			
			___ ___ : ______								Yes □ No □ N/A □ 1st administration of this instrument to this subject			
Subject Initials:			Subject ID No.								Date of Assessment (DD/MMM/YYYY)		Visit No.	
											___ ___/___ ___ ___/_________ ___			

STRUCTURED INTERVIEW GUIDE FOR THE HAMILTON DEPRESSION SCALE (SIGH-D)

OVERVIEW: **I'd like to ask you some questions about the past week. How have you been feeling since last (DAY OF WEEK)? IF OUTPATIENT: Have you been working? IF NOT: Why not?**

What's your mood been like this past week (compared to when you feel OK)? Have you been feeling down or depressed? IF YES: Can you describe what this feeling has been like for you? How bad is the feeling? Does the feeling lift at all if something good happens? How are you feeling about the future? In the last week, how often have you felt (OWN EQUIVALENT)? Every day? All day? Have you been crying at all?	**DEPRESSED MOOD** (sadness, hopeless, helpless, worthless): 0 - absent 1 - indicated only on questioning *(occasional, mild depression)* 2 - spontaneously reported verbally *(persistent, mild to moderate depression)* 3 - communicated non-verbally, i.e., facial expression, posture, voice, tendency to weep *(persistent, moderate to severe depression)* 4 - VIRTUALLY ONLY those feeling states reported in spontaneous verbal and non-verbal communication *(persistent, very severe depression, with extreme hopelessness or tearfulness)*

IF SCORED 1-4 ABOVE, ASK: How long have you been feeling this way?

NOTES:

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Subject Initials:	Subject ID No.	Date of Assessment (DD/MMM/YYYY)	Visit No.
		__ __/__ __ __/_____ __	

How have you been spending your time this past week (when not at work)? Have you felt interested in doing (THOSE THINGS), or do you feel you have to push yourself to do them? How much less interested in these things have you been this past week compared to when you're not depressed? How hard do you have to push yourself to do them? Have you stopped doing anything you used to do? (What about hobbies?) IF YES: Why? About how many hours a day do you spend doing things that interest you? Is there anything you look forward to? IF WORKING (IN OR OUT OF THE HOME): Have you been able to get as much (work) done as you usually do? How much less productive or efficient are you compared to before you were depressed?	**WORK AND ACTIVITIES:** 0 - no difficulty 1 - thoughts and feelings of incapacity, fatigue or weakness related to activities, work or hobbies *(Mild reduction in interest or pleasure; no clear impairment in functioning)* 2 - loss of interest in activity, hobbies or work - by direct report of the patient or indirect in listlessness, indecision and vacillation (feels he has to push self to work or do activities; *Clear reduction in interest, pleasure or functioning)* 3 - decrease in actual time spent in activities or decrease in productivity. In hospital, patient spends less than 3 hours/day in activities (hospital job or hobbies) exclusive of ward chores (*Profound reduction in interest, pleasure, or functioning)* 4 - stopped working because of present illness. In hospital, no activities except ward chores, or fails to perform ward chores unassisted (*Unable to work or fulfill primary role because of illness, and total loss of interest)*
Now let's talk about your sleep. What were your usual hours of going to sleep and waking up, before this began? **When have you been falling asleep and waking up over the past week?**	
Have you had any trouble falling asleep at the beginning of the night? (Right after you go to bed, how long has it been taking you to fall asleep?) How many nights this week have you had trouble falling asleep? Have you changed the time at which you try to get to sleep since you've been depressed?	**INSOMNIA EARLY (INITIAL INSOMNIA):** 0 - no difficulty falling asleep 1 - complains of occasional difficulty falling asleep (i.e., more than 1/2 hour, *2-3 nights)* 2 - complains of nightly difficulty falling asleep *(i.e., more than ½ hour, 4 or more nights)*

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	__ __ : _____	Yes □ No □ N/A □ 1st administration of this instrument to this subject

Subject Initials:	Subject ID No.	Date of Assessment (DD/MMM/YYYY)	Visit No.
		__ __/__ __ __/_____ __	

During the past week, have you been waking up in the middle of the night? IF YES: Do you get out of bed? What do you do? (Only go to the bathroom?) When you get back in bed, are you able to fall right back asleep? How long does it take you to fall back asleep? Do you wake up more than once during the night? (IF YES: How long does it take for you to fall back to sleep each time?) Have you felt your sleeping has been restless or disturbed some nights? How many nights this week have you had that kind of trouble?	**INSOMNIA MIDDLE:** 0 - no difficulty 1 - complains of being restless and disturbed during the night (or *Occasional difficulty, i.e., 2-3 nights, more than ½ hr)* 2 - waking during the night - any getting out of bed (except to void) (*Often i.e., 4 or more nights of difficulty, more than ½ hr)*
What time have you been waking up in the morning for the last time, this past week? IF EARLY: Is that with an alarm clock, or do you just wake up yourself? What time do you usually wake up (that is, when you feel well)? How many mornings this past week have you awakened early?	**INSOMNIA LATE (TERMINAL INSOMNIA):** 0 - no difficulty 1 - waking in early hours of morning but goes back to sleep *(occasional, i.e., 2-3 nights difficulty)* 2 - unable to fall asleep again if gets out of bed *(often, i.e., 4 or more nights difficulty)*
Sometimes, along with depression or anxiety, people might lose interest in sex. This week, how has your interest in sex been? (I'm not asking about actual sexual activity, but about your interest in sex.) Has there been any change in your interest in sex (from when you were feeling OK)? IF YES: How much less interest do you have compared to when you're not depressed? (Is it a little less or a lot less?)	**GENITAL SYMPTOMS** (such as loss of libido, menstrual disturbances): 0 - absent 1 - mild (*Somewhat less interest than usual)* 2 - severe (*A lot less interest than usual)*

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											___ ___/___ ___ ___/_________ ___		

How has your appetite been this past week? (What about compared to your usual appetite?) IF LESS: How much less than usual? Have you had to force yourself to eat? Have other people had to urge you to eat? (Have you skipped meals?)	**SOMATIC SYMPTOMS GASTROINTESTINAL:** 0 - none 1 - loss of appetite but eating without encouragement (*Appetite somewhat less than usual)* 2 - difficulty eating without urging (or *Appetite significantly less than usual)*
Have you lost any weight since this (DEPRESSION) began? IF YES: Did you lose any weight this last week? (Was it because of feeling depressed or down?) How much did you lose? IF NOT SURE: Do you think your clothes are any looser on you? AT FOLLOW-UP: Have you gained any of the weight back? IF YES: How much? **NOTE: RATE 1 OR 2 ONLY IF PATIENT LOST WEIGHT AND HAS NOT BEGUN TO GAIN IT BACK.**	**LOSS OF WEIGHT (Rate either A or B):** A. When rating by history: 0 - no weight loss 1 - probable weight loss due to current depression 2 - definite (according to patient) weight loss due to depression B. On weekly ratings by ward staff, when actual weight changes are measured: 0 - less than 1 lb. loss in week 1 - more than 1 lb. loss in week 2 - more than 2 lb. loss in week

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How has your energy been this past week? IF LOW ENERGY: Have you felt tired? (How much of the time? How bad has it been?) This week, have you had any aches or pains? (What about backaches or muscle aches?) (How much of the time? How bad has it been?) Have you felt any heaviness in your limbs, back, or head?	**SOMATIC SYMPTOMS GENERAL:** 0 - none 1 - heaviness in limbs, back, or head. Backaches, muscle aches. Loss of energy and fatiguability. *(Somewhat less energy than usual; mild, intermittent loss of energy or muscle aches/heaviness)* 2 - any clear-cut symptoms *(Persistent, significant loss of energy or muscle aches/heaviness)*
Have you been putting yourself down this past week, feeling you've done things wrong, or let others down? IF YES: What have your thoughts been? Have you been feeling guilty about anything that you've done or not done? IF YES: What have your thoughts been? What about things that happened a long time ago? IF UNKNOWN: How often have you thought about this the past week? Have you thought that you've brought (THIS DEPRESSION) on yourself in some way? (Have you been hearing voices or seeing visions in the last week? IF YES: Tell me about them.)	**FEELINGS OF GUILT:** 0 - absent 1 - self-reproach, feels he has let people down 2 - ideas of guilt or rumination over past errors or sinful deeds *(feelings of guilt, remorse or shame)* 3 - present illness is a punishment. Delusions of guilt. (severe, pervasive feelings of guilt) 4 - hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

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												___ ___/___ ___ ___/__________ ___		

This past week, have you had thoughts that life is not worth living? IF YES: What about thinking you'd be better off dead? Have you had thoughts of hurting or killing yourself? IF YES: What have you thought about? Have you actually done anything to hurt yourself?	**SUICIDE:** 0 - absent 1 - feels life is not worth living 2 - wishes he were dead or any thoughts of possible death to self 3 - suicidal ideas or gesture 4 - attempts at suicide
Have you been feeling especially tense this past week? IF YES: Is this more than is normal for you? Have you been unusually argumentative or impatient? Have you been worrying a lot about little things, things you don't ordinarily worry about? IF YES: Like what, for example? How often have you felt this way the past week? Has this caused you any problems or difficulties? IF YES: Like what, for example?	**ANXIETY PSYCHIC:** 0 - no difficulty 1 - subjective tension and irritability *(Mild, occasional)* 2 - worrying about minor matters (*Moderate, causes some distress)* 3 - apprehensive attitude apparent in face or speech (*Severe; significant impairment in functioning due to anxiety)* 4 - fears expressed without questioning (*Symptoms incapacitating)*

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Subject Initials:			Subject ID No.									Date of Assessment (DD/MMM/YYYY)		Visit No.
												___ ___/___ ___ ___/_________ ___		

Tell me if you've had any of the following physical symptoms in the past week. (READ LIST) FOR EACH SX ACKNOWLEDGED AS PRESENT: How much has (THE SX) been bothering you this past week? (How bad has it gotten? How much of the time, or how often, have you had it? Did (the symptom) interfere at all with your functioning or your usual activities?) NOTE: DO NOT RATE SXS THAT ARE CLEARLY RELATED TO A DOCUMENTED PHYSICAL CONDITION.	**ANXIETY SOMATIC** (physiologic concomitants of anxiety, such as Gastrointestinal - dry mouth, gas, indigestion, diarrhea, stomach cramps, belching CV - heart palpitations, headaches Respiratory - hyperventilating, sighing Urinary frequency Sweating): 0 - not present 1 - mild *(Symptom(s) present only infrequently, no impairment, minimal distress)* 2 - moderate (*Symptom(s) more persistent, or some interference with usual activities, moderate distress)* 3 - severe *(Significant impairment in functioning)* 4 - incapacitating
In the last week, how much have your thoughts been focused on your physical health or how your body is working (compared to your normal thinking)? (Have you worried a lot about being or becoming physically ill? Have you really been preoccupied with this?) Have you worried a lot that you had a specific medical illness? Do you complain much about how you feel physically? Have you seen a doctor about these problems? What did the doctor say?	**HYPOCHONDRIASIS:** 0 - not present 1 - self-absorption (bodily) (*Some inappropriate worry about his/her health OR slightly concerned despite reassurance)* 2 - preoccupation with health *(Often has excessive worries about his/her health OR definitely concerned has specific illness despite medical reassurance)* 3 - frequent complaints, requests for help, etc. *(Is certain there is a physical problem which the doctors cannot confirm; exaggerated or unrealistic concerns about body and physical health)* 4 - hypochondriacal delusions

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											___ ___/___ ___ ___/__________ ___		

RATING BASED ON OBSERVATION DURING INTERVIEW	**INSIGHT:** 0 - acknowledges being depressed and ill OR not currently depressed 1 - acknowledges illness but attributes cause to bad food, overwork, virus, need for rest, etc. 2 - denies being ill at all
RATING BASED ON OBSERVATION DURING INTERVIEW	**AGITATION:** 0 - none 1 - fidgetiness (slight agitation or mild restlessness) 2 - playing with hands, hair, etc. (moderate to marked restlessness or agitation) 3 - moving about, can't sit still (cannot remain seated) 4 - hand-wringing, nail biting, hair-pulling, biting of lips (interview cannot be conducted; severe agitation)
RATING BASED ON OBSERVATION DURING INTERVIEW	**RETARDATION** (slowness of thought and speech; impaired ability to concentrate; decreased motor activity): 0 - normal speech and thought 1 - slight retardation at interview (mild psychomotor retardation) 2 - obvious retardation at interview (moderate; some difficulty with interview, noticeable pauses and slowness of thought) 3 - interview difficult (severe psychomotor retardation; very long pauses) 4 - complete stupor (extreme retardation; interview barely possible)

TOTAL HAM-D SCORE: ___________

Rater Signature: ________________________ Date: __________________________

APPENDIX F. COLUMBIA SUICIDE SEVERITY RATING SCALE (C-SSRS) - SAMPLES

- "Baseline" Version
- "Since Last Visit" Version

Columbia-Suicide Severity Rating Scale (C-SSRS)

Baseline 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 to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

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

Rater Initials	Time Performed (24 hours)	Has the rater changed from the previous assessment?	
	__ __ : _____	Yes □ No □ N/A, 1st administration of this instrument to this	
Subject Initials:	Subject ID No.	Date of Assessment (DD/MMM/YYYY)	Visit No.
		__ __/__ __ __/__ _____	

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 12 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). Ask about time he/she was feeling the most suicidal. **Lifetime** - ***Most Severe Ideation:*** _____ ***Type # (1-5)*** _____ ***Description of Ideation*** **Past 12 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 (4) 4-8 hours/most of day (2) Less than 1 hour/some of the time (5) More than 8 hours/persistent or continuous (3) 1-4 hours/a lot of time	____	____
Controllability ***Could /can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (4) Can control thoughts with a lot of difficulty (2) Can control thoughts with little difficulty (5) Unable to control thoughts (3) Can control thoughts with some difficulty (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 (4) Deterrents most likely did not stop you (2) Deterrents probably stopped you (5) Deterrents definitively did not stop you (3) Uncertain that deterrents stopped 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 (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling (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 (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 12 Months**
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_____?***	**Yes** ☐ **No** ☐ Total # of attempts	**Yes** ☐ **No** ☐ Total # of attempts ____
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** ☐	**Yes** ☐ **No** ☐

Subject ID 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* _____

Rater Signature: _____ Date: _____

Columbia-Suicide Severity Rating Scale (C-SSRS)

Since Last Visit

Version 1/14/09

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

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Rater	Time Performed (24 hours)	Has the rater changed from the previous assessment?	
	_____ : _____	Yes □ No □ N/A □ 1st administration of this instrument to this	
Subject Initials:	Site No./ Subject ID No.	Date of Assessment (DD/MMM/YYYY)	Visit No.
		_____/_____/_____	

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

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	**Most Severe**
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	_____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (4) 4-8 hours/most of day (2) Less than 1 hour/some of the time (5) More than 8 hours/persistent or continuous (3) 1-4 hours/a lot of time	_____
Controllability ***Could /can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (4) Can control thoughts with a lot of difficulty (2) Can control thoughts with little difficulty (5) Unable to control thoughts (3) Can control thoughts with some difficulty (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 (4) Deterrents most likely did not stop you (2) Deterrents probably stopped you (5) Deterrents definitively did not stop you (3) Uncertain that deterrents stopped 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 (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling (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 (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:	**Yes** ☐ **No** ☐ **Total # of attempts** _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**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** ____

Rater Signature: _____ Date: _____

Subject ID Number:_____Visit Number_____

APPENDIX G. CLINICAL OPIATE WITHDRAWAL SCALE (COWS) - SAMPLE

Rater Initials	Time Performed (24 hours)	Has the rater changed from the previous assessment?	
	___ ___ : _____	Yes □ No □ N/A □ 1st administration of this instrument to this subject	
Subject Initials:	Subject ID No.	Date of Assessment (DD/MMM/YYYY)	Visit No.
		___ ___/___ ___ ___/_____ ___	

Clinical Opiate Withdrawal Scale

For each item, circle the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

Resting Pulse Rate: _____beats/minute *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120	**GI Upset**: *over last ½ hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 Multiple episodes of diarrhea or vomiting
Sweating: *over past ½ hour not accounted for by room temperature or patient activity.* 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	**Tremor** *observation of outstretched hands* 0 No tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching
Restlessness *Observation during assessmen*t 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 Unable to sit still for more than a few seconds	**Yawning** *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	**Anxiety or Irritability** 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable anxious 4 patient so irritable or anxious that participation in the assessment is difficult
Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/ muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	**Gooseflesh skin** 0 skin is smooth 3 piloerrection of skin can be felt or hairs standing up on arms 5 prominent piloerrection
Runny nose or tearing *Not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	Total Score _____ The total score is the sum of all 11 items Initials of person completing Assessment: _____

Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal

From: Wesson DR, Ling W J Psychoactive Drugs 2003 Apr-June; 35(2): 253-9

APPENDIX H. STRUCTURED INTERVIEW GUIDE FOR THE MONTGOMERY-ÅSBERG DEPRESSION RATING SCALE (SIGMA) - SAMPLE

STRUCTURED INTERVIEW GUIDE FOR THE MONTGOMERY AND ASBERG DEPRESSION RATING SCALE (SIGMA)

Janet B.W. Williams, D.S.W. and Kenneth A. Kobak, Ph.D.

INTERVIEWER: The questions in bold for each item should be asked exactly as written. Often these questions will elicit enough information about the severity and frequency of a symptom for you to rate the item with confidence. Follow-up questions are provided, however, for use when further exploration or additional clarification of symptoms is necessary. The specified questions should be asked until you have enough information to rate the item confidently. In some cases, you may also have to add your own follow-up questions to obtain necessary information. Note that questions in parentheses are optional, for use, for example if information is unknown.

NOTES:

Time period. The ratings should be based on the patient's condition in the past week.

Change from baseline. In general, a symptom is rated as present only when it reflects a change from before the depression began (baseline). The interviewer must identify a 2-month period of non-depressed functioning and use this as a reference point. In some cases, such as when the patient has dysthymia the referent should be to the last time the person felt all right (i.e. not depressed or high) for at least a few weeks. When a clear baseline cannot be established because of chronic depressive symptoms, current symptoms should be rated as observed over the past 7 days.

This interview guide is based on the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery SA, Asberg M: A new depression scale designed to be sensitive to change. *Br J Psychiatry* ;1979 **134:** 382-9). The scale itself has been retained in its original form, except for reversing the order of the first two items. This guide adds interview questions to aid in the assessment and application of the MADRS. Previous versions of this guide appeared in 1988, 1992, 1996, and 2005.

Rater Initials	Time Performed (24 hours)	Has the rater changed from the previous assessment?	
	___ ___ : ___ ___	Yes □ No □ N/A □	
Subject Initials:	Site No. / Subject ID No.	Date of Assessment (DD/MMM/YYYY)	Visit No.
		___ ___/___ ___ ___/___ ___ ___ ___	

OVERVIEW:
I'd like to ask you some questions about the past week. How have you been feeling since last (DAY OF WEEK)? IF OUT-PATIENT: Have you been working? (What kind of work do you do?) IF NOT: Why not?

In the past week, have you been feeling sad or unhappy? (Depressed at all?) IF YES: Can you describe what this has been like for you? (IF UNKNOWN: How bad has that been?) IF DEPRESSED: Does the feeling lift at all if something good happens? How much does your mood lift? Does the feeling ever go away completely? (What things have made you feel better?) How often did you feel (depressed/OWN EQUIVALENT) this past week? (IF UNKNOWN: How many days this week did you feel that way? How much of each day?) In the past week, how have you been feeling about the future? (Have you been discouraged or pessimistic?) What have your thoughts been? How (discouraged or pessimistic) have you been? How often have you felt that way? Do you think things will ever get better for you? **IF ACKNOWLEDGES DEPRESSED MOOD, TO GET CONTEXT ASK:** How long have you been feeling this way?	**1. REPORTED SADNESS.** Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope. Rate according to intensity, duration, and the extent to which the mood is reported to be influenced by events. 0 – Occasional sadness in keeping with the circumstances 1 – 2 – Sad or low but brightens up without difficulty 3 – 4 – Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances 5 – 6 – Continuous or unvarying sadness, misery, or despondency
RATING BASED ON OBSERVATION DURING INTERVIEW AND THE FOLLOWING QUESTIONS. In the past week, do you think you have looked sad or depressed to other people? Did anyone say you looked sad or down? How about when you've looked in the mirror? Did you look gloomy or depressed? IF YES: How sad or depressed do you think you have looked? How much of the time over the past week do you think you have looked depressed or down? IF APPEARANCE WAS DEPRESSED IN PAST WEEK: Have you been able to laugh or smile at all during the past week? IF YES: How hard has it been for you to laugh or smile, even if you weren't feeling happy inside?	**2. APPARENT SADNESS.** Representing despondency, gloom and despair. (More than just ordinary transient low spirits) reflected in speech, facial expressions, and posture. Rate by depth and inability to brighten up. 0 – No sadness 1 – 2 – Looks dispirited but does brighten up without difficulty 3 – 4 – Appears sad and unhappy most of the time 5 – 6 – Looks miserable all the time. Extremely despondent

Rater Initials			Time Performed (24 hours)									Has the rater changed from the previous assessment?	
			___ ___ : ___ ___									Yes □ No □ N/A □	
Subject Initials:			Site No. / Subject ID No.									Date of Assessment (DD/MMM/YYYY)	Visit No.
												___ ___/___ ___ ___/___ ___ ___ ___	

Have you felt tense or edgy in the last week? Have you felt anxious or nervous? IF YES: Can you describe what that has been like for you? How bad has it been? (Have you felt panicky?) What about feeling fearful that something bad is about to happen? How hard has it been to control these feelings? (What has it taken to help you feel calmer? Has anything worked to calm you down?) How much of the time have you felt this way over the past week?	**3. INNER TENSION.** Representing feelings of ill defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread, or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for. 0 – Placid. Only fleeting inner tension 1 – 2 – Occasional feelings of edginess and ill-defined discomfort 3 – 4 – Continuous feelings of inner tension or intermittent panic which the patient can master with some difficulty 5 – 6 – Unrelenting dread or anguish. Overwhelming panic

How has your sleeping been in the last week? (How many hours have you been sleeping, compared to usual?) **Have you had trouble falling asleep?** (How long has it been taking you to fall asleep this past week?) **Have you been able to stay asleep through the night?** **(**Have you been waking up at all in the middle of the night? How long does it take you to fall back to sleep?) **Has your sleeping been restless or disturbed?**	**4. REDUCED SLEEP.** Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well. 0 – Sleeps as usual 1 – 2 – Slight difficulty dropping off to sleep or slightly reduced, light, or fitful sleep 3 – 4 – Sleep reduced or broken by at least 2 hours 5 – 6 – Less than 2 or 3 hours sleep

How has your appetite been this past week? (What about compared to your usual appetite?) Have you been less interested in food? (How much less?) Does food taste as good as usual? IF LESS: How much less? Have you had to force yourself to eat? Have other people had to urge you to eat?	**5. REDUCED APPETITE.** Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat. 0 – Normal or increased appetite 1 – 2 – Slightly reduced appetite 3 – 4 – No appetite. Food is tasteless 5 – 6 – Needs persuasion to eat at all

Rater Initials	Time Performed (24 hours)	Has the rater changed from the previous assessment?	
	___ ___ : ___ ___	Yes □ No □ N/A □	
Subject Initials:	Site No. / Subject ID No.	Date of Assessment (DD/MMM/YYYY)	Visit No.
		___ ___/___ ___ ___/___ ___ ___ ___	

Have you had trouble concentrating or collecting your thoughts in the past week? (How about at home or at work?) IF YES: Can you give me some examples? (Have you been able to concentrate on reading a newspaper or magazine? Do you need to read things over and over again?) How often has that happened in the past week? Has this caused any problems for you? IF YES: Can you give me some examples? Has your trouble concentrating been so bad at any time in the past week that it has been difficult to follow a conversation? (IF YES: How bad has that been? How often has that happened this past week?) **NOTE:** ALSO CONSIDER BEHAVIOR DURING INTERVIEW.	**6. CONCENTRATION DIFFICULTIES.** Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced. 0 – No difficulties in concentration 1 – 2 – Occasional difficulties in collecting one's thoughts 3 – 4 – Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation 5 – 6 – Unable to read or converse without great difficulty

Have you had any trouble getting started at things in the past week? IF YES: What things? **Have you had to push yourself to do things?** IF YES: What things? How hard have you had to push yourself? Are you OK once you get started or is it still more of an effort to get something done? What about getting started at simple routine everyday things (like getting dressed)? **Have you done everyday things more slowly than usual?** (Have you been sluggish?) IF YES: Like what, for example? How bad has that been?	**7. LASSITUDE.** Representing a difficulty getting started, or slowness initiating and performing everyday activities. 0 – Hardly any difficulty in getting started. No sluggishness 1 – 2 – Difficulties in starting activities 3 – 4 – Difficulties in simple routine activities, which are carried out with effort 5 – 6 – Complete lassitude. Unable to do anything without help

Have you been less interested in things around you, or in activities you used to enjoy? IF YES: What things? How bad has that been? How much less interested in (those things) are you now compared to before? Have you been less able to enjoy the things you usually enjoy? Has there been any change in your ability to feel emotions? (Do you feel things less intensely than you used to, things like anger, grief, pleasure?) IF YES: Can you tell me more about that? (IF UNKNOWN: Are you able to feel any emotions at all?) How do you feel toward your family and friends? Is that different from usual? IF REDUCED: Do you feel less than you used to towards them?	**8. INABILITY TO FEEL.** Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced. 0 – Normal interest in the surroundings and in other people 1 – 2 – Reduced ability to enjoy usual interests 3 – 4 – Loss of interest in the surroundings. Loss of feelings for friends and acquaintances 5 – 6 – The experience of being emotionally paralyzed, inability to feel anger, grief or pleasure, and a complete or even painful failure to feel for close relatives and friends

Rater Initials	Time Performed (24 hours)	Has the rater changed from the previous assessment?	
	___ ___ : ___ ___	Yes □ No □ N/A □	
Subject Initials:	Site No. / Subject ID No.	Date of Assessment (DD/MMM/YYYY)	Visit No.
		___ ___/___ ___ ___/___ ___ ___ ___	

Have you been putting yourself down, or feeling that you're a failure in some way, over the past week? (Have you been blaming yourself for things that you've done, or not done?) IF YES: What have your thoughts been? How often have you felt that way? **Have you been feeling guilty about anything in the past week? What about feeling as if you have done something bad or sinful?** IF YES: What have your thoughts been? How often have you felt that way? ALSO CONSIDER RESPONSES TO QUESTIONS ABOUT PESSIMISM FROM ITEM 1.	**9. PESSIMISTIC THOUGHTS.** Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse, and ruin. 0 – No pessimistic thoughts 1 – 2 – Fluctuating ideas of failure, self-reproach, or self depreciation 3 – 4 – Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future 5 – 6 – Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakeable

This past week, have you felt like life isn't worth living? IF YES: Tell me about that. IF NO: What about feeling as if you're tired of living? **This week, have you thought that you would be better off dead?** IF YES: Tell me about that. **Have you had thoughts of hurting or even killing yourself this past week?** IF YES: What have you thought about? How often have you had these thoughts? How long have they lasted? Have you actually made plans? IF YES: What are these plans? Have you made any preparations to carry out these plans? (Have you told anyone about it?)	**10. SUICIDAL THOUGHTS.** Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparation for suicide. Suicidal attempts should not in themselves influence this rating. 0 – Enjoys life or takes it as it comes 1 – 2 – Weary of life. Only fleeting suicidal thoughts 3 – 4 – Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention 5 – 6 – Explicit plans for suicide when there is an opportunity. Active preparations for suicide

TOTAL MADRS SCALE SCORE: _____

Rater Signature: _____ Date: _____

APPENDIX I. STRUCTURED INTERVIEW GUIDE FOR THE HAMILTON RATING SCALE FOR ANXIETY (SIGH-A) - SAMPLE

STRUCTURED INTERVIEW GUIDE FOR THE HAMILTON ANXIETY SCALE (SIGH-A)

Janet B.W. Williams, D.S.W.

INTERVIEWER: The first question for each item should be asked exactly as written. Often this question will elicit enough information about the severity and frequency of a symptom for you to rate the item with confidence. Follow-up questions are provided, however, for use when further exploration or additional clarification of symptoms is necessary. The specified questions should be asked until you have enough information to rate the item confidently. In some cases, you may also have to add your own follow-up questions to obtain necessary information. For some of the HAM-A items, you may find you have already asked about some of the symptoms (for a previous item). You do not need to
repeat questions about these symptoms unless you need additional information to rate the severity.

All of the items have the same anchor points. The following may be useful as guides to rating item severity:

MILD:	Occurs irregularly and for short periods of time.
MODERATE:	Occurs more constantly and of longer duration, requiring considerable effort on the part of the subject to cope with it.
SEVERE:	Continuous and dominates the subject's life.
VERY SEVERE:	Incapacitating.

Interviewers may find it helpful to ask the patient the following questions to help clarify the severity of a symptom: How much time does (the symptom) take up? Has (the symptom) been irregular or constant? Has it been easily manageable? How severe has it been when you get it? How much time over the last week has it been bothering you?

NOTES: Time period. The ratings should be based on the patient's condition in the past week.

Panic Attacks. If the patient has panic attacks, this will affect the ratings of many of the symptoms. It is recommended that you consider the total amount of time during the past week that the panic attack symptoms occurred, as well as their severity. Therefore, for example, a patient who has few severe but short–lived panic attacks during the week, but who otherwise does not have many anxiety symptoms, would probably not have a very high total HAM-A score.

This instrument provides an interview guide for the Hamilton Anxiety Scale (Hamilton M: The assessment of anxiety states by rating. Brit J of Med Psychol 32:50-55, 1959; Hamilton M: The diagnosis and rating of anxiety, In Studies of Anxiety, MM Lader, Ed., Meedley Bros., Kent, 1969). The anchor point descriptions for the scale have been taken from the ECDEU Assessment Manuel (Guy, William, ECDEU Assessment Manual for Psychopharmacology, Revised 1976, DMEW Publication No. (ADM) 76-338), except that "sighing" and "dyspnea," which appear twice in that version, have been taken out of the item "cardiovascular symptoms," and left under "respiratory symptoms." It has been demonstrated that an interview guide strengthens the reliability of individual scale items of the Ham-D (Williams J&W: A structured guide for the Hamilton Depression Rating Scale. Arch Gen Psychiatry 45:742-767, 1988). This work was supported in part by NIMN Grant #1 P50 MH 43520. Andrea Gitow, M.S.W. contributed to the current revision of the SIGH-A.

For further information contact PPD at 722 West 168 St., Box 74, N.Y., N.Y. 10032 (Telephone: PPD Revised 3/12/93

STRUCTURED INTERVIEW GUIDE FOR THE HAMILTON ANXIETY SCALE
(SIGH-A)

OVERVIEW: I'd like to ask you some questions about the past week. How have you been feeling since last (DAY OF THE WEEK)? IF OUTPATIENT: Have you been working? IF NOT: Why not?

MILD:	Occurs irregularly and for short periods of time.
MODERATE:	Occurs more constantly and of longer duration, requiring considerable effort on the part of the subject to cope with it.
SEVERE:	Continuous and dominates the subject's life.
VERY SEVERE:	Incapacitating.

In the last week, how much have you been worrying?

How much have you been thinking about the worst that can happen, or been afraid of what's going to happen?

Have you been feeling especially irritable this past week?

ANXIOUS MOOD (worries, anticipation of the worst, fearful anticipation, irritability):

0 – not present
1 – mild
2 – moderate
3 – severe
4 – very severe

IF SCORED 1-4 ABOVE, ASK: How long have you been feeling this way?

In the past week, how much have you felt tense? Have you gotten tired easily?

How much have you been bothered by any of these things: being startled easily, crying easily, trembling, feeling restless, not being able to relax? For each SX: How bad has that been this past week?

TENSION (feelings of tension, fatigability, startle response, moved to tears easily, trembling, feelings of restlessness, inability to relax):

0 – not present
1 – mild
2 – moderate
3 – severe
4 – very severe

This past week, have you been afraid of the dark, of strangers, of being left alone, of animals, of traffic, or of crowds? IF YES: How afraid?

FEARS (of the dark, of strangers, of being left alone, of animals, of traffic, of crowds):

0 – not present
1 – mild
2 – moderate
3 – severe
4 – very severe

SIGH-A

MILD:	Occurs irregularly and for short periods of time.
MODERATE:	Occurs more constantly and of longer duration, requiring considerable effort on the part of the subject to cope with it.
SEVERE:	Continuous and dominates the subject's life.
VERY SEVERE:	Incapacitating.

In the last week, have you had trouble falling asleep, or had broken sleep, unsatisfying sleep and being tired when you wake up, bad dreams, or nightmares? FOR EACH SX: How bad has that been?

INSOMNIA (difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors):

0 – not present
1 – mild
2 – moderate
3 – severe
4 – very severe

In the last week, have you had trouble concentrating, or trouble remembering things? How much?

INTELLECTUAL (difficulty in concentrating, poor memory):

0 – not present
1 – mild
2 – moderate
3 – severe
4 – very severe

In the past week, have you felt depressed?

DEPRESSED MOOD (loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing):

Have you been less interested in things, or not enjoying things you usually enjoy doing?

0 – not present
1 – mild
2 – moderate
3 – severe
4 – very severe

This past week, what time have you been waking up in the morning for the last time? (Is that with an alarm clock, or do you just wake up yourself?)

This past week, have you been feeling better or worse at any particular time of day – morning or evening? IF VARIATION: How much worse do you feel in the (MORNING OR EVENING)? IF UNSURE: A little bit worse or a lot worse?

SIGH-A

MILD:	Occurs irregularly and for short periods of time.
MODERATE:	Occurs more constantly and of longer duration, requiring considerable effort on the part of the subject to cope with it.
SEVERE:	Continuous and dominates the subject's life.
VERY SEVERE:	Incapacitating.

In the last week, have you been bothered by aches and pains, muscle twitching, stiffness or sudden muscle jerks?

How about grinding your teeth, having an unsteady voice, or your muscles being tense?

IF YES: How bad has that been? (How much has it bothered you?)

SOMATIC (MUSCULAR) (pain and aches, twitching, stiffness, myoclonic jerk, grinding of teeth, unsteady voice, increased muscular tone):

0 – not present
1 – mild
2 – moderate
3 – severe
4 – very severe

In the past week, have you had ringing in your ears, blurred vision, hot or cold flashes, feelings of weakness, or pricking sensation? IF YES: How bad has that been? (How much has it bothered you?)

SOMATIC (SENSORY) (tinnitus, blurring of vision, hot and cold flushes, feelings of weakness, pricking sensation):

0 – not present
1 – mild
2 – moderate
3 – severe
4 – very severe

In the past week, has your heart raced, skipped, or pounded? Have you had pain in your chest, throbbing blood vessels, or fainting feelings? IF YES: How bad has that been?

CARDIOVASCULAR SYMPTOMS (tachycardia, palpitations, missing beats, pain in chest, throbbing of vessels, fainting feelings):

0 – not present
1 – mild
2 – moderate
3 – severe
4 – very severe

In the last week, have you had pressure or tightness in your chest, or choking feelings? IF YES: How bad has that been?

What about sighing, or shortness of breath? IF YES: How bad has that been?

RESPIRATORY SYMPTOMS (pressure or constriction in chest, choking feelings, sighing, dyspnea):

0 – not present
1 – mild
2 – moderate
3 – severe
4 – very severe

SIGH-A

MILD:	Occurs irregularly and for short periods of time.
MODERATE:	Occurs more constantly and of longer duration, requiring considerable effort on the part of the subject to cope with it.
SEVERE:	Continuous and dominates the subject's life.
VERY SEVERE:	Incapacitating.

In the last week, have you had trouble swallowing? Have you had stomach pain or fullness, gas, nausea, vomiting, burning or rumbling in your stomach, loose bowels, or constipation. IF YES: How bad has that been?
Have you lost weight in the past week? IF YES: How much? Have you been trying to lose weight? DO NOT RATE LOSS OF WEIGHT DUE TO DIETING.

GASTROINTESTINAL SYMPTOMS (difficulty in swallowing, wind, abdominal pain, burning sensations, abdominal fullness, nausea, borborygmi, looseness of bowels, loss of weight, constipation):

0 – not present
1 – mild
2 – moderate
3 – severe
4 – very severe

In the past week, have you had to urinate frequently? Have you had the urge to?

GENITOURINARY SYMPTOMS (frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence):

How has your interest in sex been in the past week? (Here, I'm not asking about performance but about your interest in sex. How much did you think about it?).

0 – not present
1 – mild
2 – moderate
3 – severe
4 – very severe

FOR WOMEN: Have you had trouble having an orgasm in the past week? (When did that start?) Have you had your period in the last month or so? IF NOT: Do you know why not? IF YES: Was it especially heavy?

FOR MEN: Have you had trouble with premature ejaculation (coming too soon) in the past week? How about trouble keeping an erection? (When did that start?)

In the past week, has your mouth been dry? Have you had any flushing in your face, or have you been pale? Have you felt lightheaded, or had any tension headaches? How about feeling the hair rise on your arms, the back of your neck, or your head? Have you tended to sweat a lot in the past week? FOR EACH SX: How bad has that been?

AUTONOMIC SYMPTOMS (dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair):

0 – not present
1 – mild
2 – moderate
3 – severe
4 – very severe

SIGH-A	MILD:	Occurs irregularly and for short periods of time.
	MODERATE:	Occurs more constantly and of longer duration, requiring considerable effort on the part of the subject to cope with it.
	SEVERE:	Continuous and dominates the subject's life.
	VERY SEVERE:	Incapacitating.

RATING BASED ON OBSERVATION

BEHAVIOR AT INTERVIEW (fidgeting, restless or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, belching, brisk tendon jerks, dilated pupils, exophthalmos, etc.)
0 – not present
1 – mild
2 – moderate
3 – severe
4 – very severe

TOTAL 14-ITEM HAMILTON ANXIETY SCORE

___ ___

APPENDIX J. CLINICAL GLOBAL IMPRESSION SCALE - SEVERITY (CGI-S) - SAMPLE

<table>
<tr><td colspan="13"></td></tr>
<tr><td colspan="3">Rater Initials</td><td colspan="9">Time Performed (24 hours)</td><td colspan="2">Has the rater changed from the previous assessment?</td></tr>
<tr><td></td><td></td><td></td><td colspan="9">___ ___ : ______</td><td colspan="2">Yes □ No □ N/A □
1st administration of this instrument to this subject</td></tr>
<tr><td colspan="3">Subject Initials:</td><td colspan="9">Subject ID No.</td><td>Date of Assessment (DD/MMM/YYYY)</td><td>Visit No.</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>___ ___/___ ___ ___/_________ ___</td><td></td></tr>
</table>

Clinical Global Impression – Severity (CGI-S) Scale

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- ☐ 0 = Not assessed
- ☐ 1 = Normal, not at all ill
- ☐ 2 = Borderline mentally ill
- ☐ 3 = Mildly ill
- ☐ 4 = Moderately ill
- ☐ 5 = Markedly ill
- ☐ 6 = Severely ill
- ☐ 7 = Among the most extremely ill patients

Rater Signature: ______________________ Date: ________________________

6Busner, J., Targum, S., The Clinical Global Impressions scale: *Applying a Research Tool in Clinical Practice*. Psychiatry, 2007; 4(7):28-37 as adapted from Kay, Stanley R., *Positive and Negative Symptoms in Schizophrenia: Assessment and Research.* Clinical and Experimental Psychiatry, Monograph No. 5. Brunner/Mazel, 1991.