TITLE PAGE

Protocol Number:	NAV-17A-007
Title:	A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of NV-5138 in Adults with Treatment Resistant Depression
Sponsor:	Navitor Pharmaceuticals, Inc. 6 Liberty Square PMB #284 Boston, MA 02109 USA Phone: 857 285 4328 Fax: 857 998 6313
Investigational New Drug (IND) number:	155072
Investigational Medicinal Product (IMP):	NV-5138
Indication:	Treatment-resistant depression (TRD)
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Phase:	2
Protocol Version:	5.0
Amendment:	4.0
Date:	07 Jun 2024
Good Clinical Practice (GCP) Statement:	This study is to be performed in full compliance with International Council for Harmonisation (ICH) Good Clinical Practices (GCP) and all applicable local regulations. All required study documentation will be archived as required by regulatory authorities.

INVESTIGATOR'S SIGNATURE PAGE

I, the undersigned, read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with ICH GCP and all applicable local guidelines, including the Declaration of Helsinki and all its accepted amendments to date.

Principal Investigator's Signature Date

Print Name

SUPERNUS PROTOCOL APPROVAL PAGE

NAVITOR PROTOCOL APPROVAL PAGE

Approver:

Thomas Hughes, PhD Chairman & Chief Executive Officer Navitor Pharmaceuticals	Date

CLINICAL PROTOCOL SYNOPSIS

Sponsor: Navitor Pharmaceuticals, Inc.	
Name of Product: NV-5138	**Name of Active Ingredient:** (*S*)-2-amino-5,5-difluoro-4,4-dimethylpentanoic acid
Protocol Number: NAV-17A-007	**Phase of Development:** 2
Full Title of Study: A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of NV-5138 in Adults with Treatment Resistant Depression	
Number of Study Sites: Approximately 55 sites are planned in the United States (US).	
Number of Subjects: Approximately 800 outpatient adults with treatment-resistant depression (TRD) will be screened; approximately 268 subjects will be randomized to NV-5138 or placebo in a 1:1 ratio to achieve approximately 200 subjects completing the study.	
Indication: TRD	

Objectives:

Primary Objective:

- To evaluate the efficacy of NV-5138 compared to placebo when administered to adults with TRD on the Montgomery–Åsberg Depression Rating Scale (MADRS) total score

Key Secondary Objective:

- To evaluate the efficacy of NV-5138 compared to placebo in adults with TRD on the clinician's impression of the severity of depressive symptoms

Additional Secondary Objectives:

- To evaluate the efficacy of NV-5138 compared to placebo in adults with TRD on the following:
  1) Clinical response in adults with TRD to Hamilton Depression Rating Scale-6 Item (HAM-D_6)
  2) Onset of clinical response
  3) Depressive symptoms response
  4) Depressive symptoms remission
  5) Clinician's impression of improvement of depressive symptoms
  6) Individual disability
  7) Anxiety symptoms
  8) Clinical response rate of severity
  9) Clinical response rate of improvement

[redacted]

Safety Objective:

- To assess the safety and tolerability of NV-5138 compared to placebo in adults with TRD

Exploratory Objectives:

- To evaluate the efficacy of NV-5138 compared to placebo in adults with TRD on the following:
  1) Self-reported depressive symptoms
  2) Self-reported cognitive and physical function
  3) Self-reported sexual function
- Pharmacogenomic (PGx) evaluations

Endpoints:

Primary Efficacy Endpoint:

- Change from baseline (CFB) to the end of the treatment period on the MADRS total score

Key Secondary Efficacy Endpoint:

- CFB to the end of the treatment period on the Clinical Global Impression – Severity (CGI-S) score

Additional Secondary Efficacy Endpoints:

1) CFB to the end of each scheduled week on the HAM-D_6 total score
2) CFB to the end of each scheduled week on the MADRS total score
3) Proportion of responders (defined as ≥50% reduction from baseline in the MADRS total score) at the end of each scheduled week
4) Proportion of subjects in remission (MADRS total score ≤10) at the end of each scheduled week
5) Clinical Global Impression – Improvement (CGI-I) score at the end of each scheduled week
6) CFB to the end of each scheduled week on the Sheehan Disability Scale (SDS) total score
7) CFB to the end of each scheduled week on the Generalized Anxiety Disorder 7-item (GAD-7) scale total score
8) Percentage of subjects with a CGI-S score of 1 or 2 at the end of each scheduled week
9) Percentage of subjects with a CGI-I score of 1 or 2 at the end of each scheduled week

[redacted]

Safety Endpoints:

1) Safety endpoints are adverse events (AEs), clinical safety laboratory test results, vital signs measurements (including orthostatic blood pressure/pulse rate), weight, electrocardiograms (ECGs), and physical examination
2) Suicidal ideation and behavior as measured by the Columbia-Suicide Severity Rating Scale (C-SSRS) score
3) Dissociative symptomatology as measured by the Clinician Administered Dissociative States Scale (CADSS) total score

4) Psychopathology severity as measured by the Brief Psychiatric Rating Scale-positive symptom subscale (BPRS+) score

Exploratory Endpoints:

- CFB to the end of each scheduled week on the following:
  1) Patient Health Questionnaire 9-item (PHQ-9) scale total score
  2) Massachusetts General Hospital (MGH) Cognitive and Physical Functioning Questionnaire (CPFQ) total score
  3) Changes in Sexual Functioning Questionnaire (CSFQ) total score
- PGx evaluation (optional)
  1) Correlation between baseline pharmacogenetic testing results and drug effects on efficacy, safety, and/or PK of NV-5138
  2) CFB in the concentration of brain-derived neurotrophic factor (BDNF)

Study Design:

The study will be conducted as a multicenter, randomized, double-blind, flexible-dose, placebo-controlled, parallel design of adjunctive NV-5138 in adults with TRD.

The study consists of the following: (1) a Prospective Screening Period, (2) a Double-Blind Period, and (3) a Safety Follow-up Phone Call.

Retrospective Prescreening:

The retrospective period is the time before screening when the Investigator determines the duration (without restriction) of the current major depressive episode (MDE), and also establishes the medication history of the current MDE. Subjects will not be eligible if they previously responded for more than 4 weeks while on the current antidepressant treatment (ADT) and lost response (tachyphylaxis). Those subjects may qualify for the study if, after the current MDE started, they subsequently fail a trial with a new ADT or an increased dose of the previous ADT.

At the screening visit (Visit 1), subjects must have a documented history of inadequate response to ≥1 but ≤4 prior ADTs which must include the present ADT for their current MDE. Subjects must also be taking the currently approved ADT for a minimum of 2 weeks at a stable therapeutic dose.

Screening Period (Up to 6 Weeks, Day -42 to Day -1):

The Screening Period is up to 6 weeks depending on how long subjects have been taking their current ADT and the number of failed ADTs. As shown below, subjects who have failed ≥2 ADTs and have been taking the approved ADT at a stable dose for ≥4 weeks before screening are allowed the minimum 4-week Screening Period. A longer Screening Period is required for other subjects (for example, subjects who have been on their current ADT for 2 weeks will complete 6 weeks of screening, and subjects who have been on the current ADT for 3 weeks, will be in the Screening Period for 5 weeks).

Subjects who have an inadequate response to only 1 ADT must be on the same ADT at the stable therapeutic dose for ≥2 weeks before the Screening Period and complete 6 weeks during the Screening Period.

Flexible Screening Period for Subjects Who Had Inadequate Response to ≥2 ADTs

At the initial screening visit (Visit 1, Day -42, Day -35 or Day -28, depending on the retrospective prescreening ADT history) after informed consent is obtained which includes an optional PGx consent, subjects will undergo initial screening evaluations including a blood sample to be analyzed to ensure detectable blood level of an antidepressant. Subjects will have their diagnosis of major depressive disorder (MDD) confirmed by the Mini International Neuropsychiatric Interview (MINI). Their site-rated MADRS total score must be ≥24 and CGI-S ≥4. Inadequate response (defined as <50% improvement in depressive symptoms on an ADT taken at an adequate dose and duration) to the ADT for their current MDE will be assessed by the Investigator based on the administration of the Antidepressant Treatment Response Questionnaire (ATRQ) which was developed by MGH.

[redacted]

During the Screening Period, subjects should maintain the current antidepressant stable therapeutic dose (see Appendix 11.17 for the study-approved ADTs). Dose adjustment of ADT will not be allowed during screening and throughout the duration of the study. ADTs approved for use in this study will not be supplied by the Sponsor.

Antidepressant Adherence: Subjects will download the medication adherence app on their personal smartphone or receive a provisioned device. The application will enable confirmation of the date and time of the subject's ingestion of the ADT. During the Screening Period, subject adherence to ADT must be confirmed with the medication adherence app and the ADT blood level.

Visit 2 (Day -14) will occur for subjects who have been taking their approved antidepressant at a stable dose for a total of 6 weeks (ie, 2 weeks retrospectively prior to Visit 1 and 4 weeks during screening) [redacted]. At this visit, the Investigator will measure clinical response with the administration of the MADRS and CGI-S scales. To continue in the study, subjects must have a MADRS total score ≥24 and CGI-S ≥4 and meet all other eligibility criteria. Additional laboratory sampling of the subject's antidepressant blood level will be conducted; subjects must have 2 positive test results for ADT during screening before proceeding to the baseline visit.

It is recommended to perform Investigator-rated efficacy assessments (MADRS and CGI-S) prior to performing any subject self-reported efficacy assessments.

If the MADRS total scores vary ≥25% between the highest and lowest scores during the Screening Period, subjects will be excluded from the study.

Baseline and Randomization (Visit 3): To be eligible for randomization, subjects must have inadequate response to ≥1 but ≤4 ADTs for their MDE including the current ADT administered at a stable dose and duration for a total of ≥8 weeks (see figure above). Subjects who have an inadequate response to only 1 ADT must be on the same ADT at the stable therapeutic dose for ≥2 weeks before the Screening Period and complete 6 weeks during the Screening Period before randomization. Subjects who do not meet eligibility criteria at any time during the Screening Period will be excluded. Subjects' eligibility will be reviewed by the Sponsor, and the site must receive an eligibility verification letter for each subject before proceeding to the baseline visit.

Protocol waivers in the study will be granted on a case-by-case basis after approval from the Sponsor.

Rescreening:

Subjects who screen failed under previous protocol versions and subjects who screen failed due to tachyphylaxis or due to the absence of a failed ADT for the current MDE are allowed on a case-by-case basis to rescreen after consultation with the Medical Monitor and Sponsor's approval.

Double-Blind Period (5 weeks, Day 1 to Day 36):

The Double-Blind Period consists of 4-week (28 days) flexible dosing treatment period with study medication (SM) and a 1-week placebo-washout period. On Day 1, after eligibility has been confirmed and baseline assessments conducted, subjects will be randomized (1:1) to receive either adjunctive NV-5138 or matching placebo in conjunction with their current ADT. During the Double-Blind Period, weekly study visits will be conducted. At each visit, ECG, vital signs, body weight and alcohol breath test will be performed; samples for urinalysis, hematology and chemistry laboratory tests; urine drug screen (UDS); and blood sample for ADT will be collected. Efficacy and safety scales will be assessed (see Schedules of Events and Assessments in protocol body).

The starting dose of NV-5138 group or matching placebo is 1600 mg once daily. Dose adjustments are allowed at Visit 4 (Day 8) and Visit 5 (Day 15). Subjects who experience an intolerable adverse effect at 1600 mg may have their dose reduced to 800 mg. Subjects who have an inadequate response to 800 mg may have their dose increased again to 1600 mg per Investigator judgment to maximize their treatment response; however, no dose adjustments are allowed after Visit 5. The maximum NV-5138 dose in the study is 1600 mg once daily. The minimum NV-5138 dose is 800 mg once daily. Subjects who cannot tolerate NV-5138 800 mg once daily or matching placebo should be discontinued from the study at the discretion of the Investigator. After completion of the 4-week treatment, all subjects will receive placebo in a double-blinded fashion and continue the treatment for 1 week. Throughout the duration of the Double-Blind Period, no adjustments in the ADT or dose are allowed.

[redacted]

Visit 8 (Day 36, End of Study [EOS]), EOS assessments will be performed. After completion of the EOS procedures, SM will be discontinued, and subjects should continue with their ADT.

If the subject withdraws or is early terminated (ET), the subject will complete Visit 8/EOS/ET assessments.

Safety Follow-Up (30 Days After Completion of the Study):

After the last dose of SM in the Double-Blind Period and all study visits are completed including Visit 8, the study is considered completed. A safety follow-up phone call will occur approximately 30 days after the last dose of blinded SM only for subjects who completed the study or approximately 7 days for subjects who withdraw early from the study.

Duration of Subject's Participation:

Up to 15 weeks total (including Screening and Safety Follow-up Periods).

Investigational Medicinal Products, Reference Therapy, Doses and Mode of Administration

Study Medication: NV-5138 400 mg

Dose levels: 800 mg or 1600 mg once daily (QD)

Reference Therapy: Matching placebo

Mode of Administration: Orally as intact capsules each containing 400 mg of NV-5138 or matching placebo, in the morning, approximately 3 h after breakfast

Statistical Methodology

Sample Size:

Two hundred subjects (100 per treatment group) in the Full Analysis Set (FAS) Population will yield 80% power in detecting superiority of NV-5138 to placebo at a significance level of 0.05 (two-sided) using a two-sample t-test with equal allocation to the treatment groups. This assumes an effect size of 0.40 with a mean difference of 4.8 and a standard deviation (SD) of 12. Assuming a dropout rate of 25%, approximately 268 subjects will be randomized to achieve approximately 200 completing the study.

Assuming a 67% rate of screen failure, approximately 800 potential subjects will be screened to obtain approximately 268 subjects randomized.

Analysis Populations:

The **Randomized Population** includes all subjects who are randomized.

The **Full Analysis Set (FAS)** is a subset of subjects in the Randomized Population who take at least one dose of SM and have a baseline assessment of the MADRS total score. The efficacy analyses will be conducted using the FAS according to the randomized treatment assignment.

The **Per Protocol (PP) Population** is a subset of subjects in the FAS who complete all 8 visits through EOS with no missing MADRS total score assessments and no important protocol deviations. Subjects in the PP Population will be analyzed according to the actual treatment received.

The **Safety Population** includes all subjects randomized into the study who received at least one dose of SM. The safety analysis will be performed according to the actual treatment received.

[redacted]

Statistical Methods:

Continuous variables will be summarized using descriptive statistics (number of subjects, mean, SD, median, interquartile range [Q1 and Q3], minimum, and maximum). Categorical (nominal) variables will be summarized using the number and percentage of subjects in each category.

Efficacy Analyses:

Primary Endpoint: CFB in the MADRS total score to the end of treatment period will be analyzed using a Mixed Model for Repeated Measures (MMRM). For subjects who are discontinued from the study due to AEs or lack of efficacy and for subjects who are dosed but have no post-baseline MADRS total score, missing data will be imputed based on the missing not at random (MNAR) assumption. For subjects who are discontinued from the study due to other reasons, no missing imputation will take place. The data collected at ET visit will be mapped to the next scheduled visit. The MMRM model will include baseline MADRS total score as a covariate, and treatment, visit, and treatment-by-visit interaction as fixed effects. The model parameters will be estimated using the restricted maximum likelihood method with an unstructured variance-covariance matrix and Kenward-Roger approximation to estimate the denominator degrees of freedom. If the MMRM model with the unstructured variance-covariance matrix does not converge using the default Newton-Raphson fitting algorithm by PROC MIXED in SAS, the Fisher scoring algorithm, or the no-diagonal factor analytic structure will be used (Lu & Mehrotra, 2010).

If the model still fails to converge, the following types of covariance structure with the sandwich estimators will be used to fit the model in a sequential order until the model converges:

1) Heterogeneous Toeplitz
2) Heterogeneous Autoregressive of order 1
3) Toeplitz
4) Autoregressive of order 1
5) Compound symmetry

The denominator degrees of freedom will be estimated using the BETWITHIN option in SAS when any of the covariance structures is used with the sandwich variance estimators.

One hundred (100) imputed datasets based on the MNAR assumption will be created in case of subject discontinuation due to AE(s) or lack of efficacy and for those subjects who are dosed but have no post-baseline MADRS total score. The MMRM model for the primary efficacy analysis will be performed using each of these 100 imputed datasets. PROC MIANALYZE in SAS will be used to combine all the results from these 100 MMRM models and then make a final statistical inference.

For the final statistical inference, the least squares (LS) mean of CFB to the end of treatment period for the MADRS total score for each treatment group will be presented along with the corresponding standard error (SE). The NV-5138 treatment will be compared with the placebo group by presenting the difference in the LS means between the NV-5138 and placebo groups (NV-5138 minus placebo) with its 95% confidence interval (CI) and the p-value.

Sensitivity analysis: The sensitivity analysis will be performed using the placebo-based multiple imputation (MI) to fill in missing MADRS total scores. This approach assumes that, after discontinuation, subjects from the NV-5138 treatment group would adopt the outcome that is estimated from the placebo group. The CFB in MADRS total score to the end of treatment period based on each imputed dataset will be analyzed using the same MMRM

model described for the primary analysis. To combine all the results using each of the imputed datasets, PROC MIANALYZE in SAS will be used to make a final statistical inference.

Key Secondary Endpoint: The key secondary endpoint, the CFB to the end of the treatment period in the CGI-S score, will be analyzed in the same manner as the primary efficacy endpoint.

Additional Secondary Endpoints: The CFB to the end of each scheduled week for the MADRS, HAM-D_6, SDS and GAD-7 scores and the absolute value of CGI-I at the end of each scheduled week will be analyzed using MMRM as appropriate based on the FAS. The NV-5138 treatment group will be compared with the placebo as described for the primary analysis. For dichotomous endpoints, such as responder analysis, the Pearson's Chi-squared Test, or Fisher's Exact Test, as applicable, will be used to compare the proportion of response between NV-5138 and placebo groups.

Exploratory Endpoints Analyses: The CFB to the end of each scheduled week for exploratory endpoints (PHQ-9, CPFQ, and CSFQ scores) will be analyzed using MMRM as appropriate based on the FAS. The NV-5138 treatment group will be compared with the placebo as described for the primary analysis.

[redacted]

Safety Analyses: Safety analyses will be performed by treatment group based on the safety population. The incidence rate, severity, and relationship to SM for all AEs will be summarized by treatment group for each System Organ Class (SOC) and Preferred Term (PT). Descriptive statistics will be presented for demographics, data from the clinical laboratory test results, vital signs, weight, ECGs, physical examinations, CADSS, BPRS+ and C-SSRS scores.

Pharmacogenomic Analyses: The blood samples will be stored for possible testing of genetic variation and BDNF concentration. Analyses may include the relationship between treatment effects and adverse events (eg, understand how the nonresponders react to treatment and/or subjects who show an unusual safety profile). The deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) analyses will not be used for individual genetic characterization and the subject's identity will be kept confidential. If analyzed, the results of the exploratory analyses will be presented in a stand-alone PGx report.

Inclusion Criteria:

1) Is male or female aged 18-70 years (inclusive) at screening;
2) Is able to read, understand, write, and sign the Informed Consent Form (ICF);
3) Is willing and able to follow the study protocol and procedures and attend study appointments within the specified time windows;
4) Has a body mass index (BMI) between 19.0-40.0 kg/m^2 (inclusive);
5) Is able to swallow capsules whole without crushing, chewing, or opening;
6) Has a diagnosis of major depressive disorder (MDD) according to the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5*) for either recurrent or single episode MDD without psychotic features that is confirmed by the MINI;

7) Has a MADRS total score of ≥24 for the current MDE at the screening visits and baseline visit (Day 1);
8) Has a CGI-S score of ≥4 (moderately ill or worse) at the screening visits and baseline visit;

[redacted]

10) Has a history of inadequate response to ≥1 but ≤4 prior ADT therapies (including the current ADT for the current MDE) ≥2 weeks before screening and ≥8 weeks at baseline. An inadequate response is defined as <50% improvement in depressive symptoms on an ADT (taken at an adequate dose and duration) assessed by the Investigator with the administration of the MGH-ATRQ and confirmed by documented records.

    Note: Subjects who fail to respond to either a trial with a new ADT or an increased dose for the previous ADT (both of adequate dose and duration) can be enrolled (increased doses of the same ADT are counted as only 1 failed ADT). The ADT must have been started after the current MDE began;
11) Has been on a stable therapeutic dose of one of the following study-approved ADTs for the current MDE for ≥2 weeks prior to screening: citalopram, escitalopram, paroxetine, fluoxetine, sertraline, duloxetine, venlafaxine (immediate release or extended release), desvenlafaxine, vilazodone, levomilnacipran, vortioxetine, bupropion or dextromethorphan/bupropion (see Appendix 11.17).

    Note: Subject must be on ADT monotherapy before randomization. If a subject is taking a second ADT or augmentation therapy at screening, the Investigator should decide if it is medically appropriate to discontinue the second drug before randomization into the study. If so, the second drug should be washed out at least 5 half-lives prior to baseline. If not, the subject should be excluded from the study;
12) Has a detectable blood level of the approved ADT at both Visits 1 and 2 of the Screening Period.

    Note: A negative test may be repeated with permission of the Medical Monitor and Sponsor upon additional evidence of subject adherence to ADT or evidence of sample or laboratory error;
13) Agrees to maintain a stable therapeutic dose of the approved ADT throughout the study;
14) Has discontinued prohibited hypnotic medications 6 weeks prior to randomization. See Appendix 11.16.1 for allowed sleep medications;
15) Nonpregnant females of childbearing potential (FOCP) who are exclusively in a same-sex relationship are included without the need for acceptable birth control methods.

    FOCP who are sexually active with a male partner (who is biologically capable of having children) must agree to use one of the following acceptable birth control methods after signing the ICF, throughout the study, and for 30 days following the last dose of the SM:
    a. Simultaneous use of male condom and intrauterine contraceptive device placed at least 4 weeks prior to the first SM administration;
    b. Simultaneous use of male condom and diaphragm with spermicide; or
    c. Established hormonal contraceptive (started at least 4 weeks prior to the first dose of the SM).

    Female subjects are considered not to be of childbearing potential if they are either postmenopausal (amenorrhea for at least 2 years and serum follicle-stimulating hormone

[FSH] level of >40 IU/L) or permanently sterilized (eg, bilateral tubal ligation, bilateral oophorectomy, etc.) for 6 months minimum prior to screening.

All FOCP must have a negative serum pregnancy test result before administration of SM.

16) Male subjects:
    a. Who are exclusively in a same-sex relationship or have female partners considered not to be of childbearing potential are included without the need for acceptable birth control methods;
    b. Who have been surgically sterilized (6 months minimum) prior to screening visit are eligible to participate without any contraception; or
    c. Who are biologically capable of having children and have female partners of childbearing potential must use one or more methods of contraception as stated in Inclusion Criterion #15 which must be used from the time of signing the ICF until 90 days after the last dose of SM.

All male subjects must refrain from donating sperm from the date of first administration of SM until 90 days after the last dose of the SM.

Exclusion Criteria:

1) Has a MADRS total score improvement of ≥25% from the highest to the lowest score during the Screening Period and baseline visit;
2) Has received new-onset psychotherapy or had a change in the intensity of psychotherapy within 4 weeks prior to screening. Psychotherapy initiated prior to screening must be maintained for the duration of the study;
3) Has been treated with electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), or vagal nerve stimulation (VNS) for the current MDE;
4) Has received treatment with long-acting injectable antipsychotics (LAIs) within 3 months prior to screening;
5) Has recurrent MDD, has been on an adequate dose and duration of ADT and had a >50% response for at least 4 weeks while using that ADT that was then followed by a loss of response (ie, tachyphylaxis) as assessed by the Investigator. The date of the loss of response is the start date of the current episode (from when the symptoms returned);
6) Has demonstrated a nonresponse to esketamine or off-label use of ketamine or has taken esketamine or ketamine less than 6 months prior to screening visit (see Appendix 11.16.2);
7) Is unable to discontinue treatment with trazodone at doses greater than 150 mg daily for a minimum of 5 half-lives before baseline.
    a. Trazodone 150 mg/day or less for sleep is permitted as needed if the subject has been taking the same low dose of trazodone for insomnia for at least 3 months;
8) Has unstable hypothyroidism. If the thyroid-stimulating hormone (TSH) value is out of range (>4.0 mIU/L) regardless of thyroid history, a free thyroxine (FT4) will be measured. If the FT4 value is abnormal (levels <0.8 mIU/L) and considered to be clinically significant (after discussion with the Medical Monitor), the subject will not be eligible.
    a. Treatment with thyroid hormones is allowed if prescribed at a stable dose for ≥3 months and the subject's thyroid levels are normal;
9) Has clinically significant abnormal laboratory profiles (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] values ≥3x the upper limit of normal [ULN] or total bilirubin ≥1.5 times the ULN), vital signs, or ECGs per Investigator judgment (see **Note**: below). If there are any abnormalities that are not specified in the Inclusion and Exclusion Criteria, the Investigator must determine their clinical significance and record it in the subject's source documents;

10) Has abnormal renal function as demonstrated by an estimated glomerular filtration rate (eGFR) of <60 mL/min according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation at the screening visit;
11) Has a history of substance use disorder (SUD) within 6 months prior to screening or is currently using or has a positive result (UDS) at any screening or baseline visits for drugs of abuse (see Appendix 11.16.2). Positive results for specific medications must have a confirmed medical history;
12) Has a history of alcohol use disorder within 6 months prior to screening. A subject who has a positive alcohol test result at any of the screening visits (V1 andV2), and if based on the Investigator opinion the subject does not have a history of alcohol use disorder, the subject may continue to the next visit. If the alcohol test result at baseline visit is positive, the subject should be excluded from the study. Subjects must refrain from using alcohol during the treatment phase of the study;
13) Has a diagnosis of cannabis use disorder (CUD) within 6 months before screening and has a positive UDS for cannabis at screening.
    a. At the discretion of the Sponsor, recreational use of cannabis (not daily) is allowed and should be kept consistent during the study. Subjects must agree to refrain from using cannabis 48 h prior to the study visits;
    b. Medical cannabis prescribed for a medical condition (eg, muscle spasms, nausea, vomiting, pain) other than depression, seizures, and insomnia is allowed if taken at a stable regimen for at least 3 months prior to screening. Newly prescribed cannabis treatment and/or change to the existing regimen is prohibited (see Appendix 11.16.1). When applicable, subjects should show proof of their prescription for medical cannabis;
14) Has had any suicidal behavior or suicidal ideation of type 4 (active suicidal ideation with some intent to act, without specific plan) or type 5 (active suicidal ideation with specific plan and intent) based on C-SSRS in the 2 years before screening; a history of suicide attempt in the last 6 months; or more than 2 lifetime suicide attempts;
15) Has a lifetime history of psychotic disorder including but not limited to schizophrenia, MDD with psychotic features, or bipolar I/II disorder with and without psychotic features;
16) Has a diagnosis within 12 months before screening or current diagnosis of post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), panic disorder, acute stress disorder, or has a history of intellectual disability, autism, or Cluster A or B personality disorder (per *DSM-5* criteria).
    a. Current diagnosis of comorbid generalized anxiety disorder is allowed but subject to medication restrictions (anticonvulsants and beta-blockers are allowed, if on a stable regimen for 2 months prior to screening visit);
    b. Established attention-deficit/hyperactivity disorder (ADHD) diagnosis is allowed. Subjects must provide confirmation of ADHD diagnosis (ie, provide medical records for prescribed ADHD medications) and be on a stable dose of ADHD medication for at least 3 months prior to the screening visit;
17) Has a history of a psychiatric or neurologic conditions or symptoms that could impose undue risk or compromise the study including but not limited to:
    a. History of seizure disorder or history of epilepsy (except history of absence or uncomplicated childhood febrile seizures);
    b. History of clinically significant or moderate head trauma that, in the Investigator's opinion, is likely to affect central nervous system (CNS) functioning; or
    c. Has current evidence of delirium or dementia;

18) Has a history of cardiovascular, respiratory, gastrointestinal, renal, hepatic, hematologic, or other medical disorder that could impose undue risk or compromise the study, in the Investigator's opinion, including but not limited to the following:
    a. Cardiovascular disorders:
        i. Clinically significant symptomatic orthostatic hypotension;
        ii. Uncontrolled hypertension despite diet, exercise, and antihypertensive medications (defined as a supine systolic blood pression [SBP] >140 mmHg or diastolic blood pressure [DBP] >90 mmHg) during screening and at baseline;
        iii. Acute coronary syndrome;
        iv. History of unexplained loss of consciousness, unexplained syncope, unexplained irregular heartbeats;
        v. QT interval corrected using Fridericia's method (QTcF) ≥450 ms (for men) or ≥470 ms (for women) at screening (see **Note**Note:
        vi. Patient or family history of QT congenital syndrome;
    b. Oncological disorders:
        i. Malignant tumors within 5 years prior with the exception of benign skin tumors; and/or
        ii. Diagnosis or family history of tuberous sclerosis complex (TSC).
    c. Positive result for human immunodeficiency virus (HIV), hepatitis B or hepatitis C (HCV) at screening unless:
        i. HIV positive: subjects must have a HIV Confirmation Test. If the confirmatory test is positive, the subject is eligible if on chronic suppressive antiviral medication for more than 6 months with an undetectable viral load;
        ii. HBsAg positive: subjects should be tested for anti-HBc, IgM anti-HBc, and anti-HBs to detect acute or chronic infection (ineligible). Subjects whose results indicate immunity (either by natural infection or vaccination) with no active infection are eligible; and/or
        iii. HCV positive: subjects must have undetectable HCV RNA to be eligible;
    d. Unintended recent clinically significant weight loss;
    e. Has chronic urinary tract infections (UTIs);
    f. Blood donation within 6 weeks of screening; and/or
    g. Is on any medication that could, in the Investigator's opinion, interfere with the assessments of safety, tolerability, efficacy, or the conduct or interpretation of the study;
19) Requires treatment with a medication or other substance that is prohibited by the protocol (see Section 5.8);
20) Has history of severe drug allergy or hypersensitivity, or hypersensitivity to the SM or excipients;
21) Female subjects who are pregnant, lactating, or planning to become pregnant while enrolled in the study;
22) Has previously enrolled in a NV-5138 study;
23) Is currently participating in another clinical trial or has participated in a clinical study within 30 days of screening visit.
24) Is a member of study personnel or their immediate families or is a subordinate (or immediate family member of a subordinate) to any of the study personnel.

***Note**: Repeat testing for clinical laboratory parameters, vital signs, and ECG is permitted one time for each test at the discretion of the Investigator as long as the repeat test result is available within the pre-treatment period to determine eligibility. Repeat testing is not allowed*

without justification from the site and agreement from the Medical Monitor and the Sponsor on a case-by-case basis.

Table of Contents

1 LIST OF ABBREVIATIONS

ADHD	attention deficit/hyperactivity disorder
ADR	adverse drug reaction
ADT	antidepressant therapy
AE	adverse event
ALT	alanine aminotransferase
ASSR	auditory steady-state response
AST	aspartate aminotransferase
ATC	Anatomical-Therapeutic-Chemical (code)
ATRQ	Antidepressant Treatment Response Questionnaire
AUC	area under curve
BDNF	brain-derived neurotrophic factor
BMI	body mass index
BPRS+	Brief Psychiatric Rating Scale-Positive Symptom Subscale
CADSS	Clinician Administered Dissociative States Scale
CFB	change from baseline
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression – Improvement
CGI-S	Clinical Global Impression – Severity of Illness
CI	confidence interval
CKD-EPI	Chronic Kidney Disease-Epidemiology Collaboration
CL/F	apparent clearance
ClinRO	clinical reported outcome
CLr	renal clearance
C_{max}	peak plasma concentration
CNS	central nervous system
CPFQ	Cognitive and Physical Functioning Questionnaire
CRA	clinical research associate
CRO	clinical research organization
CSF	cerebrospinal fluid
CSFQ	Changes In Sexual Functioning Questionnaire
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTNI	Clinical Trials Network Institute
CUD	cannabis use disorder
CUS	chronic unpredictable stress
CYP	cytochrome P450
DBP	diastolic blood pressure
DNA	deoxyribonucleic acid
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders – 5th Edition*
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram/electrocardiography
eCRF	electronic case report form
ECT	electroconvulsive therapy

EDC	electronic data capture
EEG	electroencephalography
eGFR	estimated glomerular filtration rate
EOS	end of study
ER	extended-release
ERP	event-related potential
ES	effect size
ET	early termination
FAS	Full Analysis Set
FCS	fully conditional specification (method)
FDA	Food and Drug Administration
FOCP	females of childbearing potential
FPC	follow-up phone call
FSH	follicle-stimulating hormone
FST	Forced Swim Test
FT4	free thyroxine
GAD-7	Generalized Anxiety Disorder 7-Item Scale
GCP	Good Clinical Practice
GLDH	glutamate dehydrogenase
GLP	Good Laboratory Practice
HAM-D_6	Hamilton Depression Rating Scale-6 Items
HIV	human immunodeficiency virus
HTT	human treat test
IB	Investigator's Brochure
ICE	intercurrent events
ICF	informed consent form
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IR	immediate release
IRB	institutional review board
IRT	interactive response technology
LS	least squares
MADRS	Montgomery–Åsberg Depression Rating Scale
MAR	missing at random
MDD	major depressive disorder
MDE	major depressive episode
MedDRA	*Medical Dictionary for Regulatory Activities*
MGH	Massachusetts General Hospital
MINI	Mini International Neuropsychiatric Review
MMRM	Mixed Model for Repeated Measures
MNAR	missing not at random
mPFC	medial prefrontal cortex
mTORC1	mammalian target of rapamycin complex 1
NMDA	N-methyl-D-aspartate

NMDAR	N-methyl-D-aspartate receptor
NOAEL	no-observed-adverse-effect-level
NSFT	novelty-suppressed feeding test
OCD	obsessive-compulsive disorder
p-EEG	pharmaco-electroencephalography
PFC	prefrontal cortex
PGx	pharmacogenomics
PHQ-9	Patient Health Questionnaire 9-Item
PK	pharmacokinetics
POC	Point of Care
PP	Per Protocol
PRR	Placebo Response Reduction (Training)
PT	preferred term
PTSD	post-traumatic stress disorder
Q1, Q3	quartile 1, quartile 3
QD	once daily
qEEG	quantitative electroencephalography
QTcF	QT corrected using Fridericia's method
RNA	ribonucleic acid
RR	respiratory rate
SADR	suspected adverse drug reaction
SAE	serious adverse event
[redacted]	
SAP	statistical analysis plan
SBP	systolic blood pressure
[redacted]	[redacted]
SD	standard deviation
SDS	Sheehan Disability Scale
SIGMA	Structured interview guide for the Montgomery–Åsberg Depression
SM	study medication
SNRI	serotonin and noradrenaline reuptake inhibitor
SOC	system organ class
SOP	standard operating procedure
SSRI	selective serotonin reuptake inhibitor
SUD	substance use disorder
$t_{½}$	terminal elimination half-life
TDD	total daily dose
TEAE	treatment-emergent adverse event
T_{max}	time to peak plasma concentration
TMS	transcranial magnetic stimulation
TR	total radioactivity
TRD	treatment-resistant depression
TSC	tuberous sclerosis complex
TSH	thyroid-stimulating hormone

UDS	urine drug screen
ULN	upper limit of normal
UTI	urinary tract infection
Vd/F	apparent volume of distribution
VNS	vagal nerve stimulation
WBC	white blood cell
WHO DD	*World Health Organization-Drug Dictionary*

2 INTRODUCTION

2.1 Background

Major Depressive Disorder (MDD) is a leading disability that affects over 25.8 million people worldwide (Q. Liu et al., 2020). MDD is made up of major depressive episodes that are usually two weeks in duration and longer and may be recurring in nature. Based on the *Diagnostic and Statistical Manual of Mental Disorders* 5th Edition (DSM-5), out of the five diagnostic criteria needed to be diagnosed with MDD, at least one of the following must be present: depressed mood or loss of interest or pleasure. In addition to one of these symptoms, the individual must also experience one of the following: changes in appetite or weight, sleep disturbances, psychomotor changes (ie, agitation or retardation); decreased energy, sense of worthlessness or guilty, impaired ability to think, and thoughts of death, suicidal ideation or suicide attempts (DSM-5, 2013).

First-line therapy for MDD is either psychotherapy, pharmacotherapy, or a combination of both. Antidepressants typically used as first-line medications are selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), bupropion, mirtazapine, and newer agents. Approximately 50-70% of patients with MDD do not achieve response or remission with at least one antidepressant treatment (ADT) of adequate dose and duration (Bartova et al., 2019; Knoth, Bolge, Kim, & Tran, 2010; Trivedi et al., 2006) resulting in treatment-resistant depression (TRD). The two currently Food and Drug Administration (FDA)-approved treatments for TRD are the Olanzapine/Fluoxetine hydrochloride combination and the nasal spray, Esketamine. There is a clear unmet need in the treatment of TRD for a novel pharmacotherapy that has less deleterious effects such as metabolic changes or potential addictive properties (Brunner, Tohen, Osuntokun, Landry, & Thase, 2014; FDA, 2019). There are novel antidepressants in clinical development and approved for the treatment of TRD that modulate the N-methyl-D-aspartate (NMDA) receptor (NMDAR), leading to rapid and sustained symptom relief in TRD patients (Abdallah, Averill, & Krystal, 2015; Moskal et al., 2017; Zarate & Machado-Vieira, 2017); however, acute modulation of the NMDAR with ketamine administration has been associated with frequent dissociative symptoms and other undesirable effects (Pennybaker, Luckenbaugh, Park, Marquardt, & Zarate, 2017). Alternative therapeutic options not involving NMDAR modulation could be of great value in treating TRD patients.

2.2 NV-5138

The investigational drug in this study is NV-5138, (S)-2-amino-5,5-difluoro-4,4-dimenthylpentanoic acid, a novel, orally bioavailable, selective, activator of mammalian target of rapamycin complex 1 (mTORC1) cellular signaling. The activation of mTORC1 involves the binding of NV-5138 to the primary cytoplasmic leucine sensor protein

isoforms sestrins 1 and 2, without binding to or modulating other synaptic receptors or other signaling proteins (eg, NMDAR).

NV-5138 is intended to provide a rapid-onset antidepressant response whereas the standard first-line and second-line antidepressant therapies (SSRIs and SNRIs) typically require a longtime course to establish an antidepressant response (Ignacio et al., 2016). The central role of mTORC1 signaling in the rapid-acting antidepressant effect suggests that an activator of mTORC1 signaling may provide rapid antidepressant efficacy without the potential neurological side effects associated with some NMDAR-modulating compounds.

2.3 Preclinical Studies

In animals, NV-5138 was rapidly and completely absorbed after oral administration. Following single oral administration in rats and monkeys, the increase in systemic exposure (area under the curve [AUC]) of NV-5138 was roughly proportional with dose. NV-5138 exhibited a moderate volume of distribution and low systemic clearance in all preclinical species.

2.3.1 In Vitro Binding Studies

The specificity of NV-5138 was evaluated in vitro by screening for binding and functional modulation across multiple categories of proteins, including multiple classes of enzymes and receptors. There was no significant binding to or modulation of several classes of enzymes, including an extensive number of kinases and over 100 different receptors, among them many of the most common receptors found in the central nervous system (CNS). This included all isoforms of the NMDAR where there was no binding or functional modulation when evaluated across ligand categories (Sengupta et al., 2019) .

2.3.2 In Vivo Pharmacology in Animals

Oral administration of NV-5138 in *ad libitum* fed rats resulted in significant activation of mTORC1 across various regions of rat brain including the prefrontal cortex (PFC), hippocampus, striatum and neocortex, with no significant activation observed in cerebellum (Sengupta et al., 2019). Similarly, oral administration of NV-5138 and leucine resulted in mTORC1 activation across multiple peripheral tissues, but not in whole brain. These data also show that the pattern of mTORC1 activation in the periphery appears to correlate with nutritional activation simulated by the use of leucine supplementation, indicating that there is no organ system other than the brain which appears more sensitive to NV-5138 versus the natural sestrin2/1 ligand leucine (Sengupta et al., 2019). The differential metabolism between NV-5138 and leucine in the brain leads to the greater relative activation of mTORC1 compared with that observed in the peripheral tissues examined, where there is greater direct competition between leucine and NV-5138 for sestrin-mediated activation and subsequent mTORC1 activation (Sengupta et al., 2019).

2.3.3 In Vivo Pharmacology Studies in Animal Models of Depression

The pharmacological efficacy of NV-5138 at different doses was evaluated using models of stress-induced depressive behavior and anxiety, including the forced swim test (FST) and the novelty-suppressed feeding test (NSFT). These studies demonstrate that the pharmacological efficacy of NV-5138 in the FST and the NSFT was observed only after one dose of 160 mg/kg, up to 3 days following administration (Kato et al., 2019). Similar studies demonstrate that the pharmacological efficacy of NV-5138 in the FST and the NSFT was observed 24 h after daily dosing for 6 days at 80 mg/kg and out to 72 h following the end of the dosing period, suggesting that alternative dose administration strategies to achieve similar efficacy at lower doses clinically may be feasible.

The chronic unpredictable stress (CUS) model is considered one of the more challenging models to evaluate antidepressant activity of new agents, since the model produces anhedonia, a core symptom of depression (Banasr et al., 2007; Li et al., 2011). Rats exposed to CUS had a significant decrease in sucrose preference compared to the non-CUS animals. The administration of a single dose of NV-5138 completely and significantly blocked the effects of CUS in the sucrose preference test. CUS also had a significant impact on the latency to feed in the NSFT which was significantly improved up to 3 days following the administration of NV-5138 (Kato et al., 2019). Since previous studies in rodents have established that ketamine and GLYX-13 require activation of the mTORC1 signaling pathway to elicit the observed rapid antidepressant efficacy (Hoeffer & Klann, 2010; Li et al., 2010; R. J. Liu et al., 2017), the effects of NV-5138 (160 mg/kg) following a single oral administration on mTORC1 pathway activation, were compared to those of ketamine (10 mg/kg) following a single injection in male rats. Similar to ketamine, there was a robust and significant induction of S2448pmTOR by NV-5138 and a significant induction of GluR1 and synapsin1 by both NV-5138 and ketamine was observed (Kato et al., 2019). This is translated in increased dendritic spine formation in the layer V pyramidal neurons of the medial prefrontal cortex (mPFC).

The human treat test (HTT) is another well-validated test procedure in the nonhuman primate which is sensitive to clinically active anxiolytics (Costall, Domeney, Gerrard, Kelly, & Naylor, 1988). NV-5138, similarly to ketamine, showed an anxiolytic/antidepressant-like profile 24 h after acute oral administration in the marmoset HTT as demonstrated by the ability to reduce the number of postures without causing a change in locomotor activity as assessed by the number of jumps performed by the animals.

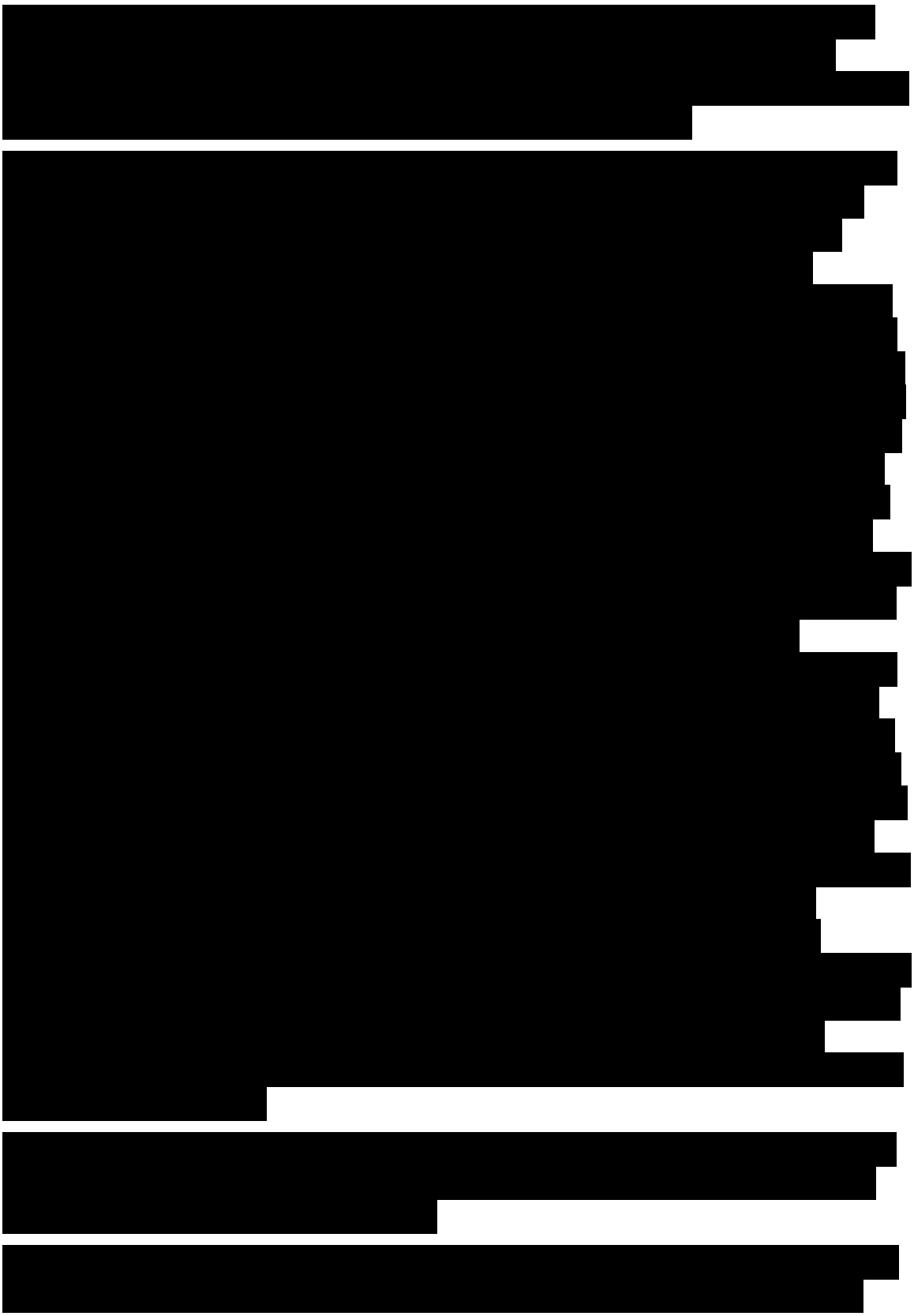
Pharmaco-electroencephalography (p-EEG) have been used extensively to characterize the impact of neuromodulating compounds, including rapid-acting antidepressants such as ketamine (Ahnaou, Huysmans, Biermans, Manyakov, & Drinkenburg, 2017; W. C. Duncan, Jr. & Zarate, 2013; W. C. Duncan et al., 2013). p-EEGs in animals and humans are being used to address extrapolation issues and to optimize the translational validity of

preclinical animal p-EEG paradigms such as quantitative electroencephalogram (qEEG). NV-5138 produces rapid and strong effects on the spectral EEG recorded from rat in both sleep and wake states. In two independent studies, induction of these effects required at least two doses (separated by 36 h) of NV-5138 with a third dose further accentuating the effects.

2.3.4 In Vivo Binding Adverse Effects

The *in vitro* plasma protein binding of NV-5138 was low (close to 0%) in all species tested, which indicates that NV-5138 is unlikely to produce adverse effects due to a pharmacokinetic drug interaction involving competition for plasma protein binding sites. After oral administration in rats, NV-5138 rapidly distributed to tissues, including the brain, where maximal concentrations in whole brain homogenates were achieved at 1 h postdose (Kato et al., 2019; Sengupta et al., 2019).

2.4 Toxicological Studies



[redacted]

2.5 Clinical Studies

2.5.1 Phase 1 Studies

Four Phase 1 studies have been conducted; each is summarized below. For additional information, please refer to the Investigator's Brochure (IB).

2.5.1.1 Study NAV-17A-001

This study was a Phase 1a/1b, randomized, two-part, double-blind, placebo-controlled, on-site study of single ascending dosage levels of NV-5138 or placebo in 48 healthy volunteers (Part A) and a single dose of NV-5138 2400 mg or placebo in 32 subjects with TRD (Part B).

In Part A of the study, a single dose of NV-5138 was generally safe and well tolerated in healthy subjects at doses ranging from 150-2400 mg. Subjects treated with NV-5138 had a higher incidence of treatment-emergent adverse events (TEAEs) overall (36.1% compared with 16.7%) and of drug-related TEAEs (19.4% compared with 0) than subjects who received placebo; this was a disparity that was generally dose related. There were no serious adverse events (SAEs) or discontinuations due to TEAEs. Only two drug-related TEAEs occurred in more than 1 subject: dizziness (NV-5138, 3 subjects [8.3%]; placebo, 0) and nausea (NV-5138, 2 subjects [5.6%]; placebo, 0). All TEAEs in NV-5138-treated subjects were mild. [redacted]

[redacted]

In Part B of the study, a single dose of NV-5138 2400 mg was generally safe and well tolerated in patients with TRD. NV-5138 was associated with a higher incidence of TEAEs (68.8% compared with 37.5%) and drug-related TEAEs (62.5% compared with 25.0%) than placebo. There were no serious or severe TEAEs, or discontinuations due to TEAEs. Only 3 drug-related TEAEs occurred in more than 1 patient: somnolence (NV-5138, 4 patients [25.0%]; placebo, 2 patients [12.5%]); dizziness (NV-5138, 2 patients [12.5%]; placebo, 0), and headache (NV-5138, 2 patients [12.5%]; placebo, 0).

There were no dissociative effects in either Part A or Part B. There were no clinically meaningful trends or individual abnormalities in laboratory test results, vital signs, ECG data, Brief Psychiatric Rating Scale-Positive Symptoms Subscale (BPRS+), and Clinician Administered Dissociative States Scale (CADSS) scores, or neurological and physical examination findings in either part of the study.

[redacted]

2.5.1.2 Study NAV-17A-002

This study was a Phase 1, randomized, double-blind, placebo-controlled, on-site, single-dose study to evaluate the safety, pharmacokinetics (PK), and metabolomic and proteomic profiles of NV-5138 in plasma and CSF in healthy male subjects between the ages of 18-55 years. A total of 13 subjects were randomly assigned to receive either a single oral 2400 mg dose of NV-5138 (N=8) or placebo (N=5).

In addition, compared to placebo, NV-5138 significantly and rapidly increased key proteomic and metabolomic biomarkers in the CSF involved in synaptic plasticity and mTORC1 activation including orotate, N-formyl methionine, and N-acetyl methionine, as hypothesized.

NV-5138 was generally well tolerated. There were no deaths, SAEs, or discontinuations due to TEAEs. Of the 20 TEAEs recorded, half were due to postlumbar puncture syndrome or back pain which are common with CSF sampling procedures and were considered not related to SM. All TEAEs were mild, and all resolved. There were no clinically significant abnormal laboratory values, vital signs, ECG data, or physical examination findings, and no treatment-related trends were identified. For further CSF results and metabolomic and proteomic data, please refer to the IB.

2.5.1.3 Study NAV-17A-003

This study was a randomized, double-blind, placebo-controlled, on-site study of the effects on qEEG and event-related potential (ERP) of two sequential doses of NV-5138 or placebo administered 48 h apart to healthy adult male subjects; 25 subjects were randomized to receive either NV-5138 2400 mg (N=12) or matching placebo (N=13).

[redacted]

NV-5138 produced dose-dependent decreases in low-frequency electroencephalography (EEG) bands (delta, theta) and increases in high-frequency EEG bands (gamma). In alpha bands, there were decreases in amplitudes (or desynchronization) at 1 h after dosing. These changes are all signs of EEG activation, and they did not occur in the placebo group.

NV-5138 was also associated with increased auditory steady-state response (ASSR) high-frequency resonance which was not evident in the placebo group. NV-5138 treatment reduced the peak latency of N100, P200, and P300A components in auditory oddball tasks, which was not evident in the placebo group.

The two doses of 2400 mg NV-5138 administered 48 h apart were generally safe and well tolerated in healthy male subjects. TEAEs were mild, with no SAEs or discontinuations due to TEAEs. The incidence of TEAEs was higher in the placebo group (15.4%) than in the NV-5138 group (8.3%) as was the incidence of drug-related TEAEs (15.4% for placebo compared with 0 for NV-5138). No dissociative effects were reported. There were no clinically meaningful abnormalities in laboratory test results, vital signs, ECG data, safety EEG data, BPRS+ or CADSS scores, or neurological and physical examination findings. There was no evidence of proconvulsant activity on safety EEGs.

2.5.1.4 Study NAV-17A-004

This study was a randomized, double-blind, placebo-controlled study of the safety, tolerability, and PK of multiple ascending doses of NV-5138 in healthy adults. The study consisted of 5 dose cohorts (400 mg, 800 mg, 1600 mg, 2400 mg, and 3000 mg). In each cohort, subjects were randomized 3:1 (NV-5138: placebo) to receive NV-5138 or placebo for 7 days under fasting conditions; subjects in the 2400 mg cohort returned to the clinic after a minimum 5-day washout to receive an additional single dose of NV-5138 or placebo with a standard high-fat breakfast. Safety, tolerability, and plasma PK were assessed in each cohort. In addition, CSF PK and biomarkers were assessed in all except the 3000 mg cohort. [redacted]

[redacted]

NV-5138 was found to be safe and tolerable in the dose range of 400 mg-3000 mg following multiple doses. Most TEAEs were mild or moderate in severity. None were serious. Two subjects in the 400 mg cohort discontinued the study due to AEs (neck strain and emesis). No early discontinuations due to AEs occurred in the other cohorts.

2.5.1.5 Study NAV-17A-005

The study was an open-label, randomized, 4-sequence crossover study to compare the relative bioavailability of capsule with oral solution following a single dose of 400 mg NV-5138 administered to healthy adults under fasted conditions and to assess dose linearity following administration of NV-5138 400 mg (1 capsule) and 1600 mg (4 capsules). [redacted]

Overall, NV-5138 was well-tolerated when administered as 400- and 1600-mg capsules and 400- and 1600-mg oral solution. All AEs were mild in severity; none were severe or serious. No AEs led to study discontinuation.

2.5.1.6 Study NAV-17A-006

This study was an open-label, single-dose study in healthy male subjects to assess the mass balance recovery, metabolite profile, and metabolite identification of carbon-14 ([^{14}C])-NV-5138. [redacted]

NV-5138 was well tolerated when administered to healthy male subjects as a single dose of 1600 mg [^{14}C]-NV-5138 oral solution in the fasted state. There were no AEs, severe AEs, SAEs, or AEs leading to subject discontinuation or to death in this study.

2.6 Study Rationale

A randomized, placebo-controlled trial is the gold standard for evaluating the efficacy of an investigational product. In preclinical antidepressant models, NV-5138 (Section 2.3) showed anxiolytic and antidepressant effects similar to ketamine. In addition in a pilot clinical study, NV-5138 has shown preliminary signals of efficacy in subjects with TRD. These efficacy signals, together with evidence of target engagement and a favorable safety and tolerability profile, support continued development of NV-5138 for TRD.

Rationale for dose regimen

Rationale for Study Primary and Secondary Endpoints

The appropriately selected scales as the primary and key secondary endpoints are the MADRS and Clinical Global Impression-Severity of Illness (CGI-S). The MADRS is a validated tool that measures the severity of depressive episodes in patients and is designed to be sensitive to changes brought on by treatment (Montgomery & Asberg, 1979). Change in MADRS total score was selected as the primary outcome measure because MADRS is a clinician/Investigator-structured interview assessing the severity of MDD symptoms per the *DSM-5* criteria. [redacted]

The CGI-S was selected as a key secondary outcome measure because it is commonly used as a reliable measure of severity of a disease/disorder in clinical research as well as a measure of change in severity over time during an experimental treatment.

The HAM-D_6 focuses on six core depression symptoms and is sensitive to measuring rapid changes in depression symptoms.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Primary Objective

- To evaluate the efficacy of NV-5138 compared to placebo when administered to adults with TRD on the MADRS total score

3.2 Key Secondary Objective

- To evaluate the efficacy of NV-5138 compared to placebo in adult subjects with TRD on the clinician's impression of the severity of depressive symptoms

3.3 Additional Secondary Objectives

- To evaluate the efficacy of NV-5138 compared to placebo in adults with TRD on the following:
  1) Clinical response to HAM-D_6
  2) Onset of clinical response
  3) Depressive symptoms response
  4) Depressive symptoms remission
  5) Clinician's impression of improvement of depressive symptoms
  6) Individual disability
  7) Anxiety symptoms
  8) Clinical response rate of severity
  9) Clinical response rate of improvement

[redacted]

3.5 Safety Objective

- To evaluate the safety and tolerability of NV-5138 compared to placebo in adults with TRD

3.6 Exploratory Objectives

- To evaluate the efficacy of NV-5138 compared to placebo in adults with TRD on the following:
  1) Self-reported depressive symptoms
  2) Self-reported cognitive and physical function
  3) Self-reported sexual function
- Pharmacogenomic evaluations

3.7 Primary Efficacy Endpoint

- CFB to the end of the treatment period on the MADRS total score

3.8 Key Secondary Endpoint

- CFB to the end of the treatment period on the CGI-S score

3.9 Additional Secondary Endpoints

1) CFB to the end of each scheduled week on the HAM-D_6 total score
2) CFB to the end of each scheduled week in the MADRS total score
3) Proportion of responders (defined as ≥50% reduction from baseline in the MADRS total score) at the end of each scheduled week
4) Proportion of subjects in remission (MADRS total score ≤10) at the end of each scheduled week
5) Clinical Global Impression – Improvement (CGI-I) score at the end of each scheduled week
6) CFB to the end of each scheduled week on the Sheehan Disability Scale (SDS) total score
7) CFB to the end of each scheduled week on the Generalized Anxiety Disorder 7 item (GAD-7) scale total score
8) Percentage of subjects with a CGI-S score of 1 or 2 at the end of each scheduled week
9) Percentage of subjects with a CGI-I score of 1 or 2 at the end of each scheduled week

3.11 Safety Endpoints

1) Safety endpoints are adverse events (AEs), clinical safety laboratory test results, vital signs (including orthostatic blood pressure/pulse rate), weight, ECGs, physical examination
2) Suicidal ideation and behavior as measured by the Columbia-Suicide Severity Rating Scale (C-SSRS) score
3) Dissociative symptomatology as measured by the CADSS total score
4) Psychopathology severity as measured by the BPRS+ score

3.12 Exploratory Endpoints

- CFB to the end of each scheduled week on the following:
  1) Patient Health Questionnaire 9-item (PHQ-9) scale total score
  2) Massachusetts General Hospital (MGH) Cognitive and Physical Functioning Questionnaire (CPFQ) total score
  3) Changes in Sexual Functioning Questionnaire (CSFQ) total score

- Pharmacogenomic (PGx) evaluation (optional)
  1) Correlation between baseline pharmacogenetic testing results and drug effects on the efficacy, safety, and/or PK of NV-5138
  2) CFB in the concentration of brain-derived neurotrophic factor (BDNF)

4 INVESTIGATIONAL STUDY PLAN

4.1 Overall Study Design and Plan

This is a multicenter, randomized, double-blind, flexible-dose, placebo-controlled, parallel design of adjunctive NV-5138 in adults with TRD. Approximately 800 outpatient subjects will be screened into the study and 268 subjects will be randomized to NV-5138 or placebo in a 1:1 ratio to achieve about 200 subjects completing the study. Following up to 6 weeks of screening, there will be a 4-week treatment period with SM, a 1-week double-blinded placebo-washout period, and a safety follow-up phone call occurring approximately 30 days after the last dose of blinded SM. The total study duration from the screening visit to the end of the Treatment Period is up to 15 weeks (see Figure 2).

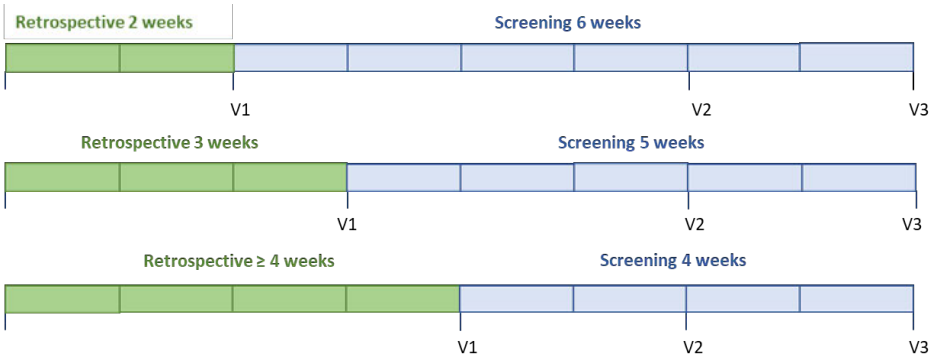
Retrospective Prescreening: The retrospective period is the time before screening when the Investigator determines the duration (without restriction) of the current major depressive episode (MDE), and also establishes the medication history of the current MDE. Subjects will not be eligible if they previously responded for more than 4 weeks while on the current ADT and lost response (tachyphylaxis). Those subjects may qualify if, after the current MDE started, they subsequently fail a trial with a new ADT or an increased dose of the previous ADT.

At the screening visit (Visit 1), subjects must have a documented history of inadequate response to ≥1 but ≤4 prior ADTs which must include the present ADT for their current MDE. Subjects must also be taking the currently approved ADT for a minimum of 2 weeks at a stable therapeutic dose.

Screening Period (Up to 6 Weeks; Day -42 to Day -1): The Screening Period is up to 6 weeks depending on how long the subjects have been taking their current ADT and the number of failed ADTs. As shown in Figure 1, subjects who have failed ≥2 ADTs and have been taking the approved ADT at a stable dose for ≥4 weeks before screening are allowed the minimum 4-week Screening Period. A longer Screening Period is required for other subjects (for example, subjects who have been on their current ADT for 2 weeks will complete 6 weeks of screening, and subjects who have been on the current ADT for 3 weeks will be in the Screening Period for 5 weeks).

Subjects who have an inadequate response to only 1 ADT must be on the same ADT at the stable therapeutic dose for ≥2 weeks before the Screening Period and complete 6 weeks during the Screening Period.

Figure 1: Flexible Screening Period for Subjects Who Had Inadequate Response to ≥2 ADTs



Visit 1:

At the initial screening visit (Visit 1, Day -42, Day -35 or Day -28, depending on the retrospective prescreening ADT history) after informed consent is obtained which includes an optional PGx consent, subjects will undergo initial screening evaluations including a blood sample to be analyzed to ensure detectable blood level of an antidepressant. Subjects will have their diagnosis of MDD confirmed by the Mini International Neuropsychiatric Interview (MINI). Their site-rated MADRS total score must be ≥24 and CGI S ≥4. Inadequate response (defined as <50% improvement in depressive symptoms on an ADT taken at ad adequate dose and duration) to the ADT for their current MDE will be assessed by the Investigator by the administration of the Antidepressant Treatment Response Questionnaire (ATRQ) which was developed by the MGH.

[redacted]

During the Screening Period, subjects should maintain the current antidepressant stable therapeutic dose (see Appendix 11.17) for the study-approved ADTs. Dose adjustment of ADT will not be allowed during screening and throughout the duration of the study. ADTs approved for use in this study will not be supplied by the Sponsor.

Antidepressant Adherence:

Subjects will download the medication adherence app on their personal smartphone or receive a provisioned device. The application will enable confirmation of date and time

of the subject's ingestion of the ADT. During the screening period, subject adherence to ADT must be confirmed with the medication adherence app and the ADT blood level.

Visit 2:

Visit 2 (Day -14) will occur for subjects who have been taking their approved antidepressant at a stable dose for a total of 6 weeks (ie, 2 weeks retrospectively prior to Visit 1 and 4 weeks during screening) [redacted]. At this visit, the Investigator will measure clinical response with the administration of the MADRS and CGI-S scales. To continue in the study, subjects must have a MADRS total score ≥24 and CGI-S ≥4 and meet all other eligibility criteria. Additional laboratory sampling of the subject's antidepressant blood level will be conducted; subjects must have 2 positive test results for ADT during screening before proceeding to the baseline visit.

It is recommended to perform Investigator-rated efficacy assessments (MADRS and CGI-S) prior to performing any subject self-report efficacy assessments.

If the MADRS total scores vary ≥25% between the highest and lowest scores during the Screening Period, subjects will be excluded from the study.

Baseline and Randomization (Visit 3): To be eligible for randomization, subjects must have inadequate response to ≥1 but ≤4 ADTs for their MDE including the current ADT administered at a stable dose and duration for a total of ≥8 weeks (Figure 1). Subjects who have an inadequate response to only 1 ADT must be on the same ADT at the stable therapeutic dose for ≥2 weeks before the Screening period and complete 6 weeks during the Screening Period before randomization. Subjects who do not meet eligibility criteria at any time during the Screening Period will be excluded. Subjects' eligibility will be reviewed by the Sponsor, and the site must receive an eligibility verification letter for each subject before proceeding to the baseline visit.

Protocol waivers in the study will be granted on a case-by-case basis after approval from the Sponsor.

Rescreening:
Subjects that screen failed under previous protocol versions and subjects who screen failed due to tachyphylaxis or, due to the absence of a failed ADT for the current MDE are allowed on a case-by-case basis to re-screen after consultation with the MM and Sponsor's approval.

Double-Blind Period (Visits 3-8): The Double-Blind Period consists of a 4-week (28 days) flexible dosing treatment period with SM (Figure 2) and a 1-week placebo-washout period. On Day 1, after eligibility has been confirmed and baseline assessments conducted, subjects will be randomized (1:1) to receive either adjunctive NV-5138 or matching placebo in conjunction with their current ADT. During the Double-Blind

Period, weekly study visits will be conducted. At each visit, ECG, vital signs, body weight and alcohol breath test will be performed; samples for urinalysis, hematology and chemistry laboratory tests; and UDS; and samples for ADT will be collected. Efficacy and safety scales will be assessed (see Table 2).

Visits 4-7 (Study Medication Treatment):

The starting dose of NV-5138 or matching placebo is 1600 mg QD. Dose adjustments are allowed at Visit 4 (Day 8) and Visit 5 (Day 15). Subjects who experience an intolerable adverse effect at 1600 mg may have their dose reduced to 800 mg. Subjects who have an inadequate response to 800 mg may have their dose increased again to 1600 mg per Investigator judgment to maximize their treatment response; however, no dose adjustments are allowed after Visit 5. The maximum NV-5138 dose in the study is 1600 mg QD. The minimum NV-5138 dose is 800 mg QD; subjects who cannot tolerate NV-5138 800 mg once daily or matching placebo should be discontinued from the study at the discretion of the Investigator. After completion of the 4-week treatment, all subjects will receive placebo in a double-blinded fashion and continue the treatment for one week. Throughout the duration of the Double-Blind Treatment Period, no adjustments in the ADT or dose are allowed (Section 6.1.4).

Visit 8 (End of Study/Early Termination):

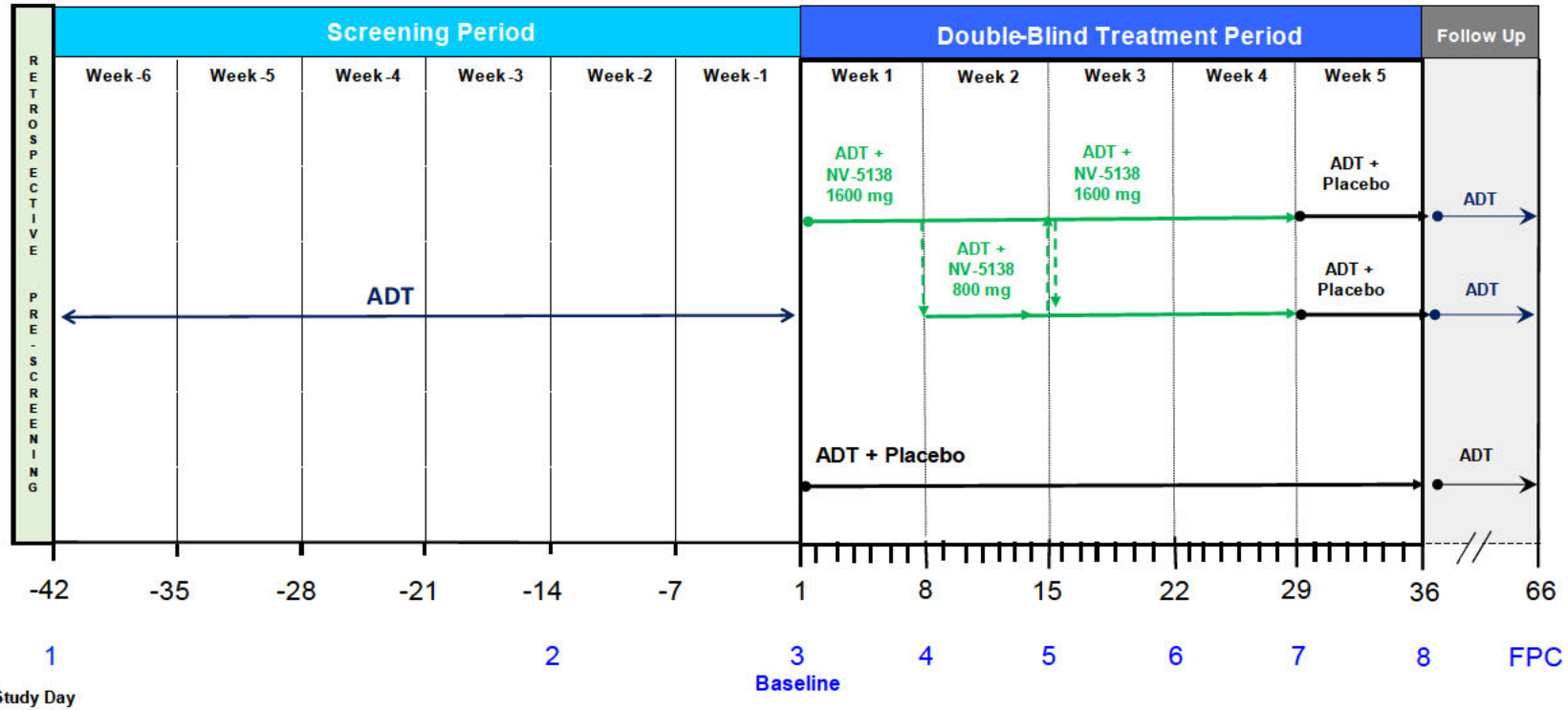
EOS assessments will be collected. After completion of the EOS study procedures, SM will be discontinued, and subjects should continue with their ADT. If the subject withdraws or is early terminated, the subject will complete Visit 8 assessments.

Unscheduled visits may be conducted at the discretion of the Investigator throughout the study. AEs and concomitant medications will be assessed at all scheduled and unscheduled visits (Section 6.1.4).

Safety Follow-up (30 Days After Completion of the Study: After the last dose of SM in the Double-Blind Period and all study visits are completed including Visit 8, the study is considered completed. A safety follow-up phone call will occur approximately 30 days

after the last dose of blinded SM only for subjects who completed the study. For subjects who withdraw from the study, a safety follow-up phone call will occur approximately 7 days after withdrawal (Section 6.1.5).

Figure 2: Study Schematic



FPC = Follow Up Phone Call

1. Visit 1 may range from Day -42 to -28 for a subject depending on the length of time in the screening period.
2. Dosing is flexible: the starting dose of NV-5138 or matching placebo is 1600 mg once daily. Dose can be adjusted per Investigator judgment, to maximi ze their treatment response at Visit 4 (Day 8) and Visit 5 (Day 15). Subjects who experience an intolerable adverse effect at 1600 mg may have their dose reduced to 800 mg at Visit 5; subjects who have an inadequate response to 800 mg may have their dose increased again to 1600 mg at Visit 5.
3. Weeks 1-4:Treatment Period, Week 5: Placebo-Washout Week

4.2 Study Population

4.2.1 Number of Subjects

Approximately 800 subjects (400 per treatment arm) will be screened; approximately 268 subjects will be randomized to NV-5138 or placebo in a 1:1 ratio to achieve approximately 200 subjects completing the study.

4.2.2 Inclusion Criteria

1. Is male or female aged 18-70 years (inclusive) at screening;
2. Is able to read, understand, write, and sign the Informed Consent Form (ICF);
3. Is willing and able to follow the study protocol and procedures and attend study appointments within the specified time windows;
4. Has a body mass index (BMI) between 19.0 to 40.0 kg/m^2 (inclusive);
5. Is able to swallow capsules whole, without crushing, chewing, or opening.
6. Has a diagnosis of major depressive disorder (MDD) according to the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5)* for either recurrent or single episode MDD without psychotic features that is confirmed by the MINI;
7. Has a MADRS total score of ≥24 for the current MDE at the screening visits and baseline visit (Day 1);
8. Has an CGI-S score of ≥4 (moderately ill or worse) at the screening visits and baseline visit;

[redacted]

10. Has a history of inadequate response to ≥1 but ≤4 prior ADT therapies (including the current ADT for the current MDE) ≥2 weeks before screening and ≥8 weeks at baseline. An inadequate response is defined as <50% improvement in depressive symptoms on an ADT (taken at an adequate dose and duration) assessed by the Investigator with the administration of the MGH-ATRQ and confirmed by documented records.

    Note: Subjects who fail to respond to either a trial with a new ADT or an increased dose for the previous ADT (both of adequate dose and duration) can be enrolled (increased doses of the same ADT are counted as only 1 failed ADT). The ADT must have been started after the current MDE began;

11. Has been on a stable therapeutic dose of one of the following study-approved ADTs for the current MDE for ≥2 weeks prior to screening: citalopram, escitalopram, paroxetine, fluoxetine, sertraline, duloxetine, venlafaxine (immediate release or extended release), desvenlafaxine, vilazodone, levomilnacipran, vortioxetine, bupropion or dextromethorphan/bupropion (see Appendix 11.17).

    Note: Subject must be on ADT monotherapy before randomization. If a subject is taking a second ADT or augmentation therapy at screening, the Investigator should decide if it is medically appropriate to discontinue the second drug before randomization into the study. If so, the second drug should be washed out at least 5 half-lives prior to baseline. If not, the subject should be excluded from the study;
12. Has a detectable blood level of the approved ADT at both Visits 1 and 2 of the Screening Period.

    Note: A negative test may be repeated with permission of the MM and Sponsor upon additional evidence of subject adherence to ADT or evidence of sample or laboratory error;
13. Agrees to maintain a stable therapeutic dose of the approved ADT throughout the study;
14. Has discontinued prohibited hypnotic medications 6 weeks prior to randomization. See Appendix 11.16.1 for allowed sleep medications;
15. Nonpregnant females of childbearing potential (FOCP) who are exclusively in a same-sex relationship are included without the need for acceptable birth control methods.

    FOCP who are sexually active with a male partner (who is biologically capable of having children) must agree to use one of the following acceptable birth control methods after signing the ICF, throughout the study, and for 30 days following the last dose of the SM:

    a. Simultaneous use of male condom and intrauterine contraceptive device placed at least 4 weeks prior to the first SM administration;
    b. Simultaneous use of male condom and diaphragm with spermicide; or
    c. Established hormonal contraceptive (started at least 4 weeks prior to the first dose of SM).

    Female subjects are considered not to be of childbearing potential if they are either postmenopausal (amenorrhea for at least 2 years and serum follicle-stimulating hormone [FSH] level of >40 IU/L) or permanently sterilized (eg, bilateral tubal ligation, bilateral oophorectomy, etc.) for 6 months minimum prior to screening.

All FOCP must have a negative serum pregnancy test result before the administration of SM;

16. Male subjects:
    a. Who are exclusively in a same-sex relationship or have female partners considered not to be of childbearing potential are included without the need for acceptable birth control methods;
    b. Who have been surgically sterilized (6 months minimum) prior to screening are eligible to participate without any contraception; or
    c. Who are biologically capable of having children and have female partners of childbearing potential must use one or more methods of contraception as stated in Inclusion Criterion #15 which must be used from the time of signing the ICF until 90 days after the last dose of SM.

    All male subjects must refrain from donating sperm from the date of first administration of SM until 90 days after the last dose of the SM.

4.2.3 Exclusion Criteria

1. Has a MADRS total score improvement of ≥25% from the highest to the lowest score during the Screening Period and baseline visit;
2. Has received new-onset psychotherapy or had a change in the intensity of psychotherapy within 4 weeks prior to screening. Psychotherapy initiated prior to screening must be maintained for the duration of the study;
3. Has been treated with electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), or vagal nerve stimulation (VNS) for the current MDE;
4. Has received treatment with long-acting injectable antipsychotics (LAIs) within 3 months prior to screening;
5. Has recurrent MDD, has been on an adequate dose and duration of ADT, and had a >50% response for at least 4 weeks while using that ADT that was then followed by a loss of response (ie, tachyphylaxis) as assessed by the Investigator. The date of the loss of response is the start date of the current episode (from when the symptoms returned);
6. Has demonstrated a nonresponse to esketamine or off-label use of ketamine or has taken esketamine or ketamine less than 6 months prior to the screening visit (Appendix 11.16.2);
7. Is unable to discontinue treatment with trazodone at doses greater than 150 mg daily for a minimum of 5 half-lives before baseline.
    a. Trazodone 150 mg/day or less for sleep is permitted as needed if the subject has been taking the same low dose of trazodone for insomnia for at least 3 months;

8. Has unstable hypothyroidism. If the thyroid-stimulating hormone (TSH) value is out of range (>4.0 mIU/L) regardless of thyroid history, a free thyroxine (FT4) will be measured. If the FT4 value is abnormal (levels <0.8 mIU/L) and considered to be clinically significant (after discussion with the Medical Monitor), the subject will not be eligible.
    a. Treatment with thyroid hormones is allowed if prescribed at a stable dose for ≥3 months and the subject's thyroid levels are normal;
9. Has clinically significant abnormal laboratory profiles (ALT or AST values ≥3x the upper limit of normal [ULN] or total bilirubin ≥1.5 times the ULN), vital signs, or ECGs, per Investigator judgment (see **Note** below). If there are any abnormalities that are not specified in the Inclusion and Exclusion Criteria, the Investigator must determine their clinical significance and record it in the subject's source documents;
10. Has abnormal renal function as demonstrated by an estimated glomerular filtration rate (eGFR) of <60 mL/min, according to the Chronic Disease Epidemiology Collaboration (CKD-EPI) equation at the screening visit;
11. Has a history of substance use disorder (SUD) within 6 months prior to screening or is currently using or has a positive result (UDS) at any screening or baseline visits for drugs of abuse (Appendix 11.16.2). Positive results for specific medications must have a confirmed medical history;
12. Has a history of alcohol use disorder within 6 months prior to screening. A subject who has a positive alcohol test result at any of the screening visits (V1 andV2) and, if based on the Investigator opinion, the subject does not have a history of alcohol use disorder, the subject may continue to the next visit. If the alcohol test result at baseline visit is positive, subjects should be excluded from the study. Subjects must refrain from using alcohol during the treatment phase of the study;
13. Has a diagnosis of cannabis use disorder (CUD) within 6 months before screening and has a positive UDS for cannabis at screening.
    a. At the discretion of the Sponsor, recreational use of cannabis (not daily) is allowed and should be kept consistent during the study. Subjects must agree to refrain from using cannabis 48 h prior to the study visits;
    b. Medical cannabis prescribed for a medical condition (eg, muscle spasms, nausea, vomiting, pain) other than depression, seizures, and insomnia is allowed if taken at a stable regimen for at least 3 months prior to screening. Newly prescribed cannabis treatment and/or change to the existing regimen is prohibited (Appendix 11.16.1). When applicable, subjects should show proof of their prescription for medical cannabis;

14. Has had any suicidal behavior or suicidal ideation of type 4 (active suicidal ideation with some intent to act, without specific plan) or type 5 (active suicidal ideation with specific plan and intent) based on C-SSRS in the 2 years before screening; a history of suicide attempt in the last 6 months; or more than 2 lifetime suicide attempts;
15. Has a lifetime history of psychotic disorder including but not limited to schizophrenia, MDD with psychotic features, or bipolar I/II disorder with and without psychotic features;
16. Has a diagnosis within 12 months before screening or current diagnosis of post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), panic disorder, acute stress disorder or has history of intellectual disability, autism, or Cluster A or B personality disorder (per *DSM-5* criteria).
    a. Current diagnosis of comorbid generalized anxiety disorder is allowed but subject to medication restrictions (anticonvulsants and beta-blockers are allowed, if on a stable regimen for 2 months prior to the screening visit);
    b. Established attention-deficit/hyperactivity disorder (ADHD) diagnosis is allowed. Subjects must provide confirmation of ADHD diagnosis (ie, provide medical records for prescribed ADHD medications) and be on a stable dose of ADHD medication for at least 3 months prior to the screening visit;
17. Has a history of a psychiatric or neurologic conditions or symptoms that could impose undue risk or compromise the study, in the Investigator's opinion, including but not limited to:
    a. History of seizure disorder or history of epilepsy (except history of absence or uncomplicated childhood febrile seizures);
    b. History of clinically significant or moderate head trauma that, in the Investigator's opinion, is likely to affect CNS functioning; or
    c. Has current evidence of delirium or dementia;
18. Has a history of cardiovascular, respiratory, gastrointestinal, renal, hepatic, hematologic, or other medical disorder that could, in the Investigator's opinion, impose undue risk or compromise the study including but not limited to the following:
    a. Cardiovascular disorders:
        i. Clinically significant symptomatic orthostatic hypotension;
        ii. Uncontrolled hypertension despite diet, exercise, and antihypertensive medications (defined as a supine systolic blood pression (SBP) >140 mmHg or diastolic blood pressure (DBP) >90 mmHg) during screening and at baseline;

iii. Acute coronary syndrome;
iv. History of unexplained loss of consciousness, unexplained syncope, or unexplained irregular heartbeats;
v. QT interval corrected using Fridericia's method (QTcF) ≥ 450 ms (for men) or ≥ 470 ms (for women) at screening (see **Note** below); and/or
vi. Patient or family history of QT congenital syndrome;

b. Oncological disorders:
i. Malignant tumors within 5 years prior with the exception of benign skin tumors; or
ii. Diagnosis or family history of tuberous sclerosis complex (TSC);

c. Positive result for human immunodeficiency virus (HIV), hepatitis B, or hepatitis C (HCV) at screening unless:
i. HIV positive: subjects must have a HIV Confirmation Test. If the confirmatory test is positive, the subject is eligible if on chronic suppressive antiviral medication for more than 6 months with an undetectable viral load;
ii. HBsAg positive: subjects should be tested for anti-HBc, IgM anti-HBc, and anti-HBs to detect acute or chronic infection (ineligible). Subjects whose results indicate immunity (either by natural infection or vaccination) with no active infection are eligible; and/or
iii. HCV positive: subjects must have undetectable HCV ribonucleic acid (RNA) to be eligible;

d. Unintended recent clinically significant weight loss;
e. Has chronic urinary tract infections (UTIs);
f. Blood donation within 6 weeks of screening; and/or
g. Is on any medication that could, in the Investigator's opinion, interfere with the assessments of safety, tolerability, efficacy, or the conduct or interpretation of the study;

19. Requires treatment with a medication or other substance that is prohibited by the protocol (see Section 5.8);
20. Has history of severe drug allergy or hypersensitivity, or hypersensitivity to the SM or excipients;
21. Female subjects who are pregnant or lactating or planning to become pregnant while enrolled in the study;
22. Has previously enrolled in a NV-5138 study;
23. Is currently participating in another clinical trial or has participated in a clinical study within 30 days of screening visit;

24. Is a member of study personnel or their immediate families or is a subordinate (or immediate family member of a subordinate) to any of the study personnel.

Note: Repeat testing for clinical laboratory parameters, vital signs, and ECG is permitted one time for each test, at the discretion of the Investigator, as long as the repeat test result is available within the pretreatment period to determine eligibility. Repeat testing is not allowed without justification from the site and agreement from the MM and the Sponsor on a case-by-case basis.

4.3 Completion of Study

Subjects will be considered to have completed the study if they complete all visits up to and including Visit 8.

All reasons for screening failure will be recorded. [redacted] if a subject does not have a history of inadequate response to ≥1 but ≤4 prior ADTs and fails the MGH-ATRQ administered by the Investigator, the reason will be recorded as Inclusion Criterion #10. If a subject experienced tachyphylaxis (ie, >50% response for at least 4 weeks while using that ADT followed by a loss of response) as assessed by the Investigator, the screening failure reason will be recorded as Exclusion Criterion #5.

4.4 Discontinuation or Early Termination of Subjects

Subjects who are randomized and dosed with SM, but who withdraw or are withdrawn from participation in the study by the Investigator before the completion of the study (ie, after Visit 3 but prior to Visit 8), should complete an Early Termination (ET) visit. Procedures listed for Visit 8 (see Table 2) should be completed at ET visit with the following exception:

If subject's ET visit occurs:

1) >4 days after the date of subject's last dose, efficacy assessments **should not** be performed/collected at ET visit; or
2) ≤4 days after the date of subject's last dose, efficacy assessments should be performed/collected at ET visit.

Subjects who are discontinued for a positive alcohol test or UDS should complete the ET visit. At that visit, efficacy assessments **should not** be performed/collected.

The Investigator(s) or subjects themselves may stop SM treatment at any time for safety or personal reasons. A subject is free to withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The Sponsor may also withdraw the subject at any time in the interest of the subject's safety. The withdrawal of a subject from the study should be discussed with the MM and Investigator before the subject stops SM. Subjects removed from the study for any reason will not be replaced.

Reasons for a subject's early discontinuation may include:

- Withdrawal of consent;
- Noncompliance with study procedures (eg, positive alcohol test or UDS, missed more than two consecutive doses of SM, use of prohibited medications);
- Occurrence of unmanageable AEs;
- Lost to follow-up;
- Lack of efficacy;
- The Investigator or the Sponsor believes it is in the best interest of the subject to discontinue the study (ie, for safety or tolerability reasons); or
- Other (eg, study is terminated by the Sponsor, subject becomes pregnant, blind is broken, subject has relocated, or death, etc).

If the subject withdraws consent or the Investigator discontinues the subject's participation in the study, the primary reason for the subject's withdrawal, or the Investigator's discontinuation of the subject should be documented and captured on the eCRF. If a subject is withdrawn for more than one reason, each reason should be documented in the source document and the most medically significant reason should be entered on the eCRF.

If the subject is lost to follow-up, every effort must be done by the study site to contact the subject and to determine the reason for discontinuation/withdrawal. This should include at minimum 3 phone calls, certified letters, email etc. The measures taken to follow-up must be documented.

Subjects who withdraw will not be replaced.

5 STUDY TREATMENT

5.1 Study Medication Identity, Packaging, and Labeling

SM is supplied by the Sponsor as capsules packaged in a double-blind configuration in bottles. Each bottle will include identical-looking capsules that contain 400 mg of NV-5138 or matching placebo. The capsule is size 00 elongated (00 EL) with white opaque cap and body. Each bottle contains 40 capsules to supply a subject with 7 days of dosing plus 3 extra days if needed. Each bottle will be labeled with the protocol number.

5.2 Study Medication Administration

SM will be administered orally QD as intact capsules. Daily dosing should occur in the morning, approximately 3 h after breakfast. Splitting the daily dose (eg, taking part of the daily dose in the morning and the remainder of the daily dose in the evening) is not permitted. SM will be dispensed to the subject following randomization on Day 1 (Visit 3). Subject will take the first dose at the site at Visit 3 and resume the morning dosing the following day. If Visit 3 occurs after noon, subject will still take the first dose at the clinic and resume the morning dose the following day. **The subject should not exceed 35 (+3) days of SM administration**.

During the first week of the Treatment Period, all subjects will take 1600 mg/day (equivalent to 4 capsules) QD. During Week 2 (starting at Visit 4) of the Treatment Period, per the Investigator's discretion based on the subject's clinical response and tolerability (adverse effects), the dose of NV-5138 can be tapered down to 800 mg/day (equivalent to 2 capsules) to a target dose of 800 mg/day during the week (Table 1). During Week 3 (starting at Visit 5), per the Investigator's discretion based on the subject's clinical response and tolerability, the dose of NV-5138 can remain at 800 mg/day (2 capsules) or be titrated up to 1600 mg/day (4 capsules) to a target dose of 1600 mg/day (Table 1). After completion of the 4-week treatment, all subjects will receive placebo in a double-blinded fashion and continue the treatment for one week. Dose adjustments are allowed at Visits 4 and 5; in the event a subject experiences intolerable AE(s) to 1600 mg/day between Visit 4 and Visit 5, an unscheduled visit may be conducted for dose adjustment before the subject's scheduled Visit 5; however, no further dose adjustments are allowed after Visit 5. The maximum NV-5138 dose in the study is 1600 mg QD. The minimum NV-5138 dose is 800 mg QD. Subjects who cannot tolerate

NV-5138 800 mg once daily or matching placebo should be discontinued from the study at the discretion of the Investigator.

Table 1: Study Medication Administration

Number of Capsules Taken per Day During the Treatment Period				
Week 1	Week 2	Week 3	Week 4	Week 5
4	2 or 4	2 or 4	2 or 4[1]	2 or 4[1,2]

[1] The dose regimen of SM established at Week 3 (800 mg/day or 1600 mg/day) will be maintained during Week 4 and Week 5.

[2] During Week 5 all subjects will receive placebo in a double-blind fashion.

5.3 Missed Dose

Adherence to SM will be monitored using a SM diary. If a subject misses the dose of SM in the morning, the subject can take the missed dose within 24 h and record the administration time in the medication adherence diary. If a subject misses doses of SM during this study, the Investigator and study coordinator shall counsel the subject on the importance of compliance and retrain the subject. If a subject has **missed doses for more than 2 consecutive days**, the subject may be discontinued from the study at the discretion of the Investigator and in consultation with the MM and the Sponsor. All procedures for discontinuation will be followed (Section 4.4).

5.4 Antidepressant Administration

All subjects must be on stable therapeutic dose of antidepressant for ≥2 weeks before screening. The following are the antidepressants approved for the study: citalopram, escitalopram, paroxetine, fluoxetine, sertraline, duloxetine, venlafaxine (immediate release or extended release), desvenlafaxine, vilazodone, levomilnacipran. vortioxetine, bupropion or dextromethorphan/bupropion (see Appendix 11.17) for study-approved ADTs. A second ADT or augmentation therapy at screening should be washed out at least 5 half-lives prior to baseline based on the Investigator's decision if it is deemed medically appropriate.

Subjects will continue to take their ADT for their current MDE after randomization and EOS/Visit 8. Antidepressant treatment dose adjustment and change of ADT will not be allowed during the duration of the study.

Adherence to ADT will be tracked by collecting blood samples at each visit and monitoring the ADT electronic clinical outcome assessment diary (eCOA).

If subjects miss doses of ADT, the Investigator and/or study coordinator should follow up with the subjects on the importance of maintaining full compliance to protocol procedures throughout the study.

Antidepressant treatments approved for use in this study will not be supplied by the Sponsor.

5.5 Method of Assigning Subjects to Treatment Arm

Eligible subjects will be randomized in a 1:1 ratio at Visit 3 (baseline) to receive active NV-5138 or matching placebo.

Allocation of study treatment will occur centrally via an interactive response technology (IRT) using a randomization schedule to determine the SM assignment for each subject being randomized. Subjects will be randomly assigned to one of the treatment groups based on the randomization schedule created by the designated Clinical Research Organization (CRO) biostatistician before the initiation of the study under the supervision of the Sponsor. The randomization files will be securely stored on the CRO's server. The IRT vendor will receive the unblinded randomization schedule from the CRO unblinded biostatistician and assign a unique treatment code for the corresponding SM (containing either the active drug or placebo) for each subject (assigned treatment) according to the subject randomization schedule. The clinical site must confirm and record that the correct corresponding SM number was dispensed to the subject (actual study treatment).

A bottle with SM will be dispensed to the subject at each study visit starting at Visit 3.

5.6 Blinding

The subject and all personnel involved with the conduct and interpretation of the study including the Investigators, study site personnel, the Sponsor and CRO clinical staff including the MM will be blinded to SM. A limited number of Supernus personnel will perform the bioanalytical PK analysis during clinical study conduct. These personnel should not have access to the randomization schedule or be associated with the clinical conduct of the study and will not reveal to any clinical personnel involved in the study the treatment to which a subject is assigned.

5.6.1 Maintaining Blind

Randomization schedule data will be kept strictly confidential, filed securely by the IRT vendor, and accessible only to authorized persons until the time of the planned unblinding.

5.6.2 Planned Unblinding

The study blind will be broken only after the study has been completed and the study database has been locked.

5.6.3 Emergency Unblinding

The Study Investigator may contact the IRT vendor and unblind a subject in situations in which the subject experiences an unexpected SAE requiring special and/or acute emergency medical services (ie, hospitalization) for which the disclosure/knowledge of their assigned/actual treatment arm in the study is critical to the subject's safety and medical care. Prior to breaking the treatment blind, it is recommended that the Investigator, who is directly responsible for the care of the subject (ie, the physician), discuss the need to unblind the subject with the Sponsor's MM (or designee). If the Sponsor's MM or designee cannot be reached, then the Investigator should unblind the subject and make every attempt to contact the Sponsor's MM (or designee) as soon as possible. If a subject's treatment assignment is unblinded, the Investigator should only share the subject's study treatment information with the individual(s) responsible for the medical treatment/care of the subject. Under no circumstances should the Investigator disclose the subject's unblinded treatment arm to any staff at the study site, CRO, Sponsor, etc. The Investigator must notify the Sponsor's MM and properly document/record the event (unblinding) in the respective subject's source documentation; this includes recording the Subject ID No., the date and time of the unblinding, the rationale/reasoning behind the necessity to unblind the subject's study treatment, and the signature of the person who unblinded the subject. It is the Investigator's responsibility to always keep the Sponsor's MM (or designee) apprised of all unblinding activities and report all cases involving emergency unblinding to the Sponsor without disclosing the unblinded information. All unblinded subjects will be discontinued from participating in the study and will not be replaced in order to preserve the integrity of the study, and each subject should be followed up by the Investigator for safety purposes.

5.7 Study Medication Handling and Accountability

All SM will be supplied by the Sponsor to the Investigator. SM supplies must be stored at 20-25^{o} C in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the SM label.

Following Sponsor instructions and in compliance with International Council for Harmonisation (ICH) E6 as well as local, state, and federal regulations, the Investigator and study staff will be responsible for the accountability of all clinical

supplies (receiving, shipment, dispensing, inventory, and record keeping) in a SM accountability log. A copy will be collected by the Sponsor at the end of the study.

Under no circumstances will the Investigator allow the SM to be used other than as directed by this protocol. Clinical supplies will not be dispensed to any individual who is not enrolled into the study.

An accurate and timely record of the receipt of all clinical supplies; dispensing of SM to the subject; collection of unused supplies; and subsequent return of unused SM to the Sponsor must be maintained with dates. This SM accountability log includes but may not be limited to: (a) documentation of receipt of clinical supplies, (b) SM inventory log, (c) SM accountability log, and (d) all shipping service receipts. Forms may be provided by the Sponsor. Any comparable forms that the study site wishes to use must be approved by the Sponsor.

The supplies and inventory records must be made available upon request for inspection by the designated representative of the Sponsor or a representative of the FDA. The assigned Clinical Research Associate (CRA) will review these documents along with all other study conduct documents at specified intervals once SM has been received by the study site. All used, partly used, and unused clinical supplies including empty containers are to be returned to the Sponsor at the conclusion of the study unless provision is made by the Sponsor for destruction of supplies and containers at the study site. Upon completion of SM accountability and reconciliation procedures by study site personnel and documentation procedures by Sponsor personnel, SM is to be returned to the Sponsor with a copy of the completed SM disposition form.

5.8 Concomitant and Prohibited Medications

Subjects may not be on any prohibited medication as indicated in the Inclusion/Exclusion Criteria. Please contact the MM for any questions related to the subject's current concomitant medication(s). Additional concomitant medications may be allowed on a case-by-case basis at the discretion of the MM and the Sponsor.

Permitted and prohibited medications are shown in Appendix 11.16.

5.8.1 Permitted Concomitant Medications

A comprehensive list of allowed medications is shown in Appendix 11.16.1. The list is not all inclusive. Contact the MM for any questions related to the subject's current concomitant medication(s). Most of the concomitant medications are allowed if on a **stable dose for at least 3 months prior to screening** or otherwise specified in Appendix 11.16.1.

- Treatment for hypercholesterolemia (eg, statins, gemfibrozil) and hyperlipidemia if on a stable dose for at least 3 months prior to screening;
- Treatment for hypertension with ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, and beta-blockers alone or in combination with diuretics if on a stable dose for 2 weeks before screening;
- Inhalers for the treatment of asthma if the subject has stable asthma control and no changes for at least 6 months prior to screening;
- Treatment for diabetes if on a stable dose for at least 3 months before screening. Insulin will not be permitted; and/or
- For ADHD treatment, psychostimulants, atomoxetine, guanfacine, and clonidine are allowed if on a stable dose for at least 3 months before screening. Confirmation of ADHD diagnosis will be required.

The stable dose of all concomitant medications allowed in the study **must be maintained** throughout the duration of the study participation.

As needed, the following treatments will also be allowed:

- For sleeping, only the following medications are allowed if on a stable dose (dose increment is prohibited) for at least 4 weeks prior to screening (Appendix 11.16.1):
  - Hypnotics (eg, zaleplon and zolpidem);
  - Benzodiazepines: lorazepam (2 mg total daily dose [TDD]), clonazepam (0.5 mg TDD), and flurazepam (30 mg TDD). Benzodiazepines should be taken more than 12 h prior to any study visits; or
  - Trazodone (150 mg/day or less) as needed if the subject has been taking the same low dose of trazodone for insomnia for at least 3 months
- Nutritional supplements (eg, multivitamins, fish oil, melatonin)
- EMLA® or other numbing cream for venipuncture
- Common over-the-counter therapies for minor transient ailments (eg, acetaminophen, ibuprofen for headache, fever, etc)
- Recreational cannabis (not daily and not exceeding 3 times per week for either vape, edible, or smoke) is allowed at the discretion of the Sponsor if taken consistently during the study. Subjects must refrain from using cannabis 48 h prior to the study visits: at each visit, it is recommended that the Investigator assess the subjects for symptoms of cannabis intoxication (ie, motor impairment, euphoria, anxiety, impaired judgment, social withdrawal, redness of eyes, increased appetite, dry mouth, tachycardia). If subjects show symptoms of intoxication or do not refrain from using cannabis for 48 h prior

to the study visits, that study visit should not be conducted and an unscheduled visit should be scheduled.

- Medical cannabis if prescribed for a medical condition (eg, muscle spasms, nausea, vomiting, pain) other than depression, seizures, and insomnia and taken at a stable regimen for at least 3 months prior to screening. When applicable, subjects should show proof of their prescription for medical cannabis.

  Note: Newly prescribed cannabis treatment and/or change to the existing regimen is prohibited.

All concomitant medications will be recorded in the eCRF.

5.8.2 Prohibited Concomitant Medications

A comprehensive list of prohibited medications is shown in Appendix 11.16.2. The list is not all inclusive. Contact the MM for any questions related to the subject's current concomitant medication(s).

Prohibited medications should be discontinued for 5 half-lives before baseline. Where washout of prohibited medications is required prior to baseline, tapering rates are at the discretion of the Investigator and are to be determined on an individual basis, with consideration to subject state, dose, and known PK of the medication being discontinued. The subject must be consented before any discontinuation or any tapering is started.

6 STUDY METHODS

6.1 Study Visits and Procedures

All subjects who are randomized and take the initial dose of SM will be followed according to the protocol regardless of the number of doses of SM taken unless consent for follow-up is withdrawn. The Sponsor or Sponsor's designee must be notified of all deviations from the protocol visit or procedures except as noted, and these procedures, if applicable, will be rescheduled or performed at the nearest possible time to the original schedule. Subjects will be instructed to call study personnel to report any AEs during the intervals in between study visits and to come to the study site if medical evaluation is needed and as the urgency of the situation indicates. For emergency and other unscheduled visits to a medical facility other than the study site, medical records will be obtained by the Investigator or qualified designee as source data for study follow-up.

Investigator-rated efficacy assessments (MADRS, CGI-S, CGI-I, SDS, GAD-7 and HAM-D_6) should be performed/conducted/collected in the order above prior to administering any self-report efficacy assessments to subjects.

The Schedule of Events and Assessments for the study is shown in Table 2**.**

Table 2: Schedule of Events and Assessments

Period	Screening		Double-Blind Treatment					Safety Follow-up*	
Visit Number	**1**	**2**	**3 (Baseline)**	**4**	**5**	**6**	**7**	**8 EOS/ET**	
Day of Study	**-42[a]**	**-14**	**1**	**8**	**15**	**22**	**29**	**36**	**66**
Week of Study	**-6**	**-2**	–	**1**	**2**	**3**	**4**	**5**	
Study Visit Window (Days)		**± 1**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 7**
Signed informed consent form (ICF) including PGx consent	√								
Relevant histories (social, medical, psychiatric, family psychiatric, neurological)	√								
Mini-International Neuropsychiatric Interview (MINI)	√								
[redacted]									
ATRQ Investigator Rated	√								
Demographics and Height	√								
Inclusion/Exclusion criteria	√	√	√						
Alcohol consumption	√		√	√	√	√	√	√	
Recreational cannabis use[c]	√	√	√	√	√	√	√	√	
Physical examination	√		√					√	
Vital signs[d] and Weight	√	√	√	√	√	√	√	√	
ECG	√		√	√	√	√	√	√	

Period	Screening		Double-Blind Treatment					Safety Follow-up*	
Visit Number	**1**	**2**	**3 (Baseline)**	**4**	**5**	**6**	**7**	**8 EOS/ET**	
Day of Study	**-42[a]**	**-14**	**1**	**8**	**15**	**22**	**29**	**36**	**66**
Week of Study	**-6**	**-2**	**–**	**1**	**2**	**3**	**4**	**5**	
Study Visit Window (Days)		**± 1**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 7**
Blood sample for FSH (post-menopausal females only)	√								
Blood sample for Hematology & Chemistry	√		√	√	√	√	√	√	
[redacted]									
Blood sample for PGx[f]			√[f]			√[f]			
Blood sample for ADT	√	√	√	√	√	√	√	√	
Serum pregnancy test (FOCP only)	√								
Urine pregnancy test (FOCP only)			√	√	√	√	√	√	
Urine sample for urinalysis	√		√	√	√	√	√	√	
Urine drug and alcohol screen[g]	√	√	√	√	√	√	√	√	
Randomization			√						
Subject PRR training video		√			√				
Register medication Diary	√								
Review medication adherence[h]		√[h]	√[h]	√[h]	√[h]	√[h]	√[h]	√[h]	

Period	Screening		Double-Blind Treatment					Safety Follow-up*	
Visit Number	1	2	3 (Baseline)	4	5	6	7	8 EOS/ET	
Day of Study	-42[a]	-14	1	8	15	22	29	36	66
Week of Study	-6	-2	–	1	2	3	4	5	
Study Visit Window (Days)		± 1	± 2	± 2	± 2	± 2	± 2	± 2	± 7
MADRS	√	√	√	√	√	√	√	√	
CGI-S	√	√	√	√	√	√	√	√	
CGI-I				√	√	√	√	√	
HAM-D6			√	√	√	√	√	√	
SDS			√			√	√	√	
GAD-7			√			√	√	√	
CADSS	√		√	√	√	√	√	√	√
C-SSRS[i]	√	√	√	√	√	√	√	√	√
BPRS+	√		√	√	√	√	√	√	√
CPFQ			√	√	√	√	√	√	
PHQ-9			√			√	√	√	
CSFQ			√			√	√	√	
Review adverse events			√	√	√	√	√	√	√
Review concomitant medication	√	√	√	√	√	√	√	√	√
SM dispensed			√	√	√	√	√		
SM returned and accountability				√	√	√	√	√	

Period	Screening		Double-Blind Treatment					Safety Follow-up*	
Visit Number	1	2	3 (Baseline)	4	5	6	7	8 EOS/ET	
Day of Study	-42[a]	-14	1	8	15	22	29	36	66
Week of Study	-6	-2	–	1	2	3	4	5	
Study Visit Window (Days)		± 1	± 2	± 2	± 2	± 2	± 2	± 2	± 7
Follow-up phone call									√

ADT = antidepressant therapy; ATRQ = Antidepressant Treatment Response Questionnaire; BPRS+ = Brief Psychiatric Rating Scale positive symptom subscale; CADSS = Clinician Administered Dissociative States Scale; CGI-I = Clinical Global Impression – Improvement scale; CGI-S = Clinical Global Impression – Severity scale; CPFQ = Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire; CSFQ = Changes in Sexual Functioning Scale; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EOS = end of study; ET=early termination; FOCP = females of childbearing potential; FSH = follicle stimulating hormone; GAD-7=Generalized Anxiety Disorder 7-item Scale; HAM-D6=Hamilton Depression Rating Scale (6 items); ICF = informed consent form; MADRS=Montgomery-Asberg Depression Rating Scale; MINI=Mini-International Neuropsychiatric Interview; PGx=Pharmacogenomics; PHQ-9 = Patient Health Questionnaire- 9 Item; PK=Pharmacokinetics; POC=Point of Care; PRR=Placebo response reduction; [redacted] SDS=Sheehan Disability Scale; SM=Study medication

* The Safety Follow-up phone call will occur approximately 30 days after the last dose of blinded SM only for subjects who completed the study. For subjects who withdraw from the study, a safety follow-up call will occur approximately 7 days after withdrawal (Section 6.1.5).

a. Day of the Study for Visit 1 will be depending on the prescreening ADT history (Day -42, Day -35 or Day -28) [redacted]

c. Recreational use of cannabis is allowed (not daily, and not exceeding 3 times per week for either vape, smoke, or edible), and should be kept consistent during the study. Subjects must agree to refrain from using cannabis 48 h prior to the study visits.

d. Orthostatic blood pressure and pulse rate, respiratory rate and oral temperature. [redacted]

f. Samples will be stored for analysis and will not be used for identification. At Visit 3 two samples will be collected: one for pharmacogenomic (DNA) and one for BDNF analysis. At Visit 6, one sample will be collected for BDNF analysis.

g. Perform "Standard" Urine Drug Screen (UDS) and alcohol at Visit 1 and Visit 2. At Baseline (Visit 3) and all post-Baseline visits POC test will be performed for UDS, while breathalyzers will be provided for alcohol screen.

h. Sites should review the use of the medication Diary at each visit and intervene with participants as needed.

i. Screening/Baseline C-SSRS version will be assessed at Visit 1 and the "since last visit" version will be assessed thereafter.

6.1.1 Visit 1 – Screening (Days -42, -35, or -28, Depending on the Prescreening ADT History)

The following assessments will be conducted:

- ICF signed including PGx consent
- Administer MINI
- Record social, medical, psychiatric, family psychiatric, and neurological histories
- Record demographics and height
- Review Inclusion/Exclusion Criteria
- Record alcohol and cannabis consumption history
- Perform physical examination
- Record vital signs and weight (orthostatic blood pressure and pulse rate, respiratory rate [RR], oral temperature)
- Perform ECG
- Collect blood samples for:
  - FSH (postmenopausal females only)
  - Serum pregnancy test (FOCP only)
  - Hematology and serum chemistry (nonfasted sample allowed)
  - ADT
- Collect urine samples for:
  - Urinalysis
  - "Standard" Urine drug and alcohol screen (Table 3)
- Administer MADRS, CGI-S, C-SSRS, CADSS, and BPRS+ scales
- Administer Investigator-rated ATRQ
- Register subject in medication adherence diary
- Record concomitant medications

At this visit, in order to record accurate information of psychiatric, family psychiatric, and neurological histories, the site should request records from the pharmacy and medical records from the doctors who previously treated the subject.

6.1.2 Visit 2 (Day -14 ± 1 Day)

The following assessments will be conducted:

- Review Inclusion/Exclusion Criteria
- Record vital signs and weight (orthostatic blood pressure and pulse rate, RR, oral temperature)

- Collect blood sample for ADT
- Collect "Standard" urine sample for urine drug and alcohol screen
- Record cannabis use
- Complete subject placebo response reduction (PRR) training video
- Review medications adherence
- Administer MADRS, CGI-S, and C-SSRS
- Review concomitant medications

6.1.3 Visit 3 – Baseline (Randomization: Day 1 ± 2 Days)

The following assessments will be conducted:

- Review Inclusion/Exclusion Criteria
- Record alcohol and cannabis use
- Perform physical examination
- Record vital signs and weight (orthostatic blood pressure and pulse rate, RR, oral temperature)
- Perform ECG
- Collect blood samples for:
  - Hematology and serum chemistry (nonfasted sample allowed)
  - PGx (optional)
  - ADT
- Collect urine samples for:
  - Urine pregnancy test (FOCP only)
  - Urinalysis
  - "Point of Care" UDS
- Breathalyzer for alcohol screen
- Randomization
- Review medications adherence
- Administer MADRS, CGI-S, HAM-D_6, SDS, GAD-7, CADSS, C-SSRS, BPRS+, CPFQ, PHQ-9, and CSFQ
- Review AEs
- Review concomitant medications
- Dispense SM

6.1.4 Visits 4-8 – Treatment Period Including End of Study

Visit 4 – End of Week 1 (Day 8 ± 2 Days)

The following assessments will be conducted:

- Record alcohol and cannabis use

- Record vital signs and weight (orthostatic blood pressure and pulse rate, RR, oral temperature)
- Perform ECG
- Collect blood samples for:
  - Hematology and serum chemistry (nonfasted sample allowed)
  - ADT
- Collect urine samples for:
  - Urine pregnancy test (FOCP only)
  - Urinalysis
  - "Point of Care" UDS
- Breathalyzer for alcohol screen
- Review medications adherence
- Administer MADRS, CGI-S, CGI-I, HAM-D_6, CADSS, C-SSRS, BPRS+, and CPFQ
- Review AEs
- Review concomitant medications
- Dispense SM
- SM return and assess drug accountability

Visit 5 – End of Week 2 (Day 15 ± 2 Days)

The following assessments will be conducted:

- Record alcohol and cannabis use
- Record vital signs and weight (orthostatic blood pressure and pulse rate, RR, oral temperature)
- Perform ECG
- Collect blood samples for:
  - Hematology and serum chemistry (nonfasted sample allowed)
  - ADT
- Collect urine samples for:
  - Urine pregnancy test (FOCP only)
  - Urinalysis
  - "Point of Care" UDS
- Breathalyzer for alcohol screen
- Complete subject PRR training video
- Review medications adherence
- Administer MADRS, CGI-S, CGI-I, HAM-D_6, CADSS, C-SSRS, BPRS+, and CPFQ
- Review AEs
- Review concomitant medications
- Dispense SM

- Collect SM and assess drug accountability

Visit 6 – End of Week 3 (Day 22 ± 2 Days)

The following assessments will be conducted:

- Record alcohol and cannabis use
- Record vital signs and weight (orthostatic blood pressure and pulse rate, RR, oral temperature)
- Perform ECG
- Collect blood samples for:
  - Hematology and serum chemistry (nonfasted sample allowed)
  - [redacted]
  - PGx (optional)
  - ADT
- Collect urine samples for:
  - Urine pregnancy test (FOCP only)
  - Urinalysis
  - "Point of Care" UDS
- Breathalyzer for alcohol screen
- Review medications adherence
- Administer MADRS, CGI-S, CGI-I, HAM-D_6, SDS, GAD-7, CADSS, C-SSRS BPRS+, CPFQ, PHQ-9, and CSFQ
- Review AEs
- Review concomitant medications
- Dispense SM
- Collect SM and assess drug accountability

Visit 7 – End of Week 4 (Day 29 ± 2 Days)

The following assessments will be conducted:

- Record alcohol and cannabis use
- Record vital signs and weight (orthostatic blood pressure and pulse rate, RR, oral temperature)
- Perform ECG
- Collect blood samples for:
  - Hematology and serum chemistry (nonfasted sample allowed)
  - ADT
- Collect urine samples for:
  - Urine pregnancy test (FOCP only)
  - Urinalysis
  - "Point of Care" UDS

- Breathalyzer for alcohol screen
- Review medications adherence
- Administer MADRS, CGI-S, CGI-I, HAM-D_6, SDS, GAD-7, CADSS, C-SSRS, BPRS+, CPFQ, PHQ-9, and CSFQ
- Review AEs
- Review concomitant medications
- Dispense SM
- Collect SM and assess drug accountability

Visit 8 – End of Week 5/EOS (Day 36 ± 2 Days)

The following assessments will be conducted:

- Record alcohol and cannabis use
- Perform physical examination
- Record vital signs and weight (orthostatic blood pressure and pulse rate, RR, oral temperature)
- Perform ECG
- Collect blood samples for:
  - Hematology and serum chemistry (nonfasted sample allowed)
  - ADT
- Collect urine samples for:
  - Urine pregnancy test (FOCP only)
  - Urinalysis
  - "Point of Care" UDS
- Breathalyzer for alcohol screen
- Review medications adherence
- Administer MADRS, CGI-S, CGI-I, HAM-D_6, SDS, GAD-7, CADSS, C-SSRS, BPRS+, CPFQ, PHQ-9, and CSFQ
- Review AEs
- Review concomitant medications
- SM return and assess drug accountability

6.1.5 Follow-up Phone Call (Day 66 ± 7 Days)

A safety follow-up phone call will occur approximately 30 days after the EOS Visit for subjects who completed the study. For subjects who withdraw from the study, a safety follow-up phone call will occur approximately 7 days after withdrawal.

- Administer CADSS, C-SSRS, and BPRS+ scales
- Review AEs
- Review concomitant medications

6.1.6 Unscheduled Visits

At the discretion of the Investigator throughout the study, unscheduled visits may be conducted to perform or repeat assessments, including record ECG, measure vital signs (orthostatic blood pressure/pulse rate) and weight, draw blood sample for hematology, ADT levels, and/or serum chemistry or serum pregnancy test (FOCP only), ethanol drug screen, obtain urine sample for urine pregnancy test and/or drug screen, administer C-SSRS and perform physical examination.

In the event a subject cannot tolerate 1600 mg/day between Visits 4 and 5, an unscheduled visit may be conducted for dose adjustment before the subject's scheduled Visit 5. AEs and concomitant medications should also be recorded at all unscheduled visits.

6.1.7 Post-Baseline Study Visits

UDS should be completed and results known before any efficacy assessments are conducted at baseline and all post-baseline study visits (Visit 3-8/EOS). UDS will be performed as "Point of Care" (POC) with POC kits provided to sites. If a subject has a positive drug screen at baseline and any post-baseline visit (Visits 3-8), then the subject's participation in the study should be terminated and **no efficacy assessments** (MADRS, CGI-S, CGI-I, HAM-D_6, SDS, and GAD-7) **should be performed at that visit (ET Visit).** All safety assessments should still be performed at this visit. A follow-up phone call with the subject should also be performed 1 week following discontinuation of SM/study.

At baseline and all post-baseline study visits, alcohol screening will be performed using breathalyzers provided by the Sponsor. Subjects should refrain from taking alcohol during the study after the first dose of SM. If a subject tested positive for ethanol at baseline and any post-baseline visit (Visits 3-8), then the subject's participation in the study should be terminated and **no efficacy assessments** (MADRS, CGI-S, CGI-I, HAM-D_6, SDS, and GAD-7) **should be performed at that visit (ET Visit)**. All safety assessments should still be performed at the visit. A follow-up phone call with the subject should also be performed 1 week following discontinuation of SM/study.

[redacted]

[redacted]

6.1.9 Pharmacogenomic Testing

Subjects who have provided consent for PGx testing will have two blood samples taken at baseline (Visit 3) for DNA analysis of genetic variation and for BDNF blood levels measurement. One additional blood sample will be collected at Visit 6 for BDNF blood levels measurement. This additional research may start at any time during the sample storage period. If PGx testing is performed, results from individual tests will be used for research purposes only, and a report separate from the CSR will be generated. Samples will be identified only by the study subject number to maintain confidentiality. Samples will be stored for up to 10 years for potential future research purposes**,** such as possible testing of genes involved in the efficacy of the drug**,** and possible association with particular AEs of the drug (ie, to facilitate an understanding of nonresponders to treatment and/or individuals who show an unusual safety profile).

Data from samples will not have diagnostic value**.** The DNA and RNA analyses will not be used for individual genetic characterization, or development of a commercial product, and the subject's identity will be kept confidential. At the end of testing or after 10 years, any remaining samples will be destroyed.

The subject may withdraw consent for PGx testing at any time. If consent is withdrawn, the subject's sample will be destroyed.

7 STUDY VARIABLES AND ASSESSMENTS

All clinical outcome assessments will be collected electronically using a tablet provided by the Sponsor, and then transferred to a portal.

All scales assessments ratings recorded in the portal are subsequently manually entered into the eCRFs.

Some of the scale assessments will be recorded for an internal independent review purpose conducted by a Sponsor's designee to ensure data consistency and accuracy from each study visit.

7.1 Rater Qualification Process

Identified raters from each site will be asked to provide information regarding their highest education degrees, field of studies, indication areas, and experience in each indication areas using an electronic platform. Once the rater's profile is complete, the platform will automatically assign any Qualification Groups to raters that are eligible. Consequently, raters will be asked to provide scale experience information, and based on the information entered, the system will determine if raters are qualified to proceed to training. Raters can appeal their qualification status; final determination will be made by the Sponsor. All qualified study coordinators, Subinvestigators, and Investigators must complete the platform trainings.

Sites will be considered activated once at least one rater per scale training is completed.

7.2 Efficacy Assessments

We suggest, when possible, that the same qualified rater administer the primary and key secondary efficacy scales for the subject.

For the administration of the MADRS and HAM-D_6 scales, two separate raters for each scale are requested; each rater's score should be blinded to the other rater's score.

It is recommended to administer the scales for the primary endpoint first (ie, MADRS and CGI-S) and then collect study visit assessments (chemistry, vital signs, etc), and lastly administer HAM-D_6 and the self-rating scales.

7.2.1 Montgomery-Åsberg Depression Rating Scale

The MADRS is a 10-item Investigator-rated diagnostic questionnaire used to measure the severity of depressive episodes in patients with mood disorders and is designed to be sensitive to changes brought on by treatment (Montgomery & Asberg, 1979). Each question is scored from 0-6, the sum of the 10 subtests score will yield a total score ranging from 0-60. A higher MADRS score indicates more severe depression. Successful therapy is indicated by a lower total score in subsequent testing (Appendix 11.1).

There are 10 subtests based on each item:

1. Reported sadness
2. Apparent sadness
3. Inner tension
4. Reduced sleep
5. Reduced appetite
6. Concentration difficulties
7. Lassitude
8. Inability to feel
9. Pessimistic thoughts
10. Suicidal thoughts

The rater will use a structured interview that standardizes the administration of the ten MADRS items known as structured interview guide for the MADRS (SIGMA), a structured interview developed by Dr. Janet Williams and Dr. Kenneth Kobak, in order to increase inter-rater reliability, thus improving signal detection (Williams & Kobak, 2008).

The standard (including comparison to euthymic baseline for 3 items) and "Past Week" versions will be administered, with Standard at Visit 1 and "Past Week" version at Visits 2-8 (Appendix 11.1.1). Euthymic baseline is autopopulated based on the information captured at the 1st administration.

The scale is a Clinician Reported Outcome (ClinRO) administered by the qualified raters at each visit during Screening Period and after Day 1 (Randomization/Baseline): Visits 1-8.

7.2.2 Clinical Global Impression – Severity of Illness

The CGI scale was developed to provide a brief, stand-alone assessment of the clinician's view of a subject's global functioning prior to and after administration of SM (Guy, 1976). The Clinical Global Impression-Severity of Illness Scale (CGI-S; Appendix 11.3) is a single-item clinician rating of the clinician's assessment of the severity of symptoms in relation to the clinician's total experience with patients with TRD. The CGI-S is evaluated on a 7-point scale where 1 = Normal not at all, 2 = Borderline depressed, 3 = Mildly depressed, 4 = Moderately depressed, 5 = Markedly depressed, 6 = Severely depressed, and 7 = Among the most extremely depressed patients. Successful therapy is indicated by a lower overall score in subsequent testing.

The scale is a ClinRO administered by the qualified raters at each visit during Screening Period and after Day 1 (Randomization/Baseline): Visits 1-8.

7.2.3 Generalized Anxiety Disorder 7-Item Scale

GAD-7 is a self-reported 7-item questionnaire for Screening and measuring the severity of generalized anxiety disorder (Spitzer, Kroenke, Williams, & Lowe, 2006; Appendix

11.4). The GAD-7 measures the severity of various symptoms of generalized anxiety disorder over the past 2 weeks according to reported response categories with assigned points. The patient scores each GAD-7 item on a 4-point Likert scale where 0 = Not at all, 1 = Several days, 2 = Over half the days, and 3 = Nearly every day. The total score is obtained by summating all 7 items. GAD-7 total scores range from 0-21, where a total score of 1-4 = None/Minimal anxiety, 5-9 = Mild anxiety, 10-14 = Moderate anxiety, and ≥15 = Severe anxiety. It takes less than 5 minutes to complete the GAD-7.

The self-reported GAD-7 scale is administered at Visits 3, 6, 7, and 8.

7.2.4 Clinical Global Impression – Improvement

CGI-I (Appendix 11.5) is an assessment of how much the patient's illness has improved or worsened relative to a baseline state at the beginning of treatment. The CGI-I is evaluated by the Investigator at each post-baseline study visit during treatment relative to the subject's condition at baseline on a 7-point scale where 1 = Very much improved, 2 = Much improved, 3 = Minimally improved, 4 = No change, 5 = Minimally worse, 6 = Much worse, and 7 = Very much worse. Successful therapy is indicated by a lower overall score in subsequent testing. The CGI-S assessment obtained at the baseline visit should serve as a basis for the Investigator's CGI-I assessment of improvement in the subject's conditions at each post-baseline study visit during the treatment period.

The scale is a ClinRO administered by the qualified raters at Visits 4-8.

7.2.5 Sheehan Disability Scale

The SDS is a short self-report tool that assesses functional impairment in three inter-related domains consisting of:

1. Work/School
2. Social Life
3. Family Life/Home Responsibilities

The subject will rate disruption in responsibilities of the three domains on a 10-point visual analog scale (Appendix 11.6). Scores from each item is summed to measure global functional impairment ranging from 0 (unimpaired) to 30 (highly impaired). On the first domain (work/school) before completing the assessment, the subject will be asked to state if have not worked/studied all during the past week due to reasons **unrelated** to depression. In such cases, subjects should **not** indicate disruption severity. If the subject's symptoms interfere with the ability to find a job or contribute in any way to the current status of not working, the subject must give the score on the scale to indicate disruption severity.

While there is no recommended cutoff score, subjects that have scores 5 and above in any of the 3 domains should be follow up as they are associated with significant functional impairment (Sheehan et al., 1998).

The self-reported SDS scale is administered at Visits 3, 6, 7 and 8.

7.2.6 Hamilton Depression Rating Scale – 6 Items

The HAM-D_6 rating scale is one of the most widely used clinician-administered depression scales (Hamilton, 1960). The original version contains 17 items related to symptoms of depression over the past week developed for hospital inpatients. The HAM-D_6, derived from the original 17-items version of the scale, offers sensitivity for measuring severity of detecting improvement of depression comparable to other more complex versions (Williams, 1988).

Five of the six items (Depressed Mood, Work and Activities, Somatic Symptoms General, Feelings of Guilt, Anxiety Psychic, Retardation) are scored on a scale of 0-4, and one item (Somatic Symptoms General) is scored on a scale of 0-2, for a possible total score of 0-22 (Appendix 11.2).

The scale is a ClinRO administered by the qualified raters at Visits 3-8.

7.3 Exploratory Assessments

7.3.1 Cognitive and Physical Functioning Questionnaire

The CPFQ is a brief self-rating scale to measure cognitive and executive dysfunction in mood and anxiety disorders (Fava, Iosifescu, Pedrelli, & Baer, 2009). It assesses the past month subjects' satisfaction with their cognitive and physical functioning (ie, alertness, motivation, attention, memory, lethargy, lexical access, and mental acuity). The CPFQ consists of 7 questions, each rated on a scale from 1-6, with 1 = greater than normal, 2 = normal, 3 = minimally diminished, 4 = moderately diminished, 5 = markedly diminished and 6 = totally absent with a max score of 42. The sum of each of the questions results in the following scoring: ≤7 = greater than normal functioning; 8-14 = normal functioning; 15-21 = minimally diminished functioning; 22-28 = moderately diminished functioning; 29-35 = markedly diminished functioning; and 36-42 = totally absent functioning. (Appendix 11.7).

The self-reported CPFQ scale is administered at Visits 3-8.

7.3.2 Patient Health Questionnaire 9-Item

The PHQ-9 is self-administered questionnaire (Spitzer, Kroenke, & Williams, 1999) consisting of the 9-item depression module derived from the full PHQ (Kroenke et al. 2001).

Major depression is diagnosed if 5 or more of the 9 depressive symptom criteria have been present at least "more than half the days" in the past 2 weeks, and 1 of the symptoms is depressed mood or anhedonia. Other depression is diagnosed if 2, 3, or 4 depressive symptoms have been present at least "more than half the days" in the past 2 weeks, and 1 of the symptoms is depressed mood or anhedonia. As a severity measure,

the PHQ-9 score can range from 0-27, since each of the 9 items can be scored from 0 (not at all) to 3 (nearly every day) (Appendix 11.8).

The self-reported questionnaire is administered at Visits 3, 6, 7, and 8.

7.3.3 Changes in Sexual Functioning Questionnaire

The CSFQ, a structured interview/questionnaire designed to measure illness and medication-related changes in sexual functioning (Clayton, McGarvey, & Clavet, 1997) and the 14-point instrument is validated for measuring sexual function in females and males (Petersen, Kristensen, Giraldi, & Giraldi, 2020). The CSFQ-14 uses 5-point Likert scales to provide the subject an opportunity to self-evaluate the subject's sexual behaviors or problems in a number of areas. For all items, higher scores reflect higher sexual functioning. For 12 of the 14 items, higher sexual functioning corresponds to greater frequency or enjoyment/pleasure (eg, 1 = never to 5 = every day). For two items (item 10, assessing loss of interest after arousal for women and priapism for men, and item 14, assessing painful orgasm), higher sexual functioning corresponds to lower frequency (eg, 1= every day to 5 = never). Items 10 and 14 are included in the total score but not in any scale score (Keller, McGarvey, & Clayton, 2006). To calculate the total score, sum up the values for each of the 14 items. The total score in woman can range from 14-70 with a cutoff of ≤41 indicating sexual dysfunction. The total score in men can also range from 14-70 but with a cutoff of ≤47 indicating sexual dysfunction (Appendix 11.9).

The self-reported scale is administered at Visits 3, 6, 7 and 8.

7.4 Safety Variables and Assessments

Safety assessments include monitoring, evaluation, and recording of all concomitant medications and AEs, and the evaluation of clinical laboratory test results, vital signs and weight, 12-lead ECGs, C-SSRS, CADSS, BPRS+ and the performance of physical examinations as detailed in the Schedule of Events and Assessments (Table 2).

Investigators are responsible for monitoring the safety of subjects who have entered this study and for alerting Supernus or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the subjects.

7.4.1 Adverse Events

As defined by the ICH Guideline for Good Clinical Practice (GCP), an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with treatment.

An AE can be, for example:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product;
- Any new disease, intercurrent injuries, or exacerbation of an existing disease;
- Any deterioration in a laboratory value or other clinical test (e.g., ECG) that results in symptoms, a change in treatment, or discontinuation from SM; and/or
- Recurrence of an intermittent medical condition (eg, headache) not present at baseline.

Surgical procedures are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required is an AE if it occurs or is detected during the study period.

7.4.2 Adverse Events of Special Interest

At the current time, no AEs of special interest (AESI) have been identified. This section will be updated when new information becomes available.

7.4.3 Overdose

No data are available. Should an overdose of NV-5138 be administered or ingested, the subject should be closely monitored for adverse signs and symptoms and appropriate medical supportive care administered.

7.4.4 Causality

Adverse events may be categorized as either adverse drug reactions (ADRs) or suspected adverse drug reactions (SADRs) based on their relationship to SM and the degree of certainty about causality.

SADRs are a subset of AEs for which there is evidence to suggest a causal relationship between the drug and the AE, ie, there is a reasonable possibility that the drug caused the AE.

ADRs are a subset of all SADRs for which there is reason to conclude that the drug caused the event.

7.4.5 Recording and Evaluation of Adverse Events

All subjects who are screened (Visit 1) will be questioned regarding any current and prior medical health status or diagnoses, and any medical records and pharmacy records will be documented as medical history. At each contact with the subject following the first dose of SM (post-Visit 3), the Investigator must seek information on AEs by specific questioning and, as appropriate, by examination. Information on all AEs should be recorded immediately in the source document, and also in the appropriate AE module of the eCRF. All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, although they may be grouped under

one diagnosis. For example, fever, elevated white blood cell (WBC), cough, abnormal chest X-ray, etc., can all be reported as “pneumonia”.

All AEs occurring after Visit 3 and throughout the study period must be recorded. A TEAE is defined as an AE with a start date on or after the first dose of SM is taken, or that worsened following first administration of SM. All AEs in this study will be recorded after administration of SM; therefore, all will be treatment emergent. The clinical course of each AE should be followed for at least 30 days following the date of last dose of SM (either due to EOS or ET), or until resolution, or until, in the medical judgment of the Investigator, the event has stabilized or is assessed as chronic.

The Investigator is responsible for evaluating AEs and determining the following:

- Serious vs. Non-serious: Is the event a Serious Adverse Event (SAE)?
- Causality: Was AE related or not related to the SM?
- Severity: How pronounced is the incapacity/discomfort caused by an AE?

7.4.6 Criteria for Assessing Severity

The Investigator will evaluate the comments of the subject and the response to treatment in order that the Investigator may judge the true nature and severity of the AE. Severity refers to the accumulated intensity of discomfort/impairment of health since the last recording of AEs and will be assessed according to the following criteria:

- **Mild:** Awareness of sign, symptom, or event, but easily tolerated
- **Moderate:** Discomfort enough to interfere with usual activity and may warrant intervention
- **Severe:** Incapacitating with inability to do usual activities or significantly affects clinical status and warrants intervention

The criteria for assessing severity are different from those used for seriousness.

7.4.7 Criteria for Assessing Causality

The Investigator is responsible for determining the relationship between the administration of SM and the occurrence of an AE as not suspected or as a suspected reaction to SM. These are defined as follows:

Not suspected: The temporal relationship of the AE to SM administration makes a causal relationship unlikely, or other drugs, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

- **Not related**: Temporal relationship to SM administration is missing or implausible, or there is an evident other cause.
- **Unlikely related**: Temporal relationship to SM administration makes a causal relationship improbable; and other drugs, chemicals, or underlying disease provide plausible explanations.

Suspected: The temporal relationship of the AE to SM administration makes a **causal relationship possible**, and other drugs, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

- **Possibly related:** Temporal relationship to SM administration is plausible, but concurrent disease, other drugs, or chemicals could also explain event. Information on drug withdrawal may be lacking or unclear. This will be reported as a **SADR**.
- **Definitely related**: Temporal relationship to SM administration is plausible, and concurrent disease, other drugs, or chemicals cannot explain event. The response to withdrawal of the medication (rechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary. This will be reported as an **ADR**.

7.4.8 Serious Adverse Events

Adverse events are classified as serious or non-serious. An AE or ADR is considered "serious" if, in the view of either the Investigator or Sponsor, it results in one of the following outcomes:

- death
- life-threatening AE (ie, the subject was at immediate risk of death from the AE as it occurred. This does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death.)
- in-patient hospitalization or prolongation of existing hospitalization
- persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening or result in death or hospitalization but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, blood dyscrasias, a seizure that did not result in in-patient hospitalization or intensive treatment for allergic bronchospasm in an emergency department would typically be considered serious.

7.4.9 Investigator Responsibilities for Reporting SAEs

The Investigator must immediately report to the Sponsor all SAEs regardless of whether the Investigator believes they are drug related.

All SAEs must be reported to the Drug Safety Contact within 24 h of first becoming aware of the SAE. The Investigator must complete an SAE Form and include a detailed description of the SAE as well as other available information pertinent to the case

(eg, hospital records, autopsy reports, and other relevant documents). The Investigator will keep a copy of this SAE Report form on file at the study site.

The Investigator or study physician, after thorough consideration of all facts that are available, must include an assessment of the causality of an AE to SM in the report to the Sponsor or designee.

SAEs should be followed until resolution or until no further/additional information can be obtained regarding the event. Follow-up information or new information available after the initial report should be actively sought and reported to the Sponsor or designee as it becomes available using the SAE Report Form.

[redacted]

7.4.10 Other Events Requiring Immediate Reporting

The Investigator must report a pregnancy that occurs in a subject during a clinical study to the Drug Safety Contact within **24 h** of first becoming aware of the event. Subjects who become pregnant during the study should be discontinued from SM immediately. Pregnancy should be reported on a Pregnancy Report Form. The Investigator should discuss the case with the Medical Monitor; the Investigator must follow any pregnant subject until 3 months after the child is born. Any AEs concerning the pregnancy of the subject during pregnancy or the child after birth must be documented and reported to the Sponsor or designee.

Acute suicidal crisis or clinically significant suicidal behavior or ideation should be reported to the Drug Safety Contact within 24 h of first becoming aware of the event.

7.4.11 Sponsor Responsibilities for Reporting SAEs

The Sponsor or designee will inform Investigators and regulatory authorities of reportable events in compliance with applicable regulatory requirements on an expedited basis (ie, within specific time frames). For this reason, it is imperative that study sites submit SAE information to the Sponsor or designee in the manner described above.

Investigators must comply with the applicable regulatory requirements related to the reporting of SAEs to the Institutional Review Board (IRB). Investigators must also submit the safety information provided by the Sponsor to the IRB unless the country legal regulation requires that the Sponsor should be responsible for the safety reporting to the IRB.

It is the responsibility of the Sponsor to notify all participating Investigators in a written IND safety report of any SADR that is both serious and unexpected. The Sponsor will also notify participating Investigators of any findings from other sources (other studies, animal, and in vitro testing, etc) that suggest a significant risk for human subjects. Such findings will typically lead to safety-related changes in the study protocol, Informed Consent, and/or Investigator's Brochure (IB).

7.4.12 Clinician-Administered Dissociative States Scale

The CADSS is a 23-item clinician administered scale that measures present-state dissociative symptoms (Bremner et al., 1998).

The subjective component consists of items administered by the clinician who begins each question with anchors and then reads the item to the subject. The subject then rates items on a 4-point Likert scale ranging from: 0 = not at all, 1 = mild, 2 = moderate, 3 =severe, to 4 = extreme with a total score ranging from 0-92 (Appendix 11.10).

The scale is a ClinRO administered by the qualified raters at screening Visit, baseline visit, Visits 4-8, and follow-up phone call (FPC).

7.4.13 Brief Psychiatric Rating Scale

The BPRS is one of the most widely-used instruments enabling the clinician to quickly gather information about the possible presence and severity of various psychiatric symptoms (Zanello, Berthoud, Ventura, & Merlo, 2013). Varying in the number and type of symptoms assessed, clarity of anchor point definitions, and administration and rating instructions, the BPRS exists in various forms. Originally in the early sixties, the BPRS was developed as a 16-item instrument (John E. Overall & Gorham, 1962), which was later extended to 18 items and was used for many years (J. E. Overall, 1967). In order to increase its sensitivity to psychotic and affective disorders as well as to be used with patients living in the community, the BPRS was expanded to 24 items-version 2 (Lukoff, Liberman, & Nuechterlein, 1986). In its latest version (version 4.0), the manual of administration of the 24-item BPRS (Ventura J, 1993(b)) not only offers a more detailed semi-structured interview containing more probe questions for each symptom but also provides supplementary rules for the rating (e.g., delusions) with better-defined anchor points. For the study, the version used is adapted from the original BPRS 4-item positive symptoms (BPRS+). The scale is comprised of 4 items assessing a subject's experience of psychosis, often referred as positive symptoms of Suspiciousness, Hallucinatory Behavior, Unusual Thought Content and Conceptual Disorganization. Of the 4 items assessed, the first three items are based on questions asked by the clinician to the subject, Conceptual Disorganization is a clinician rated item based on observation of subjects' behavior and speech during the assessment (Appendix 11.11).

The scale is a ClinRO administered by qualified raters at Screening Visit 1, Baseline Visit, Visits 4-8, and FPC.

7.5 Treatment-Emergent Suicidal Ideation

Prospective assessment of suicidal ideation and suicidal behavior is a mandatory part of the safety evaluations for any drug developed for a psychiatric indication (FDA, 2012). In this study, the initial evaluation of subjects will be conducted prior to enrollment to assess lifetime suicidal ideation and to identify subjects who must not participate in the trial due to pre-existing suicidality risk. The assessment will then be repeated at each subsequent study visit to monitor the occurrence of new suicidal and self-injurious tendencies.

7.5.1 Columbia-Suicide Severity Rating Scale

Assessment of suicidal ideation and behavior will be conducted using the C-SSRS (Posner et al., 2011; [Baseline] Appendix 11.12; [Since Last Visit] Appendix 11.13). The C-SSRS is an FDA-recommended prospective assessment instrument that directly classifies suicidal ideation and behavior events into 11 preferred categories including 5 levels of suicidal ideation, 5 levels of suicidal behavior, and the category of self-injurious behaviors with no suicidal intent.

The instrument has been validated and used successfully in adult patients with various psychiatric disorders that do not involve cognitive impairment. The C-SSRS outcomes that can be used for clinical management and safety monitoring are suicidal lethality rating, suicidal ideation score, and suicidal ideation intensity rating.

The scale is a ClinRO administered by qualified raters at each visit during the Screening Period and after Day 1 (Randomization/Baseline): at Visits 1-8, and FPC.

7.5.2 Suicide Risk Management Plan

The protocol procedures related to clinical care of patients with treatment-emergent suicidal ideation and behavior must be implemented to ensure proper management of the event and protection of subject's safety. If a disclosure of suicidal ideation is revealed as part of the C-SSRS questionnaire or when a subject spontaneously expresses that the subject may be a threat to him/herself, the study team should be prepared to quickly evaluate the event and to determine the appropriate course of action.

7.5.2.1 Assessment of Suicide Risk

Any indication of suicidal ideation should be evaluated as soon as possible by appropriately trained staff. The Investigator is responsible for making the final judgment regarding potential suicide risk and the need for subsequent action.

7.5.2.2 Acute Suicidal Crisis

A person evaluated as being at high risk should be transferred to an immediate care facility. The Investigator will guide intervention as clinically indicated and follow up

with the subject within 1 week and/or refer the subject to a qualified mental health professional.

7.5.2.3 Non-acute Suicidal Risk

The Investigator will conduct safety planning with the subject and will follow up within 1 week.

Reference materials for subjects and caregivers should include lists of mental health organizations and professionals, outpatient behavioral services, local crisis and peer support groups, and Suicide/Crisis Hotlines.

7.6 Clinical Measurements

7.6.1 Screening and Clinical Safety Laboratory Assessments

All clinical laboratory tests will be performed by a central laboratory as specified in the reference binder.

Details for collecting, handling, and shipping samples (including shipment addresses) will be detailed in a separate clinical laboratory manual. The Schedule of Events and Assessments (Table 2) shows the time points at which blood and urine samples will be collected. Table 3 presents the clinical laboratory tests to be performed.

Table 3: Clinical Laboratory Tests

Category	Parameters
Hematology	Red blood cell count, hemoglobin, hematocrit, platelet count, and WBC count with differential
Chemistry	**Electrolytes**: Chloride, phosphate, potassium, sodium
	Liver function tests: Alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, direct bilirubin
	Renal function parameters: Blood urea nitrogen, creatinine, eGFR[a]
	Other: Glucose, Ca^{+2}, albumin, total protein, bicarbonate, TSH, free T3/T4, and FSH (Postmenopausal females only)
Serology[b]	Hep B, Hep C, HIV
Urinalysis	Microscopic examination[c], pH, specific gravity, protein, glucose, ketone, occult blood, WBC, nitrites, bilirubin, urobilinogen
Standard Urine Drug Screen (UDS)[d]	Amphetamines[e], barbiturates, benzodiazepines[e], buprenorphine, cocaine, ecstasy, ethanol, methadone, methamphetamine[e], methylphenidate[e] opiates, oxycodone, phencyclidine, propoxyphene, tricyclic antidepressants, THC (cannabinoids)
Point of Care[f] Urine Drug Screen (UDS)[d]	Amphetamines[e], barbiturates, benzodiazepines[e], buprenorphine, cocaine, ecstasy, methadone, methamphetamine, opiates,

Category	Parameters
	oxycodone, phencyclidine, propoxyphene, tricyclic antidepressants, THC (cannabinoids)
Breathalyzer	Ethanol
FOCP only: pregnancy test (blood sample at Screening, urine sample at other time points)	Human chorionic gonadotropin

FOCP = females of childbearing potential; FSH=follicle stimulating hormone; Hep B=hepatitis B; Hep C=hepatitis C; HIV=human immunodeficiency virus; T4=thyroxine; TSH=thyroid-stimulating hormone; WBC=white blood cell.

[a]Glomerular filtration rate (eGFR) will be calculated using the Chronic Kidney Disease Epidemiology Collaboration equation at screening only.

[b]Confirmatory serology testing for positive HIV, hepatitis B and C at screening will be performed.

[c]A microscopic examination will be performed on abnormal findings unless otherwise specified.

[d]Standard UDS will be performed at the screenings visits (Visits 1 and 2). A positive test must be confirmed against medical history and concomitant medications.

[e]Amphetamine, methamphetamine, and methylphenidate positive test is allowed only for subjects diagnosed with ADHD confirmed by a prescription record. Benzodiazepine positive test is allowed if used for insomnia.

[f]Point of care (POC) testing and breathalyzer will be used at baseline and all post-baseline visits (Visit 3 to Visit 8/EOS).

7.6.2 Vital Signs and Weight

Vital signs measurements (including orthostatic blood pressure/pulse rate, respiratory rate, and body [oral] temperature) and body weight will be obtained at the time points shown in the Schedule of Events and Assessments (Table 2). Orthostatic blood pressure and pulse rate should be measured after the subject has been sitting for 5 minutes and again within 3 minutes of the subject standing. Vital signs may be taken at any other time, as deemed necessary by the Investigator.

7.6.3 Physical Examinations and Height

Physical examinations and measurement of height will be obtained at the time points shown in the Schedule of Events and Assessments (Table 2). The physical examination conducted at screening (Visit 1) will include assessments of all body systems except genitourinary. Any abnormal findings during screening will be recorded as medical history and any clinically significant abnormal findings following the first dose of SM (post-Visit 3) will be recorded as an AE. At the EOS physical examination, only CFB observations will be noted.

7.6.4 Electrocardiograms

A 12-lead ECG will be obtained at the time points shown in the Schedule of Events and Assessments (Table 2) Additional ECGs may be performed at other times if deemed necessary by the Investigator.

The ECG will be recorded while the subject is resting in a supine position for at least 10 minutes. The ECG will electronically measure the PR, QRS, QT, and QTc intervals, and heart rate. All ECG tracings will be reviewed within 24 h by the Investigator or qualified Subinvestigator and clinical significance will be determined by the Investigator.

PR intervals will be determined for each of these ECGs from a single reading. Invalid measurements will be repeated. QTc will be reported as QTcF (QT corrected using Fridericia's method).

[redacted]

7.8 Screening Scales and Assessment Tools

7.8.1 Mini-International Neuropsychiatric Interview

The MINI is a short, structured diagnostic interview developed by psychiatrics and clinicians in the United States (US) and Europe for DSM disorders and has been updated to map to the *DSM-5* (Hergueta & Weiller, 2013; Sheehan et al., 1998). With an administration time of approximately 15 minutes, the MINI is often used for psychiatric evaluation in clinical trials and is the most widely used psychiatric structured diagnostic interview instrument in the world (Appendix 11.14).

[redacted]

[redacted]

7.8.3 Medication Adherence Diary

This study will use a medication diary to monitor adherence. The platform is provided on a smartphone application to confirm medication ingestion. Built-in reminders allow intervention in case of missed doses. Use of the platform is required for all subjects in the study to reinforce the proper dosing schedule and improve data integrity. Visit reminders are also included.

Registration on the medication adherence platform

- The platform can be downloaded as an app on the subject's personal smartphone. If a subject does not own a smartphone or prefers not to use the subject's personal smartphone, one of the backup provisioned devices should be provided.
- The subject should be registered in the platform following completion of the screening visit to begin monitoring ADT. After completion of the registration process, a training mode will be automated and presented to the subject the first time the subject logs into the device.

Ongoing use and monitoring of medication adherence

- Subjects must use the application to record each daily intake of ADT and SM throughout the trial both remotely between visits and during the PK visit when SM is taken at the site.
- Site study coordinator as well as CRO should regularly check the dashboard to ensure consistent medication adherence throughout the study. In cases of missed doses, the study coordinator will follow up with the subject as soon as possible to assess the reason for nonadherence and reinforce the importance of complying with the SM dosing schedule. If the subject reports that a dose was taken but not logged in the app, the site study coordinator can edit the data using the Manual Cloud Diary Entry role in electronic data capture (EDC).
- Site study coordinator can perform interventions for nonadherent subjects directly through the site within EDC only under special circumstances. Sites are encouraged to document interventions performed within EDC to track their efforts in intervening.

Data Privacy and Security on the smartphone platform

The medication adherence platform is compliant with all applicable privacy and data security laws; data is captured, processed, and analyzed in a secure and compliant manner as outlined in the ICF. This includes the fact that the platform will collect a study ID and cell phone number if provided. All recordings and data are encrypted by the application and will be automatically forwarded to a secure server located in the US. Recordings are only accessible during the study by trained platform staff and all recordings and identifiable data will be deleted at the end of the study.

7.9 Placebo Response Reduction Training

The PRR training for subjects involves an approximately 5-minute long eLearning module found on the eLearning training platform that aims to teach subjects about the appropriate expectations of personal benefit while participating in a clinical trial. The eLearning module is adapted to the protocol and includes case scenarios and interactive questions throughout the course. The content provides subjects with information that helps to neutralize the typical overestimation of personal benefit expectation that drives high placebo responses in clinical studies. Neutralizing staff and study subject's expectations of benefit is a validated method used to decrease placebo response and improve the accuracy of assay sensitivity. A completion certificate is generated at the end of the course and will be filed in the subject chart.

PRR training should be completed by the subject prior to completing study assessments at Visit 2; a refresher training is also requested at Visit 5.

7.10 Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in the study. The committee will meet periodically to review safety data. After the reviews, the DSMB will make recommendations regarding the continuation of the study. The details are provided in a separate DSMB charter. The DSMB consists of two medical experts in the relevant therapeutic area; one is a qualified physician and one an independent biostatistician. The responsibilities, authorities, and procedures are documented in the DSMB charter.

8 STATISTICAL METHODS

8.1 General Considerations

All tabulations of analysis results will include summaries for treatment arms of NV-5138 and placebo.

Where appropriate, variables will be summarized descriptively (frequency count and percentage for categorical variables; number of subjects [n], mean, SD, median, interquartile range [Q1 and Q3], minimum, and maximum for continuous variables).

The data summaries will be accompanied by individual subject data listings, as specified in Sections 16.2 and 16.4 of ICH Guidance E3; these are sorted by unique subject identifier. All data available from the eCRFs will be listed. Unscheduled measurements will be excluded from the descriptive statistics and statistical analysis but will be included in listings.

Complete details of the statistical analysis will be provided in a separate statistical analysis plan (SAP).

8.2 Sample Size and Power Considerations

Two hundred subjects (100 per treatment group) in the FAS will yield 80% power in detecting superiority of NV-5138 to placebo at a significance level of 0.05 (two-sided) using a two-sample t-test with equal allocation to the treatment groups. This assumes an effect size of 0.40 with a mean difference of 4.8 and a SD of 12. Assuming a dropout rate of 25%, approximately 268 subjects will be randomized to achieve about 200 subjects completing the study.

Assuming a 67% rate of screen failure, approximately 800 potential subjects will be screened to obtain about 268 subjects randomized.

8.3 Estimand

8.3.1 Primary Estimand

The attributes below will be used to construct the primary estimand, thereby defining the treatment effect of NV-5138.

1) Treatment: To compare the treatment effect of NV-5138 versus placebo
2) Population: The population targeted for the scientific question is defined by the Inclusion and Exclusion Criteria in adults with TRD
3) Variable: CFB (Day 1) in MADRS total score to end of treatment period
4) ICE: The treatment policy strategy will be followed for handling intercurrent events. For subjects who are discontinued due to AE(s) or lack of efficacy and for subjects who are dosed but have no post-baseline MADRS total score, missing data will be imputed using MI under the MNAR assumption; no imputation will be done for subjects discontinued due to other reasons

5) Population-level summary: difference in mean change in MADRS total score between the NV-5138 and placebo groups will be compared using the MMRM methodology

8.3.2 Secondary Estimand

The attributes below will be used to construct the secondary estimand, thereby defining the treatment effect of NV-5138.

1) Treatment: To compare the treatment effect of NV-5138 versus placebo
2) Population: The population targeted for the scientific question is defined by the Inclusion and Exclusion Criteria in adults with TRD
3) Variable: CFB (Day 1) in the CGI-S score to the end of treatment period
4) ICE: The treatment policy strategy will be followed for handling ICEs. For subjects discontinued due to AE(s) or lack of efficacy and for subjects who are dosed and have no post-baseline CGI-S scores, missing data will be imputed using MI under the MNAR assumption; no imputation will be done for subjects discontinued due to other reasons
5) Population-level summary: The difference in mean change in CGI-S scores between the NV-5138 and placebo groups will be compared using the MMRM methodology

8.4 Handling of Dropout or Missing Data

With respect to the primary analysis, the MMRM method, implemented via SAS® PROC MIXED (SAS/STAT Software), will be used for handling missing MADRS total scores under the missing at random (MAR) assumption; however, for subjects who are discontinued due to AE(s) or lack of efficacy and for subjects who are dosed but have no post-baseline MADRS total score, placebo-based MI will be used to fill in missing data before performing the MMRM analysis. This approach assumes that missing data from the NV-5138 treatment group would adopt the outcomes estimated from the placebo group. The SAS procedure, PROC MI, will be used to apply the MNAR statement with the option of using the observations from the placebo group. MI will be carried out by the fully conditional specification (FCS) method. One hundred (100) imputed datasets will be created in case of subjects who are discontinued due to AE(s) or lack of efficacy and for subjects who are dosed but have no post-baseline MADRS total score. The MMRM model for the primary efficacy analysis will be performed using each of these 100 imputed datasets. PROC MIANALYZE in SAS will be used to combine all the results from these 100 MMRM models and then make a final statistical inference.

A sensitivity analysis for the primary endpoint will be performed by assuming that missing MADRS total scores are MNAR using placebo-based MI to impute all missing data in the NV-5138 group.

The same procedure will be applied to key secondary endpoint CGI-S.

For analysis of additional secondary endpoints, missing values will be using MMRM which assumes missing values as MAR.

For safety analyses, missing date for AEs and nonstudy medication use will be imputed as described in the SAP. Missing data for all other safety endpoints will not be imputed.

8.5 Analysis Populations

The **Randomized Population** includes all subjects who are randomized.

The **Full Analysis Set (FAS)** is a subset of subjects in the Randomized Population who take at least one dose of SM and have a baseline assessment of MADRS total score. The efficacy analyses will be conducted using the FAS according to the randomized treatment assignment.

The **Per Protocol (PP) Population** is a subset of subjects in the FAS who complete all 8 visits through EOS with no missing MADRS total scores assessments and no important protocol deviations. Subjects in the PP Population will be analyzed according to the actual treatment received.

The **Safety Population** includes all subjects randomized into the study who receive at least one dose of SM. The safety analysis will be performed according to the actual treatment received.

[redacted]

8.6 Demographics and Baseline Analysis

Demographic and baseline characteristics (eg, age, age group, sex, ethnicity, race, height, weight, and BMI) will be summarized using descriptive statistics for continuous variables and using counts and percentages for categorical variables. The descriptive summary will be presented by the treatment group for the FAS and Safety Populations.

8.7 Subject Disposition

A disposition of subjects will include the number and percentage of subjects in each of the analysis populations.

The number and percentage of subjects who completed and discontinued from the study and primary reason for early discontinuation will be summarized. The reason for early discontinuation may include any of the following:

- Withdrawal of consent
- Noncompliance with study procedures (eg, positive alcohol test or UDS, missed more than two consecutive doses of SM, use of prohibited medications)
- Occurrence of unmanageable AEs
- Lost to follow-up

- Lack of efficacy
- The Investigator or the Sponsor believes it is in the best interest of the subject to discontinue the study (ie, for safety or tolerability reasons)
- Other (eg, study is terminated by the Sponsor, subject becomes pregnant, blind is broken, subject has relocated or death, etc)

8.8 Study Medication Exposure and Compliance

Duration of exposure is defined as the total number of days a subject is exposed to any SM. This will be calculated for each subject by taking the difference between the date of last dose minus the date of the first dose, plus 1 (date of last dose minus date of first dose +1).

Duration of treatment exposure will be summarized by duration category (1-7 days, 8-14 days, 15-21 days, 22-28 days, 29-35 days, and 35 days or more) and will also be summarized using descriptive statistics (n, mean, SD, median, interquartile range [Q1 and Q3], minimum, and maximum).

Subject exposure will be summarized categorically by study week, dose (800 mg, 1600 mg in separate rows [eg, 1600 mg for week 1, 800 or 1600 mg for rest weeks]), and treatment group. The number and percent of subjects in each dose group will be presented for each treatment.

Percentage compliance will be calculated. For each treatment, SM compliance will be summarized by compliance category (<80%, 80-120%, and >120%) and number of subjects in each compliance category. SM compliance will also be summarized as a continuous variable using descriptive statistics (n, mean, SD, median, interquartile range [Q1 and Q3], minimum, and maximum) for each treatment.

8.9 Concomitant Medications

Concomitant medications will be assigned an 11-digit code using the World Health Organization Drug Dictionary (WHO-DD) drug codes. Concomitant medications will be further coded to the appropriate Anatomical-Therapeutic-Chemical (ATC) code indicating therapeutic classification. A tabular summary of concomitant medications by drug class will be presented for the Safety Population.

8.10 Efficacy Analysis

All efficacy endpoints will be analyzed based on the FAS. All efficacy data will be presented in data listings.

8.10.1 Primary Efficacy Analysis

The CFB in MADRS total score to the end of treatment period will be analyzed using a MMRM. For subjects who are discontinued from the study due to AE(s) or lack of efficacy and for subjects who are dosed but have no post-baseline MADRS total score,

missing data will be imputed based on the MNAR assumptions. For subjects who are discontinued from the study due to other reason, no missing imputation will take place. The data collected at the ET visit will be mapped to the next scheduled visit. The MMRM model will include baseline MADRS total score as a covariate, and treatment, visit, and treatment-by-visit interaction as fixed effects. The model parameters will be estimated using the restricted maximum likelihood method with an unstructured variance-covariance matrix and Kenward-Roger approximation to estimate the denominator degrees of freedom. If the MMRM model with the unstructured variance-covariance matrix does not converge using the default Newton-Raphson fitting algorithm by PROC MIXED in SAS, the Fisher scoring algorithm or the no-diagonal factor analytic structure will be used (Lu & Mehrotra, 2010).

If the model still fails to converge, the following types of covariance structure with the sandwich estimators will be used to fit the model in a sequential order until the model converges:

1. Heterogeneous Toeplitz
2. Heterogeneous Autoregressive of order 1
3. Toeplitz
4. Autoregressive of order 1
5. Compound symmetry

The denominator degrees of freedom will be estimated using the BETWITHIN option in SAS when any of the covariance structures is used with the sandwich variance estimator.

One hundred (100) imputed datasets based on the MNAR assumption will be created in case of subject discontinuation due to AE(s) or lack of efficacy and for subjects who are dosed but have no post-baseline MADRS total score. The MMRM model for the primary efficacy analysis will be performed using each of these 100 imputed datasets. PROC MIANALYZE in SAS will be used to combine all the results from these 100 MMRM models and then make a final statistical inference.

For the final statistical inference, the least squares (LS) mean of CFB to the end of treatment period for the MADRS total score for each treatment group will be presented along with the corresponding standard error (SE). The NV-5138 group will be compared with the placebo group by presenting the difference in the LS means between the NV-5138 and placebo groups (NV-5138 minus placebo) with its 95% CI and the p-value.

8.10.2 Sensitivity Analysis

A sensitivity analysis will be performed using the placebo-based MI to fill in missing MADRS total scores. This approach assumes that after discontinuation, subjects from the NV-5138 treatment group would adopt the outcome that is estimated from the placebo group. Placebo-based MI will be used to fill in all missing values in the NV-5138 and placebo groups. The CFB in MADRS total score to the end of Treatment Period based on

each imputed dataset will be analyzed using the same MMRM model described for the primary analysis. To combine all the results using each of the imputed datasets, PROC MIANALYZE in SAS will be used to make a final statistical inference.

8.11 Secondary Efficacy Analyses

The secondary analyses will be based on the FAS.

8.11.1 Key Secondary Efficacy Analyses

The key secondary endpoint, the CFB to the end of the Treatment Period in the CGI-S score, will be analyzed using the same MMRM model as the primary efficacy analysis. Specifically, ICEs, missing data, and statistical methods for the key secondary efficacy endpoint analysis will be handled in the same manner as described in Sections 8.3.2, 8.4, and 8.10.2. Sensitivity analysis will be conducted in the same manner as described in Section 8.10.2.

8.11.2 Additional Secondary Analyses

For the MADRS, the CFB to end of each scheduled week will be analyzed using MMRM as appropriate based on the FAS. For the SDS, HAM-D_6 and GAD-7 scores, the CFB to end of each scheduled week will be analyzed using MMRM as appropriate based on the FAS. For the CGI-I, the absolute value will be analyzed using MMRM. The NV-5138 treatment group will be compared with the placebo as described for the primary analysis.

The treatment groups for the proportion of responders (defined as ≥50% reduction from baseline in MADRS total score), the proportion of subjects in remission (MADRS total score ≤10), the percentage of subjects with a CGI-S score of 1 or 2, and the percentage of subjects with a CGI-I score of 1 or 2 at the end of each scheduled week will be compared using Pearson's Chi-squared Test or Fisher's Exact Test as applicable.

8.12 Exploratory Efficacy Analyses

The CFB to the end of each scheduled week in PHQ-9, CPFQ, and CSFQ scale scores will be analyzed using MMRM as appropriate based on the FAS. The NV-5138 treatment group will be compared with the placebo as described for the primary analysis. A subgroup analysis of the primary efficacy endpoint will be explored using the history of inadequate response to the prior ADT medications and speech latencies. If applicable, subgroup analyses of some efficacy endpoints will be explored (eg, by sex, prior ADT failure category, and speech latency category).

[redacted]

[redacted]

8.14 Interim Analysis

No interim analysis will be performed.

8.15 Pharmacogenomic Analyses

The blood samples will be stored for possible testing of genetic variation and BDNF concentration. Analyses may include the relationship to treatment effects and AEs (eg, understand how the non-responders react to treatment and/or subjects who show an unusual safety profile). The DNA and RNA analyses will not be used for individual genetic characterization and the subject identity will be kept confidential. If analyzed, the results of the exploratory analyses will be presented in a stand-alone PGx report.

8.16 Safety Analysis

Safety analyses will be performed by treatment arm based on the Safety Population.

The incidence rate of AEs will be calculated by treatment arm for each system organ class (SOC) and preferred term (PT). The severity of the AEs and the relationship to SM will be summarized by the treatment arm for each SOC and PT.

AEs, serious AEs (including deaths), and AEs leading to withdrawal will be summarized by SOC and PT, separately for each treatment arm. The verbatim descriptions with *Medical Dictionary for Regulatory Activities (MedDRA*) coded SOCs and PTs for all AEs will be contained in the subject data listings.

Clinical laboratory values will be summarized by the treatment arm for each visit using descriptive statistics. For quantitative laboratory parameters, both actual values and CFB will be summarized.

Vital signs and weight will be summarized by visit by treatment arm using descriptive statistics. Both actual values and CFB will be summarized.

ECG results will be summarized by the treatment arm for each visit using descriptive statistics (for quantitative ECG parameters) and frequency tables (for qualitative ECG parameters, including the overall ECG finding).

C-SSRS outcomes will be summarized using number and percent of subjects by categories for suicidal ideation only, suicidal behavior only, and suicidality (ideation and behavior combined). The summary will be presented by the treatment arm for each visit.

Descriptive statistics will be presented for demographics, physical examinations, CADSS, and BPRS+ scores.

9 DOCUMENTATION

9.1 Adherence to the Protocol

The Investigator agrees, when signing the protocol, to adhere to the instructions and procedures described within and to the principles of ICH GCP as well as all governing local regulations and principles for medical research.

The protocol, ICF, and appropriate related documents must be reviewed and approved by an IRB constituted and functioning in accordance with ICH E6 and any local regulations. Documentation of IRB compliance with the ICH and any local regulations regarding constitution and review conduct will be provided to the Sponsor.

A signed letter of study approval from the IRB must be sent to the Investigator with a copy to the Sponsor prior to study start and the release of SM to the site by the Sponsor or its designee. If the IRB decides to suspend or terminate the study, the Investigator will immediately send the notice of study suspension or termination by the IRB to the Sponsor.

9.2 Changes to the Protocol

Changes to the protocol will not be made without written approval from the Sponsor.

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the Sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require additional approval by the applicable IRB, and in some cases, filings to the regulatory authority. These requirements should in no way prevent any immediate action from being taken by the Investigator, or by the Sponsor, in the interest of preserving the safety of all subjects included in the study. If an immediate change to the protocol is felt by the Investigator to be necessary for safety reasons, the Medical Monitor, and IRB must be notified promptly.

Changes to the protocol which are administrative in nature do not require formal protocol amendments or IRB approval, but the IRB must be kept informed of such changes. In these cases, the Sponsor or CRO will send a letter to the IRB detailing such changes.

9.3 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures (SOPs), working practice documents, and applicable regulations and guidelines. Site visit audits may be made periodically by the Sponsor's Quality Assurance team or qualified designee, which is an independent function from the study conduct team.

9.3.1 Data Collection

The primary source document will be the subject's medical and pharmacy records. If separate research records are maintained by the Investigator(s), both the medical record and the research record will be considered the source documents for the purposes of monitoring and auditing the study.

Electronic data collection techniques will be used to collect data directly from the study sites using eCRFs. The electronic data will be stored centrally in a fully validated clinical database.

Data recorded on source documents will be transcribed into the eCRFs in accordance with the eCRF Completion Instructions that are provided to the study sites. The Investigator is responsible for ensuring that all sections of each eCRF are completed correctly, and that entries can be verified against source documents. The eCRFs will be monitored for completeness and accuracy against the source documents by the CRA(s) on a regular basis. Inconsistencies between the eCRFs and source documents will be resolved in accordance with the principles of GCP.

9.3.2 Clinical Data Management

External data outside of the clinical database (eg, laboratory data) will be reconciled with the database as specified in the data management plan. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database.

9.3.3 Database Quality Assurance

In accordance with the vendor's procedures, the clinical database will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures. The procedure for handling missing data will be addressed in the SAP. Data queries requiring clarification will be documented and returned to the study site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections will be documented in an audit trail.

9.3.4 Bioanalytical Sample Handling

Samples will be shipped according to instructions provided by the Sponsor or according to a Sponsor-reviewed sample processing/handling manual. Primary and backup samples will be transported in separate shipments to the Sponsor designated bioanalytical facility. The samples should be packed on sufficient dry ice to keep them frozen during shipment.

9.4 Retention of Records

The Investigator has the responsibility to retain all study "essential documents", as described in ICH E6 for at least two years after approval of a marketing application or after formal discontinuation of the clinical program. Essential documents include but not limited to the protocol, eCRFs, source documents, laboratory test results, SM inventory records, IBs, regulatory agency registration documents (eg, FDA form 1572, ICFs, and IRB correspondence). The Investigator must obtain written permission from Supernus prior to the destruction of any study document.

9.5 Auditing Procedures

In addition to the routine monitoring procedures, the Sponsor's Corporate Quality Assurance department or qualified designee may conduct audits of clinical research activities in accordance with the Sponsor's written SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. A government regulatory authority may also wish to conduct an inspection (during the study or after its completion). If an inspection is requested by a regulatory authority, the Investigator must inform the Sponsor and the CRO immediately that this request has been made.

These records must be made available at reasonable times for inspection and duplication, if required, by a properly authorized representative of the US FDA in accordance with the US 21 Code of Federal Regulation (CFR) 312.68 or other national or foreign regulatory authorities in accordance with regulatory requirements.

9.6 Publication of Results

Any presentation or publication of data collected as a direct or indirect result of this trial will be considered as a joint publication by the Investigator(s) and the appropriate personnel at the Sponsor's site. Authorship will be determined by mutual agreement. All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the Sponsor prior to submission for publication or presentation. No publication or presentation with respect to the study shall be made until all Sponsor comments on the proposed publication or presentation have been addressed to the Sponsor's satisfaction.

The detailed obligations regarding the publication of any data, material results, or other information, generated or created in relation to the study shall be outlined in the agreement between each Investigator and the Sponsor or designee.

9.7 Financing and Insurance

Financing and Insurance information will be set forth in a separate document between the Investigator and Sponsor (provided by the Sponsor or designee).

9.8 Disclosure and Confidentiality

The contents of this protocol, any amendments, and results obtained during the course of this study will be kept confidential by the Investigator, the Investigator's staff, and the IRB and will not be disclosed in whole or in part to others or used for any purpose other than reviewing or performing the study without the written consent of the Sponsor. No data collected as part of this study will appear in any written work including publications without the written consent of Sponsor.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in the Confidentiality Agreement between the Investigator and Sponsor.

9.9 Discontinuation of Study

The Sponsor reserves the right to discontinue the study for medical or administrative reasons at any time. The Investigator will be reimbursed for reasonable expenses covering subjects, use of live-in facilities, laboratory tests, and other professional fees. The Investigator will refund the excess of payments made in advance.

The Investigator reserves the right to discontinue the study should the Investigator's judgment so dictate. The Investigator will notify the IRB in case of study discontinuation. Study records must be retained as noted above.

10 ETHICS

10.1 Institutional Review Boards

The IRB that approved this study and the approval letters will be included in the CSRfor this protocol.

The protocol, any protocol amendments, and the ICF will be reviewed and approved by the appropriate IRB before subjects are enrolled. The Investigators or Sponsor will submit, depending on local regulations, periodic reports and inform the IRB of any reportable AEs per ICH guidelines and local IRB standards of practice.

10.2 Ethical Conduct of the Study

This study will be conducted in accordance with SOPs from both the Sponsor and the CRO. These SOPs are designed to ensure adherence to GCP guidelines as required by:

- Declaration of Helsinki, 1964 ("Recommendations Guiding Physicians in Biomedical Research Involving Human Patients"), and all its accepted amendments to date concerning medical research in humans
- ICH Guideline for GCP (Committee for Proprietary Medicinal Products/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, ICH of Pharmaceuticals for Human Use
- US CFR dealing with clinical studies (21 CFR, including parts 50 and 56 concerning Patient Informed Consent/Assent and IRB regulations)
- Local, national legal guidelines

10.3 Investigators and Study Personnel

This study will be conducted by qualified Investigators under the sponsorship of Navitor Pharmaceuticals, Inc. and its partner Supernus Pharmaceuticals, Inc.

Contact persons at the Sponsor and the CROs are listed in the reference binder provided to each investigational site. The study will be monitored by qualified personnel from the Sponsor or their designees, such as the CROs for their respective sites. Laboratory tests will be conducted by a central laboratory as designated in the reference binder.

[redacted] Data management and statistical analyses will be the responsibility of the CRO data management and biostatistics groups.

10.4 Subject Information and Consent

The Investigator (or designee) will inform the subject of all aspects pertaining to the subject's participation in the study and will provide oral and written information describing the nature and duration of the study, the procedures involved, the expected duration, the potential risks and benefits involved, and any potential discomfort.

The process for obtaining informed consent will be in accordance with all applicable regulatory requirements. The Investigator (or designee) and subject must sign and date the ICF before the subject can participate in the study. The subject will be given a copy of the signed and dated ICF, and the original will be retained in the investigational site study records.

The decision regarding subject participation in the study is entirely voluntary. The Investigator (or designee) must emphasize to the subject that consent, regarding study participation may be withdrawn at any time without penalty or loss of benefits to which the subject is otherwise entitled.

If the ICF is amended during the study, the Investigator must follow all applicable regulatory requirements pertaining to approval of the amended ICF by the IRB and use the amended ICF (including ongoing subjects).

11 APPENDIX:

11.1 MADRS

SIGMA 2011, v. 1.2

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

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

INTERVIEWING GUIDELINES: The questions in bold for each item should be asked exactly as written unless the information has been previously obtained, in which case it is appropriate to restate the information for confirmation. Follow-up questions are provided 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. Statements in ALL CAPITALS are interviewer instructions and should not be read to the subject.

RATING GUIDELINES: Ratings should be based on the subject's condition as observed in the past week (past 7 days). As specified in the item descriptions, three of the items, Reduced Sleep, Reduced Appetite, and Inability to Feel, are rated as present only when they reflect a change from before the depression began (EUTHYMIC BASELINE). The interviewer should attempt to identify the most recent 2-month period of non-depressed functioning and use this as a reference point. In some cases, such as when the subject has dysthymia, the referent should be to the last time the subject felt alright (i.e., not depressed or high) for at least a few weeks. When a clear euthymic baseline cannot be established because of chronic depressive symptoms, these three items should be rated as observed over the past 7 days instead of comparing to a previous time point.

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, 2005 and 2008.

SIGMA 2011, v. 1.2

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

PT'S INITIALS: _____ PT'S ID: _____ **TIME BEGAN SIGMA: _____ AM / PM**

INTERVIEWER: _____ **DATE: _ _ _ _ _ _**

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? (What kind of work do you do? Have you been able to work your normal hours?)
IF NOT WORKING OR WORKING LESS, CLARIFY WHY.

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? (How often have you had lifts in your mood this week? 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? **ESTABLISH EUTHYMIC BASELINE: When was the last time you were well, not depressed at all, for at least 2 months?**	**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.

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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? **Has it been hard for you to laugh or smile in the past week?**	**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.

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? **What about feeling fearful that something bad is about to happen?** How much of the time have you felt (anxious/tense/OWN EQUIVALENT) over the past week? **Have you felt panicky in the past week?** IF YES: Can you describe this feeling? How often have you felt this way? IF YES TO ANY TENSION SYMPTOM: 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?)	**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 only 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? How many nights?) **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? How many nights?) **Have there been any mornings this past week when you have awakened earlier than (EUTHYMIC BASELINE)?** IF UNKNOWN: 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.

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How has your appetite been this past week? (What about compared to your usual appetite?) IF NOT REDUCED: Have you been less interested in food? (How much less?) **Does food taste as good as usual?** IF LESS: How much less? Does it have any taste at all? (Have you had to push yourself to eat or 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.

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 book or on the computer? Do you need to read things over and over again? Are you able to follow movies or television?) How often has that happened in the past week? Has this caused any problems for you? **Have you had any trouble following 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? How bad has that been? Have you had difficulty getting started at simple routine everyday things (like getting dressed, brushing your teeth, showering)? Are you OK once you get started at things or is it still more of an effort to get something done? Has there been anything that you needed to do that you were unable to do? Have you needed help to do things? IF YES: What things? How often? Have you done everyday things more slowly than usual? 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 much less interested in (those things) are you now compared to (EUTHYMIC BASELINE)? **What things have you enjoyed this week?** How much did you enjoy them? **Has there been any change in your ability to feel emotions in the past week?** (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?) **Have your feelings towards family and friends changed at all since (EUTHYMIC BASELINE)?** IF YES: Do you feel less towards them than you used to?	**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.

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? **In the past week have you been feeling guilty about anything? 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.

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This past week, have you felt like life isn't worth living? (IF NO: What about feeling as if you're tired of living?) IF YES: Tell me about that. How often have you felt that way? **This week, have you thought that you would be better off dead?** IF YES: Tell me about that. How often have you felt that way? **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.

TIME ENDED SIGMA:	_____ **AM / PM**
TOTAL MADRS SCALE SCORE:	_____ _____

11.1.1 MADRS Past Week (Follow-up Evaluation)

SIGMA 2011, v. 1.2

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

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

INTERVIEWING GUIDELINES: The questions in bold for each item should be asked exactly as written unless the information has been previously obtained, in which case it is appropriate to restate the information for confirmation. Follow-up questions are provided 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. Statements in ALL CAPITALS are interviewer instructions and should not be read to the subject.

RATING GUIDELINES: Ratings should be based on the subject's condition as observed in the past week (past 7 days). As specified in the item descriptions, three of the items, Reduced Sleep, Reduced Appetite, and Inability to Feel, are rated as present only when they reflect a change from before the depression began (EUTHYMIC BASELINE). The interviewer should attempt to identify the most recent 2-month period of non-depressed functioning and use this as a reference point. In some cases, such as when the subject has dysthymia, the referent should be to the last time the subject felt alright (i.e., not depressed or high) for at least a few weeks. When a clear euthymic baseline cannot be established because of chronic depressive symptoms, these three items should be rated as observed over the past 7 days instead of comparing to a previous time point.

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, 2005 and 2008.

SIGMA 2011, v. 1.2

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

PT'S INITIALS: _____ PT'S ID: _____ **TIME BEGAN SIGMA: _____ AM / PM**

INTERVIEWER: _____ **DATE: _ _ _ _ _ _**

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? (What kind of work do you do? Have you been able to work your normal hours?)
IF NOT WORKING OR WORKING LESS, CLARIFY WHY.

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? (How often have you had lifts in your mood this week? 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? **ESTABLISH EUTHYMIC BASELINE: When was the last time you were well, not depressed at all, for at least 2 months?**	**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.

SIGMA 2011, v. 1.2

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? **Has it been hard for you to laugh or smile in the past week?**	**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.

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? **What about feeling fearful that something bad is about to happen?** How much of the time have you felt (anxious/tense/OWN EQUIVALENT) over the past week? **Have you felt panicky in the past week?** IF YES: Can you describe this feeling? How often have you felt this way? IF YES TO ANY TENSION SYMPTOM: 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?)	**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 only 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? How many nights?) **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? How many nights?) **Have there been any mornings this past week when you have awakened earlier than (EUTHYMIC BASELINE)?** IF UNKNOWN: 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.

SIGMA 2011, v. 1.2

How has your appetite been this past week? (What about compared to your usual appetite?) IF NOT REDUCED: Have you been less interested in food? (How much less?) **Does food taste as good as usual?** IF LESS: How much less? Does it have any taste at all? (Have you had to push yourself to eat or 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.

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 book or on the computer? Do you need to read things over and over again? Are you able to follow movies or television?) How often has that happened in the past week? Has this caused any problems for you? **Have you had any trouble following 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? How bad has that been? Have you had difficulty getting started at simple routine everyday things (like getting dressed, brushing your teeth, showering)? Are you OK once you get started at things or is it still more of an effort to get something done? Has there been anything that you needed to do that you were unable to do? Have you needed help to do things? IF YES: What things? How often? Have you done everyday things more slowly than usual? 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 much less interested in (those things) are you now compared to (EUTHYMIC BASELINE)? **What things have you enjoyed this week?** How much did you enjoy them? **Has there been any change in your ability to feel emotions in the past week?** (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?) **Have your feelings towards family and friends changed at all since (EUTHYMIC BASELINE)?** IF YES: Do you feel less towards them than you used to?	**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.

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? **In the past week have you been feeling guilty about anything? 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.

SIGMA 2011, v. 1.2

This past week, have you felt like life isn't worth living? (IF NO: What about feeling as if you're tired of living?) IF YES: Tell me about that. How often have you felt that way? **This week, have you thought that you would be better off dead?** IF YES: Tell me about that. How often have you felt that way? **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.

TIME ENDED SIGMA:	_____ **AM / PM**
TOTAL MADRS SCALE SCORE:	_____ _____

11.2 HAM-D_6

STRUCTURED INTERVIEW GUIDE FOR THE HAMILTON DEPRESSION RATING SCALE – 6-ITEM VERSION (SIGH-D-6)

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 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. You should ask for examples for any symptoms acknowledged as present (e.g., *"Can you give me an example of that?"*). For some of the HAM-D 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 their severity.

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

Administration method. This version includes interview questions to help the clinician rate psychomotor agitation and psychomotor retardation, when the interview is administered by telephone. Several research studies have demonstrated that depression scale scores are equivalent whether the scale is administered face-to-face, by telephone, or by video (Williams JBW and Kobak KA: Development and Reliability of a Structured Interview Guide for the Montgomery-Asberg Depression Rating Scale. Br J Psychiatry 192, 52-58, 2008; Kobak KA: A comparison of face-to-face and remote administration of the Hamilton Depression Rating Scale via videoconferencing. J Telemed Telecare 10, 231-235, 2004).

Referent of "usual" or "normal" condition. In the HAM-D, most items are rated positive only if they represent a change from usual functioning. For this reason, several of the interview questions in the HAM-D refer to the subject's usual or normal functioning. The referent should be to the last time they felt okay (i.e., not depressed or high and normal interest in things) for at least two months. When no clear euthymic baseline can be established, one should rate symptomatic behavior as one sees it, even if it is not a change from the subject's usual dysphoric self.

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 for all items except Helplessness, Hopelessness, and Worthlessness, 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). The loss of weight item has been simplified to eliminate the section for ratings by ward staff. 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). Additional designators were added in parentheses to the anchor points by Kobak, Lipsitz and Williams to further standardize ratings.

For further information and permission to use or translate the SIGH-D, contact Mapi Research Trust (Internet: https://eprovide.mapi-trust.org).

SIGH-D – United States/English – Original version
SIGH-D_AU2.0_eng-USori

STRUCTURED INTERVIEW GUIDE FOR THE HAMILTON DEPRESSION RATING SCALE – 6-ITEM VERSION (SIGH-D-6)

SUBJECT'S INITIALS: _____ TIME BEGAN SIGH-D: _____

INTERVIEWER: _____ DATE: _____/_____/_____

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 okay)?

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?

IF UNKNOWN: Have you been feeling discouraged or pessimistic?

IF YES: What have your thoughts been?

In the last week, how often have you felt (OWN EQUIVALENT FOR DEPRESSED MOOD)? On how many days? For how long each day?

Have you been crying at all? How often?

IF SCORED 1-4 ABOVE, ASK: How long have you been feeling this way (OWN EQUIVALENT FOR DEPRESSED MOOD)?

1. 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)*

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 to 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?	**2. 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 activities) (*clear reduction in interest, pleasure or functioning)*
	3 Decrease in actual time spent in activities or decrease in productivity. In hosp., pt. spends less than 3 hrs./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)*

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?	**3. SOMATIC SYMPTOMS GENERAL:**
	0 None
	1 Heaviness in limbs, back, or head. Backaches, muscle aches. Loss of energy and fatigability *(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? 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.)	**4. 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

Have you been feeling anxious or tense this past week? IF YES: Is this more than is normal for you? **Have you been feeling irritable this past week? (IF YES): Can you give me some example? How bad has it been?** Have you been worrying a lot about little things, things you don't ordinarily worry about? IF YES: Like what, for example? How about worrying about big problems more than you need to? How much of the time has that happened this week? Has this caused you any problems or difficulties? IF YES: Like what, for example?	**5. 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)*

RATING BASED ON OBSERVATION DURING INTERVIEW **IF INTERVIEWING BY PHONE:** During this interview have you been moving slowly, reacting slowly, or speaking more slowly than usual for you?	**6. 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*)

TIME ENDED SIGH-D-6:	_____ **AM / PM ET / CT / PT**
TOTAL HAM-D-6 SCORE:	_____

Item numbers in SIGH-D-17		**Corresponding Items in SIGH-D-6**
1. Depressed Mood	►	1. Depressed Mood
2. Work and Activities	►	2. Work and Activities
9. Somatic, General	►	3. Somatic, General
10. Guilt	►	4. Guilt
12. Anxiety, Psychic	►	5. Anxiety, Psychic
17. Retardation	►	6. Retardation

11.3 CGI-S

Clinical Global Impressions Scale - Severity (CGI-S) for Depression: Past 7 Days

Considering your total clinical experience with patients with depression, how has the patient been in the PAST 7 DAYS?

- ☐ 1. Normal, not at all
- ☐ 2. Borderline depressed
- ☐ 3. Mildly depressed
- ☐ 4. Moderately depressed
- ☐ 5. Markedly depressed
- ☐ 6. Severely depressed
- ☐ 7. Among the most extremely depressed patients

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

CGI-S Depression-7 day_en_US_v1.0_30 Nov 2020 Page 1 of 1

11.4 GAD-7

GAD-7

Over the last 2 weeks, how often have you been bothered by the following problems? *(Use "✓" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

(For office coding: Total Score T____ = ____ + ____ + ____)

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from Pfizer Inc. No permission required to reproduce, translate, display or distribute.

GAD-7_en_US_v1.0_15 Jul 2019 Page 1 of 1

11.5 CGI-I

Clinical Global Impressions Scale - Improvement (CGI-I) for Depression

Compared to the patient's symptoms of depression at the time of admission to the study, how much have their symptoms changed? Rate total change whether or not, in your judgement, it is entirely due to treatment.

- ☐ 1. Very much improved
- ☐ 2. Much improved
- ☐ 3. Minimally improved
- ☐ 4. No change
- ☐ 5. Minimally worse
- ☐ 6. Much worse
- ☐ 7. Very much worse

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

CGI-I Depression_en_US_v1.0_02 Dec 2020 Page 1 of 1

11.6 SDS

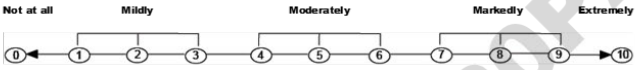
SHEEHAN DISABILITY SCALE - Depression

A BRIEF, PATIENT RATED, MEASURE OF DISABILITY AND IMPAIRMENT

Please mark ONE circle for each scale.

WORK* / SCHOOL

The symptoms of your depression have disrupted your work / school work:

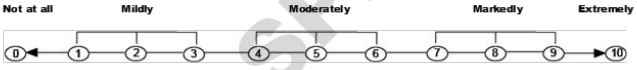


☐ I have not worked /studied at all during the past week **for reasons unrelated to depression.**

* Work includes paid, unpaid volunteer work or training. If your symptoms interfered with your ability to find or hold a job or contributed in any way to your currently not working, you must give a score on this scale.

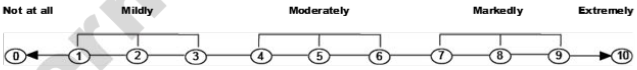
SOCIAL LIFE

The symptoms of your depression have disrupted your social life / leisure activities:



FAMILY LIFE / HOME RESPONSIBILITIES

The symptoms of your depression have disrupted your family life / home responsibilities:



DAYS LOST

How many days in the last week did the symptoms of your depression cause you to miss school or work or leave you unable to carry out your normal daily responsibilities? _____

DAYS UNDERPRODUCTIVE

How many days in the last week did you feel so impaired by the symptoms of your depression, that even though you went to school or work or had other daily responsibilities, your productivity was reduced? _____

11.7 CPFQ

MASSACHUSETTS GENERAL HOSPITAL COGNITIVE AND PHYSICAL FUNCTIONING QUESTIONNAIRE

Please answer all questions by circling the correct answer or the answer which seems the most appropriate to you (consider "normal" the time in your life prior to the past month when you were most satisfied with your cognitive and physical functioning.

a) How has your motivation/interest/enthusiasm been over the past month?

1	2	3	4	5	6
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

b) How has your wakefulness/alertness been over the past month?

1	2	3	4	5	6
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

c) How has your energy been over the past month?

1	2	3	4	5	6
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

d) How has your ability to focus/sustain attention been over the past month?

1	2	3	4	5	6
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

e) How has your ability to remember/recall information been over the past month?

1	2	3	4	5	6
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

f) How has your ability to find words been over the past month?

1	2	3	4	5	6
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

g) How has your sharpness/mental acuity been over the past month?

1	2	3	4	5	6
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

11.8 PHQ-9

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING 0 + _____ + _____ + _____

=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from

11.9 CSFQ

Male

CHANGES IN SEXUAL FUNCTIONING QUESTIONNAIRE (CSFQ-M-C)

NOTE: This is a questionnaire about sexual activity and sexual function. By sexual activity, we mean sexual intercourse, masturbation, sexual fantasies and other activity.

1. Compared with the most enjoyable it has ever been, how enjoyable or pleasurable is your sexual life right now?
☐ 1-No enjoyment or pleasure
☐ 2-Little enjoyment or pleasure
☐ 3-Some enjoyment or pleasure
☐ 4-Much enjoyment or pleasure
☐ 5-Great enjoyment or pleasure

2. How frequently do you engage in sexual activity (sexual intercourse, masturbation, etc.) now?
☐ 1-Never
☐ 2-Rarely (once a month or less)
☐ 3-Sometimes (more than once a month, up to twice a week)
☐ 4-Often (more than twice a week)
☐ 5-Every day

3. How often do you desire to engage in sexual activity?
☐ 1-Never
☐ 2-Rarely (once a month or less)
☐ 3-Sometimes (more than once a month, up to twice a week)
☐ 4-Often (more than twice a week)
☐ 5-Every day

4. How frequently do you engage in sexual thoughts (thinking about sex, sexual fantasies) now?
☐ 1-Never
☐ 2-Rarely (once a month or less)
☐ 3-Sometimes (more than once a month, up to twice a week)
☐ 4-Often (more than twice a week)
☐ 5-Every day

5. Do you enjoy books, movies, music or artwork with sexual content?
☐ 1-Never
☐ 2-Rarely (once a month or less)
☐ 3-Sometimes (more than once a month, up to twice a week)
☐ 4-Often (more than twice a week)
☐ 5-Every day

6. How much pleasure or enjoyment do you get from thinking about and fantasizing about sex?
☐ 1-No enjoyment or pleasure
☐ 2-Little enjoyment or pleasure
☐ 3-Some enjoyment or pleasure
☐ 4-Much enjoyment or pleasure
☐ 5-Great enjoyment or pleasure

7. How often do you have an erection related or unrelated to sexual activity?
☐ 1-Never
☐ 2-Rarely (once a month or less)
☐ 3-Sometimes (more than once a month, up to twice a week)
☐ 4-Often (more than twice a week)
☐ 5-Every day

8. Do you get an erection easily?
☐ 1-Never
☐ 2-Rarely (much less than half the time)
☐ 3-Sometimes (about half the time)
☐ 4-Often (much more than half the time)
☐ 5-Always

9. Are you able to maintain an erection?
☐ 1-Never
☐ 2-Rarely (much less than half the time)
☐ 3-Sometimes (about half the time)
☐ 4-Often (much more than half the time)
☐ 5-Always

10. How often do you experience painful, prolonged erections?
☐ 5-Never
☐ 4-Rarely (once a month or less)
☐ 3-Sometimes (more than once a month, up to twice a week)
☐ 2-Often (more than twice a week)
☐ 1-Every day

11. How often do you have an ejaculation?
☐ 1-Never
☐ 2-Rarely (once a month or less)
☐ 3-Sometimes (more than once a month, up to twice a week)
☐ 4-Often (more than twice a week)
☐ 5-Every day

12. Are you able to ejaculate when you want to?
☐ 1-Never
☐ 2-Rarely (much less than half the time)
☐ 3-Sometimes (about half the time)
☐ 4-Often (much more than half the time)
☐ 5-Always

13. How much pleasure or enjoyment do you get from your orgasms?
☐ 1-No enjoyment or pleasure
☐ 2-Little enjoyment or pleasure
☐ 3-Some enjoyment or pleasure
☐ 4-Much enjoyment or pleasure
☐ 5-Great enjoyment or pleasure

14. How often do you have painful orgasm?
☐ 5-Never
☐ 4-Rarely (once a month or less)
☐ 3-Sometimes (more than once a month, up to twice a week)
☐ 2-Often (more than twice a week)
☐ 1-Every day

____= Pleasure (Item 1)
____= Desire/Frequency (Item 2 + Item 3)
____= Desire/Interest (Item 4 + Item 5 + Item 6)
____= Arousal/Erection (Item 7 + Item 8 + Item 9)
____= Orgasm/Ejaculation (Item 11 + Item 12 + Item 13)
____= **Total CSFQ Score** (Items 1 to 14)

Female

CHANGES IN SEXUAL FUNCTIONING QUESTIONNAIRE (CSFQ-F-C)

NOTE: This is a questionnaire about sexual activity and sexual function. By sexual activity, we mean sexual intercourse, masturbation, sexual fantasies and other activity.

1. Compared with the most enjoyable it has ever been, how enjoyable or pleasurable is your sexual life right now?
☐ 1-No enjoyment or pleasure
☐ 2-Little enjoyment or pleasure
☐ 3-Some enjoyment or pleasure
☐ 4-Much enjoyment or pleasure
☐ 5-Great enjoyment or pleasure

2. How frequently do you engage in sexual activity (sexual intercourse, masturbation, etc.) now?
☐ 1-Never
☐ 2-Rarely (once a month or less)
☐ 3-Sometimes (more than once a month, up to twice a week)
☐ 4-Often (more than twice a week)
☐ 5-Every day

3. How often do you desire to engage in sexual activity?
☐ 1-Never
☐ 2-Rarely (once a month or less)
☐ 3-Sometimes (more than once a month, up to twice a week)
☐ 4-Often (more than twice a week)
☐ 5-Every day

4. How frequently do you engage in sexual thoughts (thinking about sex, sexual fantasies) now?
☐ 1-Never
☐ 2-Rarely (once a month or less)
☐ 3-Sometimes (more than once a month, up to twice a week)
☐ 4-Often (more than twice a week)
☐ 5-Every day

5. Do you enjoy books, movies, music or artwork with sexual content?
☐ 1-Never
☐ 2-Rarely (once a month or less)
☐ 3-Sometimes (more than once a month, up to twice a week)
☐ 4-Often (more than twice a week)
☐ 5-Every day

6. How much pleasure or enjoyment do you get from thinking about and fantasizing about sex?
☐ 1-No enjoyment or pleasure
☐ 2-Little enjoyment or pleasure
☐ 3-Some enjoyment or pleasure
☐ 4-Much enjoyment or pleasure
☐ 5-Great enjoyment or pleasure

7. How often do you become sexually aroused?
☐ 1-Never
☐ 2-Rarely (once a month or less)
☐ 3-Sometimes (more than once a month, up to twice a week)
☐ 4-Often (more than twice a week)
☐ 5-Every day

8. Are you easily aroused?
☐ 1-Never
☐ 2-Rarely (much less than half the time)
☐ 3-Sometimes (about half the time)
☐ 4-Often (much more than half the time)
☐ 5-Always

9. Do you have adequate vaginal lubrication during sexual activity?
☐ 1-Never
☐ 2-Rarely (much less than half the time)
☐ 3-Sometimes (about half the time)
☐ 4-Often (much more than half the time)
☐ 5-Always

10. How often do you become aroused and then lose interest?
☐ 5-Never
☐ 4-Rarely (much less than half the time)
☐ 3-Sometimes (about half the time)
☐ 2-Often (much more than half the time)
☐ 1-Always

11. How often do you experience an orgasm?
☐ 1-Never
☐ 2-Rarely (much less than half the time)
☐ 3-Sometimes (about half the time)
☐ 4-Often (much more than half the time)
☐ 5-Always

12. Are you able to have an orgasm when you want to?
☐ 1-Never
☐ 2-Rarely (much less than half the time)
☐ 3-Sometimes (about half the time)
☐ 4-Often (much more than half the time)
☐ 5-Always

13. How much pleasure or enjoyment do you get from your orgasms?
☐ 1-No enjoyment or pleasure
☐ 2-Little enjoyment or pleasure
☐ 3-Some enjoyment or pleasure
☐ 4-Much enjoyment or pleasure
☐ 5-Great enjoyment or pleasure

14. How often do you have painful orgasm?
☐ 5-Never
☐ 4-Rarely (once a month or less)
☐ 3-Sometimes (more than once a month, up to twice a week)
☐ 2-Often (more than twice a week)
☐ 1-Every day

____= Pleasure (Item 1)
____= Desire/Frequency (Item 2 + Item 3)
____= Desire/Interest (Item 4 + Item 5 + Item 6)
____= Arousal/Excitement (Item 7 + Item 8 + Item 9)
____= Orgasm/Completion (Item 11 + Item 12 + Item 13)
____= **Total CSFQ Score** (Items 1 to 14)

11.10 CADSS

The Clinician Administered Dissociative States Scale (CADSS)

Subjective Items:

1. Do things seem to be moving in slow motion?
   - 0= Not at all.
   - 1= Mild, things seem slightly slowed down, but not very noticeable.
   - 2= Moderate, things are moving about twice as slow as normally.
   - 3= Severe, things are moving so slowly that they are barely moving.
   - 4= Extreme, things are moving so slowly, I have the perception that everything has come to a stop, as if time is standing still.
2. Do things seem to be unreal to you, as if you are in a dream?
   - 0= Not at all.
   - 1= Mild, things seem a little unreal, but I'm well aware of where I'm at.
   - 2= Moderate, things seem dreamlike, although I know I am awake.
   - 3= Severe, things seem very dreamlike, although I know that I am here, I have the feeling like I might be asleep.
   - 4= Extreme, I feel like nothing is real, like I should pinch myself to wake up, or ask someone if this is a dream.
3. Do you have some experience that separates you from what is happening; for instance, do you feel as if you are in a movie or a play, or as if you are a robot?
   - 0= Not at all.
   - 1= Mild, I feel a little bit separated from what is happening, but I am basically here.
   - 2= Moderate, I feel somewhat separated from what is going on, or I feel as if I am in a movie or a play.
   - 3= Severe, I feel extremely separated from what is happening, but I can understand what people are saying.
   - 4= Extreme, I feel as if everyone around me is talking a foreign language, so that I cannot understand what they are saying, or I feel as if I am on the outside looking in, or like I am a robot or a machine.
4. Do you feel as if you are looking at things from outside of your body?
   - 0= Not at all.
   - 1= Mild, I feel somewhat disconnected from myself, but I am basically all together.
   - 2= Moderate, I feel like I am just outside of my body, but not looking down upon myself from far above.
   - 3= Severe, I feel like I am twenty feet or more away from my body, looking down from above.
   - 4= Extreme, I feel as if I am hundreds of feet above myself, looking down at myself and everyone else here.
5. Do you feel as if you are watching the situation as an observer or a spectator?
   - 0= Not at all.
   - 1= Mild, I feel slightly detached from what is going on, but I am basically here.
   - 2= Moderate, I feel somewhat removed as an observer or a spectator, but I am definitely in this room.
   - 3= Severe, I feel very much as if I am an observer or a spectator, but I am still here in

this room.¶
4= · · · Extreme, I feel completely removed from what is happening, as if I am not a part of this experience in any way, but totally removed from what is happening, as an observer or a spectator.¶

6. → Do you feel disconnected from your own body?
0= · · Not at all.¶
1= · · · Mild, I feel a little bit disconnected from myself, but I am basically all here.
2= · · · Moderate, I feel somewhat detached from my own body, but I am basically all¶ together.¶
3= → Severe, I feel detached from my own body, but not far removed from my body, and I feel as if it is me there.¶
4= → Extreme, I feel like I am completely out of my body, as if I am looking at my own body from a long way off, as if there is another person there.¶

7. → Does your sense of your own body feel changed: for instance, does your own body feel unusually large or unusually small?¶
0= → Not at all.¶
1= → Mild, I have a vague feeling that something about my body has changed, but I can't say exactly what it is.¶
2= → Moderate, I feel like my body has increased or decreased in size slightly, or that it feels somewhat as if it is not my body.¶
3= → Severe, I feel as if my body has increased to twice its normal size, or decreased to twice its normal size, or I very much feel as if this is not my body.¶
4= → Extreme, I feel as if my body has swelled up to at least ten times its normal size, or as if it is ten times as small, or as if my arms have become like toothpicks.¶

8. → Do people seem motionless, dead, or mechanical?
0= → Not at all.¶
1= → Mild, people seem a little bit more motionless, dead, or mechanical than would be normal.¶
2= → Moderate, people seem to be at least twice as motionless or mechanical than would be normal.¶
3= → Severe, people seem to be barely moving, or barely alive, or very mechanical.
4= → Extreme, it's as if everyone were frozen or completely like machines.¶

9. → Do objects look different than you would expect?
0= → Not at all.¶
1= → Mild, things seem slightly different than normal, although it is barely perceptible.
2= → Moderate, things are somewhat distorted, but I have no problems recognizing¶ things around me.¶
3= → Severe, things are much more distorted or unreal than normal, but I am able to recognize things in the room.¶
4= → Extreme, like everything is distorted, not real, I feel like I cannot recognize anything, everything is alien or strange.¶

10. → Do colors seem to be diminished in intensity?
0= → Not at all.¶
1= → Mild, things seem slightly paler than usual if I think about it.¶
2= → Moderate, colors are somewhat diminished, but still recognizable.¶
3= → Severe, colors are extremely pale, in no way as vivid as they usually are.¶

4= Extreme, as if everything is in black and white, or all the colors have been washed out.

11. Do you see things as if you were in a tunnel, or looking through a wide angle photographic lens?
    - 0= Not at all.
    - 1= Mild, I feel a little bit like I am looking through a tunnel, or a wide angle lens.
    - 2= Moderate, the periphery of my vision is blacked out, but I still have most of my visual field, or things are somewhat like a wide angle lens.
    - 3= Severe, it seems as if I'm looking through a tunnel, or through a wide angle lens, but I can see everything clearly.
    - 4= Extreme, as if I'm looking through a pair of binoculars backwards, where everything around the periphery is blacked out, and I can see a little point of light at the end of a tunnel, with little tiny people and objects, or I am seeing things as if through a wide lens and things are incredibly expanded.
12. Does this interview [assessment, questionnaire] seem to be taking much longer than you would have expected?
    - 0= Not at all.
    - 1= Mild, it seems as if this interview has gone on for at least twice as long as the true elapsed time.
    - 2= Moderate, it seems as if this interview has gone on for at least two hours.
    - 3= Severe, it seems as if at least ten hours have gone on since the start of the interview.
    - 4= Extreme, it seems as if time is standing still, so that we have been here at this point in time forever.
13. Do things seem to be happening very quickly, as if there is a lifetime in a moment?
    - 0= Not at all.
    - 1= Mild, things are happening slightly faster than normal.
    - 2= Moderate, things seem to be happening at least twice as fast as normal.
    - 3= Severe, things seem to be happening at least 10 times faster than normal.
    - 4= Extreme, as if this whole experience has happened at once, or as if there is a lifetime in a moment.
14. Have there been things which have happened during this interview [assessment] that now you can't account for?
    - 0= Not at all.
    - 1= Mild, there may have been things which happened which now I can't account for, but nothing pronounced.
    - 2= Moderate, at least once there were things which happened which now I can't account for.
    - 3= Severe, at least twice I have lost several minutes of time, so that now there are things I cannot account for.
    - 4= Extreme, large pieces of time are missing, of ten minutes or more, so that I am confused about what has happened.
15. Have you spaced out, or in some other way lost track of what was going on during this experience?
    - 0= Not at all.
    - 1= Mild, I have had some episodes of losing track of what is going on, but I have

followed everything for the most part.
2= Moderate, I have lost at least a minute of time, or have completely lost track of what is going on now.
3= Severe, I have lost several segments of time of one minute or more.
4= Extreme, I have lost large segments of time of at least 15 minutes or more.

16. Have sounds almost disappeared or become much stronger than you would have expected?
0= Not at all.
1= Mild, things are either a little quieter than normal, or a little louder than normal, but it is not very noticeable.
2= Moderate, things have become about twice as soft as normal, or twice as loud as normal.
3= Severe, things have become very quiet, as if everyone is whispering, or things have become very loud (although not deafening).
4= Extreme, things have become completely silent, or sounds are so loud that it is deafening, and I feel as if I am going to break my eardrums.

17. Do things seem very real, as if there is a special sense of clarity?
0= Not at all.
1= Mild, things seem to be a little bit more real than normal.
2= Moderate, things seem to be more real than normal.
3= Severe, things seem to be very real or have a special sense of clarity.
4= Extreme, things seem to have an incredible sense of realness or clarity.

18. Does it seem as if you are looking at the world through a fog, so that people and objects appear far away or unclear?
0= Not at all.
1= Mild, things seem somewhat foggy and unclear, or I do have the feeling that things are far away, but there is not a major effect on how I perceive things around me.
2= Moderate, things seem very foggy and unclear, or things seem like they are far away, but I can identify the interviewer and objects in the room easily.
3= Severe, I can barely see things around me, such as the interviewer and the objects in the room.
4= Extreme, I cannot make anything out around me.

19. Do colors seem much brighter than you would have expected?
0= Not at all.
1= Mild, colors seem a little bit brighter than normal, but not more than twice as bright.
2= Moderate, colors seem brighter, about twice as bright as normal.
3= Severe, colors seem very bright, at least five times as bright as normal.
4= Extreme, colors seem extremely bright, almost fluorescent, at least 10 times as bright as normal.

20. Do you feel confused about who you really are?
0= Not at all.
1= Mild, I feel a little bit confused about who I am.
2= Moderate, I feel confused about who I am, but I basically know who I am.
3= Severe, I feel very confused about who I am, and at times I wonder if I am a

person, or if I am many people.
4= Extreme, I feel as if there were two or more sides to myself.

21. Do you feel like there are different parts of yourself which do not fit together?
0= Not at all.
1= Mild, I feel like there are different sides of myself, but they're basically part of myself.
2= Moderate, I feel like I have different parts which don't quite fit together.
3= Severe, there are two or more sides to myself which have unique characteristics.
4= Extreme, I have two or more parts to myself with unique personality characteristics.

22. Do you have gaps in your memory?
0= Not at all.
1= Mild, there are some recent things which I cannot remember.
2= Moderate, there have been a few gaps in my memory which lasted a few minutes.
3= Severe, there have been large gaps in my memory which lasted for more than a few minutes.
4= Extreme, I cannot piece together what is happening from one moment to the next due to large gaps in my memory.

23. Do you feel like you have more than one identity?
0= Not at all.
1= Mild, I feel like there is more to me than my personality, but it's basically part of my identity.
2= Moderate, I feel like I have more than one personality, but the personalities are not really distinct.
3= Severe, I have two or more personalities, although they are not fully developed as distinct entities.
4= Extreme, I have two or more personalities which are distinct and have their own names and other unique characteristics.

11.11 BPRS+

Brief Psychiatric Rating Scale

Suspiciousness: Mistrust, belief others have malicious or discriminatory intent whether they concern past or present circumstances. Rely on verbal report and observations of suspicious behavior. Do not rely only on physical signs, although these may influence ratings.

Basis for rating: thought content expressed in the interview and its influence on behavior as reported by primary care workers or family.

Rating	Criteria
0 Not able to be assessed	Not able to be assessed
1 Not present	Not present
2 Very mild	Rare instances of mistrustfulness which may or may not be warranted by the situation; may seem on guard or describe harm to self that sounds plausible.
3 Mild	Occasional instances of suspiciousness that are definitely not warranted by the situation; may seem more guarded.
4 Moderate	More frequent suspiciousness, or transient ideas of reference; may express mistrust or refer to intention of others to cause harm; may often withdraw from approach by others.
5 Moderately severe	Subject shows pervasive suspiciousness, frequent ideas of reference, or ideas of delusional intensity; may expect harm.
6 Severe	Definite delusion(s) of reference or persecution that is (are) not wholly pervasive (e.g., an encapsulated delusion).
7 Extremely severe	As above, but more widespread, frequent, or intense.

Unusual Thought Content: Unusual, odd, strange, bizarre thought content. Rate the degree of unusualness, not the degree of disorganization of speech. In ratings, you may consider degree of conviction and its effect on actions.

Basis for rating: thought content expressed during the course of interview.
In the past seven days, did you feel like anything unusual was going on or that anything unusual was about to happen? Was anything unusual going on in your head?

Rating	Criteria
0 Not able to be assessed	Not able to be assessed
1 Not present Not reported.	Not present Not reported.
2 Very mild	Unusual thoughts, odd ideas.
3 Mild	At times, subject questions his or her belief(s) (partial delusion), or may often express odd or strange ideas with little basis in reality.
4 Moderate	Full delusional conviction, but delusion(s) may have little or no influence on behavior, or may express very odd ideas with no basis in reality.
5 Moderately severe	Subject expresses full delusional conviction, but delusion(s) may have only occasional impact on behavior.
6 Severe	Delusion(s) may have significant effect, such as neglect of responsibilities because preoccupation with belief that he/she is God; or may express bizarre beliefs or ideas.
7 Extremely severe	Delusion(s) with major impact, such as stopped eating because believes food is poisoned.

Hallucinations: Perceptions (in any sensory modality) without normal external stimulus or correspondence.
Basis for rating: verbal report and physical manifestations during the course of interview as well as reports of behavior by primary care workers or family.

In the past seven days, have you had any unusual experiences like seeing visions or hearing voices? How often did it happen? When did it happen last?

Rating	Criteria
0 Not able to be assessed	Not able to be assessed
1 Not present Not evident.	Not present Not evident.
2 Very mild	May experience unusual percepts but knows it isn't real.
3 Mild	Suspected hallucinations, or may show behavior which suggests he/she is hallucinating.
4 Moderate	Definite, may be short-lived with limited effect on behavior.
5 Moderately severe	May be persistent and/or have consistent effect on behavior, such as talking to or about voices.
6 Severe	May be pervasive and/or consistently impair functioning.
7 Extremely severe	Pervasive or severely disruptive hallucinations.

Conceptual Disorganization: Logical thought processes confused, disconnected, disorganized, disrupted.

Basis for rating: cognitive-verbal process observed during the course of interview.

Include any type of formal thought disorder (e.g., loose associations, incoherence, flight of ideas, neologisms). DO NOT include mere circumstantially or pressured speech, even if marked. DO NOT rate on the basis of subject's subjective impressions (e.g., "my thoughts are racing", "I can't hold a thought", "my thinking gets mixed up"). DO NOT rate on basis of presumed pathogenesis, e.g., aphasia.

Rating	Criteria
0 Not able to be assessed	Not able to be assessed
1 Not present	Not present.
2 Very mild	Somewhat vague, but of doubtful clinical significance.
3 Mild	Frequently vague, but the interview is able to progress smoothly; occasional loosening of associations; rambling; speech a bit hard to make sense of.
4 Moderate	Occasional irrelevant statements, infrequent use of neologisms, or moderate loosening of associations.
5 Moderately severe	As above, but more severe; blocking may interrupt conversation.
6 Severe	Formal thought disorder is present most of the time.
7 Extremely severe	Thoughts are usually incoherent.

Overall J E & Gorham D R. The brief psychiatric rating scale. Psychol. Rep. 10:799-812, 1962.

11.12 C-SSRS

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

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

Disclaimer:

This scale is intended 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 Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

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 6 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 6 Months - ***Most Severe Ideation:*** ____ ***Type # (1-5)*** ____ ***Description of Ideation***	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

C-SSRS—Baseline/Screening (Version 1/14/09)

C-SSRS B/S (6mo)_en_US_v1.0_11 Feb 2019

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past 6 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_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

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

 C-SSRS—Baseline/Screening (Version 1/14/09)

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11.13 C-SSRS Since Last Visit

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

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

Disclaimer:

This scale is intended 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 Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it".* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

 C-SSRS—Since Last Visit (Version 1/14/09)

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 ☐
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* _____

C-SSRS—Since Last Visit (Version 1/14/09)

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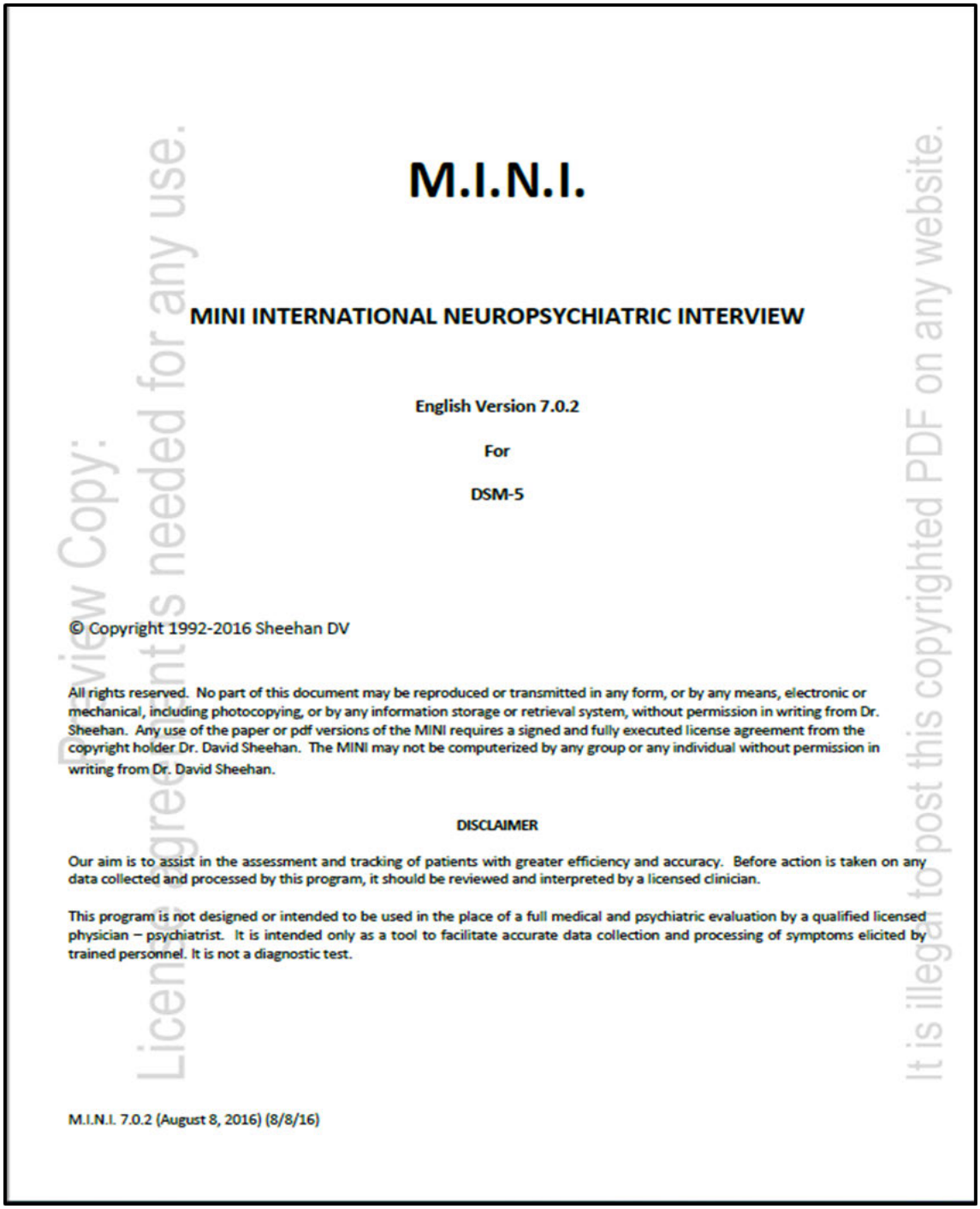
11.14 Mini-International Neuropsychiatric Interview (MINI)



M.I.N.I.

MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW

English Version 7.0.2

For

DSM-5

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. It is not a diagnostic test.

M.I.N.I. 7.0.2 (August 8, 2016) (8/8/16)

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

	MODULES	TIME FRAME	MEETS CRITERIA	ICD-10-CM	PRIMARY DIAGNOSIS
A	MAJOR DEPRESSIVE EPISODE	Current (2 Weeks)	☐		
		Past	☐		
		Recurrent	☐		
	MAJOR DEPRESSIVE DISORDER	Current (2 Weeks)	☐	F32.x	☐
		Past	☐	F32.x	☐
		Recurrent	☐	F33.x	☐
B	SUICIDALITY	Current (Past Month)	☐		☐
		Lifetime attempt	☐	☐ Low ☐ Moderate ☐ High	☐
	SUICIDE BEHAVIOR DISORDER	Current	☐	(In Past Year)	☐
		In early remission	☐	(1 - 2 Years Ago)	☐
C	MANIC EPISODE	Current	☐		
		Past	☐		
	HYPOMANIC EPISODE	Current	☐		
		Past	☐	☐ Not Explored	
	BIPOLAR I DISORDER	Current	☐	F31.0 - F31.76	☐
		Past	☐	F31.0 - F31.76	☐
	BIPOLAR II DISORDER	Current	☐	F31.81	☐
		Past	☐	F31.81	☐
	OTHER SPECIFIED BIPOLAR AND RELATED DISORDER	Current	☐	F31.89	☐
		Past	☐	F31.89	☐
D	PANIC DISORDER	Current (Past Month)	☐	F41.0/F40.01	☐
		Lifetime	☐	F41.0/F40.01	☐
E	AGORAPHOBIA	Current	☐	F40.00/F40.01/F40.02	☐
F	SOCIAL ANXIETY DISORDER (Social Phobia)	Current (Past Month)	☐	F40.10/F40.11	☐
G	OBSESSIVE-COMPULSIVE DISORDER	Current (Past Month)	☐	F42.2	☐
H	POSTTRAUMATIC STRESS DISORDER	Current (Past Month)	☐	F43.10	☐
I	ALCOHOL USE DISORDER	Past 12 Months	☐	F10.10 - F10.21	☐
J	SUBSTANCE USE DISORDER (Non-alcohol)	Past 12 Months	☐	F11.10 - F19.21	☐
K	ANY PSYCHOTIC DISORDER	Current	☐	F20.81-F29	☐
		Lifetime	☐	F20.81-F29	☐
	MAJOR DEPRESSIVE DISORDER WITH PSYCHOTIC FEATURES	Current	☐	F32.3/F33.3	☐
		Past	☐	F32.3/F33.3	☐
	BIPOLAR I DISORDER WITH PSYCHOTIC FEATURES	Current	☐	F31.2/F31.5/F31.64	☐
		Past	☐	F31.2/F31.5/F31.64	☐

M.I.N.I. 7.0.2 (August 8, 2016) (8/8/16) 2

L	ANOREXIA NERVOSA	Current (Past 3 Months)	☐	F50.01/F50.02	☐
M	BULIMIA NERVOSA	Current (Past 3 Months)	☐	F50.2	☐
MB	BINGE-EATING DISORDER	Current (Past 3 Months)	☐	F50.81	☐
N	GENERALIZED ANXIETY DISORDER	Current (Past 6 Months)	☐	F41.1	☐
O	MEDICAL, ORGANIC, DRUG CAUSE RULED OUT			☐ No ☐ Yes ☐ Uncertain	
P	ANTISOCIAL PERSONALITY DISORDER	Lifetime	☐	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?)

GENERAL INSTRUCTIONS

The M.I.N.I. was designed as a brief structured interview for the major psychiatric disorders in DSM-5 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. Clinicians can use it, 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 or diagnoses 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, questions J2b or K6b).

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. has questions that investigate these issues.

For licensing, permissions, training or questions, contact David V Sheehan, M.D., M.B.A., D.L.F.A.P.A.:
Email: davidvsheehan@gmail.com
phone: +1 813-956-8437

A. MAJOR DEPRESSIVE EPISODE

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

A1	a	Were you ever depressed or down, or did you feel sad, empty or hopeless, 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, or did you feel sad, empty or hopeless, 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

			Past 2 Weeks		Past Episode	
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:				
	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? Did anyone notice this?	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. LOOK FOR DELUSIONS OF FAILURE, OF INADEQUACY, OF RUIN OR OF GUILT, OR OF NEEDING PUNISHMENT OR DELUSIONS OF DISEASE OR DEATH OR NIHILISTIC OR SOMATIC DELUSIONS. THE EXAMPLES ARE CONSISTENT WITH A DELUSIONAL IDEA. Current Episode ☐ No ☐ Yes Past Episode ☐ No ☐ Yes				
	f	Did you have difficulty concentrating, thinking or making decisions almost every day?	NO	YES	NO	YES
	g	Did you repeatedly think about death (FEAR OF DYING DOES NOT COUNT HERE), or have any thoughts of killing yourself, or have any intent or plan to kill yourself? Did you attempt suicide? IF YES TO EITHER, CODE YES.	NO	YES	NO	YES
A4		Did these symptoms cause significant distress or problems at home, at work, at school, socially, in your relationships, or in some other important way, and are they a change from your previous functioning?	NO	YES	NO	YES

M.I.N.I. 7.0.2 (August 8, 2016) (8/8/16) 5

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? N/A NO YES

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

AND

IS "RULE OUT ORGANIC CAUSE (O2 SUMMARY)" CODED YES?

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

	In the past month did you:			Points
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 by not avoiding a risk or by causing the accident on purpose? 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	Think (even momentarily) that you would be better off dead or wish you were dead or needed to be dead?	NO	YES	1
B3	Think (even momentarily) about harming or of hurting or of injuring yourself - with at least some intent or awareness that you might die as a result - or think about suicide (i.e. about killing yourself)? IF NO TO **B2 + B3**, SKIP TO **B4**. OTHERWISE ASK:	NO	YES	6

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

B4	Hear a voice or voices telling you to kill yourself or have a dream with any suicidal content? IF YES, mark either or both: ☐ was it a voice or voices? ☐ was it a dream?	NO	YES	4
B5	Have a suicide method in mind (i.e. how)?	NO	YES	8
B6	Have a suicide means in mind (i.e. with what)?	NO	YES	8
B7	Have any place in mind to attempt suicide (i.e. where)?	NO	YES	8
B8	Have any date/timeframe in mind to attempt suicide (i.e. when)?	NO	YES	8
B9	Think about any task you would like to complete before trying to kill yourself? (e.g. writing a suicide note)	NO	YES	8
B10	Intend to act on thoughts of killing yourself? IF YES, mark either or both: ☐ did you intend to act at the time? ☐ did you intend to act at some time in the future?	NO	YES	8
B11	Intend to die as a result of a suicidal act? IF YES, mark either or both: ☐ did you intend to die by suicide at the time? ☐ did you intend to die by suicide at some time in the future?	NO	YES	8
B12	Feel the need or impulse to kill yourself or to plan to kill yourself sooner rather than later? IF YES, mark either or both: ☐ was this to kill yourself? ☐ was this to plan to kill yourself? IF YES, mark either or both: ☐ was this largely unprovoked? ☐ was this provoked? IN ASSESSING WHETHER THIS WAS LARGELY UNPROVOKED ASK: "5 minutes before this impulse, could you have predicted it would occur at that time?" IF NO TO **B12**, SKIP TO **B14**.	NO	YES	8
B13	Have difficulty resisting these impulses?	NO	YES	8

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B14	Take any active steps to prepare for a suicide attempt in which you expected or intended to die (include anything done or purposely not done that put you closer to making a suicide attempt)? This includes times when you were going to kill yourself, but were interrupted or stopped yourself, before harming yourself. IF NO TO **B14**, SKIP TO **B15**.	NO	YES	
B14a	Take active steps to prepare to kill yourself, but you **did not start** the suicide attempt?	NO	YES	9
B14b	Take active steps to prepare to kill yourself, but then **you stopped yourself just before** harming yourself ("aborted")?	NO	YES	10
B14c	Take active steps to prepare to kill yourself, but then **someone or something stopped you just before** harming yourself ("interrupted")?	NO	YES	11
B15	Injure yourself on purpose without intending to kill yourself? (B15 IS NOT COUNTED AS SUICIDAL BEHAVIOR)	NO	YES	0
B16	Attempt suicide (to kill yourself)? IF NO TO **B16**, SKIP TO **B17**.	NO	YES	
B16a	Start a suicide attempt (to kill yourself), but then **you decided to stop** and did not finish the attempt?	NO	YES	12
B16b	Start a suicide attempt (to kill yourself), but then **you were interrupted** and did not finish the attempt?	NO	YES	13
B16c	Go through with a suicide attempt (to kill yourself), **completely** as you meant to? A suicide attempt means you did something where you could possibly be injured, with at least a slight intent to die. IF NO TO **B16c**, SKIP TO **B17**: Hope to be rescued / survive ☐ Expected / intended to die ☐	NO	YES	14

B17 **TIME SPENT PER DAY WITH ANY SUICIDAL IMPULSES, THOUGHTS OR ACTIONS:**
Usual time spent per day: ____ hours ____ minutes.
Least amount of time spent in any day: ____ hours ____ minutes.
Most amount of time spent in any day: ____ hours ____ minutes.

In your lifetime:

B18	Did you ever make a suicide attempt (try to kill yourself)? If **YES**, how many times? _____ If **YES**, when was the last suicide attempt? Current: within the past 12 months ☐ In early remission: between 12 and 24 months ago ☐ In remission: more than 24 months ago ☐	NO	YES	4

"A suicide attempt is any self-injurious behavior, with at least some intent (> 0) to die as a result of the act. Evidence that the individual intended to kill him-or herself, at least to some degree, can be explicit or inferred from the behavior or circumstance. For example, it is defined as a suicide attempt if it is clearly not an accident or if the individual thinks the act could be lethal, even though denying intent." (FDA Guidance for Industry Suicidal Ideation and Behavior Document 2012 and C-CASA definition). Posner K et al. Am J Psychiatry 2007; 164 (7): 1035-1043 &
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm/

B19	How likely are you to try to kill yourself within the next 3 months on a scale of 0-100% _____% ANY LIKELIHOOD > 0% ON **B19** SHOULD BE CODED YES	NO	YES	13

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IS AT LEAST **1** OF THE ABOVE (EXCEPT **B1** AND **B15**) CODED YES?

IF YES, ADD THE TOTAL POINTS FOR THE ANSWERS (**B1-B19**) CHECKED 'YES' AND SPECIFY THE SUICIDALITY SCORE CATEGORY AS INDICATED IN THE DIAGNOSTIC BOX:

INDICATE WHETHER THE SUICIDALITY IS CURRENT (PAST MONTH) OR A LIFETIME SUICIDE ATTEMPT OR BOTH BY MARKING THE APPROPRIATE BOXES OR BY LEAVING EITHER OR BOTH OF THEM UNMARKED.
CURRENT = ANY POSITIVE RESPONSE IN **B1a** THROUGH **B16c** (EXCEPT **B15**) OR ANY TIME SPENT IN **B17**.
LIFETIME ATTEMPT = **B18** CODED YES.
LIKELY IN THE NEAR FUTURE = **B19** CODED YES.

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

NO	YES
SUICIDALITY	
1-8 points Low	☐
9-16 points Moderate	☐
≥ 17 points High	☐
CURRENT	☐
LIFETIME ATTEMPT	☐
LIKELY IN NEAR FUTURE	☐

IS **B18** CODED YES?

AND A YES RESPONSE TO

WAS THE SUICIDAL ACT STARTED WHEN THE SUBJECT WAS NOT IN A STATE OF CONFUSION OR DELIRIUM?

AND A YES RESPONSE TO

WAS THE SUICIDAL ACT DONE WITHOUT A POLITICAL OR RELIGIOUS PURPOSE?
IF YES, SPECIFY WHETHER THE DISORDER IS CURRENT, IN EARLY REMISSION OR IN REMISSION.

NO	YES
SUICIDAL BEHAVIOR DISORDER	
Current	☐
In early remission	☐
In remission	☐

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' and so active or 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 or increased activity; 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 EPISODE FIRST AND THEN THE MOST SYMPTOMATIC PAST EPISODE, OTHERWISE
IF **C1b** AND **C2b** = NO: EXPLORE ONLY THE MOST SYMPTOMATIC PAST EPISODE

WHEN EXPLORING THE CURRENT EPISODE, PREFACE EACH QUESTION AS FOLLOWS:
Over the past few days including today, when you felt high and full of energy or irritable, did you:

WHEN EXPLORING THE PAST EPISODE, PREFACE EACH QUESTION AS FOLLOWS:
Over a period of a few days in the past, when you felt most high and most full of energy or most 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.	NO	YES	NO	YES
THE EXAMPLES ARE CONSISTENT WITH A DELUSIONAL IDEA. Current Episode ☐ No ☐ Yes Past Episode ☐ No ☐ Yes				
b Need less sleep (for example, feel rested after only a few hours sleep)?	NO	YES	NO	YES

		Current Episode		Past Episode	
c	Talk too much without stopping, or felt a pressure to keep talking?	NO	YES	NO	YES
d	Notice your thoughts going very fast or running together or racing or moving very quickly from one subject to another?	NO	YES	NO	YES
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? This increase in activity may be with or without a purpose.	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 INCLUDING **C3f** CODED YES?
IF **C1b** IS YES, ARE **3** OR MORE **C3** ANSWERS INCLUDING **C3f** CODED YES?

NV WHEN RATING PAST EPISODE:
IF **C1a** IS NO, ARE **4** OR MORE **C3** ANSWERS INCLUDING **C3f** CODED YES?
IF **C1a** IS YES, ARE **3** OR MORE **C3** ANSWERS INCLUDING **C3f** CODED YES?

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

RULE: ELATION/EXPANSIVENESS REQUIRES ONLY **3** OF THE **C3** SYMPTOMS, WHILE IRRITABLE MOOD ALONE REQUIRES **4** OF THE **C3** SYMPTOMS.

C4 What is the longest time these symptoms lasted (most of the day nearly every day)?
ASSESS THIS DURATION FROM THE VERY START TO THE VERY END OF SYMPTOMS, NOT JUST THE PEAK.

a)	3 consecutive days or less		☐		☐
b)	4, 5, or 6 consecutive days, or more		☐		☐
c)	7 consecutive 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, at school or in some other important way?	NO	YES	NO	YES
C7	Were these symptoms associated with a clear change in the way that you previously functioned and that was different from the way that you usually are?	NO	YES	NO	YES

ARE **C3** SUMMARY AND **C7** AND (**C4c** OR **C5** OR **C6** OR ANY PSYCHOTIC FEATURE IN **K1** THROUGH **K8**) CODED YES?

AND

IS "RULE OUT ORGANIC CAUSE (**O2** SUMMARY)" CODED YES?

SPECIFY IF THE EPISODE IS CURRENT AND / OR PAST.

NO	YES
MANIC EPISODE	
CURRENT	☐
PAST	☐

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IS **C3** SUMMARY CODED YES AND ARE **C5** AND **C6** CODED NO AND **C7** CODED YES,
AND IS EITHER **C4b** OR **C4c** CODED YES?
AND
IS "RULE OUT ORGANIC CAUSE (**O2** SUMMARY)" CODED YES?
AND
ARE ALL PSYCHOTIC FEATURES IN **K1** THROUGH **K8** 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?

NV

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

C8

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 4 days or more (**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: GO TO THE DIAGNOSTIC BOX, CIRCLE NO AND MOVE TO THE NEXT MODULE)

D1	a	Have you, on more than one occasion, had spells or attacks when you **suddenly** felt anxious, very 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 any significant change in your behavior because of the attacks (e.g., avoiding unfamiliar situations, or avoiding leaving your house or shopping alone, or doing things to avoid having a panic attack or visiting your doctor or the emergency room more frequently)?	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 or a smothering sensation?	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 feel faint?	NO	YES
	i	Did you have hot flushes or chills?	NO	YES
	j	Did you have tingling or numbness in parts of your body?	NO	YES
	k	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
	l	Did you fear that you were losing control or going crazy?	NO	YES
	m	Did you fear that you were dying?	NO	YES
D5		ARE BOTH **D3,** AND **4** OR MORE **D4** ANSWERS, CODED YES?	➡ NO	YES *PANIC DISORDER LIFETIME*
D6		In the past month 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*

IS EITHER **D5** OR **D6** CODED YES?

AND

IS "RULE OUT ORGANIC CAUSE (**O2** SUMMARY)" CODED YES?

SPECIFY IF THE EPISODE IS CURRENT AND / OR LIFETIME.

NO	YES
PANIC DISORDER	
LIFETIME	☐
CURRENT	☐

E. AGORAPHOBIA

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

E1	Do you feel anxious or uneasy in places or situations where help might not be available or escape might be difficult if you had a panic attack or panic-like or embarrassing symptoms, like: being in a crowd, or standing in a line (queue), being in an open space or when crossing a bridge, being in an enclosed space, when you are alone away from home, or alone at home, or traveling in a bus, train or car or using public transportation?	➡ NO	YES
	ARE **2** OR MORE OF THE ABOVE SITUATIONS IN **E1** CODED YES?	➡ NO	YES
E2	Do these situations almost always bring on fear or anxiety?	➡ NO	YES
E3	Do you fear these situations so much that you avoid them, or suffer through them, or need a companion to face them?	➡ NO	YES
E4	Is this fear or anxiety excessive or out of proportion to the real danger in the situation?	➡ NO	YES
E5	Did this avoidance, fear or anxiety persist for at least 6 months?	➡ NO	YES
E6	Did these symptoms cause significant distress or problems at home, at work, socially, at school or in some other important way?	➡ NO	YES

IS **E6** CODED YES?

NO	YES
AGORAPHOBIA CURRENT	

F. SOCIAL ANXIETY DISORDER (Social Phobia)

(➡ 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 or rejected? This includes things like speaking in public, eating in public or with others, writing while someone watches, performing in front of others or being in social situations.	➡ NO	YES

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,
- PERFORMING IN FRONT OF OTHERS,
- URINATING IN A PUBLIC WASHROOM, ETC.

F2	Do these social situations almost always bring on fear or anxiety?	➡ NO	YES
F3	Do you fear these social situations so much that you avoid them, or suffer through them, or need a companion to face them?	➡ NO	YES
F4	Is this social fear or anxiety excessive or unreasonable in these social situations?	➡ NO	YES
F5	Did this social avoidance, fear or anxiety persist for at least 6 months?	➡ NO	YES
F6	Did these social fears cause significant distress or interfere with your ability to function at work, at school or socially or in your relationships or in some other important way?	➡ NO	YES

IS **F6** CODED YES?

AND

IS "RULE OUT ORGANIC CAUSE (**O2** SUMMARY)" CODED YES?

NOTE TO CLINICIAN: PLEASE SPECIFY IF THE SUBJECT'S FEARS ARE RESTRICTED TO SPEAKING OR PERFORMING IN PUBLIC.

NO	YES

SOCIAL ANXIETY DISORDER
(Social Phobia)
CURRENT

RESTRICTED TO PERFORMANCE
SAD ONLY ☐

G. OBSESSIVE-COMPULSIVE DISORDER

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

G1a	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 religious obsessions.)	NO YES ↓ SKIP TO G3a
G1b	In the past month, did you try to suppress these thoughts, impulses, or images or to neutralize or to reduce them with some other thought or action? (DO NOT INCLUDE SIMPLY EXCESSIVE WORRIES ABOUT REAL LIFE PROBLEMS. DO NOT INCLUDE OBSESSIONS DIRECTLY RELATED TO HOARDING, HAIR PULLING, SKIN PICKING, BODY DYSMORPHIC DISORDER, 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 G3a
G2	Did they keep coming back into your mind even when you tried to ignore or get rid of them?	NO YES obsessions
G3a	In the past month, did you feel driven to do something repeatedly in response to an obsession or in response to a rigid rule, like washing or cleaning excessively, counting or checking things over and over, or repeating or arranging things, or other superstitious rituals?	NO YES ↓ SKIP TO G4
G3b	Are these rituals done to prevent or reduce anxiety or distress or to prevent something bad from happening and are they excessive or unreasonable?	NO YES compulsions
G4	ARE (G1a AND G1b AND G2) OR (G3a AND G3b) CODED YES?	➡ NO YES
G5	In the past month, did these obsessive thoughts and/or compulsive behaviors cause significant distress, or interfere with your ability to function at home, at work, at school or socially or in your relationships or in some other important way or did they take more than one hour a day? AND IS "RULE OUT ORGANIC CAUSE (O2 SUMMARY)" CODED YES? (CHECK FOR ANY OBSESSIVE-COMPULSIVE SYMPTOMS STARTING WITHIN 3 WEEKS OF AN INFECTION) SPECIFY THE LEVEL OF INSIGHT AND IF THE EPISODE IS TIC-RELATED.	NO YES ***O.C.D. CURRENT*** **INSIGHT:** GOOD OR FAIR ☐ POOR ☐ ABSENT ☐ DELUSIONAL ☐ TIC-RELATED ☐

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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 or sexual violence 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	Starting after the traumatic event, did you repeatedly re-experience the event in an unwanted mentally distressing way, (such as in recurrent dreams related to the event, intense recollections or memories, or flashbacks or as if the event was recurring) or did you have intense physical or psychological reactions when you were reminded about the event or exposed to a similar event?	➡ NO	YES
H3	**In the past month:**		
a	Did you persistently try to avoid thinking about or remembering distressing details or feelings related to the event?	NO	YES
b	Did you persistently try to avoid people, conversations, places, situations, activities or things that bring back distressing recollections of the event?	NO	YES
	ARE **1** OR MORE **H3** ANSWERS CODED YES?	➡ NO	YES
H4	**In the past month:**		
a	Did you have trouble recalling some important part of the trauma? (but not because of or related to head trauma, alcohol or drugs).	NO	YES
b	Were you constantly and unreasonably negative about yourself or others or the world?	NO	YES
c	Did you constantly blame yourself or others in unreasonable ways for the trauma?	NO	YES
d	Were your feelings always negative (such as fear, horror, anger, guilt or shame)?	NO	YES
e	Have you become much less interested in participating in activities that were meaningful to you before?	NO	YES
f	Did you feel detached or estranged from others?	NO	YES
g	Were you unable to experience any good feelings (such as happiness, satisfaction or loving feelings)?	NO	YES
	ARE **2** OR MORE **H4** ANSWERS CODED YES?	➡ NO	YES

H5	**In the past month:**		
a	Were you especially irritable or did you have outbursts of anger with little or no provocation?	NO	YES
b	Were you more reckless or more self-destructive?	NO	YES
c	Were you more nervous or constantly on your guard?	NO	YES
d	Were you more easily startled?	NO	YES
e	Did you have more difficulty concentrating?	NO	YES
f	Did you have more difficulty sleeping?	NO	YES
	ARE **2** OR MORE **H5** ANSWERS CODED YES? →	NO	YES
H6	Did all these problems start after the traumatic event and last for more than one month? →	NO	YES

NV

H7 During the past month, did these problems cause significant distress, or interfere with your ability to function at home, at work, at school or socially or in your relationships or in some other important way?

AND

IS "RULE OUT ORGANIC CAUSE (**O2 SUMMARY**)" CODED YES?

SPECIFY IF THE CONDITION IS ASSOCIATED WITH DEPERSONALIZATION, DEREALIZATION OR WITH DELAYED EXPRESSION.

NO YES

POSTTRAUMATIC STRESS DISORDER CURRENT

WITH
DEPERSONALIZATION ☐
DEREALIZATION ☐
DELAYED EXPRESSION ☐

I. ALCOHOL USE DISORDER

(➡ MEANS: GO TO DIAGNOSTIC BOX, CIRCLE NO 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?	NO	YES
I2	**In the past 12 months**:		
a	During the times when you drank alcohol, did you end up drinking more than you planned when you started?	NO	YES
b	Did you repeatedly want to reduce or control your alcohol use? Did you try to cut down or control your alcohol use, but failed? IF YES TO EITHER, CODE YES.	NO	YES
c	On the days that you drank, did you spend substantial time obtaining alcohol, drinking, or recovering from the effects of alcohol?	NO	YES
d	Did you crave or have a strong desire or urge to use alcohol?	NO	YES
e	Did you spend less time meeting your responsibilities at work, at school, or at home, because of your repeated drinking?	NO	YES
f	If your drinking caused problems with your family or other people, did you still keep on drinking?	NO	YES
g	Were you intoxicated more than once in any situation where you or others were physically at risk, for example, driving a car, riding a motorbike, using machinery, boating, etc.?	NO	YES
h	Did you continue to use alcohol, even though it was clear that the alcohol had caused or worsened psychological or physical problems?	NO	YES
i	Did you reduce or give up important work, social or recreational activities because of your drinking?	NO	YES
j	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
k1	When you cut down on heavy or prolonged drinking did you have any of the following:	NO	YES
	1. increased sweating or increased heart rate ☐ 2. hand tremor or "the shakes" ☐ 3. trouble sleeping ☐ 4. nausea or vomiting ☐ 5. hearing or seeing things other people could not see or hear or having sensations in your skin for no apparent reason ☐ 6. agitation ☐ 7. anxiety ☐ 8. seizures ☐		
	IF YES TO 2 OR MORE OF THE ABOVE 8, CODE k1 AS YES.		
k2	Did you drink alcohol to reduce or avoid withdrawal symptoms or to avoid a hangover?	NO	YES

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ARE **2** OR MORE **I2** ANSWERS FROM **I2a** THROUGH **I2k2** CODED YES?
(**I2k1** AND **I2k2** TOGETHER COUNT AS ONE AMONG THESE CHOICES)

NO	YES

ALCOHOL USE DISORDER

PAST 12 MONTHS

SPECIFIERS FOR ALCOHOL USE DISORDER:

MILD = **2-3** OF THE **I2** SYMPTOMS
MODERATE = **4-5** OF THE **I2** SYMPTOMS
SEVERE = **6** OR MORE OF THE **I2** SYMPTOMS

IV

IN EARLY REMISSION = CRITERIA NOT MET FOR BETWEEN 3 & 12 MONTHS.
IN SUSTAINED REMISSION = CRITERIA NOT MET FOR 12 MONTHS OR MORE.
(BOTH WITH THE EXCEPTION OF **CRITERION d** [CRAVING] ABOVE.)

IN A CONTROLLED ENVIRONMENT = WHERE ALCOHOL ACCESS IS RESTRICTED.

SPECIFY IF:

MILD ☐
MODERATE ☐
SEVERE ☐

IN EARLY REMISSION ☐
IN SUSTAINED REMISSION ☐

IN A CONTROLLED ENVIRONMENT ☐

J. SUBSTANCE USE DISORDER (NON-ALCOHOL)

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

			➡	
		Now I am going to show you / read to you a list of street drugs or medicines.		
J1	a	**In the past 12 months**, did you take any of these drugs more than once, to get high, to feel elated, to get "a buzz" or to change your mood?	NO	YES

CIRCLE EACH DRUG TAKEN:

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

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

Opiates: heroin, morphine, Dilaudid, opium, Demerol, methadone, Darvon, codeine, Percodan, Vicodin, OxyContin, cough medicine containing opiates.

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

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

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

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

Sedatives, Hypnotics, Anxiolytics, or Benzodiazepines: Quaalude, Seconal ("reds"), Valium, Xanax, Librium, Ativan, Dalmane, Halcion, barbiturates, Miltown, GHB, Roofinol, "Roofies".

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

SPECIFY THE MOST USED DRUG(S): _____

WHICH DRUG(S) CAUSE THE BIGGEST PROBLEMS? _____

FIRST EXPLORE THE CRITERIA BELOW FOR THE DRUG CLASS CAUSING THE BIGGEST PROBLEMS AND THE ONE MOST LIKELY TO MEET CRITERIA FOR SUBSTANCE USE DISORDER. IF SEVERAL DRUG CLASSES HAVE BEEN MISUSED, EXPLORE AS MANY OR AS FEW AS REQUIRED BY THE PROTOCOL.

J2		**Considering your use of (NAME OF DRUG / DRUG CLASS SELECTED), in the past 12 months:**		
	a	During the times when you used the drug, did you end up using more (NAME OF DRUG / DRUG CLASS SELECTED) than you planned when you started?	NO	YES
	b	Did you repeatedly want to reduce or control your (NAME OF DRUG / DRUG CLASS SELECTED) use? Did you try to cut down or control your (NAME OF DRUG / DRUG CLASS SELECTED) use, but failed? IF YES TO EITHER, CODE YES.	NO	YES
	c	On the days that you used more (NAME OF DRUG / DRUG CLASS SELECTED), did you spend substantial time obtaining (NAME OF DRUG / DRUG CLASS SELECTED), using it, or recovering from the its effects?	NO	YES
	d	Did you crave or have a strong desire or urge to use (NAME OF DRUG / DRUG CLASS SELECTED)?	NO	YES
	e	Did you spend less time meeting your responsibilities at work, at school, or at home, because of your repeated (NAME OF DRUG / DRUG CLASS SELECTED) use?	NO	YES
	f	If your (NAME OF DRUG / DRUG CLASS SELECTED) use caused problems with your family or other people, did you still keep on using it?	NO	YES
	g	Did you use the drug more than once in any situation where you or others were physically at risk, for example, driving a car, riding a motorbike, using machinery, boating, etc.?	NO	YES

h Did you continue to use (NAME OF DRUG / DRUG CLASS SELECTED), even though it was clear that the (NAME OF DRUG / DRUG CLASS SELECTED) had caused or worsened psychological or physical problems? NO YES

i Did you reduce or give up important work, social or recreational activities because of your (NAME OF DRUG / DRUG CLASS SELECTED) use? NO YES

j1 Did you need to use (NAME OF DRUG / DRUG CLASS SELECTED) a lot more in order to get the same effect that you got when you first started using it or did you get much less effect with continued use of the same amount? NO YES
THIS CRITERION IS CODED NO IF THE MEDICATION IS PRESCRIBED AND USED UNDER APPROPRIATE MEDICAL SUPERVISION.

j2 IS THE DRUG CLASS CURRENTLY BEING EXPLORED HALLUCINOGENS, OR DISSOCIATIVE DRUGS, OR INHALANTS, OR 'MISCELLANEOUS' DRUGS OF ABUSE? NO YES
IF YES, SKIP ALL THE **J2x** QUESTIONS BELOW, AND GO TO THE CODING DIRECTIONS FOR THESE CLASSES ADJACENT TO THE DIAGNOSTIC BOX BELOW.

k1 When you cut down on heavy or prolonged use of the drug did you have any of the following withdrawal symptoms: NO YES
IF YES TO THE REQUIRED NUMBER OF WITHDRAWAL SYMPTOMS FOR EACH CLASS, CODE **J2k1** AS YES.
THIS CRITERION IS CODED NO IF THE MEDICATION IS PRESCRIBED AND USED UNDER APPROPRIATE MEDICAL SUPERVISION.

Sedatives, Hypnotics, or Anxiolytics (2 or more withdrawal symptoms)
1. increased sweating or increased heart rate ☐
2. hand tremor or "the shakes" ☐
3. trouble sleeping ☐
4. nausea or vomiting ☐
5. hearing or seeing things other people could not see or hear or having sensations in your skin for no apparent reason ☐
6. agitation ☐
7. anxiety ☐
8. seizures ☐

Opiates (3 or more withdrawal symptoms)
1. feeling depressed ☐
2. nausea or vomiting ☐
3. muscle aches ☐
4. runny nose or teary eyes ☐
5. dilated pupils, goose bumps or hair standing on end or sweating ☐
6. diarrhea ☐
7. yawning ☐
8. hot flashes ☐
9. trouble sleeping ☐

Stimulants and Cocaine (2 or more withdrawal symptoms)
1. fatigue ☐
2. vivid or unpleasant dreams ☐
3. difficulty sleeping or sleeping too much ☐
4. increased appetite ☐
5. feeling or looking physically or mentally slowed down ☐

Cannabis (3 or more withdrawal symptoms)

1. irritability, anger or aggression ☐
2. nervousness or anxiety ☐
3. trouble sleeping ☐
4. appetite or weight loss ☐
5. restlessness ☐
6. feeling depressed ☐
7. significant discomfort from one of the following: "stomach pain", tremors or "shakes", sweating, hot flashes, chills, headaches. ☐

k2 Did you use (NAME OF DRUG / DRUG CLASS SELECTED) to reduce or avoid withdrawal symptoms? NO YES

FOR STIMULANTS, COCAINE, OPIATES, CANNABIS, SEDATIVES, HYPNOTICS, OR ANXIOLYTICS:
ARE **2** OR MORE **J2** ANSWERS FROM **J2a** THROUGH **J2k2** CODED YES
(**J2k1** AND **J2k2** TOGETHER COUNT AS ONE AMONG THESE CHOICES)?

NV

OR

FOR HALLUCINOGENS, DISSOCIATIVE DRUGS, INHALANTS, OR 'MISCELLANEOUS' DRUGS:
ARE **2** OR MORE **J2** ANSWERS FROM **J2a** THROUGH **J2j1** CODED YES?

NO YES

SUBSTANCE (Drug or Drug Class Name) USE DISORDER

PAST 12 MONTHS

SPECIFIERS FOR SUBSTANCE USE DISORDER:

MILD = **2-3** OF THE **J2** SYMPTOMS
MODERATE = **4-5** OF THE **J2** SYMPTOMS
SEVERE = **6** OR MORE OF THE **J2** SYMPTOMS

IN EARLY REMISSION = CRITERIA NOT MET FOR BETWEEN 3 & 12 MONTHS.
IN SUSTAINED REMISSION = CRITERIA NOT MET FOR 12 MONTHS OR MORE.
(BOTH WITH THE EXCEPTION OF **CRITERION d** [CRAVING] ABOVE.)

IN A CONTROLLED ENVIRONMENT = WHERE SUBSTANCE / DRUG ACCESS IS RESTRICTED.

SPECIFY IF:

MILD ☐
MODERATE ☐
SEVERE ☐

IN EARLY REMISSION ☐
IN SUSTAINED REMISSION ☐

IN A CONTROLLED ENVIRONMENT ☐

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. 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.

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
	b	IF YES: do you currently believe these things?	NO	YES
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
	b	IF YES: do you currently believe these things?	NO	YES
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
	b	IF YES: do you currently believe these things?	NO	YES
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
	b	IF YES: do you currently believe these things?	NO	YES
K5	a	Have your relatives or friends ever considered any of your beliefs odd or unusual? CLINICIAN: ASK FOR EXAMPLES. ONLY CODE YES IF THE EXAMPLES ARE CLEARLY DELUSIONAL IDEAS NOT EXPLORED IN QUESTIONS **K1** TO **K4**. FOR EXAMPLE, RELIGIOUS, DEATH, DISEASE OR SOMATIC DELUSIONS, DELUSIONS OF GRANDIOSITY, JEALOUSY OR GUILT, OR OF FAILURE, INADEQUACY, RUIN, OR DESTITUTION, OR NIHILISTIC DELUSIONS.	NO	YES
	b	IF YES: do they currently consider your beliefs strange or unusual?	NO	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 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

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K7	a	Have you ever had visions when you were awake or have you ever seen things other people couldn't see? CLINICIAN: CHECK TO SEE IF THESE ARE CULTURALLY INAPPROPRIATE.	NO	YES
	b	IF YES: have you seen these things in the past month?	NO	YES

CLINICIAN'S JUDGMENT

K8	a	DID THE PATIENT EVER IN THE PAST EXHIBIT DISORGANIZED, INCOHERENT OR DERAILED SPEECH, OR MARKED LOOSENING OF ASSOCIATIONS?	NO	YES
K8	b	IS THE PATIENT CURRENTLY EXHIBITING INCOHERENCE, DISORGANIZED OR DERAILED SPEECH, OR MARKED LOOSENING OF ASSOCIATIONS?	NO	YES
K9	a	DID THE PATIENT EVER IN THE PAST EXHIBIT DISORGANIZED OR CATATONIC BEHAVIOR?	NO	YES
K9	b	IS THE PATIENT CURRENTLY EXHIBITING DISORGANIZED OR CATATONIC BEHAVIOR?	NO	YES
K10	a	DID THE PATIENT EVER IN THE PAST HAVE NEGATIVE SYMPTOMS OF SCHIZOPHRENIA, E.G. SIGNIFICANT REDUCTION OF EMOTIONAL EXPRESSION OR AFFECTIVE FLATTENING, POVERTY OF SPEECH (ALOGIA) OR AN INABILITY TO INITIATE OR PERSIST IN GOAL-DIRECTED ACTIVITIES (AVOLITION)?	NO	YES
K10	b	ARE NEGATIVE SYMPTOMS OF SCHIZOPHRENIA, E.G. SIGNIFICANT REDUCTION OF EMOTIONAL EXPRESSION OR 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? **AND IS EITHER:** MAJOR DEPRESSIVE EPISODE, (CURRENT, RECURRENT OR PAST) **OR** MANIC OR HYPOMANIC EPISODE, (CURRENT OR PAST) CODED YES? **AND** HOW LONG HAS THE MOOD EPISODE LASTED? _____ HOW LONG HAS THE PSYCHOTIC EPISODE LASTED? _____ IF SUCH A MOOD EPISODE IS PRESENT, CODE YES TO **K11a** ONLY IF THE MOOD DISTURBANCE IS PRESENT FOR THE MAJORITY OF THE TOTAL DURATION OF THE ACTIVE AND RESIDUAL PERIODS OF THE PSYCHOTIC SYMPTOMS. OTHERWISE CODE NO.	NO ↳ K13	YES

IF NO TO **K11a** AND THE TOTAL DURATION OF THE MOOD EPISODE IS **LESS THAN** THE TOTAL DURATION OF THE PSYCHOTIC EPISODE, THEN 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 EXPERIENCE (PSYCHOTIC SYMPTOMS) WHEN THEY WERE NOT DEPRESSED/HIGH/IRRITABLE, CODE NO TO THIS DISORDER.

IF THE ANSWER IS NO TO THIS DISORDER GROUPING, ALSO CIRCLE NO TO **K12** AND MOVE TO **K13**

NO YES

MOOD DISORDER WITH PSYCHOTIC FEATURES

LIFETIME

K12 ARE **1** OR MORE « **b** » QUESTIONS FROM **K1b** TO **K7b** CODED YES?

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 **K8b**, CODED YES?

AND

ARE **2** OR MORE « **b** » QUESTIONS FROM **K1b** TO **K10b**, CODED YES?

AND DID AT LEAST **2** OF THE PSYCHOTIC SYMPTOMS OCCUR DURING THE SAME **1**-MONTH PERIOD?

AND

IS "RULE OUT ORGANIC CAUSE (**O2** SUMMARY)" CODED YES?

NO YES

PSYCHOTIC DISORDER
CURRENT

K14 IS **K13** CODED YES?

OR

(ARE **1** OR MORE « **a** » QUESTIONS FROM **K1a** TO **K8a**, CODED YES?

AND

ARE **2** OR MORE « **a** » QUESTIONS FROM **K1a** TO **K10a**, CODED YES

AND

DID AT LEAST **2** OF THE PSYCHOTIC SYMPTOMS OCCUR DURING THE SAME **1**-MONTH PERIOD?)

AND

IS "RULE OUT ORGANIC CAUSE (**O2** SUMMARY)" CODED YES?

NO YES

PSYCHOTIC DISORDER
LIFETIME

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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 or to restrict your food intake?	➡ NO	YES
L3		Have you intensely feared gaining weight or becoming fat, even though you were under-weight?	➡ 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

IS L5 CODED YES?

NO	YES
	ANOREXIA NERVOSA CURRENT

HEIGHT / WEIGHT TABLE CORRESPONDING TO A **BMI THRESHOLD** OF 17.0 KG/M²

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	79	82	84	87	90	93	96	99	102	106	109	112	115	119
cm	145	147	150	152	155	158	160	163	165	168	170	173	175	178
kg	36	37	38.5	39.5	41	42.5	43.5	45.5	46.5	48	49	51	52	54

Height/Weight					
ft/in	5'11	6'0	6'1	6'2	6'3
lb	122	125	129	133	136
cm	180	183	185	188	191
kg	55	57	58.5	60	62

The weight thresholds above are calculated using a body mass index (BMI) equal to or below 17.0 kg/m² for the patient's height using the Center of Disease Control & Prevention BMI Calculator. This is the threshold guideline below which a person is deemed underweight by the DSM-5 for Anorexia Nervosa.

M. BULIMIA NERVOSA

(➡ MEANS: GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN THE BULIMIA NERVOSA AND IN THE ANOREXIA NERVOSA BINGE EATING / PURGING TYPE DIAGNOSTIC BOXES. BUT IF ANOREXIA NERVOSA (IN MODULE L) IS CODED YES, CONTINUE WITH THE QUESTIONS TO BE ABLE TO PROPERLY CODE ANOREXIA NERVOSA RESTRICTING TYPE)

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	During these binges, did you feel that your eating was out of control?	➡ NO	YES
	In the past 3 months:		
M3	Did you have eating binges as often as once a week?	➡ NO	YES
M4	Did you do anything to compensate for, or to prevent a weight gain, like vomiting, fasting, exercising or taking laxatives, enemas, diuretics (fluid pills), or other medications? Did you do this as often as once a week?	➡ NO	YES
M4a	Number of Episodes of Inappropriate Compensatory Behaviors per Week? _____ Number of Days of Inappropriate Compensatory Behaviors per Week? _____		
M5	Did your body weight or shape greatly influence how you felt about yourself?	➡ NO	YES
M6	DO THE PATIENT'S SYMPTOMS MEET CRITERIA FOR ANOREXIA NERVOSA?	NO ↓ Skip to M8	YES
M7	Did these binges occur only when you were under (_____lb/kg)? CLINICIAN: 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**

DO THE PATIENT'S SYMPTOMS MEET CRITERIA FOR ANOREXIA NERVOSA?

AND

IS **M2** OR **M4** CODED NO?

NO	YES

ANOREXIA NERVOSA
Restricting Type
CURRENT

SPECIFIERS OF EATING DISORDER:

MILD = **1-3** EPISODES OF INAPPROPRIATE COMPENSATORY BEHAVIORS
MODERATE = **4-7** EPISODES OF INAPPROPRIATE COMPENSATORY BEHAVIORS
SEVERE = **8-13** EPISODES OF INAPPROPRIATE COMPENSATORY BEHAVIORS
EXTREME = **14** OR MORE EPISODES OF INAPPROPRIATE COMPENSATORY BEHAVIORS

SPECIFY IF:

- MILD ☐
- MODERATE ☐
- SEVERE ☐
- EXTREME ☐

NV

MB. BINGE EATING DISORDER

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

MB1	DO THE PATIENT'S SYMPTOMS MEET CRITERIA FOR ANOREXIA NERVOSA?	NO	➡ YES
MB2	DO THE PATIENT'S SYMPTOMS MEET CRITERIA FOR BULIMIA NERVOSA?	NO	➡ YES
MB3	IS **M2** CODED YES?	➡ NO	YES
MB4	IS **M3** CODED YES?	➡ NO	YES
MB5	IS **M4** CODED YES? IF **M4** WAS BYPASSED IN MODULE M (BULIMIA NERVOSA), ASK **M4** NOW TO CODE **MB5**.	NO	➡ YES
	In the last 3 months during the binging did you:		
MB6a	Eat more rapidly than normal?	NO	YES
MB6b	Eat until you felt uncomfortably full?	NO	YES
MB6c	Eat large amounts of food when you were not hungry?	NO	YES
MB6d	Eat alone because you felt embarrassed about how much you were eating?	NO	YES
MB6e	Feel guilty, depressed or disgusted with yourself after binging?	NO	YES
	ARE **3** OR MORE **MB6** QUESTIONS CODED YES?	➡ NO	YES

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MB7 Does your binging distress you a lot? ➡ NO YES

MB8 Number of Binge Eating Episodes per Week? _____

Number of Binge Eating Days per Week? _____

IS **MB7** CODED YES?

NO	YES

BINGE-EATING DISORDER

CURRENT

SPECIFIERS OF EATING DISORDER:

NV

MILD = **1-3** EPISODES OF BINGE EATING PER WEEK
MODERATE = **4-7** EPISODES OF BINGE EATING PER WEEK
SEVERE = **8-13** EPISODES OF BINGE EATING PER WEEK
EXTREME = **14** OR MORE EPISODES OF BINGE EATING PER WEEK

SPECIFY IF:

MILD ☐
MODERATE ☐
SEVERE ☐
EXTREME ☐

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 worrier or a "worry wart"?) AND GET EXAMPLES.	➡ NO	YES
	b	Are these anxieties and worries present most days?	➡ NO	YES
N2		Do you find it difficult to control the worries?	➡ NO	YES
N3		**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 significantly disrupt your ability to work, to function socially, or in your relationships, or in other important areas of your life, or cause you significant distress?	➡ NO	YES
N5		ARE THE PATIENT'S ANXIETY SYMPTOMS IN **N3**, OR THE WORRIES, RESTRICTED EXCLUSIVELY TO: a. ☐ a depressive disorder? b. ☐ a bipolar disorder? c. ☐ a psychotic disorder? IF YES TO ANY, CODE YES AND ASK **N6.** IF NO TO ALL, SKIP TO **N7.**	NO	YES
N6		IF YES TO ANY CHECKBOX IN **N5:** IS THE ANXIETY OR WORRY ITSELF SUFFICIENTLY SEVERE TO REQUIRE SPECIAL ATTENTION BEYOND THE STANDARD TREATMENT FOR THE DEPRESSIVE, BIPOLAR, OR PSYCHOTIC DISORDER?	➡ NO	YES
N7		ARE THE PATIENT'S ANXIETY SYMPTOMS IN **N3**, OR THE WORRIES, RESTRICTED EXCLUSIVELY TO, OR BETTER EXPLAINED BY ANY PSYCHIATRIC DISORDER?	NO	➡ YES

IS **N7** CODED NO?

AND

IS "RULE OUT ORGANIC CAUSE (**O2 SUMMARY**)" CODED YES?

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 OR A MAJOR DEPRESSIVE EPISODE OR A MANIC OR A HYPOMANIC EPISODE ASK:

Just before these symptoms began:

O1a	Were you taking any drugs or medicines, or in withdrawal from any of these?	☐ No ☐ Yes ☐ Uncertain
O1b	Did you have any medical illness?	☐ No ☐ Yes ☐ Uncertain
O2	IF **O1a** OR **O1b** IS CODED YES, IN THE CLINICIAN'S JUDGMENT, IS EITHER LIKELY TO BE A DIRECT CAUSE OF THE PATIENT'S DISORDER? IF NECESSARY, ASK ADDITIONAL OPEN-ENDED QUESTIONS.	☐ No ☐ Yes ☐ Uncertain
	O2 SUMMARY: HAS AN "ORGANIC" / MEDICAL / DRUG RELATED CAUSE BEEN RULED OUT?	☐ No ☐ Yes ☐ Uncertain

IF **O2** IS YES, THEN **O2** SUMMARY IS NO.
IF **O2** IS NO, THEN **O2** SUMMARY IS YES.
OTHERWISE IT IS UNCERTAIN.

NV

P. ANTISOCIAL PERSONALITY DISORDER

(➔ MEANS: SKIP ALL THE P2 QUESTIONS, 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 or stayed out at night against your parent's rules?		NO	YES
	b repeatedly lie, cheat, "con" others, or steal or break into someone's house or car?		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 into sexual activity?		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 done things that are illegal or would be grounds to get arrested, even if you didn't get caught (for example destroying property, shoplifting, stealing, selling drugs, or committing a felony)?		NO	YES
	b often lied or "conned" other people to get money or pleasure, or lied just for fun?		NO	YES
	c been impulsive and didn't care about planning ahead?		NO	YES
	d been in physical fights repeatedly or assaulted others (including physical fights with your spouse or children)?		NO	YES
	e exposed others or yourself to danger without caring?		NO	YES
	f 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
	g 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

NO	YES
ANTISOCIAL PERSONALITY DISORDER **LIFETIME**	

MOOD DISORDERS: DIAGNOSTIC ALGORITHM

Consult Modules:

- A Major Depressive Episode
- C (Hypo)manic Episode
- K Psychotic Disorders
- O "Rule out medical, organic or drug causes for all disorders"

MODULE K:

1a	IS **K11b** CODED YES?	NO	YES
1b	IS **K12** CODED YES?	NO	YES

MODULES A and C:

			Current	Past
2	a	FOR EACH TIMEFRAME, CIRCLE YES IF A DELUSIONAL IDEA IS IDENTIFIED IN **A3e** OR IF ANY PSYCHOTIC FEATURE IS PRESENT IN **K1** THROUGH **K7**	YES	YES
	b	FOR EACH TIMEFRAME, CIRCLE YES IF A DELUSIONAL IDEA IS IDENTIFIED IN **C3a** OR IF ANY PSYCHOTIC FEATURE IS PRESENT IN **K1** THROUGH **K7**	YES	YES

c IS MAJOR DEPRESSIVE EPISODE CODED YES (CURRENT, OR PAST, OR RECURRENT)?
AND
IS MANIC EPISODE CODED NO (CURRENT AND PAST)?
AND
IS HYPOMANIC EPISODE CODED NO (CURRENT AND PAST)?
AND
IS "RULE OUT ORGANIC CAUSE (**O2** SUMMARY)" CODED YES?

SPECIFY:

- IF THE DEPRESSIVE EPISODE IS **CURRENT**, OR **PAST**, OR **BOTH**, AND/OR **RECURRENT**
- WITH PSYCHOTIC FEATURES, CURRENT: IF **1b** OR **2a** (CURRENT) = YES
  WITH PSYCHOTIC FEATURES, PAST: IF **2a** (PAST) = YES
- AS RECURRENT MAJOR DEPRESSIVE **DISORDER** (MDD) IF:

  MAJOR DEPRESSIVE **DISORDER** (MDD) IN THIS MOOD DISORDER ALGORITHM IS CODED YES
  AND IF, IN MODULE A, EITHER

  (MD **EPISODE** CURRENT + MD **EPISODE** PAST + **A5** ARE ALL CODED YES
  OR
  MD **EPISODE** PAST AND **A5** ARE BOTH CODED YES)

MAJOR DEPRESSIVE DISORDER

NO ***YES***

	Current	Past	Recurrent
MDD	☐	☐	☐

With Psychotic Features

Current ☐
Past ☐

d IS MANIC EPISODE CODED YES (CURRENT OR PAST)?
AND
IS "RULE OUT ORGANIC CAUSE (O2 SUMMARY)" CODED YES?

SPECIFY:

- IF THE BIPOLAR I DISORDER IS **CURRENT** OR **PAST** OR **BOTH**
- WITH SINGLE MANIC EPISODE: IF MANIC EPISODE (CURRENT OR PAST) = YES AND MAJOR DEPRESSIVE EPISODE (CURRENT AND PAST) = NO
- WITH PSYCHOTIC FEATURES, CURRENT: IF **1b** OR **2a** (CURRENT) OR **2b** (CURRENT) = YES
  WITH PSYCHOTIC FEATURES, PAST: IF **2a** (PAST) OR **2b** (PAST) = YES
- IF THE MOST RECENT EPISODE IS MANIC, DEPRESSED, OR HYPOMANIC (MUTUALLY EXCLUSIVE)

NV

BIPOLAR I DISORDER

	NO	*YES*	
		Current	Past
Bipolar I Disorder		☐	☐
Single Manic Episode		☐	☐
With Psychotic Features			
Current		☐	
Past		☐	
Most Recent Episode			
Manic		☐	
Depressed		☐	
Hypomanic		☐	
Most Recent Episode			
Mild		☐	
Moderate		☐	
Severe		☐	

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)?
AND
IS "RULE OUT ORGANIC CAUSE (O2 SUMMARY)" CODED YES?

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

	NO	*YES*	
		Current	Past
Bipolar II Disorder		☐	☐
Most Recent Episode			
Hypomanic		☐	
Depressed		☐	
Most Recent Episode			
Mild		☐	
Moderate		☐	
Severe		☐	

f IS MAJOR DEPRESSIVE EPISODE 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 **C8b** 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 **C8c** CODED YES?

SPECIFY IF THE OTHER SPECIFIED BIPOLAR AND RELATED DISORDER IS **CURRENT** OR **PAST** OR BOTH.

OTHER SPECIFIED BIPOLAR AND RELATED DISORDER

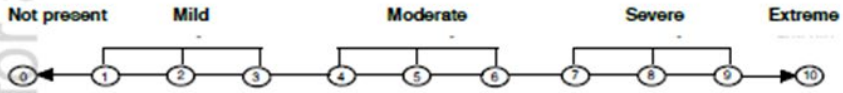
	NO	***YES***	
		Current	Past
Other Specified Bipolar and Related Disorder		☐	☐

OPTIONAL ASSESSMENT MEASURES TO TRACK CHANGES OVER TIME

A: CROSS CUTTING MEASURES

SEVERITY OF SYMPTOM

Use this scale to rate the severity of your symptom in the score column in the table below:



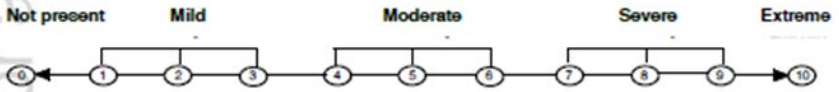
Assessment of Symptoms That Cut Across Disorders

	Symptom Name	Score
1	Depression	
2	Anger	
3	Mania (feeling up or high or hyper or full of energy with racing thoughts)	
4	Anxiety	
5	Physical (somatic) symptoms	
6	ANY suicidal thoughts (thoughts of killing yourself), or ANY suicidal impulses, plans, intent, or ANY preparations to kill yourself or ANY attempt to kill yourself	
7	Hearing sounds or voices others can't hear or fearing someone can hear or read your thoughts or believing things others don't accept as true e.g. that people are spying on you or plotting against you or talking about you (Psychosis)	
8	Sleep problems	
9	Memory problems	
10	Repetitive or obsessive thoughts or compulsive behaviors	
11	Feeling things around you are strange, unreal, detached or unfamiliar, or feeling outside or detached from part or all of your body (Dissociation)	
12	Ability to function at work, at home, in your life, or in your relationships	
13	Overusing alcohol or drugs	

B: DISABILITY / FUNCTIONAL IMPAIRMENT

SEVERITY OF DISABILITY / IMPAIRMENT

Use this scale to rate in the score column of the table below, how much your symptoms have disrupted your ability to function in the following areas of your life:



Assessment of Impairment of Functioning /Disability

	Domain Name	Score
1	Work or schoolwork	
2	Social life or leisure activities (like hobbies or things you do for enjoyment)	
3	Family life and / or home responsibilities	
4	Ability to get along with people	
5	Personal and social relationships	
6	Ability to understand and to communicate with others	
7	Ability to take care of yourself (washing, showering, bathing, dressing properly, brushing teeth, laundry, combing / brushing hair, eating regularly)	
8	Made you disruptive or aggressive towards others	
9	Financially (ability to manage your money)	
10	Ability to get around physically	
11	Spiritual or religious life	
12	How much did your condition have an impact on other people in your family?	

11.15 Antidepressant Treatment Response Questionnaire (ATRQ)

Non-Geriatric

MASSACHUSETTS GENERAL HOSPITAL (MGH)
ANTIDEPRESSANT TREATMENT RESPONSE QUESTIONNAIRE (ATRQ)

(Non-Geriatric Population: 18 to 64 years of age)(Global)

Note: The minimum therapeutic dose and the minimum optimized dose for each antidepressant treatment in Section I is based on prescribing information, relevant literature, and consultation with expert clinicians.

Section I. Antidepressant Medications

Instructions:

1. Please **check (√)** the names of any medications that the patient has taken since the beginning of **THIS CURRENT EPISODE** of depression.
2. Please **check (√)** if the daily dosage of the medication was **equal to or greater than the minimum** therapeutic dose for at least 8 weeks.
3. Only for those taken at the minimum therapeutic dose or the minimal dose at an optimal level for at least 8 weeks, indicate the amount (%) of improvement in depression that the patient reported when they felt it was working at its best.
4. If the subject initially experienced an improvement of ≥50% and then lost that response (tolerance/tachyphylaxis), that medication will not be counted towards a failed antidepressant trial.

Tricyclic Antidepressants

Generic Name	Taken during THIS current episode of depression(√)	Took at least this dose *for at least 8 weeks*? (√)				Only for those taken at minimum therapeutic dose for at least 8 weeks: Based on subject's feedback, indicate the amount (%) of improvement in depression he/she reported when they feel it was working at its best. A. 75% to 100% B. 50% to <75% C. 26% to <50% D. ≤ 25%
		Minimally adequate dose		Minimal dose at optimal level		
doxepin		150mg/d		250mg/d		
clomipramine		150mg/d		250mg/d		
amoxapine		150mg/d		250mg/d		
amitriptyline		150mg/d		250mg/d		
maprotiline		150mg/d		250mg/d		
desipramine		150mg/d		250mg/d		
nortriptyline		75 mg/d		125mg/d		
trimipramine		150mg/d		250mg/d		
imipramine		150mg/d		250mg/d		
protriptyline		30mg/d		60mg/d		
pipofezine		150mg/d		300mg/d		
noxiptiline		100mg/d		200mg/d		

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Monoamine Oxidase Inhibitors (MAOIs)

Generic Name	Taken during THIS current episode? (√)	Took at least this dose *for at least 8 weeks?* (√)				Only for those taken at minimum therapeutic dose for at least 8 weeks: Based on subject's feedback, indicate the amount (%) of improvement in depression he/she reported when they feel it was working at its best. A. 75% to 100% B. 50% to <75% C. 26% to <50% D. ≤ 25%
		Minimally adequate dose		Minimal dose at optimal level		
isocarboxazid		30mg/d		60mg/d		
phenelzine		45mg/d		90mg/d		
tranylcypromine		30mg/d		60mg/d		
selegiline patch		6 mg/ 24 hrs		12 mg/ 24 hrs		
moclobemide		300 mg/d		600 mg/d		
pirlindole		200 mg/d		300 mg/d		

Selective Serotonin Reuptake Inhibitors (SSRIs)

Generic Name	Taken during THIS current episode? (√)	Took at least this dose *at least 8 weeks?* (√)				Only for those taken at minimum therapeutic dose for at least 8 weeks: Based on subject's feedback, indicate the amount (%) of improvement in depression he/she reported when they feel it was working at its best. A. 75% to 100% B. 50% to <75% C. 26% to <50% D. ≤ 25%
		Minimally adequate dose		Minimal dose at optimal level		
fluvoxamine		50mg/d		150mg/d		
paroxetine		20/25mg/d		60/75mg/d		
fluoxetine		20 mg/d		60 mg/d		
sertraline		50 mg/d		150 mg/d		
citalopram		20mg/d		60mg/d		
escitalopram		10 mg/d		30 mg/d		
vilazodone		40 mg/d		80 mg/d		
vortioxetine		10 mg/d		20 mg/d		

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Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

Generic Name	Taken during THIS current episode? (√)	Took at least this dose for *at least 8 weeks?* (√)				Only for those taken at minimum therapeutic dose for at least 8 weeks: Based on subject's feedback, indicate the amount (%) of improvement in depression he/she reported when they feel it was working at its best. A. 75% to 100% B. 50% to <75% C. 26% to <50% D. ≤ 25%
		Minimally adequate dose		Minimal dose at optimal level		
venlafaxine / venlafaxine XR		150 mg/d		250 mg/d		
duloxetine		60mg/d		120mg/d		
desvenlafaxine		50mg/d		100mg/d		
milnacipran		100mg/d		200mg/d		
levomilnacipran		40mg/d		120mg/d		

Other Antidepressants

Generic Name	Taken during THIS current episode? (√)	Took at least this dose for at least 8 weeks? (√)				Only for those taken at minimum therapeutic dose for at least 8 weeks: Based on subject's feedback, indicate the amount (%) of improvement in depression he/she reported when they feel it was working at its best. A. 75% to 100% B. 50% to <75% C. 26% to <50% D. ≤ 25%
trazodone		300mg/d		600mg/d		
bupropion		300mg/d		450mg/d		
mirtazapine		15 mg/d		45 mg/d		
mianserin		30 mg/d		90 mg/d		
opipramol		150 mg/d		300 mg/d		
nefazodone		300 mg/d		600 mg/d		
agomelatine		25 mg/d		50 mg/d		
tianeptine		37.5 mg/d		75 mg/d		
reboxetine		4 mg/d		8 mg/d		
esketamine		56 mg		84 mg		
dextromethorphan/bupropion		45/105mg		90/210mg		

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Section II. FDA-Approved Medications added to Augment /Boost Antidepressant Effect

Instructions:

1. Please **check** (√) the names of any medication you have taken to augment or boost the antidepressant effect during **THIS CURRENT EPISODE** of depression.
2. Please **check** (√) if the subject took at least this dose for at least 8 weeks in combination with an antidepressant treatment from Section I.
3. Please indicate the name of antidepressant treatment from Section I this drug was taken with to augment /boost its antidepressant effect.
4. Please indicate the amount (%) of improvement in depression that the patient reported when they felt this combination was working at its best.

Generic Name	Taken during THIS current episode? (√)	Took at least this dose for *at least* 8 weeks in combination with an antidepressant treatment from Section I**? (√)		Name of Antidepressant Treatment from Section I (see above) this drug was taken with	Only for those taken at minimum therapeutic dose for at least 8 weeks: Based on subject's feedback, indicate the amount (%) of improvement in depression he/she reported when they feel the combination was working at its best. A. 75% to 100% B. 50% to <75% C. 26% to <50% D. ≤ 25%
Aripiprazole		5 mg/d			
Quetiapine		200 mg/d			
Brexpiprazole		1 mg/d			
Cariprazine		1.5 mg/d			
**The antidepressant treatment from Section I must also have been taken at the minimum therapeutic dose during the 8 weeks that the medication was taken to augment/boost antidepressant effect.					

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**
Did you receive transcranial magnetic stimulation (TMS) during **this current** episode (please circle one): **YES** **NO**

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Geriatric

MASSACHUSETTS GENERAL HOSPITAL (MGH)
ANTIDEPRESSANT TREATMENT RESPONSE QUESTIONNAIRE (ATRQ)

(Geriatric Population: ≥65 years of age) (Global)

Note: The minimum therapeutic dose and the minimum optimized dose for each antidepressant treatment in Section I is based on prescribing information, relevant literature, and consultation with expert clinicians.

Section I. Antidepressant Medications

Instructions:

1. Please **check (√)** the names of any medications that the patient has taken since the beginning of **THIS CURRENT EPISODE** of depression.
2. Please **check (√)** if the daily dosage of the medication was **equal to or greater than the minimum** therapeutic dose for at least 8 weeks.
3. Only for those taken at the minimum therapeutic dose or the minimal dose at an optimal level for at least 8 weeks, indicate the amount (%) of improvement in depression that the patient reported when they felt it was working at its best.
4. If the subject initially experienced an improvement of ≥50% and then lost that response (tolerance/tachyphylaxis), that medication will not be counted towards a failed antidepressant trial.

Tricyclic Antidepressants

Generic Name	Taken during THIS current episode of depression(√)	Took at least this dose *for at least 8 weeks*? (√)				Only for those taken at minimum therapeutic dose for at least 8 weeks: Based on subject's feedback, indicate the amount (%) of improvement in depression he/she reported when they feel it was working at its best. A. 75% to 100% B. 50% to <75% C. 26% to <50% D. ≤ 25%
		Minimally adequate dose		Minimal dose at optimal level		
doxepin		100mg/d		250mg/d		
clomipramine		100mg/d		250mg/d		
amoxapine		100mg/d		250mg/d		
amitriptyline		100mg/d		250mg/d		
maprotiline		100mg/d		250mg/d		
desipramine		100mg/d		250mg/d		
nortriptyline		50mg/d		125mg/d		
trimipramine		100mg/d		250mg/d		
imipramine		100mg/d		250mg/d		
protriptyline		20mg/d		60mg/d		
pipofezine		100mg/d		300mg/d		
noxiptiline		100mg/d		200mg/d		

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Monoamine Oxidase Inhibitors (MAOIs)

Generic Name	Taken during THIS current episode? (√)	Took at least this dose *for at least 8 weeks?* (√)				Only for those taken at minimum therapeutic dose for at least 8 weeks: Based on subject's feedback, indicate the amount (%) of improvement in depression he/she reported when they feel it was working at its best. A. 75% to 100% B. 50% to <75% C. 26% to <50% D. ≤ 25%
		Minimally adequate dose		Minimal dose at optimal level		
isocarboxazid		20mg/d		60mg/d		
phenelzine		30mg/d		90mg/d		
tranylcypromine		20mg/d		60mg/d		
selegiline patch		6 mg/ 24 hrs		12 mg/ 24 hrs		
moclobemide		150mg/d		600 mg/d		
pirlindole		100mg/d		300 mg/d		

Selective Serotonin Reuptake Inhibitors (SSRIs)

Generic Name	Taken during THIS current episode? (√)	Took at least this dose *at least 8 weeks?* (√)				Only for those taken at minimum therapeutic dose for at least 8 weeks: Based on subject's feedback, indicate the amount (%) of improvement in depression he/she reported when they feel it was working at its best. A. 75% to 100% B. 50% to <75% C. 26% to <50% D. ≤ 25%
		Minimally adequate dose		Minimal dose at optimal level		
fluvoxamine		25mg/d		150mg/d		
paroxetine		10/12.5mg/d		60/75mg/d		
fluoxetine		10 mg/d		60 mg/d		
sertraline		25 mg/d		150 mg/d		
citalopram		10mg/d		60mg/d		
escitalopram		5 mg/d		30 mg/d		
vilazodone		30 mg/d		80 mg/d		
vortioxetine		5 mg/d		20 mg/d		

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Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

Generic Name	Taken during THIS current episode? (√)	Took at least this dose for *at least 8 weeks?* (√)				Only for those taken at minimum therapeutic dose for at least 8 weeks: Based on subject's feedback, indicate the amount (%) of improvement in depression he/she reported when they feel it was working at its best. A. 75% to 100% B. 50% to <75% C. 26% to <50% D. ≤ 25%
		Minimally adequate dose		Minimal dose at optimal level		
venlafaxine / venlafaxine XR		75 mg/d		250 mg/d		
duloxetine		30mg/d		120mg/d		
desvenlafaxine		50mg/d		100mg/d		
milnacipran		50mg/d		200mg/d		
levomilnacipran		20mg/d		120mg/d		

Other Antidepressants

Generic Name	Taken during THIS current episode? (√)	Took at least this dose for at least 8 weeks? (√)				Only for those taken at minimum therapeutic dose for at least 8 weeks: Based on subject's feedback, indicate the amount (%) of improvement in depression he/she reported when they feel it was working at its best. A. 75% to 100% B. 50% to <75% C. 26% to <50% D. ≤ 25%
trazodone		200mg/d		600mg/d		
bupropion		150mg/d		450mg/d		
mirtazapine		7.5 mg/d		45 mg/d		
mianserin		20 mg/d		90 mg/d		
opipramol		150 mg/d		300 mg/d		
nefazodone		300 mg/d		600 mg/d		
agomelatine		25 mg/d		50 mg/d		
tianeptine		37.5 mg/d		75 mg/d		
reboxetine		4 mg/d		8 mg/d		
esketamine		56 mg		84 mg		
dextromethorphan/bupropion		45/105mg		90/210mg		

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Section II. FDA-Approved Medications added to Augment /Boost Antidepressant Effect

Instructions:

1. Please **check** (√) the names of any medication you have taken to augment or boost the antidepressant effect during **THIS CURRENT EPISODE** of depression.
2. Please **check** (√) if the subject took at least this dose for at least 8 weeks in combination with an antidepressant treatment from Section I.
3. Please indicate the name of antidepressant treatment from Section I this drug was taken with to augment /boost its antidepressant effect.
4. Please indicate the amount (%) of improvement in depression that the patient reported when they felt this combination was working at its best.

Generic Name	Taken during THIS current episode? (√)	Took at least this dose for *at least* 8 weeks in combination with an antidepressant treatment from Section I**? (√)		Name of Antidepressant Treatment from Section I (see above) this drug was taken with	Only for those taken at minimum therapeutic dose for at least 8 weeks: Based on subject's feedback, indicate the amount (%) of improvement in depression he/she reported when they feel the combination was working at its best. A. 75% to 100% B. 50% to <75% C. 26% to <50% D. ≤ 25%
Aripiprazole		5 mg/d			
Quetiapine		200 mg/d			
Brexpiprazole		1 mg/d			
Cariprazine		1.5 mg/d			

**The antidepressant treatment from Section I must also have been taken at the minimum therapeutic dose during the 8 weeks that the medication was taken to augment/boost antidepressant effect.

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**
Did you receive transcranial magnetic stimulation (TMS) during **this current** episode (please circle one): **YES** **NO**

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11.16 Prohibited and Permitted Concomitant Medications

This list of medications is not all inclusive: please contact the Medical Monitor for any questions related to the subject's current concomitant medication(s). Additional concomitant medications may be allowed on a case-by-case basis at the discretion of the Investigator, the Medical Monitor, and the Sponsor.

The prohibited medications listed should be discontinued for 5 half-lives, whichever is longer prior to the first dose of SM.

Where washout of prohibited medications is required prior to baseline, tapering rates are at the discretion of the Investigator and are to be determined on an individual basis, with consideration to subject state, dose, and known pharmacokinetics of the medication being discontinued. The subject must be consented before any discontinuation, or any tapering is started.

Note: *if a medication is part of the antidepressant treatment (FDA approved at a stable dose) regimen initiated prior screening, it must be continued until the end of the study.*

11.16.1: Permitted Concomitant Medications

Permitted concomitant medications for pre-existing medical conditions should be taken at a stable dose for at least 3 months prior to Screening or as otherwise specified in the list below:

Drug Class/Medications	PRN Use	Comments
Antidepressants (refer to Appendix 11.17) for the FDA approved antidepressants allowed for this study)		Only **1** of the predefined oral antidepressant treatment options are permitted as specified in the medication list of the ATRQ A second antidepressant or an augmentation therapy at screening, must be discontinued at least 5 half-lives prior to baseline per the Investigator's decision
Antidiabetic medication(s) (e.g., metformin, sulfonylureas, DDP-4 inhibitors, SGLT-2 inhibitors, and GLP-1 agonists)		Allowed, if on a stable regimen for at least 3 months prior to Screening
Antihypertensive medication(s): angiotensin-converting-enzyme (ACE) inhibitors, beta-blockers, angiotensin receptor blockers and calcium-blockers (alone or in combination with diuretics)		Allowed, if on a stable regimen for at least 2 weeks before Screening

Drug Class/Medications	PRN Use	Comments
Antihistamine (eg, loratadine, cetirizine)	Yes	Allowed for seasonal allergies
Antimigraine medication(s), and combinations: NSAIDs, antihistamines, antiemetics, corticosteroids, muscle relaxants, beta-blockers, calcium channel blockers and calcitonin gene-related peptide receptor (CGPR) blockers		Allowed, if used for migraine prevention and on a stable regimen for at least 3 months before screening. *Note: Antimigraine medications for mood disorders (including bipolar disorders) are excluded. Rescue or prn use is not allowed.*
Anti-retroviral for HIV therapy	No	Allowed if on a stable regimen for at least 6 months prior to screening
Aspirin (81mg) for cardiovascular protection		
Benzodiazepines for insomnia: • 2 mg/day lorazepam, • 0.5 mg/day clonazepam • 30 mg/day flurazepam	Yes	Allowed, if on a stable regimen 4 weeks before screening Benzodiazepines should be taken more than 12 h prior to any study visits Newly prescribed benzodiazepines and/or an increment of the existing dose are prohibited during the study
Bisphosphonates (eg, alendronate)		
Cholesterol-lowering agents (e.g., statins, gemfibrozil)		Allowed, if on a stable regimen for at least 3 months prior to Screening
Corticosteroids (oral, IV or IM, Inhaled, intranasal, topical, and ophthalmic steroids)	Yes	Inhalers for asthma are allowed if the subject has a stable asthma control and no changes for the last 6 months prior to Screening Intermittent IM/IV corticosteroids are allowed
Cough/cold remedies (i.e., acetaminophen, ibuprofen)	Yes	Intranasal decongestants are allowed.
Diphenhydramine	Yes	Allowed if taken more than 12 h prior to any study visit.
Diuretics		Allowed if on a stable regimen for at least 2 weeks before Screening.

Drug Class/Medications	PRN Use	Comments
EMLA® or other numbing cream for venipuncture	Yes	
Esketamine and off-label ketamine		Responders who have taken esketamine or off-label ketamine for the treatment of depression more than 6 months prior to screening and discontinued it are eligible Other uses of ketamine should be discussed with the MM for approval
Gabapentin and Pregabalin		Allowed, if on a stable regimen for at least 3 months prior to Screening Gabapentin and Pregabalin should be taken in the evening
Medical cannabis prescribed for medical conditions other than depression, seizures and insomnia		Medical cannabis is allowed if taken on a stable regimen for at least 3 months prior to Screening
Non-benzodiazepine sleep medications: • Zolpidem • Zaleplon • Ramelteon • Tasimelteon	Yes	Allowed, if the medication has been taken at the same dose for at least 4 weeks prior to Screening Dose increment is prohibited during the study
Non-stimulants (atomoxetine, clonidine and guanfacine)		Allowed only in subjects with an established ADHD diagnosis Treatment much be confirmed with prescription records
Nutritional supplements (eg, multivitamins, fish oil, melatonin)	Yes	
Over-the-counter NSAIDs	Yes	
Paxlovid		
Psychostimulants (eg, amphetamine, methylphenidate, modafinil)		Allowed only in subjects with an established ADHD diagnosis. Treatment much be confirmed with prescription records.
Proton-pump inhibitors and H2 blockers		Allowed if on a stable regimen for at least 3 months prior to Screening
Thyroid hormone supplement for treatment of thyroid condition only (not for depression)		During the study TSH levels will be monitored

Drug Class/Medications	PRN Use	Comments
Trazodone for insomnia only (150 mg/day or less)	Yes	Allowed, if on the same low dose for at least 3 months prior to Screening

ACE = angiotensin-converting enzyme; ADHD = attention-deficit/hyperactivity disorder; IM = intramuscular; IV = intravascular; NSAID = nonsteroidal anti-inflammatory drug; PRN = pro re nata (as needed); TSH = thyroid stimulating hormone.

11.16.2: Prohibited Concomitant Medications

Drug Class/Medications	Comments
Amantadine	
Anorexiants (eg, phentermine, phendimetrazine)	
Antibiotics (cefaclor, ceftizoxime, cephaloridine, penicillin G), and antiviral (acyclovir, valacyclovir, ganciclovir, oseltamivir carboxylate)	*Note:* The e*fficacy of these antibiotics will be minimally affected by SM, we recommend using a different class*
Anticholinesterase inhibitors	
Antipsychotics and long-acting injectable	
Anti-Parkinson medications (apomorphine, L-dopa, carbidopa-levodopa, COMT inhibitors, MAO-B inhibitors)	
Baclofen	
Barbiturates	
Chloral hydrate, valerian	
Dextromethorphan	
Epidiolex	Discuss with Medical Monitor for any newly approved cannabinoids.
Esketamine and off-label Ketamine use for the treatment of depression <6 months prior to screening.	*Note: Use of Esketamine and off-label Ketamine is allowed for the treatment of depression in responders if taken >6 months prior to screening and discontinued*
Eszopiclone	
Famotidine	*Note: efficacy of Famotidine can be minimally affected by SM, we recommend a different class of antiacid*

Drug Class/Medications	Comments
Furosemide	*Note: efficacy of Furosemide can be minimally affected by SM, we recommend a different diuretic*
Ketanserin	
Insulin	
Lithium, lamotrigine	
Memantine	
Methotrexate	*Note: efficacy of Methotrexate can be minimally affected by SM, when possible we recommend using a different class of medication*
Viloxazine	
Opioids, tramadol	
Induced-QTc prolongation medications such as (not limited to): quinidine, disopyramide, chlorpromazine, haloperidol, risperidone, thioridazine, azithromycin, erythromycin, fluoroquinolones, levofloxacin, moxifloxacin, ketoconazole, terfenadine and astemizole	
Reserpine	
Scopolamine	
St. John's Wort	
Tricyclic antidepressants	
Thyroxine/ triiodothyronine (T3), thyroid hormone prescribed for depression	
Trazodone (>150 mg/day)	Trazodone treatment before screening should be discontinued for a minimum of 5 half-lives before baseline.
Warfarin, anticoagulants medications, coumarins and indandiones, factor Xa inhibitors, heparins, antiplatelets, direct thrombin inhibitors	

COMT = catechol-O-methyltransferase; MAO-B = monoamine oxidase B; QTc = corrected QT interval; SM = study medication; T3 = triiodothyronine

11.17 Approved Antidepressant Treatment

This list includes all the FDA approved ADTs allowed in the study including the adequate doses for the non-geriatric population (see Appendix 11.15 for the doses in the geriatric population).

Subjects should be on one of the medications listed at a stable therapeutic dose for at least 2 weeks before screening. If a subject is taking a second ADT or augmentation therapy at screening, the Investigator should decide if it is medically appropriate to discontinue the second drug before randomization. In that case, the second drug should be washed out at least 5 half-lives prior to baseline. If not, the subject should be excluded from the study.

Selective Serotonin Reuptake Inhibitors (SSRIs)

Drug Name	Commercial name	Minimally adequate dose	Minimal dose at optimal level
Paroxetine	PAXIL, PAXIL CR, PEXEVA	20/25/25 mg/day	60/62.5/75 mg/day
Fluoxetine	PROZAC, SARAFEM, SYMBYAX	20 mg/day	60 mg/day
Sertraline	ZOLOFT	50 mg/day	150 mg/day
Citalopram	CELEXA	20 mg/day	60 mg/day
Escitalopram	LEXAPRO	10 mg/day	30 mg/day
Vortioxetine	BRINTELLIX/TRINTELLIX	10 mg/day	20 mg/day
Vilazodone	VIIBRYD	40 mg/day	80 mg/day

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

Drug Name	Commercial name	Minimally adequate dose	Minimal dose at optimal level
Venlafaxine / Venlafaxine XR	EFFEXOR, EFFEXOR XR	150 mg/day	250 mg/day
Duloxetine	CYMBALTA	60 mg/day	120 mg/day
Desvenlafaxine	PRISTIQ, KHEDEZIA	50 mg/day	100 mg/day
Levomilnacipran	FETZIMA	40 mg/day	120 mg/day

Other Antidepressants

Drug Name	Commercial name	Minimally adequate dose	Minimal dose at optimal level
Bupropion	WELLBUTRIN	300 mg/day	450 mg/day

Dextromethorphan/Bupropion	AUVELITY	45/105 mg/day	90/210 mg/day

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