Minerva Neurosciences, Inc.

Clinical Protocol

A Randomized, Double-Blind, Parallel-Group, Placebo Controlled Study to Evaluate the Efficacy and Safety of 2 Fixed Doses (5.0 mg or 2.5 mg) of MIN-117 in Adult Patients with Major Depressive Disorder

Protocol MIN-117C03; Phase 2b
AMENDMENT 1

MIN-117

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Compliance: This study will be conducted in compliance with this protocol, Good Clinical Practice, and applicable regulatory requirements.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

SYNOPSIS

Title, Protocol Number/Phase

A Randomized, Double-Blind, Parallel-Group, Placebo Controlled Study to Evaluate the Efficacy and Safety of 2 Fixed Doses (5.0 mg or 2.5 mg) of MIN-117 in Adult Patients with Major Depressive Disorder

MIN-117C03 / Phase 2b

Objectives:

Primary

To evaluate the efficacy of 2 fixed doses (5.0 mg or 2.5 mg) of MIN-117 compared with placebo in reducing the symptoms of major depression measured by the change in Montgomery-Asberg Depression Rating Scale (MADRS) total score over 6 weeks of treatment in adult patients with major depressive disorder (MDD).

Secondary

1. To assess the change from Baseline of 2 fixed doses (5.0 mg or 2.5 mg) of MIN-117 compared with placebo over 6 weeks of treatment on:
   - The symptoms of anxiety using the Hamilton Anxiety Scale (HAM-A).
   - The severity of illness and improvement using the Clinical Global Impression of Severity Scale and Clinical Global Impression of Improvement Scale (CGI-S and CGI-I).
2. To evaluate the safety of 2 fixed doses (5.0 mg or 2.5 mg) of MIN-117 compared with placebo over 6 weeks of treatment in adult patients with MDD.

Exploratory

1. To assess the change from Baseline of 2 fixed doses (5.0 mg or 2.5 mg) of MIN-117 compared with placebo over 6 weeks of treatment on:
   - Commonly associated symptoms of MDD by using the Inventory of Depressive Symptoms - Subject-Rated [IDS-SR_{30}].
   - The ability to experience hedonic capacity by using the Snaith-Hamilton Pleasure Scale (SHAPS).
   - Cognitive function as measured by digit symbol substitution test (DSST).
   - Perception of stress using the Perceived Stress Scale (PSS).
   - Sexual functioning by using the Arizona Sexual Experiences Scale (A-SEX).
   - Sleep parameters as assessed by Somno-Art methodology.
   - Neurotrophic/inflammatory factors.
2. To explore the pharmacokinetics (PK) of MIN-117 [redacted] and assess the pharmacokinetic/pharmacodynamics (PK/PD) relationship.

Hypotheses

The primary hypothesis is that at least 1 dose of MIN-117 will be superior to placebo on the change from Baseline in the MADRS total score at the end of 6 weeks of treatment.

Study Design

This is a 6-week, 3-arm, randomized, double-blind, placebo- controlled study to investigate the safety and efficacy of MIN-117 in male and female patients with MDD, aged 18 to 65. Approximately 324 patients will be randomly assigned to 1 of 3 treatment arms, including placebo, 5.0 mg MIN-117, or 2.5 mg MIN-117, in a 2:1:1 ratio (i.e., approximately 162 patients in the placebo group and approximately 81 patients in each of the MIN-117 treatment groups).

The study design has 3 phases: a screening phase of up to 3 weeks (including washout), a 6-week double-blind treatment phase, and a post-study follow-up visit, occurring approximately 2 weeks after completing the double-blind treatment phase.

Screening Phase: Patients with an acute exacerbation of a major depressive episode will be screened for this study. Screening will include informed consent (for the overall study as well as for optional pharmacogenomic research), evaluation for eligibility in the study, and assessment of medical history . Patients must meet Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5) diagnostic criteria for moderate to severe MDD, with anxious distress and without psychotic features. The diagnosis should be confirmed by the Structured clinical interview for DSM-5 (SCID-5). Patients will undergo additional physical and psychiatric evaluations, as well as safety evaluations. If patients give informed consent to participate and meet all study entry criteria at Screening, they will be tapered off their current psychotropic medications. Patients will be free of any psychotropic medications for a period of 1 week [or 2 weeks for a monoamine oxidase (MAO) inhibitor, 4 weeks for fluoxetine] prior to randomization.

Double-blind Treatment Phase: After at least 1-week of psychotropic drug-free period, patients will undergo evaluation for eligibility, and if they still meet the study entry criteria, they will be randomly assigned in a 2:1:1 ratio to receive placebo, 5.0 mg MIN-117, or 2.5 mg MIN-117,respectively, once daily for 6 weeks. Clinic visits will occur at Visits 2, 3, 4, and 5/Early Withdrawal (Weeks 1, 2, 4, and 6, respectively).

Post-Study Visit: At the end of the study, patients will be evaluated for safety/tolerability at the Post-Study Visit, approximately 2 weeks after completing the Double-blind Treatment Phase. Any patient who terminates from the study early will undergo the Early Withdrawal visit procedures and will have a Post-Study Visit within approximately 2 weeks.

Study Population

Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for participation in this study:

1. Patients must be able to read and understand the consent forms, complete study-related procedures, and communicate with the study staff.

2. Patients must have provided written consent to participate in the study and understand that they are free to withdraw from the study at any time.
3. Patients must have signed the informed consent form for pharmacogenomic research indicating willingness to participate in the pharmacogenomic component of the study in order to participate in the optional pharmacogenomic component of this study. Refusal to consent for this component does not exclude a patient from participation in the clinical study.
4. Patients must be aged 18 to 65 years, inclusive, at Screening (Visit 1).
5. Meet DSM-5 criteria for diagnosis of moderate or severe[a] major depression with anxious distress and without psychotic features at Screening based on clinical assessment and on the SCID-5 (DSM-5 codes: 296.32, 296.33; ICD-10 codes: F33.1, F33.2). Their major depressive episode must be deemed "valid" using the Massachusetts General Hospital (MGH) SAFER[b] criteria interview administered by remote, independent raters.
6. Patients must be within a body mass index (BMI) of ≥ 18 to < 35 kg/m^2 [BMI = weight (kg)/height (m)^2] at Screening (Visit 1).
7. Patients have a history of at least one previous episode of depression prior to the current episode.
8. Patient must have been treated with an antidepressant administered at an adequate dose and duration in the past for the treatment of Major Depression. An adequate treatment is defined as an antidepressant treatment for at least 4 weeks at at least the minimum therapeutic dose, for any particular antidepressant.
9. Current major depressive episode of at least 4 weeks in duration.
10. At Screening (Visit 1) and Baseline (Visit 2), patients must have a score ≥ 40 on the patient rated IDS-SR$_{30}$.
11. At Screening (Visit 1) and Baseline (Visit 2), patients must have a score ≥ 18 on HAM-A.
12. At Screening (Visit 1) and Baseline (Visit 2), patients must have a score ≥ 4 on the investigator-rated CGI-S.
13. Patients must be outpatients at the time of randomization (Baseline [Day 1]).
14. Patients must be in good general health prior to study participation with no clinically relevant abnormalities as assessed by the investigator and determined by: medical history, physical examination, vital signs, blood chemistry, hematology, urinalysis, and electrocardiogram (ECG).

[a] Several symptoms in excess of those required to make the diagnosis of MDD AND symptoms markedly interfere with occupational functioning or with usual social activities or relationships with others.

b The acronym SAFER stands for interview's attention to the following criteria: State versus trait; Assessability; Face validity; Ecological validity; and Rule of three Ps [pervasive, persistent, and pathological].

15. If female, the patient must:
    - be post-menopausal, or
    - have had a hysterectomy or tubal ligation or be otherwise incapable of pregnancy, or
    - must agree to consistent use of 2 methods of contraception for the duration of the study and until 90 days after the last dose of study medication. One of which must be a highly effective method defined as one that results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly. The following highly effective contraception methods acceptable for this study are hormonal contraception (oral or parenteral hormonal contraceptive) or placement of an intrauterine device. The following methods can be used as a second form of contraception during the study: Barrier methods for female patients include their partner's use of a condom or the subject's use of an occlusive cap (diaphragm or cervical/ vault caps) with spermicidal foam, gel, film, cream or suppository.
16. If male with partner of childbearing potential, must be willing to use one barrier method of contraception with his partner throughout the study (a condom or his partner's use of an occlusive cap [diaphragm or cervical/ vault caps]). His partner must also be using a highly effective method of birth control defined as one that results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly such as sterilization, implants, injectables, combined oral contraceptives, and intrauterine devices for up to 90 days after the last dose of study treatment. The patient must agree to inform the investigator if his partner becomes pregnant during the course of the study.
17. Male patients who have been sterilized or have partners of non-childbearing potential (including homosexual men) are required to use one barrier method of contraception. This is to prevent unintended exposure of the partner to the study drug via seminal fluid (for male subjects, this must be a condom or their partner's use of an occlusive cap [diaphragm or cervical/vault caps].
18. Female patients of childbearing potential must have a negative serum pregnancy test at Screening (Visit 1) and negative serum and urine pregnancy test at Baseline (Visit 2)

<u>Exclusion Criteria</u>

Potential patients who meet any of the following criteria will be excluded from participating in the study:

1. A DSM-5 diagnosis of current (active): panic disorder, obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD), anorexia nervosa, or bulimia nervosa.
2. History or current diagnosis of a psychotic disorder, bipolar disorder, mental retardation, or borderline personality disorders, mood disorder with postpartum onset, somatoform disorders, fibromyalgia, or idiopathic medical conditions.
3. At significant clinical risk for suicidal or violent behavior.

4. History of treatment within last 6 months with electroconvulsive therapy (ECT), Vagus Nerve Stimulation (VNS), Deep Brain Stimulation (DBS), or Transcranial Magnetic Stimulation (TMS).
5. Potential patient who in the opinion of the investigator should not discontinue, or participate in washout of a prohibited concomitant medication.
6. Potential patient who demonstrate a greater than 25% decrease in depressive symptoms as reflected by the IDS-SR_{30} total score from Screening visit to Baseline visit.
7. Active cardiovascular disease (including but not limited to: atrial fibrillation or flutter, second and third-degree atrioventricular heart block, resting supraventricular tachycardia >100 beats per minute, unstable ischemic heart disease, valvular abnormality, sick sinus syndrome or other condition requiring pacemaker) or diastolic blood pressure > 105 mmHg.
8. Any serious, untreated, or unstable illnesses, such as: liver or renal insufficiency.
9. Any significant pulmonary, endocrine, or metabolic disturbances.
10. Documented disease of the central nervous system that could interfere with the study assessments (including but not limited to: stroke, tumor, multiple sclerosis, Parkinson's disease, Alzheimer's disease, Huntington's disease, seizure disorder requiring current anti-convulsants, traumatic brain injury or trauma, and neurosyphilis.
11. Hypothyroidism or hyperthyroidism, unless stabilized by appropriate medication for at least 3 months prior to Screening (a normal thyroid-stimulating hormone [TSH] is required prior to randomization at Baseline).
12. Any medical condition that can potentially alter oral enteral absorption (e.g., gastrectomy), metabolism (e.g., liver failure), or excretion (e.g., renal failure) of the study drug.
13. History of alcohol or substance use disorders (except nicotine and caffeine) meeting DSM-5 criteria within 1-year prior to Screening visit.
14. Positive alcohol and urine drug screen for opiates, cocaine, barbiturates, tetrahydrocannabinol, methadone, tricyclic antidepressants, benzodiazepines and amphetamine/methamphetamine at Screening or Baseline. Patients with positive testing due to prescribed benzodiazepines, tricyclic antidepressants, barbiturates, or opiates at Screening are accepted but must test negative at Baseline (Visit 2).
15. Male patients who have pregnant partners.
16. Female patients who are breastfeeding.
17. Received an experimental drug or used an experimental medical device within 60 days before the planned start of treatment (Day 1) or have participated in 2 or more clinical trials in the previous 2 years.
18. QTcF interval at Screening or Baseline greater than 450 msec for males and 470 msec for females.
19. Patients requiring treatment with drugs likely to prolong QT.

20. Patients with known hypersensitivity to MIN-117 or placebo or their excipients (refer to Section 13.1 of the protocol).
21. Positive hepatitis B surface antigen, or hepatitis C antibody or Human Immunodeficiency Virus (HIV) 1 and 2 antibodies at Screening.
22. Employees of the investigator or study center, when the employee has direct involvement in the proposed study or other studies under the direction of that investigator or study center; also family members of the employee or the investigator.

Treatments

Patients will be free of any psychotropic medications for a period of 1 week (or 2 weeks for a MAO inhibitor, 4 weeks for fluoxetine) prior to randomization. Eligible patients will the be randomized in a 2:1:1 ratio to the following groups:

- Placebo
- 5.0 mg MIN-117
- 2.5 mg MIN-117

Treatments will be administered orally, once a day in the morning for up to 6 weeks.

Efficacy Evaluations

The primary efficacy endpoint will be the change in MADRS total score from Baseline (i.e., the start of double-blind treatment) to the end of the double-blind treatment period (i.e., Week 6). The primary comparisons will be between each MIN-117 dose group (5.0 mg and 2.5 mg) and the placebo group.

Secondary and exploratory efficacy evaluations include the: HAM-A, CGI-S, CGI-I, IDS-SR_{30}, SHAPS, DSST, PSS, ASEX, and sleep parameters as assessed by Somno-Art (at select sites).

Safety Evaluations

Safety and tolerability will be assessed by monitoring adverse events, clinical laboratory tests (including hematology, serum chemistry, urinalysis, lipid profile, and pregnancy tests), vital sign assessments, physical and neurologic examinations, and ECGs. Suicidal ideation/behavior will be assessed using the Columbia Suicide Severity Rating Scale (C-SSRS).

Pharmacokinetic Evaluations

Blood samples (6 mL) for assessing MIN-117 concentration in plasma will be obtained at Baseline (Visit 2), during the double-blind period at Weeks 2, 4, and 6 (Visits 3, 4, and 5), and during the Post-Study Visit (Visit 6). Samples will be taken at pre-dose (within 1 hour of dosing) and at approximately 2 to 4 hours after dosing (C_{max}) at Baseline (Visit 2) and Weeks 2, 4, and 6 (Visits 3, 4 and 5/Early Withdrawal). Only 1 sample will be taken at the Post-Study Visit (Visit 6).

Pharmacodynamic Evaluations

Blood samples will be collected for pharmacodynamic assessment of brain derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF), vascular

endothelial growth factor (VEGF), insulin-like growth factor-1 (IGF-1), fibroblast growth factor-2, C-reactive protein, cortisol, amyloid-A, interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and interleukin-10 (IL-10) at Baseline and Week 6 (Visit 5).

Statistical Methods

Sample Size Determination

The sample size for this study is based on the assumption of a treatment difference of at least 4 points in the mean change from Baseline to end point in MADRS total score between any MIN-117 dose group and placebo. A standard deviation of 9 in the change in MADRS total score from Baseline is used. Using the Bonferroni multiplicity adjustment for multiple comparisons of 2 MIN-117 dose groups with placebo and assuming an allocation of 2:1:1 for placebo and the 2 MIN-117 doses, 146 patients in the placebo group and 73 patients in each MIN-117 dose group are required to detect the treatment difference of 4 points with a power of 80% at an overall 2-sided significance level of 0.05. When adjusted for a rate of 10% of patients who will not have either Baseline or post-Baseline efficacy assessments, the required number of patients becomes 162 for the placebo group and 81 for each of the two MIN-117 dose groups. Therefore, the total number of patients across the 3 treatment groups will be 324.

Efficacy Analyses

The intent-to-treat analysis set is defined as all randomized patients who receive at least 1 dose of study drug during the 6-week double-blind period. This analysis set will be used for efficacy and safety analyses of the 6-week double-blind period. Analyses of change from Baseline will include only patients who have both Baseline and post-Baseline data during the 6-week double-blind period.

The primary efficacy endpoint will be the change in the MADRS total score from Baseline to Week 6. This endpoint will be analyzed using a mixed model repeated measures (MMRM) model with treatment arm (5.0 mg MIN-117, 2.5 mg MIN-117, and placebo), pooled study center (by country or region based on enrollment), visit, and treatment arm-by-visit interaction as fixed effects, patient nested in treatment as random effect, and Baseline total MADRS score as covariate. An unstructured covariance matrix will be used to model the covariance of within-patient scores. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. In this analysis in which the MMRM is fitted to all post-Baseline data, patients in the intent-to-treat (ITT) analysis set who do not have complete data will still contribute to the estimates at Week 6, but will have less weight in the analysis than those patients with complete data. Comparisons against placebo will be performed using the appropriate contrasts from this model at Week 6. An analysis of observed scores available at each visit will also be performed.

The adjustment for multiplicity within the family of primary hypotheses will utilize the conventional Hochberg procedure for the purpose of reporting of results. This procedure will allow the null hypothesis of no treatment difference for both the 5.0 mg and 2.5 mg doses versus placebo to be rejected if largest p-value of comparing either of these 2 doses versus placebo is at or below 0.050. Otherwise, the lowest of these 2 p-values must be at or below 0.025 to allow for rejecting the null hypothesis for the representative dose.

The overall type I error rate for testing the 2 MIN-117 doses versus placebo for the primary and the key secondary endpoint will be controlled at the 2-sided 0.05 level. The primary

family of hypotheses (corresponding to the primary endpoint) and the secondary family of hypotheses (corresponding to the key secondary endpoint, the change from Baseline in HAM-A total score) will be tested in a sequential manner with suitable adjustment for multiplicity within the family of primary hypotheses and within the family of the secondary hypotheses such that a MIN-117 dose versus placebo null hypothesis contrast testing within the secondary family can be evaluated only when the same null hypothesis contrast in the primary family was rejected.

Sensitivity analyses of the primary endpoint will also be performed and will be detailed further in the statistical analysis plan. These will include an analysis of covariance (ANCOVA) model with factors for treatment and region and Baseline MADRS total score as a covariate. In this analysis, patients without a MADRS total score at Week 6 will have an earlier post-Baseline score imputed using the last-observation-carried-forward (LOCF) method. Other sensitivity analyses may also be performed to investigate the robustness of treatment estimates to the observed pattern of, and/or reason for, early withdrawals.

The change from Baseline in CGI-S and observed CGI-I scores will be analyzed by means of an ANCOVA of ranked data, with treatment (MIN-117 and placebo) as a factor, and Baseline CGI-S value as a covariate.

Change from Baseline for efficacy parameters, IDS-SR_{30}, SHAPS, DSST, PSS, A-SEX, and sleep parameters will be analyzed using the same MMRM model and weighted combination test procedure as described above.

Pharmacokinetic Analyses

Individual plasma levels of MIN-117 [redacted] will be tabulated with the corresponding time related to study drug administration. Descriptive statistics will be summarized for MIN-117 [redacted]. Population pharmacokinetic analysis of plasma concentration-time data of MIN-117 [redacted] will be performed using nonlinear mixed-effects modeling. Data may be combined with those of a selection of Phase 1 studies to support a relevant structural model. Available patient characteristics (demographics, laboratory variables, genotypes, etc.) will be tested as potential covariates affecting pharmacokinetic parameters.

Safety Evaluations

All patients randomized to treatment who receive at least one dose of double-blind study drug will be included in the safety analyses. Summary statistics will be provided for all safety data using appropriate descriptive statistics adverse events, C-SSRS, laboratory tests, ECGs, and vital signs.

TIME AND EVENTS SCHEDULE

Procedures and Evaluations	Screening	Baseline	Double-Blind Phase			Post Study Follow-Up
Visit#[a]	**1**	**2**	**3**	**4**	**5 / EW[b]**	**6**
Week	**-3**	**1**	**2**	**4**	**6**	**8**
Day	**-21 to -1**	**1**	**15**	**29**	**43**	**57**
Screening/Administrative						
Informed consent	X					
Pharmacogenomic informed consent[c]	X					
Inclusion/exclusion criteria	X	X				
Medical history, SCID-5, MGH-SAFER	X					
Prior medications	X	X				
Preplanned surgery/procedures	X					
Height	X					
Pregnancy test[d]	X	X		X	X	X
Alcohol and Drug Screen	X	X				
TSH, serology	X					
Taper of psychotropic drugs	X[e]	X[e]				
Randomization		X[f]				
Study Drug						
Administer/Dispense study drug		X	X	X	X[g]	
Study drug accountability			X	X	X	
Pharmacokinetics						
Blood sample collection[h]		X	X	X	X	X
Pharmacodynamics						
Blood sample collection		X			X	
Pharmacogenomics						
Blood sample collection		X[i]				
Efficacy						
Investigator-Rated: MADRS, HAM-A, CGI-S	X	X	X	X	X	
Investigator-Rated: CGI-I			X	X	X	
Investigator-Rated: DSST		X	X	X	X	
Subject-Rated: SHAPS, A-SEX	X	X	X	X	X	
Subject-Rated: IDS-SR_{30}	X	X			X	
Subject-Rated: PSS		X			X	
Sleep recording (Somno-Art)[j]	X	X			X	
Safety						
Physical examination	X	X			X	X
12-Lead ECG (triplicate)[k]	X	X		X	X	X
Vital signs, temperature, weight[l]	X	X	X	X	X	X
Clinical laboratory tests[m]	X	X			X	X
C-SSRS	X	X	X	X	X	X
Adverse Events	Continuous					
Concomitant therapy	Continuous					

Abbreviations and footnotes on the following page.

Abbreviations: A-SEX = Arizona Sexual Experiences Scale; CGI-I = Clinical Global Impression of Improvement Scale; CGI-S = Clinical Global Impression of Severity Scale; C-SSRS = Columbia Suicide Severity Rating Scale; DSST = digit symbol substitution test; HAM-A = Hamilton anxiety scale; IDS-SR_{30} = Inventory of Depressive Symptoms - Subject-Rated; MADRS = Montgomery-Asberg Depression Rating Scale; PSS = Perceived Stress Scale; SCID-5 = Structured clinical interview for DSM-5; SHAPS = Snaith-Hamilton Pleasure Scale.

[a] Visits 3 to 6 may occur within a ±3-day window relative to Baseline (Visit 2). Visit 2 may occur within +7 day window relative to Visit 1 (i.e., the sceening period may be extended to 28 days) upon Sponsor's decision.

[b] Visit 5 represents the end-of-treatment or early withdrawal (EW) visit, and patients who discontinue the study prematurely should undergo all assessments indicated for this visit.

[c] To participate in the optional pharmacogenomic component of this study, patients must sign the pharmacogenomic informed consent form, indicating their willingness to participate.

[d] For all women of childbearing potential, serum pregnancy testing will be performed at Screening (Visit 1), Baseline (Visit 2), and post study visit (Visit 6). Urine pregnancy testing will be performed at Baseline (Visit 2), and Visits 4, 5, and 6.

[e] After meeting eligibility criteria during their Screening visit, patients will taper off their current psychotropic medications. Patients will be free of any psychotropic medications for a period of 1 week (or 2 weeks for a MAO inhibitor, 4 weeks for fluoxetine) prior to randomization.

[f] All procedures (except dispensing of study medication) should be completed on Day 1 before randomization.

[g] Only drug administration at Visit 5.

[h] Samples will be obtained within 1 hour prior to dosing, and approximately 2 to 4 hours after dosing (the approximate time of maximum plasma concentration for MIN-117) on Visits 2, 3, 4, and 5. Additionally, 1 sample will be taken on Visit 6.

[i] A 10-mL blood sample will be collected only from patients who give informed consent for the pharmacogenomic component of this study. A sample collected at a later time point does not constitute a protocol violation and would not require protocol amendment.

[j] Sleep recording by using Somno-Art for 1 night after Screening, 1 night before dosing, and 1 night after dosing on Visit 2 and Visit 5.

[k] Triplicate ECGs to be performed at least 1 minute apart within 5 minutes, while the patient is supine for ≥10 minutes.

[l] Patients will be weighed clothed (lightly) and without shoes.

[m] Clinical laboratory tests will include hematology, serum chemistry (including serum lipid profile, and fasting blood glucose), and urinalysis. Patients must fast for 8 hours before the blood sample is taken.

ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
APD_{90}	Action potential duration at 90%
aPTT	Activated partial thromboplastin time
A-SEX	Arizona Sexual Experience
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
BSE	Bovine spongiform encephalopathy
BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
BUN	Blood urea nitrogen
C-SSRS	Columbia Suicide Severity Rating Scale (C-SSRS)
CGI-I	Clinical Global Impression - Improvement Scale
CGI-S	Clinical Global Impression - Severity Scale
CHMP	Committee for Medicinal Products for Human Use
CL	Clearance
C_{max}	Maximum drug concentration (in plasma or serum)
CMS	Chronic mild stress
CNS	Central nervous system
CPK	Creatinine phosphokinase
CRO	Contract research organization
CSF	Cerebrospinal fluid
CYP	Cytochrome
DA	Dopamine
DAT	Dopamine transport
DBS	Deep brain stimulation
DOPAC	Dihydroxyphenylacetic acid
DSM-5	Diagnostic And Statistical Manual Of Mental Disorders-Fifth Edition
DSST	Digit Symbol Substitution Test
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECT	Electroconvulsive therapy
ED_{50}	Median effective dose
EEG	Electroencephalogram
EOS	End-of-Study
F	bioavailability
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GDNF	Glial cell line-derived neurotrophic factor
GGT	Gamma-glutamyl transferase
5HIAA	5-Hydroxyindoleacetic acid
5-HT	5-Hydroxytryptamine
5-HTT	5-Hydroxytryptamine transporter
5-HTTLPR	Serotonin transporter gene promoter polymorphism
HAM-A	Hamilton Anxiety Scale
HBsAg	Hepatitis B surface antigen
HDL	High density lipoprotein
hERG	Human ether-à-go-go-related gene

HIV	Human immunodeficiency virus
HVA	Homovanillic acid
IC_{50}	Median inhibitory concentration
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IGF-1	Insulin like growth factor-1
IL	Interleukin
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous, intravenously
IWRS	Interactive Web Response System
LC-MS/MS	Liquid chromatography-mass spectrometry
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LOCF	Last observation carried forward
MADRS	Montgomery-Asberg Depression Rating Scale
MAO	Monoamine oxidase
MB	Marble burying
MGH	Massachusetts General Hospital
MDD	Major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model repeated measures
NE	norepinephrine
NET	Norepinephrine transporter
NOAEL	No observed adverse effect level
NOEL	No observed effect level
NOR	Novel object recognition test
OCD	Obsessive compulsive disorder
8-OH-DPAT	8-hydroxy-2-(di-n-propylamino) tetralin
OR	Odds ratio
PCA	p-chloroamphetamine
PD	Pharmacodynamic
PK	Pharmacokinetic
PO	Orally, by mouth
PQC	Product quality complaint
PTSD	Post-traumatic stress disorder
QD	Quaque Die (ie, once daily)
QTc	QT interval value corrected for heart rate
QTcB	QT interval value corrected for heart rate using Bazett's formula
QTcF	QT interval value corrected for heart rate using Fridericia's formula
RBC	Red blood cell
REM	Rapid eye movement
SAE	Serious adverse event
SAFER	State versus trait, assessability, face validity, ecological validity; and Rule of three Ps [pervasive, persistent, and pathological]
SAP	Statistical Analysis Plan
SCID-5	Structured clinical interview for DSM-5
SNRI	Serotonin norepinephrine reuptake inhibitor
SSRI	Serotonin reuptake inhibitor
TEAE	Treatment-emergent adverse event
$T_{1/2}$	Terminal elimination half-life
TCA	Tricyclic antidepressant

T_{max}	Time to maximum drug concentration (in plasma or serum)
TMS	Transcranial magnetic stimulation
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
Vd/F	Volume of distribution
VEGF	Vascular endothelial growth factor
VNS	Vagal nerve stimulation
Vss	Volume of distribution at steady state
WBC	White blood cell
WHO	World Health Organization
WHO-DD	World Health Organization-drug dictionary

1. INTRODUCTION

1.1. Background on the Disease

Major depressive disorder (MDD) is a common, serious, recurrent disorder, with worldwide lifetime prevalence estimates ranging from 1% in the Czech Republic to 17% in the United States (US). Its negative impact on role functioning in various settings (e.g., school performance, marriage, parenting, and the workplace), quality of life, physical health, and life expectancy has been well-documented. Loss of work production and absenteeism due to major depressive episodes or MDD has been estimated to account for approximately 30 to 50 billion dollars in annual human capital (Kessler 2013). In fact, as of October 2015, and with an estimated 350 million sufferers, depression has been ranked by the World Health Organization as the leading cause of disability worldwide, and the prevalence is rising (WHO 2015). MDD is associated with significant comorbid medical conditions which include diabetes, hypertension, and cardiovascular disease, and there is an increased risk of early mortality in patients with MDD (Kessler 2013).

While existing therapies for this disease are available, their effectiveness is limited due to unacceptable side effects, different levels of efficacy for individual subjects requiring a physician to test, check, and alter (or change) therapies during treatment, and subject adherence due to the need for multiple daily doses (Rush 2006).

The use of antidepressants for the treatment of MDD is well established. However, effect sizes of currently available antidepressants are rather small than medium (Kirsch 2008; Turner 2008). Most subjects with major depression are best treated with a combination of antidepressants and psychotherapy. It is generally 1 to 4 weeks before antidepressants take effect. This delayed clinical response to the antidepressant makes it difficult to establish the optimal dose quickly, which is of paramount importance for the treatment of a clinically depressed subject. The individual dose is usually decided by trial and error, with the subject's previous response being the most useful guide (Spigset 1999).

1.2. MIN-117 Pharmacological Profile and Rationale as a Unique Antidepressant

MIN-117 is an investigational antidepressant belonging to a new chemical class, the benzofuran derivatives. The chemical designation is (*2S*)-1-[4-(3,4-Dichlorophenyl) piperidin-1-yl]-3-[2-(5-methyl-1,3,4-oxadiazol-2-yl)benzo[*b*]furan-4-yloxy]propan-2-ol monohydrochloride. MIN-117 is characterized by its affinity for 5-HT_{1A} pre-synaptic auto-receptors and 5-hydroxytryptamine transporters (5-HTT). The K_i values for 5-HT_{1A} receptors and 5-HTT of human were 5.0 and 0.81 nmol/L, respectively. MIN-117 acts as a serotonin reuptake inhibitor. In addition, MIN-117 has high affinity for adrenergic alpha (α)1 and serotoninergic 5-HT_{2A} and acts as antagonist to each receptor. MIN-117 is also active as a dopamine transport (DAT), by inhibiting reuptake of dopamine from the synaptic cleft. Furthermore, MIN-117 has moderate affinity for 5-HT_{2C} and also acts as a moderate norepinephrine transporter (NET) inhibitor.

For the most accurate and current information regarding the efficacy and safety of MIN-117, refer to the latest version of the Investigator's Brochure for MIN-117.

1.3. Nonclinical Studies

1.3.1. Pharmacologic Profile

An in vitro functional assay, MIN-117 showed a slight antagonist activity at 5-HT_{2B} receptor (Kb=0.79µM) and no agonist activity at 5-HT_{2B}.

MIN-117 inhibited monoamine uptake of the cells transfected with human recombinant transporters. Median inhibitory concentration (IC_{50}) values for the inhibiting effects of MIN-117 on 5-HT, norepinephrine and dopamine uptake are 6.0, 170 and 20 nmol/L, respectively. Reuptake inhibition of MIN-117 on 5-HT uptake was evaluated *in vivo* and compared with fluvoxamine, fluoxetine, and paroxetine of SSRI, venlafaxine of serotonin norepinephrine reuptake inhibitor (SNRI), and imipramine of tricyclic antidepressant (TCA). MIN-117 inhibited *ex vivo* binding to 5-HTT and 5-HT uptake and p-chloroamphetamine (PCA)-induced hyper-locomotion in rats at the dose range of 1-10 mg/kg, orally (PO) and the median effective dose (ED_{50}) values were 1.1, 7.1, and 1.7 mg/kg, PO, respectively.

The effects of MIN-117 on the release of the three main catecholamines, 5-HT, dopamine (DA) and norepinephrine (NE) were investigated in rats using microdialysis. Citalopram (10 mg/kg) was included as the reference compound of the SSRI type with clinically proven efficacy in patients with MDD. MIN-117 at the three tested doses induced modifications in the levels of the catecholamines. The findings showed no dose proportional effects. For the dose 0.1 mg/kg a very important increase in 5-HT (300%) and DA levels (235%) accompanied by some minor increases in the two metabolites dihydroxyphenylacetic acid (DOPAC) and Homovanillic acid (HVA) were observed. For the dose of 0.3 mg/kg an increase of 5-HT was observed (120%). For DA the observed increase was very important (270%) accompanied by some minor effects on DOPAC and HVA. An increase in NE levels could also be described at this dose (140%). For the dose of 3 mg/kg 5-HT levels increased (150%) concomitantly with a decrease of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) levels.

1.3.2. Safety Pharmacology

The effects of MIN-117 on the general condition and behavior, central nervous system (CNS), respiratory and cardiovascular systems, digestive system, and water and electrolytes metabolisms were investigated. In *in vivo* experiments, MIN-117 was administered orally at doses of 1, 10, and 100 mg/kg, except that the rabbit orthostatic hypotension study employed intravenous doses of 0.1, 0.3, and 1 mg/kg and oral doses of 30, 100, and 300 mg/kg. As for *in vitro* experiments, MIN-117 was applied at concentrations of 3×10^{-7}, 3×10^{-6}, and 3×10^{-5} mol/L for measurements of action potential parameters in the isolated guinea pig papillary muscle and at 2×10^{-8}, 2×10^{-7}, and 2×10^{-6} mol/L for an ion channel assay (hERG or human ether-a-go-go-related gene).

MIN-117 at 1 mg/kg PO had no effects on general condition or behavior in rats. Decrease in spontaneous activity, suppression of reactivity, and narrowing of palpebral opening were observed at ≥ 10 mg/kg. Diarrhea was also observed at 100 mg/kg. All the noted changes disappeared within 24 hours after dosing.

MIN-117 at 1 mg/kg PO had no effect on the central nervous system in rats. Decrease in body temperature was noted at ≥ 10 mg/kg, and a decrease in spontaneous locomotor

activity and an inhibition of motor coordination at 100 mg/kg. There was no pro-convulsive effect at doses up to 100 mg/kg.

The telemetry study was conducted in conscious monkeys. MIN-117 increased heart rate at 100 mg/kg, but no effects on blood pressure or ECG parameters (PR interval, QRS duration, QT interval, or QTc) at doses up to 100 mg/kg. In the *in vitro* electrophysiology studies, MIN-117 blocked hERG channel (human Ikr channel expressed in CHO cells) at IC_{50} of 0.43×10^{-6} mol/L. MIN-117 showed a prolongation of action potential duration in the isolated guinea pig papillary muscle preparations (5% prolongation for action potential duration at 90% (APD_{90}) compared to the pretreatment value) at the highest concentration of 3×10^{-5} mol/L. Effects on the orthostatic hypotension were evaluated by the head-up method in rabbits. There were no effects on any cardiovascular parameter by intravenous (IV) administration at doses up to 1 mg/kg. In the oral administration study, MIN-117 at 300 mg/kg decreased systolic and diastolic pressures after the recovery from tilting at 2, 8, 12, and 24 hours after dosing. At 100 mg/kg, low levels in diastolic pressure were also noted at 12 hours after dosing.

1.3.3. Toxicology

The toxicity of MIN-117 was characterized in rats and monkeys in oral single dose (1000 & 2000 mg/kg) and repeated dose studies (1, 3, 10, 30, 100, & 300 mg/kg) for up to 13 weeks duration.

At both doses in the single dose studies in rats, blepharoptosis was observed from 1 hour after dosing in both males and females; reddening of scrotum from 2 hours after dosing in males; and soiled perineal region from Day 1 in females. All the clinical signs disappeared by Day 10. Decreases in body weight gain were observed on Day 1 in both males and females, and continued to Day 7 in males at 2000 mg/kg.

At both doses in the single dose studies in monkeys, yellowish-white stool was observed in males and females from the day of dosing in the 2000 mg/kg group or from Day 2 in the 1000 mg/kg group and disappeared by Day 7. Increase of blood urea nitrogen (BUN) in males at both doses observed on Day 7.

At the 1000 mg/kg dose, vomiting was observed immediately after dosing in females. A decrease in triglycerides was observed in males and females and an increase of alanine aminotransferase (ALT) observed in males on Day 1. An increase in triglycerides was observed in males on Day 7.

At the 2000 mg/kg dose, soft stool was observed only on the dosing day in both males and females. Also observed was a decrease in food consumption on Day 1 and activated partial thromboplastin time (aPTT) prolongation on Day 13 in males. There was also an increase in triglycerides observed in males and females on Day 7.

In the 13-week (3, 10, 30, 100 mg/kg/day) rat study, 13 rats died or were sacrificed during the study: 8 males and 5 females at 100 mg/kg. Test article-changes in clinical signs, food consumption and body weight were only observed at 100 mg/kg/day: incomplete eyelid opening was sporadically observed until Day 7 of dosing; a decrease in body weight or suppression of body weight gain, together with a decrease in food consumption was noted from week 4; decrease in spontaneous activity and edema in the face, swelling in the extremities, and signs of deterioration were observed.

In the 13-week (3, 10, 100 and 300 mg/kg/day) monkey study, 5 monkeys died or were sacrificed during the study: 2 males and 2 females at 300 mg/kg, and 1 male at 100 mg/kg. Test article-changes in clinical signs, food consumption and body weight were observed from 100 mg/kg/day: increase in spontaneous activity for the first 2 weeks of dosing, stereotypy only at 300 mg/kg, decrease in spontaneous activity observed thereafter at 300 mg/kg and in monkey that died at 100 mg/kg; lateral position, disappearance of sound and touch response, decrease in papillary light reflex, hypothermia observed in monkeys that died or were sacrificed; soft stool, diarrhea, vomiting and emaciation; salivation observed in the latter half of the dosing in monkeys that survived at both doses; decreases in food consumption and body weight.

No lethal effect of MIN-117 was seen up to 30 mg/kg/day in rats and 10 mg/kg/day in monkeys in any of the repeated dose toxicity studies performed in both species. In the 13-week long-term toxicity studies, the No Observable Adverse Effect Level (NOAEL) was considered to be 3 mg/kg/day in rats, and 10 mg/kg/day in monkeys.

Reprotoxicity studies were performed in rats and rabbits. In rats, the NOAEL for maternal parameters was considered to be 30 mg/kg/day (corresponding to an AUC0-t of 18540 ng.h/mL and a C_{max} of 850 ng/mL for MIN-117). The No Observed Effect Level (NOEL) for effects on embryo-fetal development was considered to be 30 mg/kg/day. In the pregnant rabbits after oral (gavage) administration of MIN-117 the NOAEL for maternal toxicity is therefore 5 mg/kg/day (corresponding to a mean $AUC_{0\text{-}24h}$ of test item MIN-117 of 578 ng.h/m). There was no overt teratogenic potential of MIN-117. The NOAEL for embryo-foetal toxicity is therefore set at 45 mg/kg/day (corresponding to a mean $AUC_{0\text{-}24h}$ of test item MIN-117 of 3449 ng.h/mL).

No genotoxic potential of MIN-117 was demonstrated in mutagenicity tests including the Bacterial reverse mutation tests in *Salmonella typhimurium* and *Escherichia coli* and the in vitro chromosomal aberration test with Chinese hamster lung cells; and the micronucleus test in mice and the in vivo/in vitro Unscheduled DNA Synthesis test in rat hepatocytes, where animals were adequately exposed to MIN-117.

1.3.4. Pharmacokinetic Profile

Pharmacokinetic studies of MIN-117 have been performed mainly in rats and monkeys.

After oral administration of ^{14}C-MIN-117 in rats and monkeys, the plasma concentration of radioactivity reached C_{max} at 9.8 hours and 5.0 hours, respectively. It then declined with a terminal elimination half-life ($t_{1/2}$) (12 to 72 hours) of 19.9 hours in rats and 20.7 hours in monkeys and $t_{1/2}$ (72 h-t) of 33.2 hours in rats and 50.1 hours in monkeys (t: last quantifiable time point). The absorption rate estimated by dividing $AUC_{0\text{-}\infty}$, PO by $AUC_{0\text{-}\infty}$, IV was 85.3% for rats and 73.3% for monkeys.

The plasma concentration of unchanged MIN-117, detected after oral administration of MIN-117 in rats, reached the maximum level (C_{max}) at 6.0-6.8 h and then declined with a $t_{1/2}$ of 8.8 to 9.6 hours. The bioavailabilities (F) at 0.3, 1, and 3 mg/kg were 81.3, 95.5, and 95.2%, respectively. After intravenous administration at a dose of 1 mg/kg, total clearance (CL) and volume of distribution at steady state (V_{ss}) were 1.15 L/h/kg and 10.04 L/kg, respectively. In monkeys, the plasma concentration of unchanged MIN-117 reached C_{max} at 1.0 to 1.5 hours and then declined with a $t_{1/2}$ of 3.0 to 6.8 hours. F at 0.3, 1, and 3 mg/kg

were 14.4, 14.6, and 12.3%, respectively and after intravenous administration at a dose of 1 mg/kg, CL and V_{ss} were 0.78 L/h/kg and 2.40 L/kg, respectively.

Following a single oral administration to male rats, the tissue concentration of radioactivity reached the peak level at 3 hours after administration in thyroid gland, trachea, liver, stomach and small intestine and at 7 to 12 hours after administration in the other tissues. In almost all the tissues, the concentration of radioactivity was higher than that in plasma. At 3 to 24 hours after administration, relatively higher levels of radioactivity are detected in harderian gland, liver, lung, adrenal gland, pancreas, pituitary gland, fat and brown fat except gastro-intestinal tissues. At 168 hours after administration, the radioactivity concentration in all of the tissues was declined to 2% or less of the maximum concentration. Following repeated oral administration rats, mostly all radioactivity concentrations in the tissues reached their maxima at 7 h after administration on Day 1 and after 7, 14, and 21 days of administration, and declined after single, 7 days, 14 days, and 21 days of administration to 0%, 4% or less, 16% or less and 18% or less (33% or less for females) of their maxima at 168h post-dosing respectively.

Finally distribution rate of radioactivity in blood cells was 33.8% to 42.9% in rats, 8.6% to 12.2% in monkeys, and 2.1% to 9.6% in humans. The plasma protein binding rate of ^{14}C-labeled MIN-117 or unlabeled MIN-117 was 82.3 to 96.1% in rats, and over 96.5% in monkeys and humans. The protein binding rate was over 99.6% in human serum albumin, 84.4% in human ϒ-globulin, and 97.1% in human α1-acid glycoprotein.

The major route of elimination of radioactivity was fecal excretion via the bile. The excretion rates in feces of radioactivity of the dose after oral administration were 78.3% in rats and 65.2% in monkeys up to 168 hours. The enterohepatic circulation rate was 50.2% in rats.

1.3.5. Behavioral and Pharmacodynamics Studies

MIN-117 was tested in four kinds of animal models to evaluate its antidepressant effects. Successive oral administration of MIN-117 0.3 mg/kg for 3 days completely reversed the locomotor activities reduced by the handling stress in F344 rats. In this model, fluoxetine, venlafaxine and imipramine also reversed the motor activity, but the onset of these drugs was prominently slower than that of MIN-117. MIN-117 also reversed sucrose consumption of rats in the depression model of chronic mild stress (CMS). The magnitude of action of the most active doses of MIN-117 (0.001 and 1.0 mg/kg) was comparable to that of imipramine (10 mg/kg); by the end-of-treatment period the sucrose consumption in stressed animals treated with these doses was restored to the pre-stress level. The onset of action of these doses was clearly faster than that of imipramine; the enhancement of sucrose intakes reached statistical significance already following the first week of administration, compared to four weeks required by imipramine. The CMS procedure decreased the recognition index measured in the Novel Object recognition test. In stressed animals MIN-117, administered at doses of 0.001, 0.01 and 0.1 mg/kg, restored the recognition index to the level of the vehicle- or drug-treated control animals, while Imipramine was ineffective.

In the forced swimming test, MIN-117 shortened the immobility time with an ED_{50} of 15 mg/kg PO. In the marble burying (MB) test, results showed that MIN-117 suppresses the MB behavior without affecting locomotor activity in mice.

The reinforcing effect of MIN-117 was investigated in the self-administration experiment in monkeys. Results suggested that MIN-117 possessed a reinforcing effect but of very weak intensity considered compared to that of cocaine.

MIN-117 was tested in order to evaluate potential sexual side effects following acute (1 day), subchronic (7 days) and chronic (14 days) of treatment in a model of sexual dysfunction in rats. The serotonin reuptake inhibitor (SSRI) compounds Paroxetine Hydrochloride (10 mg/kg) and Citalopram (10 mg/kg) were used as reference compounds as SSRIs have a known inhibitory effect on the display of male sexual behavior. In the study, the SSRI reference compounds, Citalopram and Paroxetine, decrease sexual performance as measured by different parameters (increased latencies to display the first mount and the first ejaculation, slight reduction in the total number of ejaculations). MIN-117 had a significant effect to decrease the latency to display the first mount attempt. The dose of 0.03 mg/kg displayed a significant increase in number of mount attempts compared to vehicle group. The MIN-117 compound had no significant effect on the number of intromissions displayed by male rats, nor in the total number of ejaculations.

1.4. Clinical Studies

To date, 97 healthy subjects have received at least one oral dose of MIN-117, with 24 subjects receiving placebo, in a total of 2 completed and 1 ongoing clinical pharmacology studies (Studies Wf-516-E01, SON-117C01, and MIN-117C02, respectively). To date, 42 patients with MDD have recieved up to 6-weeks of daily dosing of 0.5 mg (N=21) or 2.5 mg (N=21) of MIN-117, with 21 patients receiving placebo, in one completed phase 2a study (MIN-117C01).

Study Wf-516-E01: assessed the safety, tolerability, PK, and PD profiles of 6 single-ascending doses of SON-117 (now known as MIN-117; 2.5, 5.0, 7.5, 10.0, 12.5, and 15.0 mg) in healthy male subjects. A total of 50 subjects participated in the study with 38 subjects exposed to MIN-117 and 12 subjects exposed to placebo.

Study SON-117C01: assessed the safety, tolerability, pharmacokinetic, and pharmacodynamic profile of 3 multiple ascending (14 days) doses (doses 1, 3, and 7.5 mg) of MIN-117 in healthy male subjects. A total of 50 subjects participated in the study with 29 subjects exposed to MIN-117, 12 to placebo, and 9 to escitalopram (positive control).

Study MIN-117C01: assessed the efficacy of MIN-117 0.5 and 2.5 mg compared to placebo in reducing the symptoms of a major depressive episode as measured by the change from Baseline in the MADRS total score over 6 weeks of treatment in a randomized, double-blind study. The study also assessed the efficacy of MIN-117 using CGI-S, CGI-I, HAM-A, A-SEX, cognitive testing, sleep parameters,and the safety of tolerability of MIN-117 as compared to placebo over a 6-week dusration of daily dosing. A total of 84 patients participated in the study with 42 patients exposed to MIN-117 (21 patients each to 0.5 mg and 2.5 mg doses), 20 to placebo, and 20 to 20 mg of paroxetine (positive control).

Study MIN-117C02: assessed the effect of food on the PK of a single MIN-117 dose in Healthy male and female subjects in a randomized, open-label, 2-way, crossover study. A total of 30 subjects completed both periods of the study and received a single 2.5 mg dose under both fasted and fed conditions. The study is currently ongoing.

1.4.1. Pharmacokinetics

Healthy Subjects

After a single oral dose, MIN-117 was rapidly absorbed, with time to maximimum drug concentration (T_{max}) occurring approximately between 2.5 and 4.5 hours post-dose. The $t_{1/2}$ of MIN-117 in plasma was between 43 and 52 hours post-dose. Dose-proportionality between 2.5 and 15 mg single oral doses was demonstrated.

[redacted]

Urine concentrations of MIN-117 [redacted] were also evaluated. Urinary excretion of MIN-117 [redacted] were very low and burdened with high inter-individual variability. Primary mechanism of elimination for [redacted] MIN-117 [redacted] appear to be non-renal clearance.

After multiple oral doses, MIN-117 was rapidly absorbed with a T_{max} varying from 3 to 4 hours. Steady state was estimated to be reached after 10 days of MIN-117 administration. Pharmacokinetic parameters (concentrations and AUCs) increased with MIN-117 dose on Day 1 and Day 14. Median T_{max} was in the same range for each MIN-117 dose on Day 1 and Day 14. Systemic clearance and apparent volume of distribution (Vd/F) were in the same range for each MIN-117 dose. Moderate value of Vd/F suggested that [redacted] MIN-117 is distributed in water and some tissues. Fluctuation index and accumulation rate were in the same range for each MIN-117 dose.

[redacted]

The accumulation ratio was around 4 multiples for the [redacted] drug with a terminal half-life of 50-60 hours [redacted] with a $t_{1/2}$ of 82 to 105 hours.

For each MIN-117 dose studied (1 mg, 3 mg, 7.5 mg), after single dose or last dose, PK parameters increased with MIN-117 exposure, for [redacted] MIN-117 [redacted].

The effect of co-administration with food is not known as yet.

Patients with MDD

Blood samples were collected during the study pre-dose and approximately 3 to 4 hours post-dose (approximate time of maximum plasma concentration for MIN-117). The respective mean plasma levels of MIN-117 [redacted] in the treatment groups were:

- MIN-117: mean post-dose levels of ≥ 4 ng/mL for the MIN-117 0.5 mg group and post-dose levels of ≥ 18 ng/mL for the MIN-117 2.5 mg group.

[redacted]

1.4.2. Efficacy

The primary efficacy endpoint of the MIN-117C01 study was change from Baseline to Week 6 in Montgomery-Asberg Depression Rating Scale (MADRS). MIN-117 treatment resulted in a reduction of depression severity as measured by MADRS total score change compared to Baseline, and showed a dose-dependent reduction in MADRS total score values at the end of the treatment phase as compared to placebo.

For the secondary efficacy analyses, MIN-117 had no effect on Clinical Global Impression—Severity Scale (CGI-S) and Clinical Global Impression—Improvement Scale (CGI-I) scores. MIN-117 treatment resulted in an improvement in Arizona Sexal Experience (A-SEX) scores after 4 weeks of treatment, which continued until the end of the 6-weeks treatment phase. Cognition assessed by the Digit Symbol Substitution Test (DSST) and Digit Span Backwards task was improved after MIN-117 treatment. No clear trend was observed for the comparison of the MIN-117 groups with placebo for the Tower of London Test.

Exploratory efficacy analyses on MADRS responder rates found all odds ratios (ORs) >1 for the MIN-117 dose groups as compared to placebo, with the largest OR at Week 4 for the 2.5 mg dose group. Concerning the influence of MIN-117 on sleep architecture and continuity, sleep parameter analysis showed only a minimal influence of MIN-117 treatment compared to placebo, in contrast to known effects of antidepressants like paroxetine where, after treatment, a number of sleep parameters deteriorated. An MDD treatment effect as measured by HAM-A scores was seen: after MIN-117 treatment, a trend of reduction in anxiety scores was seen starting at Week 2 compared to placebo treatment.
Safety

1.4.3. Safety

Healthy Subjects

Overall, single MIN-117 doses up to 15 mg and repeated MIN-117 doses up to 7.5 mg were well tolerated. No dose-limiting adverse events were reported. At this time, the most commonly reported adverse drug reactions (ADRs) related to MIN-117 include insomnia, somnolence, diarrhea, and nervousness.

In Study Wf-516-E01, no significant changes in laboratory tests, physical and neurological examinations, vital signs, or electrocardiogram (ECG) parameters (12-lead or 24-hour Holter) were observed. In particular, no symptomatic postural hypotension or clinically relevant increase in QTc duration was reported. No clinically significant prolonged QTc value was observed around T_{max}, in any subject and at any dose.

Of the 34 reported treatment emergent adverse events (TEAEs), 17 events occurred in the placebo group and 17 events occurred in the MIN-117 group. The body systems most frequently affected were the nervous system and the musculoskeletal and connective tissue body systems. These TEAEs were mild (11) or moderate (22) in severity. One vasovagal malaise was severe in intensity.

The most common TEAEs were 4 episodes of somnolence (1, placebo; 3, MIN-117 2.5 mg), and 4 episodes of back pain (1, placebo; 3, MIN-117 15 mg). Two vasovagal malaise cases were reported: one was moderate (MIN-117 15 mg) and one was severe (placebo) in intensity, both were considered not related to study drug.

Six events were considered by the investigator to be related to study drug including 2 events occurring in the placebo group: headache (1, placebo 1; 1, MIN-117 2.5 mg) and somnolence (1, placebo; 3 MIN-117 2.5 mg).

One serious adverse event was reported in the Wf-516-E01 study. The subject (MIN-117 15.0 mg group) presented with an acute paranoid psychosis 61 days post-dosing that required hospitalization and treatment with neuroleptics. This event occurred further to the End of Study (EOS) visit. According to the subject's relatives, sleep disorders and mild changes in his behavior were already noticed before he entered the study. This event was considered as severe in intensity and not related to study drug.

The maximum tolerated dose could not be established in this study as the highest dose was well tolerated.

In the SON-117-C01 study, 132 TEAEs were reported (40 with placebo, 40 with MIN-117 1 mg, 22 with MIN-117 3 mg and 30 with MIN-117 7.5 mg). The body systems most frequently affected were the Nervous system (36), Skin and subcutaneous system (26), and Gastrointestinal system (23). The most frequently reported TEAEs were headache (15 episodes: 7 with placebo, 1 with MIN-117 1 mg, 2 with MIN-117 3 mg and 5 with MIN-117 7.5 mg dose) and insomnia (10 episodes; 5 with placebo, 2 with 1 mg dose, 1 with 3 mg dose and 2 with 7.5 mg dose). All TEAEs were mild or moderate in intensity. Only 1 TEAE was rated as severe (fatigue, MIN-117 7.5 mg).

Among the reported TEAE, 62 were considered related to the study drug: 22 with placebo (66,7% of the subjects) and 40 with MIN-117: 22 with MIN-117 1 mg (60% of the subjects); 8 with MIN-117 3 mg (40% of the subjects) and 10 with MIN-117 7.5 mg (44% of the subjects).

The most frequently reported ADRs were insomnia (9 episodes: 5 with placebo,1 with MIN-117 1 mg; 1 with MIN-117 3 mg and 2 with MIN-117 7.5 mg), headache (6 episodes: 5 with placebo and 1 with MIN-117 1 mg) and diarrhea (5 episodes: 2 with placebo, 2 with MIN-117 1 mg and 1 with MIN-117 7.5 mg).

Of note, in the SON-117-C01 study, escitalopram was administered as a positive control to 9 subjects. In this group, 28 ADRs were reported (88,9% of the subjects). The most frequently reported ADRs were asthenia (5 episodes) and headache (3 episodes).

Results on the SSRI withdrawal scale indicated that there were no more self-perceived adverse events with MIN-117 than with placebo or escitalopram.

No significant biological abnormalities were evidently related to MIN-117.

Repeated doses of MIN-117 induced no clinically relevant changes in blood pressure. All mean values of supine systolic and diastolic blood pressure as well as heart rate were within the normal range. There was a trend toward a slight decrease in supine DBP with MIN-117 3 mg (Day 1, Day 14 and Day 18) when compared to placebo. The incidence of abnormal orthostatic tests was also higher with MIN-117 3 mg, although none of them were symptomatic. Heart rate tended to increase following MIN-117 3 mg administration. This

increase was observed on Day 1 starting at H4 with a maximum at H12 (MIN-117 3 mg: +15.6 ± 7.00; placebo: + 1.083 ± 7.192). A similar pattern was observed on Day 8 (max at H6) and Day 14 (max at H12). An increase in heart rate was also observed after MIN-117 7.5 mg but this effect was less marked when compared to the 3 mg dose.

All mean ECG parameters were in the normal ranges. As for vital signs, an increase in heart rate (and concomitant decrease in RR interval) was observed in the MIN-117 3 and 7.5 mg dose groups. However, all those changes were considered as clinically not relevant. With regards to QTcB, the mean changes from Baseline were mainly negative for placebo and MIN-117 1 mg. They were mainly positive for MIN-117 3 and 7.5 mg. It could be explained by the concomitant increase in heart rate. Given the study design and the high inter-subject variability, these changes were judged not clinically relevant. Only a few subjects reported QTcB values over 450 msec: 1 episode in one subject with placebo (476 msec Day 3 predose); two episodes in two subjects with MIN-117 1 mg (451 msec Day 1 T+2H and 460 msec Day 5 T+3H) and one episode in one subject with MIN-117 3 mg (453 msec Day 11 predose). No QTcB value over 480 msec was reported.

No SAEs were reported in this study.

The maximum tolerated dose could not be established in this study as the highest dose was well tolerated.

Patients with MDD

A total of 44 patients (53.7%) experienced TEAEs, with the highest percentage in the paroxetine 20 mg group (65.0%, 13 patients) and the lowest in the placebo group (45.0%, 9 patients). All TEAEs were mild or moderate in intensity, with the exception of 2 severe events of nausea (MIN-117 2.5 mg: 1; paroxetine 20 mg: 1). The events of nausea were considered possibly/probably related (MIN-117 2.5 mg) and definitively related (paroxetine 20 mg) to study medication. 40.2% of patients experienced TEAEs that were considered to be related to the double-blind study medication by the investigator. For 6 patients (7.3%), TEAEs were deemed to be definitively related. Overall, 2 patients were withdrawn from the study due to adverse events occurrence (both of whom were randomized to the paroxetine 20 mg group): one female patient with severe nausea (non-serious, definitely related to the study medication) and one female patient with moderate transaminases increased (considered as an adverse event as it occurred before the start of the study medication) and moderate blood alkaline phosphatase increased (TEAE). Both events were considered unrelated to study medication.

The highest frequencies of TEAEs were reported in the system organ classes Nervous system disorders (19.5% of patients), Investigations (17.1%), Gastrointestinal disorders (12.2%), and Infections and infestations (11.0%). The most commonly reported TEAE was nausea (9.8%, 8 patients). Dizziness as well as headache were reported for 7 (8.5%) patients, and upper respiratory tract infection was reported for 4 (4.9%) patients. The remainder of reported TEAEs occurred in ≤ 3 (≤ 3.7%) patients.

In general, Sheehan-Suicide Tracking Scale scores were low for all treatment groups throughout the study and no consistent pattern of change was observed.

1.5. Overall Rationale for the Study

Major depressive disorder (MDD) is a common, severe, chronic and often life-threatening illness. It is now the third leading cause of disability worldwide (WHO 2006). It is a heterogeneous disorder, with a variable course. The prevalence of the disorder is approximately 10% in men and 20% in women. It is associated with high morbidity with significant deleterious health risk and high risk for mortality. Suicide is estimated to be the cause of death in up to ~10-15% of individuals with MDD (Belmaker 2008).

Despite important advances in the treatment of depression, many with this illness remain inadequately treated. Although options for pharmacologic treatment for depression have grown over the past decades, the current armamentarium of antidepressants continues to have limitations in both efficacy and tolerability. With the first antidepressant, approximately 60 to 70%, and with 2 consecutive antidepressants 30 to 40%, of subjects treated for Major Depression do not achieve sufficient control of their symptoms (Trivedi 2009; CHMP 2013).

There is a clear need to develop novel and improved therapeutics for major depression that can improve on tolerability and efficacy. The unique mechanism of action, good tolerability, and good efficacy based on animal models of depression make MIN-117 an attractive compound to test for efficacy in major depression.

The combination of the different pharmacological activities of MIN-117 (please refer to Investigator's Brochure and information given above) confers to this molecule a unique efficacy profile, which might address particularly some of the major unmet medical needs and shortcomings of existing therapies, like delayed onset of mood improvement, cognitive impairment and sexual dysfunction.

In terms of speeding up onset of improving mood, both the effect of MIN-117 on the 5-HT1a auto-receptor seems key as well as the effect on the DAT as described below.

A published Cochrane review (Geddes 2003) reviewed 98 randomized controlled trials comparing the efficacy of selective serotonin reuptake inhibitors (SSRIs) with other classes of antidepressants. Analysis of efficacy was based upon 5044 subjects treated with SSRIs or related drugs and 4510 subjects treated with an alternative antidepressant. Overall, no clinically significant difference between SSRIs and tricyclic antidepressants were reported. Treatment decisions need to be based on considerations of relative subject acceptability, toxicity, and cost (Geddes 2003). Although the pharmacological activity of these drugs is rapid, there is a certain delay in the onset of clinical improvement in the depressive symptoms of subjects.

SSRIs inhibit the serotonin reuptake system (Hyttel 1994), which leads to an increase in extracellular serotonin. Higher levels of serotonin in the synaptic cleft lead to an activation of somatodendritic 5-HT_{1A} autoreceptors, which in turn results in reduced serotonergic neuron firing activity (Scuvee-Moreau 1979) and reduced extracellular serotonin in the forebrain (Romero 1994). This initial inhibition of serotonin synaptic release mediated by presynaptic 5 HT_{1A} receptors could contribute to the delayed onset of action of SSRIs (which are gradually down regulated and desensitized during continuing treatment). Therefore, the additional administration of 5-HT_{1A} auto-receptor antagonists), would be expected to prevent the negative feedback caused by the initial decrease in the firing rate; this may accelerate and enhance the therapeutic efficacy of SSRIs (Artigas 1993; Savitz

2009). More recently, interest has turned to the role of DA in depression. This is based on a wide body of preclinical data, the postulation that loss of interest and pleasure (anhedonia) are the core symptoms of depression and that all other depressive symptoms are causally related, and clinical evidence identifying low concentrations of homovanillic acid (HVA, a metabolite of DA) in the cerebrospinal fluid (CSF) and plasma of depressed patients (Lambert 2000).

Furthermore, data from clinical studies have shown that DA agonists, such as bromocriptine, pramipexole and ropinirole, exhibit antidepressant properties. Amineptine, a TCA-derivative that predominantly inhibits DA re-uptake and has minimal noradrenergic and serotonergic activity has also been shown to possess antidepressant activity (Boyer 1999). However, amineptine is no longer available as a treatment for depression, and thus, MIN-117 might be an alternative treatment. Indeed, MIN-117 was found to be active in the CMS model of depression. The magnitude of action of the most active doses (0.001 and 1.0 mg/kg) was comparable of that of imipramine. The onset of action of these doses was clearly faster than that of imipramine (after the first week of treatment with MIN-117).

In terms of cognitive improvement, preclinical data obtained on a novel object recognition test indicates that compared to imipramine, MIN-117 is restoring cognitive skills in experimental conditions after repeated stress. As found in the Novel Object Recognition test (NOR), MIN-117 prevented the stressed animals from CMS-induced deficit in working memory at the lowest doses of 0.001, 0.01 and 0.1 mg/kg, while the highest dose of 1.0 mg/kg was ineffective against the CMS-induced deficit in the NOR (see Investigator's Brochure). Motivation, psychomotor speed, concentration, and the ability to experience pleasure are all linked in that they are regulated in part by DA – containing circuits in the CNS and impairment of these functions are prominent features of depression. Although, some other pharmacological targets on which MIN-117 is binding, it seems that the DAT activity might be the main driver of the beneficial effect of the drug on vigilance, attention and as a consequence cognition (Dunlop 2007).

In terms of sexual function, MIN-117 might also exhibit a potent pharmacological profile. A preclinical study exploring this function in rats and comparing MIN-117 to paroxetine clearly demonstrated a preserved sexual function unlike paroxetine, which induced its known impairments (see the Investigator's Brochure). In terms of underlying pharmacological pathways, mostly 5-HT1a binding of MIN-117, might be responsible for this preserved function. As proposed by Baldwin and colleagues (2013), future management options may be extended through the development of new antidepressant treatments with a lower risk of causing sexual problems. These could include compounds with effects on the 5-HT1a receptor or with noradrenaline reuptake inhibitor properties.

At present, the evidence relating to the effects of drugs acting on the 5-HT1a receptor is intriguing. The partial agonist, buspirone, has been used to reduce sexual dysfunction associated with SSRIs, and the partial agonist, gepirone, improves sexual functioning in depressed men, independent of antidepressant or anxiolytic effects. The novel antidepressant drug vilazodone, which has both SSRI and 5-HT1a partial agonist properties, appears to have a low incidence of adverse effects on sexual functioning, as does the "multimodal" compound vortioxetine, whose pharmacological properties include full agonism at the 5-HT1a receptor.

While existing therapies for this disease are available, their effectiveness is limited due to unacceptable side effects, varying and different levels of efficacy for individual subjects requiring physicians to test, check, and alter doses, or change medication during treatment (Rush 2006). As such, the need for new drugs that are equally or more efficacious with better safety profile to address unmet medical needs exists, and MIN-117 is one such candidate.

Finally, because MIN-117 has shown, in addition to all the key pharmacological targets highlighted above, clear SSRI activity and treatment effect with moderate effect size on both depression and anxiety, it is therefore justified to test in a larger pool of depressed patients due to the potential AD and anxiolytic effect.

2. OBJECTIVES

Primary

To evaluate the efficacy of 2 fixed doses (5.0 mg or 2.5 mg) of MIN-117 compared with placebo in reducing the symptoms of major depression measured by the change in Montgomery-Asberg Depression Rating Scale (MADRS) total score over 6 weeks of treatment in adult patients with MDD.

Secondary

1. To assess the change from Baseline of 2 fixed doses (5.0 mg or 2.5 mg) of MIN-117 compared with placebo over 6 weeks of treatment on:
   - The symptoms of anxiety using the HAM-A.
   - The severity of illness and improvement using the CGI-S and CGI-I.
2. To evaluate the safety of 2 fixed doses (5.0 mg or 2.5 mg) of MIN-117 compared with placebo over 6 weeks of treatment in adult patients with MDD.

Exploratory

1. To assess the change from Baseline of 2 fixed doses (5.0 mg or 2.5 mg) of MIN-117 compared with placebo over 6 weeks of treatment on:
   - Commonly associated symptoms of MDD by using the IDS-SR_{30}.
   - The ability to experience hedonic capacity by using the SHAPS.
   - Cognitive function as measured by DSST.
   - Perception of stress using the PSS.
   - Sexual functioning by using the A-SEX.
   - Sleep parameters as assessed by Somno-Art methodology (at select sites).
   - Neurotrophic/inflammatory factors.
2. To explore the PK of MIN-117 [redacted] and assess the PK/PD relationship.

Hypothesis

The primary hypothesis is that at least 1 dose of MIN-117 will be superior to placebo on the change from Baseline in the MADRS total score at the end of 6 weeks of treatment.

3. OVERVIEW OF STUDY DESIGN

This is a 6-week, 3-arm, randomized, double-blind, placebo- controlled study to investigate the safety and efficacy of MIN-117 in male and female patients with MDD, aged 18 to 65. Approximately 324 patients will be randomly assigned to 1 of 3 treatment arms, including placebo, 5.0 mg MIN-117, or 2.5 mg MIN-117, in a 2:1:1 ratio (i.e., approximately 162 patients in the placebo group and approximately 81 patients in each of the MIN-117 treatment groups).

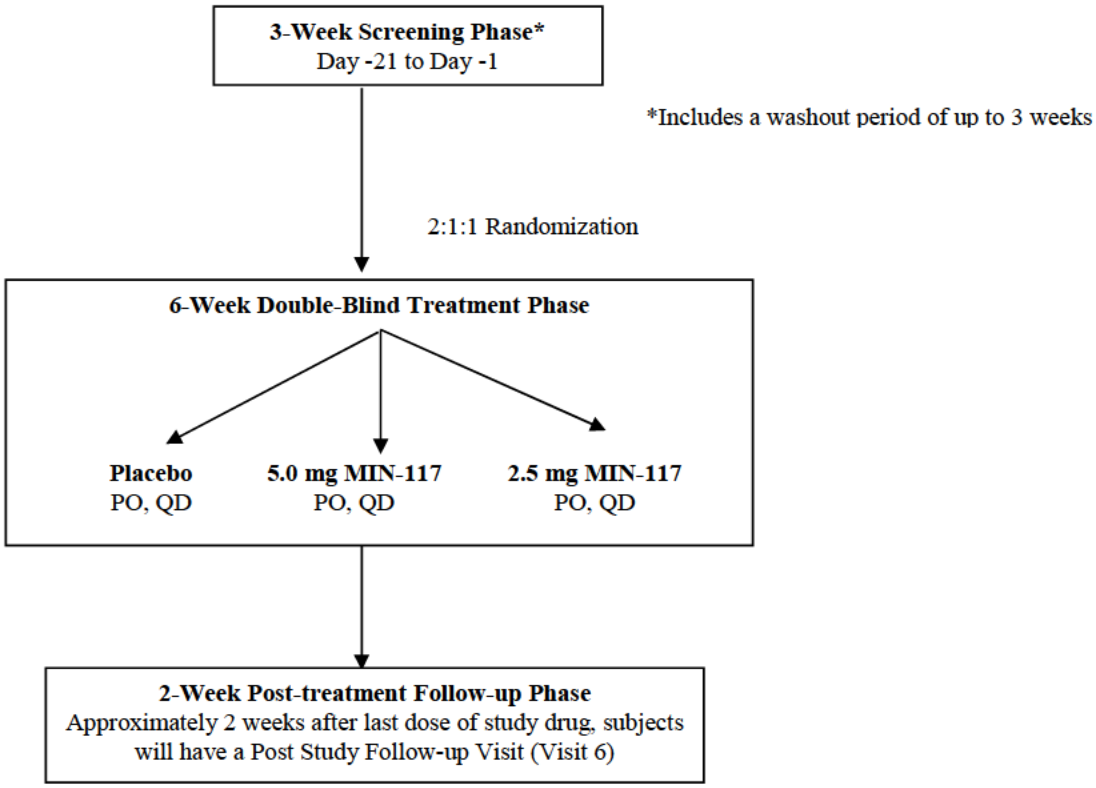
The study design has 3 phases: a screening phase of up to 3 weeks (including washout), a 6-week double-blind treatment phase, and a post-study follow-up visit, occurring approximately 2 weeks after completing the double-blind treatment phase.

Screening Phase: Patients with an acute exacerbation of a major depressive episode will be screened for this study. Screening will include informed consent (for the overall study as well as for optional pharmacogenomic research), evaluation for eligibility in the study, and assessment of medical history . Patients must meet Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5) diagnostic criteria for moderate to severe MDD, with anxious distress and without psychotic features. The diagnosis should be confirmed by the SCID-5. Patients will undergo additional physical and psychiatric evaluations, as well as safety evaluations. If patients give informed consent to participate and meet all study entry criteria at Screening, they will be tapered off their current psychotropic medications. Patients will be free of any psychotropic medications for a period of 1 week (or 2 weeks for MAO inhibitor, 4 weeks for fluoxetine) prior to randomization.

Double-blind Treatment Phase: After at least 1-week of psychotropic drug-free period, patients will undergo evaluation for eligibility, and if they still meet the study entry criteria, they will be randomly assigned in a 2:1:1 ratio to receive placebo, 5.0 mg MIN-117, or 2.5 mg MIN-117, respectively, once daily for 6 weeks. Clinic visits will occur at Visits 2, 3, 4, and 5/Early Withdrawal (Weeks 1, 2, 4, and 6, respectively).

Post-Study Visit: At the end of the study, patients will be evaluated for safety/tolerability at the Post-Study Visit, approximately 2 weeks after completing the Double-blind Treatment Phase. Any patient who terminates from the study early will undergo the Early Withdrawal visit procedures and will have a Post-Study Visit within approximately 2 weeks.

Figure 1: Study Design Diagram (Timelines not to scale)



Study Evaluations

The primary efficacy endpoint will be the change in MADRS total score from Baseline (i.e., the start of double-blind treatment) to the end of the double-blind treatment period (i.e., Week 6). Secondary and exploratory efficacy evaluations include the: HAM-A, CGI-S, CGI-I, IDS-SR_{30}, SHAPS, DSST, PSS, A-SEX, and sleep parameters as assessed by Somno-Art, at specified time-points as outlined in the Time and Events Schedule.

Blood samples (6 mL) for assessing MIN-117 concentration in plasma will be obtained at Baseline (Visit 2), during the double-blind period at Weeks 2, 4, and 6 (Visits 3, 4, and 5), and during the Post-Study Visit (Visit 6). Samples will be taken at pre-dose (within 1 hour) and approximately 2 to 4 hours after dosing (C_{max}) at Baseline (Visit 2) and Weeks 2, 4, and 6 (Visits 3, 4 and 5). Only 1 sample will be taken at the Post-Study Visit (Visit 6).

Blood samples will be collected for pharmacodynamic assessment of BDNF, GDNF, VEGF, IGF-1, fibroblast growth factor-2, C-reactive protein, cortisol, amyloid-A, IL-1β, IL-6, and IL-10 at Baseline and the Week 6 visit.

A pharmacogenomic blood sample will be obtained (at sites where local regulations permit) at Visit 2 or later to allow for pharmacogenomic research, as necessary. Patients will also be asked for consent for storage of their DNA sample for future research.

Safety will be assessed by monitoring adverse events, clinical laboratory tests (including hematology, serum chemistry, urinalysis, lipid profile, and pregnancy tests), vital sign assessments, physical and neurologic examinations, and ECGs. Suicidal ideation/behavior will be assessed using the C-SSRS.

3.1. Study Design Rationale

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active treatment.

Randomization will be used to minimize bias in the assignment of patients to treatment groups, to increase the likelihood that known and unknown patient attributes (e.g., demographic and Baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

Study Population

The study population will consist of adult men and women with a diagnosis of moderate or severe MDD [i.e., met DSM-5 criteria for diagnosis of moderate or severe major depression with anxious distress and without psychotic features at Screening based on clinical assessment and on the SCID-5 (DSM-5 codes: 296.32, 296.33; ICD-10 codes: F33.1, F33.2)]. Patients should have at least one previous episode of depression prior to the one qualifying them for this study.

To minimize rating inflation, patients will qualify for the study by their own self ratings of their severity of depression by using the IDS-SR_{30}. Additional safeguards such as utilizing the Massachusetts General Hospital Clinical Trials Network Institute to conduct the "SAFER" interviews will be utilized (see Inclusion Criterion # 5). The SAFER inventory helps to facilitate identification of the *valid* patient for clinical trials. The inventory addresses specific elements adapted from the SAFER criteria that comprise a valid symptom and one SAFER element (face validity) that considers the entire symptom cluster as a valid nosological entity. Such criteria seek to confirm that identified patients have acute symptoms that reflect the current state of illness and that these symptoms can be reliably assessed with validated measurement tools. Beyond mere presence or absence, valid patients must have relevant symptoms that are pervasive, persistent (and not fluctuating over a defined period of time), and pathological in nature (Targum 2008).

Length of Study Phases and Periods

In any clinical study there is always some risk to removing current psychotropic medications and starting an investigational compound. All patients will undergo a Screening period including a washout period and a drug-free period of at least 7 days prior to randomization. Most patients will tolerate this washout period well without significant symptoms and can remain as outpatients with appropriate clinical monitoring and rescue medications. Only patients who have not had sufficient clinical benefit from their current psychotropic medication will be included in the study. Patients who are benefitting from their current psychotropic medications at the time of Screening will not be included in the study.

Tapering and discontinuation of the previous psychotropic medications will allow for the study drug to be assessed for efficacy and safety as monotherapy instead of an add-on therapy.

The 6-week duration of the double-blind study is adequate to assess the potential efficacy of MIN-117 in the treatment of MDD.

Dosage Selection and Interval

Clinical studies with MIN-117 have been shown the drug to be well tolerated at up to 7.5 mg/day for up to 14 days, and at up to 2.5 mg for 6 weeks. The selected doses (5.0 mg and 2.5 mg) are considered to be pharmacologically potent to show antidepressant effect as doses as low as 0.001 and 1.0 mg/kg were found to be effective in the CMS model of depression in mice. A once daily dosing interval is customary in depression trials and the PK properties of MIN-117 support such dosing interval without undue accumulation.

Choice of Efficacy Measurements

Mood and Anxiety

The MADRS was designed for use in subjects with MDD to measure the overall severity of depressive symptoms. The scale has been validated, is reliable and is acceptable to regulatory health authorities as a primary scale to determine efficacy in major depression.

The CGI will provide an overall clinician-determined summary measure that takes into account all available information, including knowledge of the subject's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the subject's ability to function. The CGI comprises two companion one-item measures evaluating the following: severity of psychopathology (CGI-S) from 1 to 7 and change from the initiation of treatment on a similar seven-point scale (CGI-I).

Hamilton Anxiety Scale (HAM-A) measures the severity of a subject's anxiety, based on 14 parameters, including anxious mood, tension, fears, insomnia, somatic complaints and behavior at the interview. The subject is asked to rate the gravity of each item using a 5-level scale – from 0 to 4, with 4 being the most severe – and afterwards, the results are collated and tabulated to determine the severity of anxiety.

Stress and Anhedonia

MIN-117 pharmacological profile and hypothesized mechanism of action suggest it will have beneficial effect on the perceived levels of stress and hedonic capacity. To that end, the PSS and SHAPS scales will be used in an exploratory fashion to help validate such potential benefit.

Sleep

Sleep dysfunction, manifesting as too much or too little sleep, can be an indicator of depression. In addition, sleep dysfunction can be a side effect of antidepressant medications. Sleep-related adverse effects range from somnolence to insomnia, and from interrupted sleep to lack of restful, refreshing sleep. The consequences of sleep dysfunction may extend to daytime functioning and health-related quality of life. (Devine 2005).

To date, numerous studies have explored the effects of antidepressants on sleep but less research has focused on the use of sleep-electroencephalogram (EEG) parameters as biomarkers for the therapeutic effects of antidepressant medication. In a prospective case-

control study with a relatively large sample size, abnormal sleep-EEG profiles were associated with poor cognitive behavioral therapy response (Thase 1996). Two commonly reported biomarkers for therapeutic response are (i) a pretreatment elevated rapid eye movement (REM) disinhibition and (ii) an initial tonic REM suppression measured at beginning of treatment. Furthermore, recorded sleep EEGs at Day 7 and at Day 42 of treatment with paroxetine and tianeptine show that REM density served as a predictor of paroxetine treatment response: changes in REM density showed an inverse correlation with changes in HAM-D scores (Murk 2003). In summary, most studies point toward REM disinhibition before treatment and REM suppression at treatment initiation as predictors for better antidepressant treatment outcome.

Sexual Functioning

Another common side effect of certain antidepressant medications is sexual dysfunction; sexual dysfunction can also be a symptom of depression. Sexual dysfunction can occur in any one or more phases of the sexual cycle, including desire, arousal, orgasm and resolution (Derogatis 2008). The Arizona Sexual Experiences Scale (A-SEX) addresses the areas of sexual functioning most commonly impaired by psychotropic drugs while being brief, easy to understand and less intrusive than other sexual functioning measures. It will be used in this study to explore the effect of MIN-117 on sexual dysfunction.

Neurotrophic/Inflammatory Markers

Several studies have suggested that major depression is associated with reduced neurotrophic and elevated inflammatory markers. Depressed subjects who respond to antidepressant treatment show quantitative reversal in these markers. Exploratory assessment of these factors is included as potential biomarkers to predict response, subject to confirmation in larger studies.

Cognition

Cognitive impairments are now widely acknowledged as an important aspect of MDD, and the DSM-5 lists impairment in cognition (i.e., diminished ability to think or concentrate or indecisiveness) as a criterion item in the diagnosis of a major depressive episode. Although executive function and memory seem to be particularly impaired in patients with MDD, other domains can be affected including processing speed (Keefe 2014). In the present study, DSST (processing speed) will be performed.

4. STUDY POPULATION

4.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for participation in this study:

1. Patients must be able to read and understand the consent forms, complete study-related procedures, and communicate with the study staff.
2. Patients must have provided written consent to participate in the study and understand that they are free to withdraw from the study at any time.
3. Patients must have signed the informed consent form for pharmacogenomic research indicating willingness to participate in the pharmacogenomic component of the study

in order to participate in the optional pharmacogenomic component of this study. Refusal to consent for this component does not exclude a patient from participation in the clinical study.

4. Patients must be aged 18 to 65 years, inclusive, at Screening (Visit 1).
5. Meet DSM-5 criteria for diagnosis of moderate or severe[a] major depression with anxious distress and without psychotic features at Screening based on clinical assessment and on the SCID-5 (DSM-5 codes: 296.32, 296.33; ICD-10 codes: F33.1, F33.2). Their major depressive episode must be deemed "valid" using the Massachusetts General Hospital (MGH) SAFER[b] criteria interview administered by remote, independent raters.
6. Subjects must be within a body mass index (BMI) of ≥ 18 to < 35 kg/m^2 [BMI = weight (kg)/height (m)^2] at Screening (Visit 1).
7. Subjects have a history of at least one previous episode of depression prior to the current episode.
8. Patient must have been treated with an antidepressant administered at an adequate dose and duration in the past for the treatment of Major Depression. An adequate treatment is defined as an antidepressant treatment for at least 4 weeks at at least the minimum therapeutic dose, for any particular antidepressant.
9. Current major depressive episode of at least 4 weeks in duration.
10. At Screening (Visit 1) and Baseline (Visit 2), patients must have a score ≥ 40 on the patient rated IDS-SR$_{30}$.
11. At Screening (Visit 1) and Baseline (Visit 2), patients must have a score ≥ 18 on HAM-A.
12. At Screening (Visit 1) and Baseline (Visit 2), patients must have a score ≥ 4 on the investigator-rated CGI-S.
13. Patients must be outpatients at the time of randomization (Baseline [Day 1]).
14. Patients must be in good general health prior to study participation with no clinically relevant abnormalities as assessed by the investigator and determined by: medical history, physical examination, vital signs, blood chemistry, hematology, urinalysis, and electrocardiogram (ECG).
15. If female, the patient must:
    a. be post-menopausal, or
    b. have had a hysterectomy or tubal ligation or be otherwise incapable of pregnancy, or

[a] Several symptoms in excess of those required to make the diagnosis of MDD AND symptoms markedly interfere with occupational functioning or with usual social activities or relationships with others.

b The acronym SAFER stands for interview's attention to the following criteria: State versus trait; Assessability; Face validity; Ecological validity; and Rule of three Ps [pervasive, persistent, and pathological].

c. must agree to consistent use of 2 methods of contraception for the duration of the study and until 90 days after the last dose of study medication. One of which must be a highly effective method defined as one that results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly. The following highly effective contraception methods acceptable for this study are hormonal contraception (oral or parenteral hormonal contraceptive) or placement of an intrauterine device. The following methods can be used as a second form of contraception during the study: Barrier methods for female patients include their partner's use of a condom or the subject's use of an occlusive cap (diaphragm or cervical/ vault caps) with spermicidal foam, gel, film, cream or suppository.

16. If male with partner of childbearing potential, must be willing to use one barrier method of contraception with his partner throughout the study (a condom or his partner's use of an occlusive cap [diaphragm or cervical/ vault caps]). His partner must also be using a highly effective method of birth control defined as one that results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly such as sterilization, implants, injectables, combined oral contraceptives, and intrauterine devices for up to 90 days after the last dose of study treatment. The patient must agree to inform the investigator if his partner becomes pregnant during the course of the study.
17. Male patients who have been sterilized or have partners of non-childbearing potential (including homosexual men) are required to use one barrier method of contraception. This is to prevent unintended exposure of the partner to the study drug via seminal fluid (for male subjects, this must be a condom or their partner's use of an occlusive cap [diaphragm or cervical/vault caps].
18. Female patients of childbearing potential must have a negative serum pregnancy test at Screening (Visit 1) and negative serum and urine pregnancy test at Baseline (Visit 2).

4.2. Exclusion Criteria

Potential patients who meet any of the following criteria will be excluded from participating in the study:

1. A DSM-5 diagnosis of current (active): panic disorder, obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD), anorexia nervosa, or bulimia nervosa.
2. History or current diagnosis of a psychotic disorder, bipolar disorder, mental retardation, or borderline personality disorders, mood disorder with postpartum onset, somatoform disorders, fibromyalgia, or idiopathic medical conditions.
3. At significant clinical risk for suicidal or violent behavior.
4. History of treatment within last 6 months with electroconvulsive therapy (ECT), Vagus Nerve Stimulation (VNS), Deep Brain Stimulation (DBS), or Transcranial Magnetic Stimulation (TMS).
5. Potential patient who in the opinion of the investigator should not discontinue, or participate in washout of a prohibited concomitant medication.
6. Potential patient who demonstrate a greater than 25% decrease in depressive symptoms as reflected by the IDS-SR_{30} total score from Screening visit to Baseline visit.

7. Active cardiovascular disease (including but not limited to: atrial fibrillation or flutter, second and third-degree atrioventricular heart block, resting supraventricular tachycardia >100 beats per minute, unstable ischemic heart disease, valvular abnormality, sick sinus syndrome or other condition requiring pacemaker) or diastolic blood pressure > 105 mmHg.
8. Any serious, untreated, or unstable illnesses, such as: liver or renal insufficiency.
9. Any significant pulmonary, endocrine, or metabolic disturbances.
10. Documented disease of the central nervous system that could interfere with the study assessments (including but not limited to: stroke, tumor, multiple sclerosis, Parkinson's disease, Alzheimer's disease, Huntington's disease, seizure disorder requiring current anti-convulsants, traumatic brain injury or trauma, and neurosyphilis.
11. Hypothyroidism or hyperthyroidism, unless stabilized by appropriate medication for at least 3 months prior to Screening (a normal thyroid-stimulating hormone [TSH] is required prior to randomization at Baseline).
12. Any medical condition that can potentially alter oral enteral absorption (e.g., gastrectomy), metabolism (e.g., liver failure), or excretion (e.g., renal failure) of the study drug.
13. History of alcohol or substance use disorders (except nicotine and caffeine) meeting DSM-5 criteria within 1-year prior to Screening visit.
14. Positive alcohol and urine drug screen for opiates, cocaine, barbiturates, tetrahydrocannabinol, methadone, tricyclic antidepressants, benzodiazepines, and amphetamine/methamphetamine at Screening or Baseline. Patients with positive testing at Screening due to prescribed benzodiazepines, tricyclic antidepressants, barbiturates or opiates are accepted but must test negative at Baseline (Visit 2).
15. Male patients who have pregnant partners.
16. Female patients who are breast-feeding.
17. Received an experimental drug or used an experimental medical device within 60 days before the planned start of treatment (Day 1) or have participated in 2 or more clinical trials in the previous 2 years.
18. QTcF interval at Screening or Baseline greater than 450 msec for males and 470 msec for females.
19. Patients requiring treatment with drugs likely to prolong QT.
20. Patients with known hypersensitivity to MIN-117 or placebo or their excipients (refer to section 13.1 p. 64 of the protocol).
21. Positive hepatitis B surface antigen, or hepatitis C antibody or Human Immunodeficiency Virus (HIV) 1 and 2 antibodies at Screening.
22. Employees of the investigator or study center, when the employee has direct involvement in the proposed study or other studies under the direction of that investigator or study center; also family members of the employee or the investigator.

4.3. Prior and Concomitant Therapy

4.3.1. Prior Therapy

Any medication (including, but not limited to, over-the-counter medicines such as aspirin, antacids, vitamins, mineral supplements, and herbal preparations) that the patient is receiving at the time of Screening, or receives during the study, must be recorded on the appropriate eCRF along with the reason for use, dates of administration, and dosages.

- Women must remain on a highly effective method of birth control (see Section 4.1, Inclusion Criteria).
- Patients must not use antidepressant within 1 week of the time they will take their first dose of study medication, or MAO inhibitor medications within 2 weeks, or fluoxetine (Prozac) within 4 weeks of the time they will take their first dose of study medication (i.e., 5 half-lives of the antidepressant).
- Patients must not use other prescription medication within 7 days (or per study physician's recommendation) prior to Baseline (Day 1) visit except those allowed in Attachment 1 (Allowed and Prohibited Concomitant Medications). An exception is that women using hormone replacement therapy or hormonal contraception who have been using it continuously for at least 30 days before dosing may take the medication.

  Other exceptions justified by the patient's medical condition could be allowed after the Sponsor's Responsible Medical Officer approval (refer to Section 4.3.2).
- Patients must not use herbal medications (e.g., St. John's Wort, ephedra, ginkgo, ginseng, and kava kava) within 7 days prior to Baseline visit or during the study.

Information on the dose, date of last administration, length of time on medication and reason for stopping or changing the medication will be collected in the source documents and appropriate eCRF pages.

4.3.2. Concomitant Therapy

All medications except study drug, administered to a patient during the study, should be documented in the eCRF as concomitant medications.

In general, concomitant medications with primary CNS activity, as well as CYP 2C8 and CYP 3A4/5 inhibitors, CYP 2C8 and CYP 3A4/5 inducers, and concomitant medications metabolized through CYP 2C9 are not allowed in this study (refer to Attachment 1).

As the list of prohibited/allowed concomitant medications (Attachment 1) is not exhaustive, other concomitant medications justified by the patient's medical condition could be allowed on a case by case basis after Sponsor's Responsible Medical Officer approval.

As a general rule:

- Patients must not use psychotropic drugs other than the study medications at any time during the study. For a complete list of prohibited therapies, please refer to Attachment 1.

- Patients must be strongly discouraged from using alcohol or illicit substances during the entire study.
- Ongoing psychological treatment (eg, Cognitive Behavior Therapy, Interpersonal Psychotherapy, Psychodynamic Psychotherapy, etc.) if it started > 3 months prior to the double-blind treatment phase, if the investigator deems the psychological treatment to continue during the study.

Patients should be discontinued from the study if any prohibited medications are used during the study (the Sponsor's Responsible Medical Officer can allow exceptions).

4.3.3. Contraception

Patients who are sexually active must use, with their partner, 2 approved methods of highly effective contraception from the time of study drug administration until 90 days after the last dose of study drug.

Two or more of the following methods are acceptable and must include at least 1 barrier method:

- Surgical sterilization (i.e., bilateral tubal ligation/salpingectomy, hysterectomy for female patients or partners; vasectomy for male patients or partners).
- Placement of an intrauterine device or intrauterine system.
- Hormonal contraception (implantable, patch, oral, injectable).
- Barrier methods (for male patients, this must be a condom or their partner's use of an occlusive cap [diaphragm or cervical/vault caps]; for female patients, either their partner's use of a condom or the patient's use of an occlusive cap [diaphragm or cervical/vault caps] with spermicidal foam/gel/film/cream/suppository).

Male patients who have been sterilized or have partners of non-childbearing potential (including homosexual men) are required to use one barrier method of contraception (condom). This is to prevent unintended exposure of the partner to the study drug via seminal fluid.

Female patients who are not of childbearing potential, i.e., women who are post-menopausal (defined as spontaneous amenorrhea for at least 1 year or spontaneous amenorrhea for at least 6 months confirmed by an follicle stimulating hormone [FSH] result of ≥ 40 IU/mL) or permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy), are not required to use any contraception during this study.

Alternatively, true abstinence is acceptable when it is in line with the patient's preferred and usual lifestyle. If a patient is usually not sexually active but becomes active, they, with their partner, must comply with the contraceptive requirements detailed above.

4.3.4. Exposure to Partners During the Study

As there is a significant risk of drug exposure through the ejaculate (which also applies to vasectomized males) that might be harmful to the sexual partners, including pregnant partners, of male patients, barrier contraception should be used throughout the study and for 90 days after the last day of study drug administration.

4.3.5. Sperm Donation

Male patients should not donate sperm for the duration of the study and for at least 90 days after the last day of study drug administration.

4.3.6. Pregnancy

Patients will be instructed that if they/their partner become pregnant during the study, the pregnancy should be reported to the investigator. The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a patient/patient's partner is subsequently found to be pregnant after the patient is included in the study, then consent will be sought from the partner and, if granted, any pregnancy will be followed and the status of mother and/or child will be reported to the sponsor after delivery. Any patient reporting a pregnancy during the study will be withdrawn from the study.

Men who plan to father a child or to donate sperm within 90 days after last study drug administration (Day 43 or early withdrawal) are not allowed to participate in the study.

Woman who are currently pregnant or nursing, or are planning to conceive a child within 90 days after the last study drug administration (Day 43 or early withdrawal) are not allowed to participate in the study.

5. TREATMENT ALLOCATION AND BLINDING

5.1. Randomization

Central randomization will be implemented in this study. Patients will be randomized to 1 of 3 treatment arms, based on a computer-generated randomization schedule prepared by or under the supervision of the sponsor before the study. The randomization will be balanced by using permuted blocks. The Interactive Web Response System (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the patient.

Approximately 324 eligible patients will be randomized in a 2:1:1 ratio to the following groups:

- Placebo
- 5.0 mg MIN-117
- 2.5 mg MIN-117

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual patient, if needed.

5.2. Blinding

Under normal circumstances, the blind should not be broken until all patients have completed the study and the database is locked. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment the patient is receiving. In such cases, the investigator may in an emergency determine the identity of the treatment by IWRS. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week.

In the event the blind is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented by the investigator in the appropriate section of the electronic case report form (eCRF), and in the source document. The documentation received from the IWRS indicating the code break must be retained with the patient's source documents in a secure manner (e.g., sealed envelope) so as not to unblind the treatment assignment to the study site, sponsor/contract research organization (CRO) personnel. The investigator is also advised not to reveal the study treatment assignment to the study site or sponsor personnel.

6. DOSAGE AND ADMINISTRATION

On Day 1 (Visit 2) of the double-blind treatment phase, patients will be randomized to receive placebo, 5.0 mg MIN-117, or 2.5 mg MIN-117, PO, once daily for 6 weeks (Table 1).

Study drugs will be packaged using a double-dummy, double-blind design. The study drugs will be packaged in individual patient kits containing 6 weekly blisters, with each blister containing medication sufficient for 8 days (1 week of treatment and 1 day of overage). Medications blisters will be dispensed to the patients at Visit 2 (3 blisters), Visit 3 (2 blisters), and Visit 4 (1 blister) to ensure intra-visit daily dosing, including the allowed visit windows (±3 days), are covered. Daily dose will consist of 2 capsules containing the intended dose (MIN-117 or Placebo). MIN-117 capsules are available in 2.5 mg strength.

Table 1: Characteristics of the Treatment and Dosage

Treatment	Capsule Strength / Number		Total Number of Capsules	
	No. of MIN 2.5 mg capsules	No. of MIN-117 placebo capsules	During Study Participation	Total Capsules Dispensed
5.0 mg MIN-117	2	-	84	96
2.5 mg MIN-117	1	1	84	96
Placebo	-	2	84	96

Placebo and MIN-117 capsules are identically matched in appearance.

The study drug should be administered in a single dose in the morning at approximately the same time each day with or without food per patient's food intake habit. Capsules should be swallowed whole with water and not divided, crushed, chewed, or placed in water.

7. TREATMENT COMPLIANCE

The investigator or designated study center personnel will maintain a log of all study drug dispensed and returned during the study. Study drug supplies for each patient will be inventoried and accounted for throughout the study to verify the patient's compliance with the dosage regimen. Patients will be counseled regarding compliance at every visit.

8. STUDY EVALUATIONS

8.1. Study Procedures

8.1.1. Overview

The Time and Events Schedule that follows the Synopsis summarizes the frequency and timing of efficacy, PK, PD, and safety measurements applicable to this study.

With the exception of fasting safety laboratory and pre-dose PK blood draws, all visit-specific efficacy assessments during any study visit should be conducted first, before other scheduled tests, procedures, or medical consultations planned for the patients at any specific visit.

A serum pregnancy test is required at Screening, Baseline, and the post-study follow-up visit for all women of childbearing potential. Additional urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy throughout the study.

During the study, including the end-of-study visit, the total blood volume to be collected from each patient will be 136.5 mL (Table 2).

These estimates are for required blood samples and do not include additional blood samples that may be collected at the investigator's discretion for drug level monitoring or other clinical laboratory tests deemed necessary for appropriate patient care in case of occurrence of adverse events.

Table 2: Estimated Blood Volume Drawn

Type of Sample	Volume per Sample (mL)	No. of Samples per Patient	Total Volume of Blood (mL)[a]
Safety			
Hematology	3.5	4	14
Chemistry	5.0	4	20
TSH and Serology[b]	8.5	1	8.5
PK	6	9	54
PD	15	2	30
Pharmacogenomic	10	1	10
Total blood volume drawn			136.5

[a] Calculated as number of samples multiplied by amount of blood per sample.
[b] Includes HBsAg, anti-HCV, and anti-HIV.

8.1.2. Screening Period (Visit 1)

At the Screening visit, a signed informed consent form for study participation will be obtained. Informed consent must be freely given by the patient and documented by signature before any procedures are performed. The inclusion and exclusion criteria will be reviewed to verify the patient's eligibility, and Screening procedures will be performed as detailed in the Time and Events Schedule.

Patients must meet the DSM-5 diagnostic criteria for moderate to severe MDD, without psychotic features. The diagnosis should be confirmed by using the SCID-5. If patients

give informed consent to participate and meet all study entry criteria at Screening, they will be tapered off their current psychotropic medications. Patients will be free of any psychotropic medications for a period of 1 week or 2 weeks for MAO inhibitors (including reversible inhibitors of monoamine oxidase A), and up to 4 weeks for fluoxetine (i.e., a minimum of 5 half-lives of the drug). This visit may be extended to 4 weeks on a case-by-cases basis after consultation with the sponsor.

8.1.3. Double-Blind Treatment Phase

8.1.3.1. Visits 2 (Baseline Visit /Randomization) 3, 4, and 5/Early Withdrawal (Weeks 1, 2, 4, and 6) – Double-Blind Phase

Patients will undergo 2 consecutive nights of sleep assessments using Somno-Art on the evenings of Day -1, and Day 1. Sleep recording will be done in outpatient settings at select sites. On the morning of Day 1, all inclusion and exclusion criteria will be verified, including all efficacy and safety assessments as per the Time and Events Schedule, and eligible patients will be randomized to 1 of 3 treatment groups: placebo, 5.0 mg MIN-117, or 2.5 mg MIN-117, to receive the first dose of study treatment. Pharmacokinetic blood samples will be drawn within 1 hour before and 2-4 hours after dosing.

Refer to the Time and Events Schedule for evaluations and procedures to be performed during the double-blind treatment phase.

If patients terminate from the study early, they will undergo the Visit 5/Early Withdrawal Visit.

8.1.3.2. Visit 6 (Post-Study Follow-up; Week 8 or 2 Weeks after Early Withdrawal)

At the end of the study, patients will be evaluated for safety/tolerability at the Post-Study Visit, approximately 2 weeks after completing the double-blind treatment phase. Any patient who terminates from the study early will have a Post-Study Follow-up Visit approximately 2 weeks following Early Withdrawal. If any of the laboratory results indicate an abnormality that warrants repeating the test, the patient should be fasting for the repeat assessment. Also, patients with ongoing adverse events at the time of the follow-up visit will be followed until all significant changes have resolved or become medically stable.

8.2. Efficacy

8.2.1. Efficacy Evaluations

Efficacy will be evaluated based on the change from Baseline in the MADRS total score after 6 weeks of treatment or at Early Withdrawal. In addition, other efficacy evaluations will be based on the change from Baseline in the CGI-S, HAM-A total score, A-SEX, DSST score, IDS-SR_{30}, SHAPS, and PSS, and observed CGI-I score. Sleep parameters as assessed by Somno-Art (at select sites) will also be used to evaluate efficacy at specific time points as outlined in the Time and Events Schedule.

Every effort should be made to ensure that all clinician-reported objective measurements are completed by the same individual who made the initial Baseline determinations.

The Montgomery-Asberg Depression Rating Scale (MADRS) – The MADRS is a physician-rated scale designed to measure depression severity and detects changes due to antidepressant treatment. The test consists of 10 items, each of which is scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms), for a total score of 60 (Attachment 2). Higher scores represent a more severe condition. The MADRS evaluates apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, interest level, pessimistic thoughts, and suicidal thoughts. The test exhibits high inter-rater reliability and its capacity to differentiate between responders and non-responders to antidepressant treatment has been shown to be comparable to the Hamilton Rating Scale for Depression.

Hamilton Anxiety Scale (HAM-A) – HAM-A is composed of 14 items, each defined by a series of symptoms (Attachment 3). The subject is asked to rate the gravity of each item using a 5-level scale – from 0 to 4, where 0 being not present and 4 being severe – and afterwards, the results are collated and tabulated to determine the severity of anxiety.

Clinical Global Impression- Severity and Improvement (CGI-S and CGI-I) – The CGI-S is a physician-rated scale that is designed to rate the severity of the subject's illness at the time of assessment, relative to the clinician's past experience with subjects who have the same diagnosis and improvement with treatment. Considering total clinical experience, a subject is assessed on severity of mental illness at the time of rating according to: normal (not at all ill)=1; borderline mentally ill=2; mildly ill=3; moderately ill=4; markedly ill=5; severely ill=6; or extremely ill=7. The CGI-I is a 7-point scale that requires the clinician to assess how much the subject's illness has improved or worsened relative to a Baseline state at the beginning of the intervention and rated as: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; or 7, very much worse.

See Attachment 4 and Attachment 5 for an example of these scales.

Inventory of Depressive Symptoms - Subject-Rated – IDS-SR_{30} – The 30-item IDS (Attachment 6; Rush 1996) is designed to assess the severity of depressive symptoms. The IDS is available in the clinician (IDS-C) and self-rated versions (IDS-SR). The IDS assess all the criterion symptom domains designated by the American Psychiatry Association DSM-5 to diagnose a major depressive episode. This assessment can be used to screen for depression, although it has been used predominantly as measures of symptom severity, and is sensitive to change, with medications, psychotherapy, or somatic treatments, making it useful for both research and clinical purposes. The psychometric properties of the IDS have been established in various study samples. The IDS requires minimal training to administer and should be completed in one sitting, and rates symptoms for the prior seven days.

The IDS-SR_{30} is scored by summing responses to 28 of the 30 items to obtain a total score ranging from 0 to 84. Either appetite increase or decrease, but not both, and weight increase or decrease, but not both, are used to calculate the total score. Higher scores indicate increase in severity of depression.

Snaith-Hamilton Pleasure Scale (SHAPS) – The 14-item SHAPS is a self-administered instrument that is used to measure hedonic capacity (Snaith, 1993). The SHAPS has excellent internal consistency, with construct validity, and is unidimensional in assessing hedonic capacity among adult outpatients with major depressive disorder (Attachment 7).

The pattern of the SHAPS mean scores is consistent with the scoring direction on the pleasure/enjoyment item of the IDS (Clinician-administered, sub-item 21); that is, those who rarely or are unable to derive pleasure from activities (as coded/scored on IDS sub-item 21) also have higher levels of anhedonia or lower levels of hedonic capacity (as measured via the SHAPS). The SHAPS is not influenced by age, gender, race, education, duration of the current depressive episode, length of illness, or first versus recurrent episode of depression. Each of the items has a set of four response categories--Definitely Agree, Agree, Disagree, and Strongly Disagree, with either of the Disagree responses receiving a score of 1 and either of the Agree responses receiving a score of 0. Thus, the SHAPS is scored as the sum of the 14 items so that total scores ranged from 0 to 14. A higher total SHAPS score indicated higher levels of present state of anhedonia.

Perceived Stress Scale – PSS – The PSS is the most widely used psychological instrument for measuring the perception of stress (Attachment 8). It is a measure of the degree to which situations in one's life are appraised as stressful. Items were designed to tap how unpredictable, uncontrollable, and overloaded respondents find their lives. The scale also includes a number of direct queries about current levels of experienced stress. Moreover, the questions are of a general nature and hence are relatively free of content specific to any sub-population group. The questions in the PSS ask about feelings and thoughts during the last month. In each case, respondents are asked how often they felt a certain way (Cohen 1983).

The Arizona Sexual Experience Scale (A-SEX) – The A-SEX scale is a subject-completed scale designed to measure five specific areas that are the core elements of sexual function (Attachment 9). The self-reported 5-item scale has male and female specific versions and has been commonly used in clinical studies of depression. The items are answered on 6-point Likert scales, ranging from hyperfunction (1) to hypofunction (6). The recall period is the past week. The total A-SEX score is calculated by adding scores of the five items. Each response option for each item is assigned a score from 1-6 (e.g., 1=extremely strong to 6=none), with the total score ranging on a scale from 5 to 30. Lower scores reflect higher sexual functioning. A total A-SEX score of > 19 indicates sexual dysfunction.

Digit Symbol Substitution Test (DSST) – The DSST will be used to evaluate cognition. The DSST is a neuropsychological test sensitive to brain damage, dementia, age, and depression. It consists of digit-symbol pairs (e.g., 1/-,2/⊥ ... 7/Λ,8/X,9/=) followed by a list of digits. Under each digit the subject should write down the corresponding symbol as fast as possible. The number of correct symbols within the allowed time (e.g., 90 or 120 sec) is measured.

See Attachment 10 for an example of this test.

Somno-Art – Somno-Art is a new methodology to score sleep. The device is worn on the non-dominant forearm and records the cardiac cycle by photoplethysmography, while body movements are recorded by the integrated actimetry. The actimetry is measured through the vector magnitude of accelerations obtained every second in the three dimensions of the space

The cardiac and actimetry data are sampled and stored at 1 Hz. The data are then post-processed in 1-second average ".srt" files that are used for sleep analysis using the Somno-Art methodology.

The following sleep parameters will then be extracted:

Sleep Onset Latency (SOL): elapsed time between light out time and the first occurrence of any sleep stage other than stage W.

REM sleep Latency (REML): elapsed time between sleep onset and the first occurrence of REM sleep.

Wake After Sleep Onset (WASO): cumulative time of wake episodes occurring between sleep onset and light on time.

Time spent in each sleep stage: cumulative time spent in each sleep stages (N1, N2, N3 or REM sleep) between sleep onset and light on time.

Total Sleep Time (TST): cumulative time spent in N1, N2, N3 and REM sleep from sleep onset to light on time.

Sleep Efficiency Index (SEI): ratio between total sleep time divided by time in bed.

Number of awakenings (NAW): number of wake episodes exceeding 15 seconds, between sleep onset and light on time.

Number of Sleep Cycles (NSC): a sleep cycle was defined as the elapsed time between sleep onset and the end of the first REM sleep phase (1st cycle) or the end of one REM sleep phase to the end of the following REM sleep phase (2nd and following cycles). A REM sleep phase can be constituted by several REM sleep episodes. Two successive REM sleep episodes were considered as parts of the same REM sleep phase when they were separated by less than 20 min of any other sleep stage.

8.2.2. Efficacy Criteria

The primary efficacy endpoint will be the change in MADRS total score from Baseline (i.e., the start of double-blind treatment) to the end of the double-blind treatment period (i.e., Week 6). The primary comparisons will be between each MIN-117 dose group (5.0 mg and 2.5 mg) and the placebo group.

The key secondary endpoint will be the change from Baseline in HAM-A, and it will be evaluated similar to the primary efficacy endpoint. Change from Baseline in CGI-S and observed CGI-I scores will also be evaluated as measures of the clinical meaningfulness of the changes in the objective measures of depression and anxiety. The primary comparisons will be between each MIN-117 dose groups (5.0 mg and 2.5 mg) and the placebo group.

The change from Baseline for the remaining efficacy endpoints will be analysed similarly to primary endpoint.

Time to onset of antidepressant effect will include criteria of sustained pre-defined decrease in depressive symptomatology and will be analysed using conditional survival analysis.

In order to establish the clinical relevance of the primary analysis results, the rate of responders defined as a MADRS score of $\geq$ 50%, will be calculated at each assessment between Week 1 and Week 6 and the 95% confidence interval for the odds ratio of MIN-117 versus placebo computed using a logistic regression model.

Time to clinical response (first assessment with a ≥ 50% improvement from Baseline in total MADRS score scale) will be analysed using a survival analysis method assuming proportional hazard. Time to ≥ 30% will also be explored.

The rate of early and sustained full responders (≥ 50% improvement from Baseline in total MADRS score and a CGI-I score ≤ 2 at every time points) and the rate of remission in MADRS (defined as a score < 12) will be analysed using the same method as for the clinical response. The rate of early and sustained response based on ≥ 30% will also be explored.

The following efficacy evaluations will be performed at the scheduled visits according to the time points provided in the Time and Events Schedule in the following order and in the morning (between 8:00 a.m. to 1:00 p.m.) during the 6-week, double-blind treatment phase, as applicable:

- MADRS
- CGI-S
- CGI-I
- HAM-A
- IDS-SR_{30}
- SHAPS
- PSS
- A-SEX
- DSST

8.3. Pharmacokinetic Evaluations

8.3.1. Sample Collection and Handling

Blood samples (6 mL) will be collected for assessing the plasma concentration of MIN-117 [redacted] during the Double-blind Treatment Period at Visits 2, 3, 4, and 5, at pre-dose (within 1 hour from dosing) and approximately 2 to 4 hours post-dose (approximate time of maximum plasma concentration for MIN-117). Additionally one sample will be collected at the post-study follow-up visit (Visit 6).

The actual time and date of the blood draw and actual date and time of the last study drug administration prior to collection of the PK sample must be accurately recorded on eCRF.

8.3.2. Analytical Procedures

Plasma samples will be analyzed to determine concentrations of MIN-117 [redacted] using validated, specific, and sensitive liquid chromatography-mass spectrometry (LC-MS/MS) methods under the supervision of the sponsor's bioanalytical facility or designee.

Plasma samples will be disposed after the clinical study report is finalized.

8.3.3. Pharmacokinetic Evaluations

Plasma levels of MIN-117 [redacted] will be tabulated.

Population pharmacokinetic analyses will be performed on the data of this study in combination with data pooled from other studies. An objective of these analyses is to investigate the potential effects of covariates, such as demographics and concomitant drugs, on the pharmacokinetics of MIN-117 [redacted]. An integrated population pharmacokinetic model for MIN-117 will be used combining the data sets of Phase 1 and 2 studies. Standard population pharmacokinetic parameters will be estimated. The effects of demographic characteristics, concomitant medications, laboratory values, and other covariates on MIN-117 pharmacokinetics will be evaluated. Results of the population pharmacokinetic analysis will be presented in a separate report.

8.4. Pharmacodynamic Evaluations

Blood samples will be collected for pharmacydynamic assessment of BDNF, GDNF, VEGF, IGF-1, fibroblast growth factor-2, C-reactive protein, cortisol, amyloid-A, IL-1β, IL-6, and IL-10 at Baseline and the Week 6 visit.

8.5. Pharmacogenomic Evaluations

A pharmacogenomic blood sample (10 mL) will be obtained (at sites where local regulations permit) at Visit 2 or any time during the double-blind phase to allow for pharmacogenomic research, as necessary. Pharmacogenomic research may be performed to explain variability in the data or to address emerging clinical issues. Candidate genes from previous pharmacogenomic studies conducted by the Sponsor on similar compounds may be analyzed as well as genes known to be associated with depression or response to anti-depressive treatment [e.g., serotonin transporter gene promoter polymorphism (5-HTTLPR)]. Patients will also be asked for consent for storage of their DNA sample for future research.

8.6. Safety Evaluations

Any clinically significant abnormalities persisting at the end of the study will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the Time and Events Schedule

Adverse Events

Adverse events will be reported by the patient for the duration of the study. Adverse events will be followed by the investigator as specified in Section 11, Adverse Event Reporting.

Clinical Laboratory Tests

Blood samples for serum chemistry (collected after an overnight fast) and hematology and urine samples for urinalysis will be collected according to the Time and Events Schedule. In women of childbearing potential, a serum pregnancy will be performed at Screening, Baseline, Visit 5/Early Withdrawal, and EOS visit. In addition, urine sample for drug and alcohol testing and urine samples from women of childbearing potential for pregnancy testing will be collected (refer to the Time and Events Schedule). The investigator must

review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF. The following tests will be performed:

- ***Hematology:***
  - hemoglobin
  - hematocrit
  - white blood cell (WBC) count with differential
  - platelet count
  - red blood cell (RBC) count
- ***Serum Chemistry:***
  - sodium
  - potassium
  - chloride
  - blood urea nitrogen (BUN)
  - creatinine
  - glucose (fasting)
  - AST
  - ALT
  - total bilirubin
  - alkaline phosphatase
  - gamma-glutamyl transferase (GGT)
  - creatine phosphokinase (CPK)
  - lactic acid dehydrogenase (LDH)
  - uric acid
  - calcium
  - phosphorous (inorganic)
  - albumin
  - total protein
  - cholesterol (total)
  - triglycerides
  - high density lipoprotein (HDL)
  - low density lipoprotein (LDL)
  - thyroid-stimulating hormone (TSH) (at Screening only)
- ***Urinalysis***

  Dipstick
  - specific gravity
  - pH
  - glucose
  - protein
  - blood
  - ketones
  - bilirubin
  - urobilinogen
  - nitrite
  - leukocyte esterase

  Sediment (if dipstick result is abnormal)
  - RBC
  - white blood cell (WBC)
  - epithelial cells
  - crystals
  - casts
  - bacteria

  If dipstick result is abnormal, the sediment will be examined microscopically.

- Serum Pregnancy Testing for women of childbearing potential: at Screening, Baseline (Visit 2) and Post study Visit (Visit 6). .
- Urine Pregnancy Testing for women of childbearing potential only: at Baseline (Visit 2), Visits 4, 5 and 6.

If results of the pregnancy test(s) are positive, the patient will be excluded or withdrawn from the study. Of note, at Baseline (Visit 2), both a urine and a serum pregnancy test will be performed. Enrollment will be based on the result of the urine test performed locally in

order not to postpone the randomization. Nevertheless, this urine pregnancy test will have to be confirmed by the serum pregnancy test assessed centrally. Should there be a discrepancy in the results, the result of serum test will prevail.

- Serology (HBsAg, HCV antibody, and HIV antibodies 1 and 2).
- Urine Drug Screen and Urine Alcohol: Potential patients will be tested for drugs of abuse (cocaine, methadone, amphetamines, cannabinoids, opiates, benzodiazepines, barbiturates, tricyclic antidepressants) and alcohol according to the Time and Events Schedule. If the results of the urine drug screen (except for prescription benzodiazepines, prescription barbiturates, prescription tricyclic antidepressants or prescription opiates at Screening) or the urine alcohol test are positive at Screening or Baseline, the patient will not be enrolled. If the screen is positive for cannabinoids, they will be excluded.

Electrocardiogram (ECG)

Triplicate ECGs will be performed according to the Time and Events Schedule. The visits, three 12-lead ECGs will be recorded at least 1 minute apart within 5 minutes after the patient is supine for at least 10 minutes. ECG assessments during the double-blind phase should occur prior to the post-dose PK sample.

Twelve-lead ECGs will be recorded at a paper speed of 25 mm per second until 4 regular consecutive complexes are available.

The following intervals will be assesed: RR, PR, QRS, and QT. Electrocardiogram monitoring will include the evaluation of lengthening of the QTc interval using QTcF.

Vital Signs

Vital signs will include oral/aural temperature, respiratory rate, pulse, and blood pressure.

Three consecutive blood pressure and pulse readings will be taken at each visit. Blood pressure and pulse should be taken in the arm with the highest pressure, using the same arm for each reading and for all visits. An appropriately sized arm cuff will be used, and the size of the cuff should remain constant for all visits.

Blood pressure and pulse will be taken after the patient has been resting quietly in supine position for 5 minutes. Vital signs assessments during the double-blind phase should occur prior to the post-dose PK sample, and after the ECG assessments.

Physical Examination

Physical examinations, height, and weight will be performed at the times specified in the Time and Events Schedule.

Any abnormalities present at Baseline, or subsequent changes, will be documented in the appropriate sections of the CRF. Any clinically significant abnormalities persisting at the end of the study will be followed by the investigator until resolution or until reaching a clinically stable endpoint.

Columbia Suicide Severity Rating Scale (C-SSRS)

Emergence of suicidal ideation will be assessed using the C-SSRS, a prospective rating scale that tracks both treatment-emergent suicidal ideation and behaviors, and will be

performed at the times specified in the Time and Events Schedule. The C-SSRS has been used frequently in clinical studies, is a standard measure for suicidal ideation assessment, and its use is in accordance with FDA guidance.

See Attachment 11 for an example of this scale.

9. PATIENT COMPLETION/WITHDRAWAL

9.1. Completion

A patient will be considered to have completed the study if he or she has completed assessments at Week 6 of the double-blind treatment phase. Patients who prematurely discontinue study treatment for any reason before completion of the double-blind treatment phase will not be considered to have completed the study. The investigational drug will not be available after the completion of the study.

9.2. Withdrawal from the Study and Replacement.

The patients have the right to withdraw from the study at any time for any reason, without the need to justify.

A patient will be withdrawn from the study for any of the following reasons:

- Patient withdraws consent.
- Lost to follow-up.
- Termination of the study.
- The investigator believes that for safety reasons (e.g., adverse event) it is in the best interest of the patient to stop treatment.
- The patient becomes pregnant.
- Failure to use an acceptable method of birth control.
- Significant deviation from the protocol.
- Occurrence of a treatment-related serious adverse event.
- Concurrent illness and requirement of a prohibited medication.
- The patient meets one of the following .stopping criteria:
    - Patient with significant increase in ALT [i.e., > 5 upper limit of normal (ULN)].
    - Patient with abnormal laboratory results with simultaneous increases of total bilirubin (> 2 ULN), ALT (> 3 ULN) and alkaline phosphatases (< 1.5 ULN).
    - Patient with sustained mean QTcF (calculated using Fridericia's formula) value > 500 msec (confirmed by a second ECG under strict resting position and at minimum at ½ hour distant from the first measurement).
    - Patient with sustained increase of more than 60 msec in the mean QTcF compared to Baseline (confirmed by a second ECG under strict resting conditions).

If a patient discontinues treatment before the double-blind phase ends, attempts to obtain end-of-treatment and follow-up assessments must be made. In case a patient is lost to

follow-up, every possible effort must be made by the study site personnel to contact the patient and determine the reason for discontinuation/withdrawal. The measures taken to follow-up must be documented. When a patient withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study drug assigned to the withdrawn patient may not be assigned to another patient. Patients who withdraw will not be replaced.

10. STATISTICAL METHODS

10.1. Sample Size Determination

The sample size for this study is based on the assumption of a treatment difference of at least 4 points in the mean change from Baseline to end point in MADRS total score between any MIN-117 dose group and placebo. A standard deviation of 9 in the change in MADRS total score from Baseline is used. Using the Bonferroni multiplicity adjustment for multiple comparisons of 2 MIN-117 dose groups with placebo and assuming an allocation of 2:1:1 for placebo and the 2 MIN-117 doses, 146 patients in the placebo group and 73 patients in each MIN-117 dose group are required to detect the treatment difference of 4 points with a power of 80% at an overall 2-sided significance level of 0.05. When adjusted for a rate of 10% of patients who will not have either Baseline or post-Baseline efficacy assessments, the required number of patients becomes 162 for the placebo group and 81 for each of the two MIN-117 dose groups. Therefore, the total number of patients across the 3 treatment groups will be 324.

10.2. Data Set

One analysis set is included in this study, the Intent-to-Treat (ITT) analysis set. The ITT analysis set will consist of all patients as all randomized patients who receive at least 1 dose of study drug during the 6-week double-blind period. This analysis set will be used for efficacy and safety analyses of the 6-week double-blind period. Analyses of change from Baseline will include only patients who have both Baseline and post-Baseline data during the 6-week double-blind treatment period.

Details about the analysis of the efficacy analyses will be explained in the Statistical Analysis Plan (SAP).

10.3. Patient Information

For all patients who received at least one dose of study drug, descriptive statistics by dose group and also totaled over all dose groups will be provided for age, body mass index, weight in kilograms, and height in centimeters. Gender will be tabulated by dose group and overall. The BMI will be calculated and presented using the following formula: BMI = (weight in kg/height in meters^2).

The number and percentage of patients who complete the double-blind treatment period and of patients who prematurely discontinue during the same period will be presented for each treatment arm and pooled across treatment arms for the ITT analysis set. The reasons for premature discontinuation from the double-blind treatment period as recorded on the termination pages of the eCRFs will be summarized (number and percentage) by treatment arm for the ITT analysis set. The percentage of premature discontinuations will be

compared overall and for each discontinuation reason between treatment groups using the Fisher exact test.

The number and percent of patients with a current or historical presence of abnormal finding in medical history will be summarized by dose group and totaled over all dose groups.

10.4. Extent of Exposure and Treatment Compliance

Investigational Product

Exposure to double-blind treatment for the ITT analysis set during the double-blind treatment period will be summarized for treatment duration, calculated as the number of days from the date of the first dose of double-blind treatment taken to the date of the last dose taken, inclusive, for the double-blind treatment period. Descriptive statistics will be presented by treatment group.

Prior and Concomitant Medications

Prior medications are defined as any medication taken before the date of the first dose of double-blind treatment. Concomitant medications are defined as any medication taken on or after the date of the first dose of double-blind treatment.

Both prior medication use and concomitant medication use (during the double-blind treatment period) will be coded using the World Health Organization-Drug Dictionary (WHO-DD) and will be presented in data listings, and only concomitant medication will be summarized by the number and proportion of patients in each treatment arm receiving each medication within each therapeutic class for the ITT analysis set. Multiple medication use by a patient will only be counted once.

Measurement of Treatment Compliance

Dosing compliance for a specified period is defined as the total number of tablets actually taken by a patient during that period divided by the number of tablets prescribed during the same period multiplied by 100. The total number of tablets actually taken will be calculated from the study medication record. The number of tablets prescribed for a specific treatment period will be calculated by multiplying the number of days in that period by the number of tablets prescribed per day. Descriptive statistics for treatment compliance will be presented by treatment arm for each period between 2 consecutive visits when medication dispensation occurred, as well as for the entire double-blind treatment period.

10.5. Efficacy Analyses

Primary Estimand

The primary estimand, the main clinical quantity of interest to be estimated in the study, is defined by the following 3 components:

Population: patients with a pre-defined minimum threshold and fluctuation of depressive symptoms as captured by IDS-SR_{30} score.

Endpoint: change in MADRS total score from Baseline to the end of Week 6.

Measure of Intervention: the effect of the initially randomized treatment that would have been observed had all patients remained on their treatment throughout the double-blind phase.

The primary efficacy analysis will be based on the ITT Population. Baseline for efficacy is defined as values recorded at Visit 2 (Baseline).

Analyses of change from Baseline will include only patients who have both Baseline and post-Baseline data during the 6-week double-blind period.

All statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance. All confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise.

Additionally, by-visit analyses will be done for all efficacy parameters using the MMRM and last observation carried forward (LOCF) approaches (described in Section 10.5.1), unless stated otherwise.

10.5.1. Primary Endpoint

The primary efficacy endpoint will be the change in the MADRS total score from Baseline to Week 6. This endpoint will be analyzed using MMRM with treatment arm 5.0 mg MIN-117 dose, 2.5 mg MIN-117 dose, placebo), pooled study center (by country or region based on enrollment), visit, and treatment arm-by-visit interaction as fixed effects, patient nested in treatment as random effect, and Baseline total MADRS score as covariate. An unstructured covariance matrix will be used to model the covariance of within-patient scores. The Kenward-Roger approximation (Kenward 1997) will be used to estimate denominator degrees of freedom. In this analysis in which the MMRM is fitted to all post-Baseline data, patients in the ITT analysis set who do not have complete data will still contribute to the estimates at Week 6, but will have less weight in the analysis than those patients with complete data (i.e., only the observed cases without imputation of missing values will be used in this analysis). Comparisons against placebo will be performed using the appropriate contrasts from this model at Week 6. An analysis of observed scores available at each visit will also be performed.

The adjustment for multiplicity within the family of primary hypotheses will utilize the conventional Hochberg procedure for the purpose of reporting of results. This procedure will allow the null hypothesis of no treatment difference for both the 5.0 mg and 2.5 mg doses versus placebo to be rejected if largest p-value of comparing either of these 2 doses versus placebo is at or below 0.050. Otherwise, the lowest of these 2 p-values must be at or below 0.025 to allow for rejecting the null hypothesis for the representative dose.

The overall type I error rate for testing the 2 MIN-117 doses versus placebo for the primary and the key secondary endpoint will be controlled at the 2-sided 0.05 level. The primary family of hypotheses (corresponding to the primary endpoint) and the secondary family of hypotheses (corresponding to the key secondary endpoint, the change from Baseline in HAM-A total score) will be tested in a sequential manner with suitable adjustment for multiplicity within the family of primary hypotheses and within the family of the secondary hypotheses such that a MIN-117 dose versus placebo null hypothesis contrast testing within the secondary family can be evaluated only when the same null hypothesis contrast in the primary family was rejected.

Sensitivity analyses of the primary endpoint will also be performed and will be detailed further in the statistical analysis plan. These will include an ANCOVA model with factors for treatment and region and Baseline MADRS total score as a covariate. In this analysis, patients without a MADRS total score at Week 6 will have an earlier post-Baseline score imputed using the last-observation-carried-forward (LOCF) method. Other sensitivity analyses may also be performed to investigate the robustness of treatment estimates to the observed pattern of, and/or reason for, early withdrawals.

10.5.2. Secondary and Exploratory Endpoints

The change from Baseline in CGI-S and observed CGI-I scores will be analyzed by means of an ANCOVA of ranked data, with treatment (MIN-117 doses and placebo) as a factor, and Baseline CGI-S value as a covariate.

Change from Baseline for efficacy parameters, HAM-A, IDS-SR_{30}, SHAPS, DSST, PSS, A-SEX, and sleep parameters will be analyzed using the same MMRM model and weighted combination test procedure as described above.

10.5.3. Additional Efficacy Analyses

- The rate of responders defined as a decrease in MADRS score of ≥ 50%, will be calculated at each assessment between Week 1 and Week 6 and will be analyzed using a logistic regression model with the treatment group and the corresponding Baseline score as explanatory variable for the LOCF approach only.
- Time to clinical response (first assessment with a ≥ 50% improvement from Baseline in total MADRS score scale, and ≥ 30% improvement from Baseline in total MADRS score scale) will be analyzed using cox-regression model with treatment group and the corresponding Baseline score as covariate.
- The rate of early responders (≥ 50% improvement from Baseline in total MADRS score and a CGI-I score ≤ 2 at each post-Baseline visit) will be analyzed using a logistic regression model with the treatment group and the corresponding Baseline score as explanatory variable for the LOCF approach only. Early responders defined using ≥ 30% improvement from Baseline in total MADRS score and a CGI-I score ≤ 2 at each post-Baseline visit will also be analyzed.
- The rate of sustained full responders (≥ 50% improvement from Baseline in total MADRS score at every time points and a CGI-I score ≤ 2 at every post-Baseline visit, once achieved) using a logistic regression model with the treatment group and the corresponding Baseline score as explanatory variable for the LOCF approach only. Sustained full responders defined using ≥ 30% improvement from Baseline in total MADRS score at every time points and a CGI-I score ≤ 2 at every post-Baseline visit, once achieved, will also be analyzed.
- The rate of remission in MADRS (defined as a score < 12) will be analyzed using a logistic regression model with the treatment group and the corresponding Baseline score as explanatory variable for the LOCF approach only.
- Changes from Baseline in single MADRS rating scale items and for core mood items (items 1 & 2 combined) will be analyzed using an ANCOVA of ranked data, with treatment as a factor, and Baseline value as a covariate.

10.6. Interim Analysis

No interim analyses are planned for this study.

10.7. Pharmacokinetics

Individual plasma levels of MIN-117 [redacted], will be tabulated with the corresponding time related to study drug administration. Descriptive statistics will be summarized for MIN-117[redacted]

Population pharmacokinetic analysis of plasma concentration-time data of MIN-117 [redacted] will be performed using nonlinear mixed-effects modeling. Data may be combined with those of a selection of Phase 1 studies to support a relevant structural model. Available patient characteristics (demographics, laboratory variables, genotypes, etc.) will be tested as potential covariates affecting pharmacokinetic parameters. Details will be given in a population pharmacokinetic analysis plan and results of the population pharmacokinetic analysis will be presented in a separate report.

10.8. Safety Analyses

All patients randomized to treatment who receive at least one dose of double-blind study drug will be included in the safety analyses. Summary statistics will be provided for all safety data using appropriate descriptive statistics adverse events, C-SSRS, laboratory tests, ECGs, and vital signs.

10.8.1. Adverse Events

The original terms used in the eCRFs by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported adverse events with onset during the 6-week double-blind period (i.e., treatment-emergent adverse events or TEAE) will be included in the analysis. For each adverse event, the percentage of patients who experienced at least one occurrence of the given event will be summarized by treatment group.

Special attention will be given to those patients who died, or who discontinued treatment due to an adverse event, or who experienced a severe or a serious adverse event (e.g., summaries, listings, and narrative preparation may be provided, as appropriate).

A TEAE that occurs > 14 days after the date of the last dose of double-blind treatment will not be summarized.

10.8.2. Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the SAP) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at Baseline and at each scheduled time point. Changes from Baseline results will be presented in pre- versus post-treatment cross tabulations (with classes for below, within, and above normal ranges). A listing of patients with any laboratory results outside the reference ranges will be provided. A listing of patients with any markedly abnormal laboratory results will also be provided.

10.8.3. Vital Signs

Descriptive statistics of body temperature, pulse, respiratory rate, and blood pressure (systolic and diastolic) values and changes from Baseline will be summarized at each scheduled time point. The percentage of patients with values beyond clinically important limits will be summarized. Clinically important limits will be defined in the SAP.

10.8.4. Electrocardiogram (ECG)

The effects on cardiovascular variables will be evaluated by means of descriptive statistics and frequency tabulations. These tables will include observed values and changes from Baseline values (the pre-dose ECG will be used as Baseline) to allow detection of clinically relevant changes in individuals.

The ECG variables that will be analyzed are heart rate, PR interval, QRS interval, QT interval, and QTc interval corrected for heart rate using QTcF. QTcF values will be tabulated for their absolute values and also tabulated relative to Baseline measurements in order to detect individual QTcF changes (ICH-E14 2005).

Descriptive statistics of QTcF intervals and changes from Baseline will be summarized at each scheduled time point. The percent of patients with QTc interval > 450 msec, > 480 msec, or > 500 msec will be summarized as will the percent of patients with QTcF interval increases from Baseline of 30 to 60 msec or > 60 msec.

All important abnormalities in ECG waveform that are changes from the Baseline readings will be reported (e.g., changes in T-wave morphology or the occurrence of U-waves).

10.8.5. Physical Examination

Physical examination abnormalities will be listed.

10.8.6. Other Safety Parameters

Observed and changes from Baseline in heart rate will be summarized in tabular format showing descriptive statistics.

10.8.6.1. Columbia Suicide Severity Rating Scale (C-SSRS)

Results from the C-SSRS will be tabulated by treatment.

11. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of patients, investigators, and the sponsor, and are mandated by regulatory agencies worldwide.

11.1. Definitions

11.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study patient administered a medicinal (investigational or non-investigational) product. An adverse event

does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the Baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the informed consent form (refer to Section 11.3.1, all Adverse Events for time of last adverse event recording).

Serious Adverse Event

An SAE is defined as any AE that results in any of the following:

- **Death**: The patient died as the result of the event.
- **Life-threatening event**: Any AE that places the patient, in the view of the Investigator or Sponsor, at immediate risk of death from the AE as it occurred, i.e., does not include an AE that had it occurred in a more severe form, might have caused death.
- **Required or prolonged inpatient hospitalization**: The AE resulted in hospitalization or prolonged an existing hospitalization. Since hospitalization may be part of the study, only hospitalizations that are longer than expected based on Investigator judgment, will be considered prolonged hospitalizations.
- **Persistent or significant disability/incapacity**: An AE that results in a substantial disruption of a person's ability to conduct normal life functions.
- **Congenital anomaly/birth defect**: A congenital anomaly/birth defect that occurs in the offspring of a patient exposed to the IP.
- **Important medical events**: An AE that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

Note: Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in situations other than those listed above. For example, important medical events may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above (e.g., suspected transmission of an infectious agent by a medicinal product is considered a serious adverse event). Any adverse event is considered a serious adverse event if it is associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An unlisted AE, the nature or severity of which is not consistent with the applicable product reference safety information. For an investigational product, the expectedness of an AE will be determined by whether or not it is listed in the Investigator's Brochure.

Adverse Event Associated With the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or definite as per the definitions listed in Section 11.1.2.

11.1.2. Attribution Definitions

Every effort should be made by the investigator to try to explain each AE and assess its relationship, if any, to the study drug. The temporal relationship of the event to study drug administration should be considered in the causality assessment (i.e., if the event starts soon after study drug administration and resolves when the study drug is stopped).

Causality should be assessed using the following categories

Unrelated: An adverse event that is not related to the use of the drug.

Possibly/probably related: An adverse event that might be due to the use of the drug. An alternative explanation, e.g., concomitant drug(s), concomitant disease(s), is inconclusive or unlikely. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Definitely: An adverse event that cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive.

11.1.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the intensity of events not directly experienced by the patient (e.g., laboratory abnormalities).

11.1.4. Action Taken and Outcome

For all AEs reported, the following will also be specified:

- Actions taken: none, medication required, tests required, hospitalization required or prolonged, treatment unblinded, study drug withdrawn/interrupted, other-specify
- Outcome and date of outcome according to the following definitions:
  - Recovered/resolved

- Recovering/resolving
- Not recovered/not resolved
- Recovered with sequelae/resolved with sequelae
- Fatal
- Unknown
- Seriousness: yes or no (criteria for SAE see above)

11.2. Special Reporting Situations

Safety events of interest on a sponsor study drug that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug.
- Suspected abuse/misuse of a sponsor study drug, defined as 3 x daily dose within any 24-hour period.
- Accidental or occupational exposure to a sponsor study drug.
- Medication error involving a sponsor product (with or without patient/patient exposure to the sponsor study drug, e.g., name confusion).
- Exposure to a sponsor study drug during pregnancy or breastfeeding.

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of a SAE should be recorded on the SAE page of the eCRF.

11.3. Procedures

11.3.1. All Adverse Events

All AEs, whether serious or non-serious, will be reported from the time a signed and dated informed consent form is obtained until completion of the last study-related procedure (may include contact for follow-up of safety). Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments.

All AEs, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as “upper respiratory infection”). Investigators must record in the eCRF their opinion concerning the relationship of the AE to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator all SAEs that are unlisted (unexpected) and associated with the use of the drug. The investigator (or sponsor where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

Patients (or their designees, if appropriate) must be provided with a "study card" indicating the name of the investigational study drug, the study number, the investigator's name, a 24-hour emergency contact number, and, if applicable, excluded concomitant medications.

11.3.2. Serious Adverse Events

All SAEs occurring during the study must be reported by the investigational staff within 24 hours of their knowledge of the event. The following contact information must be used:

Email: [redacted]

In the unlikely event that the email address results in a delivery failure, one of the following backup fax numbers must be used:

For US cases: [redacted]

For Europe/Rest of the world cases: [redacted]

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a member of the investigational staff, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a SAE should be made by email.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the patient's participation in the study, must be followed until any of the following occurs:

- The event resolves.
- The event stabilizes.
- The event returns to Baseline, if a Baseline value is available.
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct.
- It becomes unlikely that any additional information can be obtained (patient or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a patient's participation in a clinical study must be reported as a SAE, except hospitalizations for the following:

- Social reasons in absence of an adverse event.
- Surgery or procedure planned before entry into the study (must be documented in the eCRF).

Suspected transmission of an infectious agent by a medicinal product should be reported as a SAE.

- The cause of death of a patient in the study within 30 days of the last dose of study drug, whether or not the event is expected or associated with the study drug, is considered a SAE.

11.3.3. Pregnancy

All initial reports of pregnancy must be reported to the sponsor by the investigational staff within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any patient who becomes pregnant during the study must be promptly withdrawn from the study.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male patients included in the study will be reported by the investigational staff within 24 hours of their knowledge of the event using the appropriate pregnancy notification form.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

11.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed on the Contact Information page(s), which will be provided as a separate document.

12. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, i.e., any dissatisfaction relative to the identity, quality, durability, and reliability of a product, including its labeling or package integrity. PQCs may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from clinical studies are crucial for the protection of patients, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

12.1. Procedures

All initial PQCs must be reported to the sponsor by the investigational staff as soon as possible after being made aware of the event.

If the defect is combined with a serious adverse event, the investigational staff must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 11.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

12.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed on the Contact Information page(s), which will be provided as a separate document.

13. STUDY DRUG INFORMATION

13.1. Physical Description of Study Drug(s)

MIN-117 will be available in capsules of 2.5 mg strength. [redacted] All excipients of the MIN-117 capsules are derived from sources that are in compliance with Committee for Proprietary Medicinal Products guidelines on minimizing the risk of transmitting animal spongiform encephalopathy agents via medicinal products. [redacted] Certificate of Analysis and TSE/BSE statement of the batch to be used in the proposed clinical trial are checked and accepted according to the regulatory requirements.

MIN-117 placebo will be [redacted] made of white hard gelatin containing silicified microcrystalline cellulose and vegetable magnesium stearate. All excipients of the MIN-117 placebo capsules are derived from sources that are in compliance with Committee for Proprietary Medicinal Products guidelines on minimizing the risk of transmitting animal spongiform encephalopathy agents via medicinal products. [redacted] Certificate of Analysis and TSE/BSE statement of the batch to be used in the proposed clinical trial are checked and accepted according to the regulatory requirements.

13.2. Packaging

The study drug will be packaged in individual patient kits containing sufficient medication with overage for each intra-visit duration.

13.3. Labeling

Each kit containing study drug will have a product and study-specific label containing information that meets the applicable regulatory requirements. The study dispensing labels will contain dosing instructions, quantity of product dispensed, and spaces to record subject number, visit number, date dispensed, and investigator's name/site number.

13.4. Preparation, Handling, and Storage

All study drugs must be stored in a controlled environment at room temperature (i.e., from 15 to 25 °C).

13.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the

patient, and the return of study drug from the patient (if applicable), must be documented on the drug accountability form. Patients must be instructed to return all original containers, whether empty or containing study drug. Study drug returned by study patients will be stored and disposed of according to the sponsor's instructions. Site staff must not combine contents of the study drug containers.

Study drug must be handled in strict accordance with the protocol and the container label and will be stored in a limited access area or in a locked cabinet under appropriate environmental conditions. Unused study drug, and study drug returned by the patient (if applicable), must be available for verification by the sponsor's site monitor during on-site monitoring visits. The return to the sponsor of unused study drug, or used returned study drug for destruction, will be documented on the Drug Return Form. When the site is an authorized destruction unit and study drug supplies are destroyed on site, this must also be documented on the Drug Return Form.

Study drug should be dispensed under the supervision of the investigator, a qualified member of the investigational staff, or by a hospital/clinic pharmacist. Study drug will be supplied only to patients participating in the study. Returned study drug must not be dispensed again, even to the same patient. Returned study drug may not be relabeled or reassigned for use by other patients. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

14. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- eCRF and infrastructure
- Forms and questionnaires for special assessments
- Pharmacokinetic blood sampling supplies
- PD blood sampling supplies
- Safety laboratory sampling supplies
- Patient education material
- Somno-Art device
- ECG device
- Patient trial card indicating the IMP, the study number, the investigator's name and an emergency telephone number providing 24-hour service.

15. ETHICAL ASPECTS

15.1. Study-Specific Design Considerations

Clinical Trial in Major Depressive Disorder

Major depression is a serious and common illness that can run a chronic course and is associated with both frequent morbidity and high mortality (WHO 2006). There is a clear need to develop novel and improved therapeutics for major depressive disorders.

MIN-117 has shown antidepressant-like effects in animal models and has unique mechanism of action and good tolerability. These characteristics make MIN-117 an attractive compound to test for efficacy in major depression.

Selection of Patients

The primary aim of the study is to evaluate the efficacy, safety and tolerability of MIN-117 for the treatment of patients MDD. Thus, the study cannot be completed in healthy subjects. Patients selected in the study will have adequate capacity to give consent for participation in the study.

Justification for Using Placebo

Assessing the potential efficacy of a new compound for the treatment of patients with MDD requires adequate and well-controlled clinical studies. For a new compound this can be achieved either through a placebo-controlled study or through a study comparing it to an active comparator through a non-inferiority design. For non-inferiority studies, previous placebo-controlled studies have to show consistently the superiority of the active standard drug to placebo. A large proportion of studies with antidepressant fail even with previously proven antidepressant, making assay sensitivity difficult to establish and thus, a non-inferiority design invalid (Laughren 2001). Therefore, randomized, controlled studies that rely on comparison with the standard of care drug(s) alone may generate unreliable results with limited assay sensitivity.

Though some continue to consider it unethical to do placebo-controlled studies due to the potential risk of irreversible harm (Rothman 1994), the use of a placebo-controlled study design remains the gold standard for assessment of efficacy of new compound to allow for scientifically meaningful results. Placebo-controlled studies in major depressive disorders are ethically and scientifically justifiable (Temple 2000; Laughren 2001).

Precautions to Ensure Patient Safety in the Study

Patients may participate in the study only if they have adequate capacity to give consent and after fully understanding the potential risks and giving an informed consent. Patients may discontinue the study at any time. The probability of receiving placebo and the concept of random assignment will be explained to the patient. The duration of the study is short, minimizing the time on placebo. Potential disadvantages and adverse events of participating in the study and alternative treatment options will be discussed. Patients at high risk of suicide will be excluded from participating. Patients who do not respond during the study may drop out during the study and clinical care will be arranged between the study investigator and their physician.

Compensation for any study requirements or procedure will be fair per local standards and approved by the participating sites EC in order to not offer any undue incentive to participate in the study.

Specific entry criteria, including exclusion of patients with clinically apparent liver disease, hepatic insufficiency, and other medically unstable systemic diseases, and significantly abnormal ALT, bilirubin, hematology, or other test results at Screening or Baseline, will further ensure the appropriate selection and safety of patients who enter the study. During the study, patients who are unable to tolerate study drug will be discontinued from the study. Only patients who have not adequately responded to their antidepressant where a clinician would consider changing it for lack of response or poor tolerability in addition to meeting the severity criteria for the study will be enrolled.

Only highly qualified and experienced investigators will be participating in the study.

15.2. Regulatory Ethics Compliance

15.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study patients are protected, consistent with the principles that originated in the Declaration of Helsinki and that the clinical study data are credible.

15.2.2. Independent Ethics Committee or Institutional Review Board (IEC/IRB)

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents:

- Final protocol and, if applicable, amendments
- Sponsor-approved informed consent form (and any other written materials to be provided to the patients)
- Investigator's Brochure (or equivalent information) and amendments
- Sponsor-approved patient recruiting materials
- Information on compensation for study-related injuries or payment to patients for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for patients
- Any other documents that the IEC/IRB requests to fulfill its obligation.

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any), the informed consent form, applicable recruiting materials, and patient compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments
- Revision(s) to informed consent form and any other written materials to be provided to patients
- If applicable, new or revised patient recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to patients for participation in the study, if applicable
- Investigator's Brochure amendments or new edition(s)
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)

- Reports of adverse events that are serious, unexpected, and related with the investigational drug
- New information that may adversely affect the safety of the patients or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the patients
- Report of deaths of patients under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Annual Safety Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB.

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for patients, data or trial conduct), the amendment and applicable informed consent form revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

15.2.3. Informed Consent

Each patient must give written consent according to local requirements after the nature of the study has been fully explained. The consent form must be signed before performance of any study-related activity. The consent form that is used must be approved by both the sponsor and by the reviewing IEC/IRB. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the investigational staff must explain to potential patients (or their legal representatives) the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Patients will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the patient will receive for the treatment of his or her disease. Patients will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a patient identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor staff without violating their confidentiality, to the extent permitted by the applicable law(s) or regulations. By signing the informed consent form the patient (or legal representative) is authorizing such access, and agrees to allow his or her study physician to re-contact the patient for the purpose of obtaining consent for additional safety evaluations, if needed, or to obtain information about his or her survival status.

The patient will be given sufficient time to read the informed consent form and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the patient’s personally dated signature. After having obtained the consent, a copy of the informed consent form must be given to the patient.

If the patient is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the informed consent form after the oral consent of the patient is obtained.

15.2.4. Privacy of Personal Data

The collection and processing of personal data from patients enrolled in this study will be limited to those data that are necessary to investigate the efficacy, safety, quality, and utility of the investigational study drug(s) used in this study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of study patients confidential.

The informed consent obtained from the patient (or legal representative) includes explicit consent for the processing of personal data and for the investigator to allow direct access to his or her original medical records for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The patient has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

15.2.5. Country Selection

This study is being conducted in United States of America and select European countries.

16. ADMINISTRATIVE REQUIREMENTS

16.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the patients, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor or its designee.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative (see Contact Information pages provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the

CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

16.2. Regulatory Documentation

16.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, as applicable. A study may not be initiated until all local regulatory requirements are met.

16.2.2. Required Pre-study Documentation

The following documents must be provided to the sponsor before shipment of study drug to the investigational site:

- Protocol and amendment(s), if any, signed and dated by the investigator.
- A copy of the dated and signed written IEC/IRB approval of the protocol, amendments, informed consent form, any recruiting materials, and if applicable, patient compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed by the chairman or authorized designee.
- Name and address of the IEC/IRB including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the investigational staff is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable.
- Documentation of investigator qualifications (e.g., curriculum vitae).
- Completed investigator financial disclosure form from the investigator, where required.
- Signed and dated clinical trial agreement, which includes the financial agreement.
- Any other documentation required by local regulations.

The following documents must be provided to the sponsor before enrollment of the first patient:

- Documentation of subinvestigator qualifications (e.g., curriculum vitae).
- Name and address of the laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests.
- Laboratory documentation demonstrating competence and test reliability (e.g., accreditation/license), if applicable.

16.3. Patient Identification, Enrollment, and Screening Logs

The investigator agrees to complete a patient identification and enrollment log to permit easy identification of each patient during and after the study. This document will be reviewed by the sponsor site contact for completeness.

The patient identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure patient confidentiality, no copy will be

made. All reports and communications relating to the study will identify patients by initials and assigned number only.

The investigator must also complete a patient-screening log, which reports on all patients who were seen to determine eligibility for inclusion in the study.

16.4. Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the CRF: patient identification, eligibility, and study identification; study discussion and date of informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events; and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion, and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

It is recommended that the author of an entry in the source documents be identifiable.

At a minimum, the type and level of detail of source data available for a study patient should be consistent with that commonly recorded at the site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

16.5. Case Report Form Completion

Case report forms are provided in electronic format for each patient who is enrolled in this study.

Data must be entered into eCRFs in English. The investigator must verify that all data entries in the eCRFs are accurate and correct. All eCRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel.

16.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, review of protocol procedures with the investigator and associated personnel before the study, and periodic monitoring visits by the sponsor. Written instructions will be provided for collection, preparation, and shipment of blood, plasma, and urine samples.

Guidelines for eCRF completion will be provided and reviewed with study personnel before the start of the study.

The sponsor will review eCRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After entry of the data into the clinical study database they will be verified for accuracy.

16.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRFs and all source documents that support the data collected from each patient, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the

Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

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

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator must permit access to such reports.

16.8. Monitoring

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study center visit log that will be kept at the site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and investigational staff and are accessible for verification by the sponsor site contact. If electronic records are maintained at the investigational site, the method of verification must be discussed with the investigational staff.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the eCRF are consistent with the original source data. Findings from this review of eCRF and source documents will be discussed with the investigational staff. The sponsor expects that, during monitoring visits, the relevant investigational staff will be available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

16.9. Study Completion/Termination

16.9.1. Study Completion

The study is considered completed with the last visit of the last patient participating in the study. The final data from the investigational site will be sent to the sponsor (or designee) after completion of the final patient visit at that site. Investigational sites will be closed

upon study completion. An investigational site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

16.9.2. Study Termination

The sponsor reserves the right to close the investigational site or terminate the study at any time for any reason at the sole discretion of the sponsor. Investigational sites will be closed upon study termination. An investigational site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended closure.

Reasons for the early closure of an investigational site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the investigator
- Discontinuation of further drug development.

16.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the eCRF. Patient privacy must, however, be respected. The investigator and staff are responsible for being present and available for consultation during routinely scheduled site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

16.11. Use of Information and Publication

All information, including but not limited to information regarding MIN-117 or the sponsor's operations (e.g., patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the clinical study will be used by the sponsor in connection with the continued development of MIN-117, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To

permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report (CSR) generated by the sponsor and will contain CRF data from all investigational sites that participated in the study. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator, if needed. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

The sponsor shall have the right to publish such data and information without approval from the investigator. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information.

For multicenter study designs and substudy approaches, results may need to be published in a given sequence (e.g., substudies) should not generally be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not publishing data derived from the individual site until the combined results from the completed study have been published in full, within 12 months after conclusion, abandonment, or termination of the study at all sites, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

16.12. Registration of Clinical Studies and Disclosure of Results

The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

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ATTACHMENT 1: ALLOWED/PROHIBITED CONCOMITANT MEDICATIONS

The list is not exhaustive; other concomitant medications could be allowed after Sponsor's Responsible Medical Officer approval – As a general rule, CYP 2C8 and CYP3A4/5 inducers and inhibitors as well as drugs metabolized through CYP2C9 are **always** prohibited.

Drug Class	As Needed	Chronic Use	Comments
Analgesics	Y	N	Non-opiate analgesics only.
Anorexics	N	N	
Antacids	Y	N	
Antianginal Agents	N	N	
Antiarrhythmics	N	N	
Antiasthma Agents	Y	Y	Inhaled agents only.
Antibiotics	Y	N	
Anticholinergics	N	N	
Anticoagulants	N	Y (1)	Aspirin (max. 325 mg/day) is allowed as chronic anti-platelet treatment.
Anticonvulsants	N	N	
Antidepressants	N	N	
Antidiarrheal Preparations	Y	N	
Antifungal Agents:			
Systemic	N	N	
Topical	Y	Y	
Antihistamines	Y	N	Allegra, Claritin, and Zyrtec are allowed.
Antihypertensives	N	Y (1)	Telmisartan, ramipril, atenolol are allowed
Anti-inflammatory Drugs	N	N	
Antinauseants	Y	N	
Antineoplastics	N	N	
Antiobesity	N	N	
Antipsychotics	N	N	
Anxiolytics	N	N	
Cough/Cold Preparations	Y	N	Use of cough and cold preparations containing pseudoephedrine or phenylpropanolamine is not permitted. Decongestants containing narcotics are not permitted.
Diuretics	Y	Y (1)	Amiloride and hydrochlorothiazide are allowed
H2-Blockers	Y	N	
Hormones	N	Y	Only thyroid hormone replacement, oral contraceptives and estrogen replacement therapy are allowed.
Hypoglycemic Agents	N	Y (1)	Metformine is allowed
Hypolipidemics	N	Y (1)	Rosuvastatin is allowed
Insulin	N	N	
Benign Prostatic Hypertrophy	N	Y(1)	Finasteride, dutasteride are allowed
Muscle Relaxants	N	N	
Psychotropic drugs not otherwise specified (including herbal products)	N	N	No drugs with psychomotor effects or with anxiolytic, stimulant, antipsychotic, or sedative properties are allowed.
Sedatives/Hypnotics	N	N	

(1) Allowed for some specific medications. Please contact the Medical Monitor as needed.

ATTACHMENT 2: MONTGOMERY-ASBERG DEPRESSION RATING SCALE (MADRS)

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones, which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5) and then report the appropriate number. The items should be rated with regards to the patient has done over the past week.

1. Apparent sadness Representing despondency, gloom and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.	
0 = No sadness.	☐
2 = Looks dispirited but does brighten up without difficulty.	☐
4 = Appears sad and unhappy most of the time.	☐
6 = Looks miserable all the time. Extremely despondent	☐

2. 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.	
0 = Occasional sadness in keeping with the circumstances.	☐
2 = Sad or low but brightens up without difficulty.	☐
4 = Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.	☐
6 = Continuous or unvarying sadness, misery or despondency.	☐

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.	☐
2 = Occasional feelings of edginess and ill-defined discomfort.	☐
4 = Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.	☐
6 = Unrelenting dread or anguish. Overwhelming panic.	☐

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 normal.	☐
2 = Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.	☐
4 = Moderate stiffness and resistance	☐
6 = Sleep reduced or broken by at least 2 hours.	☐

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.	☐
2 = Slightly reduced appetite.	☐
4 = No appetite. Food is tasteless.	☐
6 = Needs persuasion to eat at all.	☐

6. Concentration difficulties Representing difficulties in collecting one's thoughts mounting to an incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.	
0 = No difficulties in concentrating.	☐
2 = Occasional difficulties in collecting one's thoughts.	☐
4 = Difficulties in concentrating and sustaining thought which reduced ability to read or hold a conversation.	☐
6 = Unable to read or converse without great difficulty.	☐

7. Lassitude Representing difficulty in getting started or slowness in initiating and performing everyday activities.	
0 = Hardly any difficulty in getting started. No sluggishness.	☐
2 = Difficulties in starting activities.	☐
4 = Difficulties in starting simple routine activities which are carried out with effort.	☐
6 = Complete lassitude. Unable to do anything without help.	☐

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.	☐
2 = Reduced ability to enjoy usual interests.	☐
4 = Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.	☐
6 = The experience of being emotionally paralysed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends.	☐

9. Pessimistic thoughts Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse and ruin.	
0 = No pessimistic thoughts.	☐
2 = Fluctuating ideas of failure, self-reproach or self- depreciation.	☐
4 = Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future.	☐
6 = Delusions of ruin, remorse or irredeemable sin. Self- accusations which are absurd and unshakable.	☐

10. Suicidal thoughts Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicide attempts should not in themselves influence the rating.	
0 = Enjoys life or takes it as it comes.	☐
2 = Weary of life. Only fleeting suicidal thoughts.	☐
4 = Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intenstion.	☐
6 = Explicit plans for suicide when there is an opportunity. Active preparations for suicide.	☐

ATTACHMENT 3: HAMILTON ANXIETY SCALE (HAM-A)

1. Anxious mood **This item covers the emotional condition of uncertainty about the future, ranging from worry, insecurity, irritability and apprehension to overpowering dread.**	
0 – The patient is neither more or less insecure or irritable than usual.	☐
1 – Doubtful whether the patient is more insecure or irritable than usual.	☐
2 – The patient expresses more clearly to be in a state of anxiety, apprehension or irritability, which he may find difficult to control. However, the worrying still is about minor matters and thus without influence on the patient's daily life.	☐
3 – At times the anxiety or insecurity is more difficult to control because the worrying is about major injuries or harms which might occur in the future. Has occasionally interfered with the patient's daily life.	☐
4 – The feeling of dread is present so often that it markedly interferes with the patient's daily life.	☐

2. Tension **This item includes inability to relax, nervousness, bodily tensions, trembling and restless fatigue.**	
0 – The patient is neither more nor less tense than usual.	☐
1 – The patient seems somewhat more nervous and tense than usual.	☐
2 – Patient expresses clearly unable to relax and full of inner unrest, which he finds difficult to control, but it is still without influence on the patient's daily life.	☐
3 – The inner unrest and nervousness is so intense or frequent that it occasionally interferes with the patient's daily work.	☐
4 – Tensions and unrest interfere with the patient's life and work at all times.	☐

3. Fears **This item includes fear of being in a crowd, of animals, of being in public places, of being alone, of traffic, of strangers, of dark etc. It is important to note whether there has been more phobic anxiety during the present episode than usual.**	
0 – Not present.	☐
1 – Doubtful whether present.	☐
2 – The patient experiences phobic anxiety but is able to fight it.	☐
3 – It is difficult to fight or overcome the phobic anxiety, which thus to some extent interferes with the patient's daily life and work.	☐
4 – The phobic anxiety clearly interferes with the patient's daily life and work.	☐

4. Insomnia **This item covers the patient's subjective experience of sleep duration and sleep depth during the three preceding nights. Note: Administration of hypnotics or sedatives is disregarded.**	
0 – Usual sleep duration and sleep depth.	☐
1 – Sleep duration is doubtfully or slightly reduced (e.g. due to difficulties falling asleep), but no change in sleep depth.	☐
2 – Sleep depth is also reduced, sleep being more superficial. Sleep as a whole is somewhat disturbed.	☐
3 – Sleep duration and sleep depth is markedly changed. Sleep periods total only a few hours per 24 hours.	☐
4 – Sleep depth is so shallow that the patient speaks of short periods of slumber or dozing, but no real sleep.	☐

5. Difficulties in concentration and memory **This item covers difficulties in concentration, making decision about everyday matters, and memory.**	
0 – The patient has neither more nor less difficulty in concentration and/or memory that usual.	☐
1 – Doubtful whether the patient has difficulty in concentration and/or memory.	☐
2 – Even with a major effort it is difficult for the patient to concentrate on his daily routine work.	☐
3 – The patient has pronounced difficulties with concentration, memory, or decision making, e.g. in reading a newspaper article or watching a television programme to the end.	☐
4 – During the interview the patient shows difficulty in concentration, memory or decision making.	☐

6. Depressed mood **This item covers both the verbal and the non-verbal communication of sadness, depression, despondency, helplessness and hopelessness.**	
0 – Not present.	☐
1 – Doubtful whether the patient is more despondent or sad than usual, or is only vaguely so.	☐
2 – The patient is more clearly concerned with unpleasant experiences, although he still lacks helplessness or hopelessness.	☐
3 – The patient shows clear non-verbal signs of depression and/or hopelessness.	☐
4 – The patient remarks on despondency and helplessness or the non-verbal signs dominate the interview and the patient cannot be distracted.	☐

7. General somatic symptoms: Muscular **Weakness, stiffness, soreness or real pain, more or less diffusely localized in the muscles, such as jaw ache or neck ache.**	
0 – The patient is neither more nor less sore or stiff in the muscles than usual.	☐
1 – The patient seems somewhat more stiff or sore in the muscles than usual.	☐
2 – The symptoms have the character of pain.	☐
3 – Muscle pain interferes to some extent with the patient's daily work and life.	☐
4 – Muscle pain is present most of the time and clearly interferes with the patient's daily work and life.	☐

8. General somatic symptoms: Sensory **This item includes increased fatigability and weakness or real functional disturbances of the senses, including tinnitus, blurring of vision, hot and cold flashes and prickling sensations.**	
0 – Not present.	☐
1 – Doubtful whether the patient's indications of symptoms are more pronounced than usual.	☐
2 – The sensations of pressure reach the character of buzzing in the ears, visual disturbances and prickling or itching sensations in the skin.	☐
3 – The generalized sensory symptoms interfere to some extent with the patient's daily life and work.	☐
4 – The generalized sensory symptoms are present most of the time and clearly interfere with the patient's daily life and work.	☐

9. Cardiovascular symptoms **This item includes tachycardia, palpitations, oppression, chest pain, throbbing in the blood vessels, and feelings of faintness.**	
0 – Not present.	☐
1 – Doubtful whether present.	☐
2 – Cardiovascular symptoms are present, but the patient can still control them.	☐
3 – The patient has occasional difficulty controlling the cardiovascular symptoms, which thus to some extent interfere with his daily life and work.	☐
4 – Cardiovascular symptoms are present most of the time and clearly interfere with the patient's daily life and work.	☐

10. Respiratory symptoms **Feelings of constriction or contraction in throat or chest, 89dyspnoea or choking sensations and sighing respiration.**	
0 – Not present.	☐
1 – Doubtful whether present.	☐
2 – Respiratory symptoms are present, but the patient can still control them.	☐
3 – The patient has occasional difficulty controlling the respiratory symptoms, which thus to some extent interfere with his daily life and work.	☐
4 – Respiratory symptoms are present most of the time and clearly interfere with the patient's daily life and work.	☐

11. Gastro-intestinal symptoms **This item covers difficulties in swallowing, "sinking" sensation in stomach, dyspepsia (heartburn or burning sensation in the stomach, abdominal pains related to meals, fullness, nausea and vomiting), abdominal rumbling and diarrhoea.**	
0 – Not present.	☐
1 – Doubtful whether present (or doubtful whether different from usual).	☐
2 – One or more gastro-intestinal symptoms are present, but the patient can still control them.	☐
3 – The patient has occasional difficulty controlling the gastro-intestinal symptoms, which to some extent interfere with his daily life and work.	☐
4 – The gastro-intestinal symptoms are present most of the time and interfere clearly with the patient's daily life and work.	☐

12. Genito-urinary symptoms **This item includes non-organic or psychic symptoms such as frequent or more pressing passing of urine, menstrual irregularities, anorgasmia, dyspareunia, premature ejaculation, loss of erection.**	
0 – Not present.	☐
1 – Doubtful whether present (or doubtful whether different from usual).	☐
2 – One or more genito-urinary symptoms are present, but do not interfere with the patient's daily life and work.	☐
3 – Occasionally, one or more genito-urinary symptoms are present to such a degree that they interfere to some extent with the patient's daily life and work.	☐
4 – The genito-urinary symptoms are present most of the time and interfere clearly with the patient's daily life and work.	☐

13. Other autonomic symptoms **This item includes dryness of the mouth, blushing or pallor, sweating and dizziness.**	
0 – Not present.	☐
1 – Doubtful whether present.	☐
2 – One or more autonomic symptoms are present, but they do not interfere with the patient's daily life and work.	☐
3 – Occasionally, one or more autonomic symptoms are present to such a degree that they interfere to some extent with the patient's daily life and work.	☐
4 – Autonomic symptoms are present most of the time and clearly interfere with the patient's daily life and work.	☐

14. Behaviour during interview **The patient may appear tense, nervous, agitated, restless, tremulous, pale, hyperventilating or sweating during the interview. Based on such observations a global estimate is made.**	
0 – The patient does not appear anxious.	☐
1 – It is doubtful whether the patient is anxious.	☐
2 – The patient is moderately anxious.	☐
3 – The patient is markedly anxious.	☐
4 – Patient is overwhelmed by anxiety, for example with shaking and trembling all over.	☐

Total score _____

HAM-A score level of anxiety
<17: mild
18 – 24: mild to moderate
25 – 30: moderate to severe

ATTACHMENT 4: CLINICAL GLOBAL IMPRESSION – SEVERITY RATING (CGI-S)

Severity of illness

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

0 = Not assessed

1 = Normal, not at all ill

2 = Borderline mentally ill

3 = Mildly ill

4 = Moderately ill

5 = Markedly ill

6 = Severely ill

7 = Among the most extremely ill patients

ATTACHMENT 5: CLINICAL GLOBAL IMPRESSION – IMPROVEMENT RATING (CGI-I)

Global Improvement: Rate total improvement whether or not, in your judgment, it is due entirely to drug treatment.

Compared to the patient's condition at admission to the study, how much has this patient changed?

0 = Not assessed

1 = Very much improved

2 = Much improved

3 = Minimally improved

4 = No change

5 = Minimally worse

6 = Much worse

7 = Very

ATTACHMENT 6: INVENTORY OF DEPRESSIVE SYMPTOMS - SUBJECT-RATED (IDS-SR$_{30}$)

INVENTORY OF DEPRESSIVE SYMPTOMATOLOGY (SELF-REPORT)
(IDS-SR)

NAME: _____ TODAY'S DATE _____

Please circle the one response to each item that best describes you for the past seven days.

1. Falling Asleep:
   - 0 I never take longer than 30 minutes to fall asleep.
   - 1 I take at least 30 minutes to fall asleep, less than half the time.
   - 2 I take at least 30 minutes to fall asleep, more than half the time.
   - 3 I take more than 60 minutes to fall asleep, more than half the time.

2. Sleep During the Night:
   - 0 I do not wake up at night.
   - 1 I have a restless, light sleep with a few brief awakenings each night.
   - 2 I wake up at least once a night, but I go back to sleep easily.
   - 3 I awaken more than once a night and stay awake for 20 minutes or more, more than half the time.

3. Waking Up Too Early:
   - 0 Most of the time, I awaken no more than 30 minutes before I need to get up.
   - 1 More than half the time, I awaken more than 30 minutes before I need to get up.
   - 2 I almost always awaken at least one hour or so before I need to, but I go back to sleep eventually.
   - 3 I awaken at least one hour before I need to, and can't go back to sleep.

4. Sleeping Too Much:
   - 0 I sleep no longer than 7-8 hours/night, without napping during the day.
   - 1 I sleep no longer than 10 hours in a 24-hour period including naps.
   - 2 I sleep no longer than 12 hours in a 24-hour period including naps.
   - 3 I sleep longer than 12 hours in a 24-hour period including naps.

5. Feeling Sad:
   - 0 I do not feel sad
   - 1 I feel sad less than half the time.
   - 2 I feel sad more than half the time.
   - 3 I feel sad nearly all of the time.

6. Feeling Irritable:
   - 0 I do not feel irritable.
   - 1 I feel irritable less than half the time.
   - 2 I feel irritable more than half the time.
   - 3 I feel extremely irritable nearly all of the time.

7. Feeling Anxious or Tense:
   - 0 I do not feel anxious or tense.
   - 1 I feel anxious (tense) less than half the time.
   - 2 I feel anxious (tense) more than half the time.
   - 3 I feel extremely anxious (tense) nearly all of the time.

8. Response of Your Mood to Good or Desired Events:
   - 0 My mood brightens to a normal level which lasts for several hours when good events occur.
   - 1 My mood brightens but I do not feel like my normal self when good events occur.
   - 2 My mood brightens only somewhat to a rather limited range of desired events.
   - 3 My mood does not brighten at all, even when very good or desired events occur in my life.

9. Mood in Relation to the Time of Day:
   - 0 There is no regular relationship between my mood and the time of day.
   - 1 My mood often relates to the time of day because of environmental events (e.g., being alone, working).
   - 2 In general, my mood is more related to the time of day than to environmental events.
   - 3 My mood is clearly and predictably better or worse at a particular time each day.

   9A. Is your mood typically worse in the morning, afternoon or night? (circle one)

   9B. Is your mood variation attributed to the environment? (yes or no) (circle one)

10. The Quality of Your Mood:
    - 0 The mood (internal feelings) that I experience is very much a normal mood.
    - 1 My mood is sad, but this sadness is pretty much like the sad mood I would feel if someone close to me died or left.
    - 2 My mood is sad, but this sadness has a rather different quality to it than the sadness I would feel if someone close to me died or left.
    - 3 My mood is sad, but this sadness is different from the type of sadness associated with grief or loss.

Please complete either 11 or 12 (not both)

11. Decreased Appetite:

0 There is no change in my usual appetite.
1 I eat somewhat less often or lesser amounts of food than usual.
2 I eat much less than usual and only with personal effort.
3 I rarely eat within a 24-hour period, and only with extreme personal effort or when others persuade me to eat.

12. Increased Appetite:

0 There is no change from my usual appetite.
1 I feel a need to eat more frequently than usual.
2 I regularly eat more often and/or greater amounts of food than usual.
3 I feel driven to overeat both at mealtime and between meals.

Please complete either 13 or 14 (not both)

13. Decreased Weight (Within the Last Two Weeks):

0 I have not had a change in my weight.
1 I feel as if I've had a slight weight loss.
2 I have lost 2 pounds or more.
3 I have lost 5 pounds or more.

14. Increased Weight (Within the Last Two Weeks):

0 I have not had a change in my weight.
1 I feel as if I've had a slight weight gain.
2 I have gained 2 pounds or more.
3 I have gained 5 pounds or more.

15. Concentration/Decision Making:

0 There is no change in my usual capacity to concentrate or make decisions.
1 I occasionally feel indecisive or find that my attention wanders.
2 Most of the time, I struggle to focus my attention or to make decisions.
3 I cannot concentrate well enough to read or cannot make even minor decisions.

16. View of Myself:

0 I see myself as equally worthwhile and deserving as other people.
1 I am more self-blaming than usual.
2 I largely believe that I cause problems for others.
3 I think almost constantly about major and minor defects in myself.

17. View of My Future:

0 I have an optimistic view of my future.
1 I am occasionally pessimistic about my future, but for the most part I believe things will get better.
2 I'm pretty certain that my immediate future (1-2 months) does not hold much promise of good things for me.
3 I see no hope of anything good happening to me anytime in the future.

18. Thoughts of Death or Suicide:

0 I do not think of suicide or death.
1 I feel that life is empty or wonder if it's worth living.
2 I think of suicide or death several times a week for several minutes.
3 I think of suicide or death several times a day in some detail, or I have made specific plans for suicide or have actually tried to take my life.

19. General Interest:

0 There is no change from usual in how interested I am in other people or activities.
1 I notice that I am less interested in people or activities.
2 I find I have interest in only one or two of my formerly pursued activities.
3 I have virtually no interest in formerly pursued activities.

20. Energy Level:

0 There is no change in my usual level of energy.
1 I get tired more easily than usual.
2 I have to make a big effort to start or finish my usual daily activities (for example, shopping, homework, cooking or going to work).
3 I really cannot carry out most of my usual daily activities because I just don't have the energy.

21. Capacity for Pleasure or Enjoyment (excluding sex):

0 I enjoy pleasurable activities just as much as usual.
1 I do not feel my usual sense of enjoyment from pleasurable activities.
2 I rarely get a feeling of pleasure from any activity.
3 I am unable to get any pleasure or enjoyment from anything.

22. Interest in Sex (Please Rate Interest, not Activity):

0 I'm just as interested in sex as usual.
1 My interest in sex is somewhat less than usual or I do not get the same pleasure from sex as I used to.
2 I have little desire for or rarely derive pleasure from sex.
3 I have absolutely no interest in or derive no pleasure from sex.

23. Feeling slowed down:

0 I think, speak, and move at my usual rate of speed.
1 I find that my thinking is slowed down or my voice sounds dull or flat.
2 It takes me several seconds to respond to most questions and I'm sure my thinking is slowed.
3 I am often unable to respond to questions without extreme effort.

24. Feeling restless:

0 I do not feel restless.
1 I'm often fidgety, wring my hands, or need to shift how I am sitting.
2 I have impulses to move about and am quite restless.
3 At times, I am unable to stay seated and need to pace around.

25. Aches and pains:

0 I don't have any feeling of heaviness in my arms or legs and don't have any aches or pains.
1 Sometimes I get headaches or pains in my stomach, back or joints but these pains are only sometime present and they don't stop me from doing what I need to do.
2 I have these sorts of pains most of the time.
3 These pains are so bad they force me to stop what I am doing.

26. Other bodily symptoms:

0 I don't have any of these symptoms: heart pounding fast, blurred vision, sweating, hot and cold flashes, chest pain, heart turning over in my chest, ringing in my ears, or shaking.
1 I have some of these symptoms but they are mild and are present only sometimes.
2 I have several of these symptoms and they bother me quite a bit.
3 I have several of these symptoms and when they occur I have to stop doing whatever I am doing.

27. Panic/Phobic symptoms:

0 I have no spells of panic or specific fears (phobia) (such as animals or heights).
1 I have mild panic episodes or fears that do not usually change my behavior or stop me from functioning.
2 I have significant panic episodes or fears that force me to change my behavior but do not stop me from functioning.
3 I have panic episodes at least once a week or severe fears that stop me from carrying on my daily activities.

28. Constipation/diarrhea:

0 There is no change in my usual bowel habits.
1 I have intermittent constipation or diarrhea which is mild.
2 I have diarrhea or constipation most of the time but it does not interfere with my day-to-day functioning.
3 I have constipation or diarrhea for which I take medicine or which interferes with my day-to-day activities.

29. Interpersonal Sensitivity:

0 I have not felt easily rejected, slighted, criticized or hurt by others at all.
1 I have occasionally felt rejected, slighted, criticized or hurt by others.
2 I have often felt rejected, slighted, criticized or hurt by others, but these feelings have had only slight effects on my relationships or work.
3 I have often felt rejected, slighted, criticized or hurt by others and these feelings have impaired my relationships and work.

30. Leaden Paralysis/Physical Energy:

0 I have not experienced the physical sensation of feeling weighted down and without physical energy.
1 I have occasionally experienced periods of feeling physically weighted down and without physical energy, but without a negative effect on work, school, or activity level.
2 I feel physically weighted down (without physical energy) more than half the time.
3 I feel physically weighted down (without physical energy) most of the time, several hours per day, several days per week.

Which 3 items (questions) were the easiest to understand? _____

Thank you

Range 0-84 Score: _____

ATTACHMENT 7: SNAITH–HAMILTON PLEASURE SCALE (SHAPS)

Each of the items has a set of four response categories--Definitely Agree, Agree, Disagree, and Strongly Disagree, with either of the Disagree responses receiving a score of 1 and either of the Agree responses receiving a score of 0.

Domain
1. I would enjoy my favorite television or radio program
2. I would enjoy being with family or close friends
3. I would find pleasure in my hobbies and pastimes
4. I would be able to enjoy my favorite meal
5. I would enjoy a warm bath or refreshing shower
6. I would find pleasure in the scent of flowers or the smell of a fresh sea breeze or freshly baked bread
7. I would enjoy seeing other people's smiling faces
8. I would enjoy looking smart when I have made an effort with my appearance
9. I would enjoy reading a book, magazine or newspaper
10. I would enjoy a cup of tea or coffee or my favorite drink
11. I would find pleasure in small things; e.g., bright sunny day, a telephone call from a friend
12. I would be able to enjoy a beautiful landscape or view
13. I would get pleasure from helping others
14. I would feel pleasure when I receive praise from other people

ATTACHMENT 8: PERCEIVED STRESS SCALE (PSS)

Perceived Stress Scale

A more precise measure of personal stress can be determined by using a variety of instruments that have been designed to help measure individual stress levels. The first of these is called the Perceived Stress Scale.

The Perceived Stress Scale (PSS) is a classic stress assessment instrument. The tool, while originally developed in 1983, remains a popular choice for helping us understand how different situations affect our feelings and our perceived stress. The questions in this scale ask about your feelings and thoughts during the last month. In each case, you will be asked to indicate how often you felt or thought a certain way. Although some of the questions are similar, there are differences between them and you should treat each one as a separate question. The best approach is to answer fairly quickly. That is, don't try to count up the number of times you felt a particular way; rather indicate the alternative that seems like a reasonable estimate.

For each question choose from the following alternatives:
0 - never 1 - almost never 2 - sometimes 3 - fairly often 4 - very often

_____ 1. In the last month, how often have you been upset because of something that happened unexpectedly?

_____ 2. In the last month, how often have you felt that you were unable to control the important things in your life?

_____ 3. In the last month, how often have you felt nervous and stressed?

_____ 4. In the last month, how often have you felt confident about your ability to handle your personal problems?

_____ 5. In the last month, how often have you felt that things were going your way?

_____ 6. In the last month, how often have you found that you could not cope with all the things that you had to do?

_____ 7. In the last month, how often have you been able to control irritations in your life?

_____ 8. In the last month, how often have you felt that you were on top of things?

_____ 9. In the last month, how often have you been angered because of things that happened that were outside of your control?

_____ 10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?

PSS Scoring

- First, reverse the scores for questions 4, 5, 7, and 8. On these 4 questions, change the scores like this:

  0 = 4, 1 = 3, 2 = 2, 3 = 1, 4 = 0.

- Now add up the scores for each item to get a total. **Total score is** _____.

- Individual scores on the PSS can range from 0 to 40 with higher scores indicating higher perceived stress.
  - Scores ranging from 0-13 would be considered low stress.
  - Scores ranging from 14-26 would be considered moderate stress.
  - Scores ranging from 27-40 would be considered high perceived stress.

The Perceived Stress Scale is interesting and important because your perception of what is happening in your life is most important. Consider the idea that two individuals could have the exact same events and experiences in their lives for the past month. Depending on their perception, total score could put one of those individuals in the low stress category and the total score could put the second person in the high stress category.

ATTACHMENT 9: ARIZONA SEXUAL EXPERIENCES SCALE (A-SEX)

ARIZONA SEXUAL EXPERIENCES SCALE (ASEX)-MALE

For each item, please indicate your OVERALL level during the PAST WEEK, including TODAY.

1. How strong is your sex drive?

1	2	3	4	5	6
extremely strong	very strong	somewhat strong	somewhat weak	very weak	no sex drive

2. How easily are you sexually aroused (turned on)?

1	2	3	4	5	6
extremely easily	very easily	somewhat easily	somewhat difficult	very difficult	never aroused

3. Can you easily get and keep an erection?

1	2	3	4	5	6
extremely easily	very easily	somewhat easily	somewhat difficult	very difficult	never

4. How easily can you reach an orgasm?

1	2	3	4	5	6
extremely easily	very easily	somewhat easily	somewhat difficult	very difficult	never reach orgasm

5. Are your orgasms satisfying?

1	2	3	4	5	6
extremely satisfying	very satisfying	somewhat satisfying	somewhat unsatisfying	very unsatisfying	can't reach orgasm

COMMENTS:

ARIZONA SEXUAL EXPERIENCES SCALE (ASEX)-FEMALE

For each item, please indicate your OVERALL level during the PAST WEEK, including TODAY.

1. How strong is your sex drive?

1	2	3	4	5	6
extremely strong	very strong	somewhat strong	somewhat weak	very weak	no sex drive

2. How easily are you sexually aroused (turned on)?

1	2	3	4	5	6
extremely easily	very easily	somewhat easily	somewhat difficult	very difficult	never aroused

3. How easily does your vagina become moist or wet during sex?

1	2	3	4	5	6
extremely easily	very easily	somewhat easily	somewhat difficult	very difficult	never

4. How easily can you reach an orgasm?

1	2	3	4	5	6
extremely easily	very easily	somewhat easily	somewhat difficult	very difficult	never reach orgasm

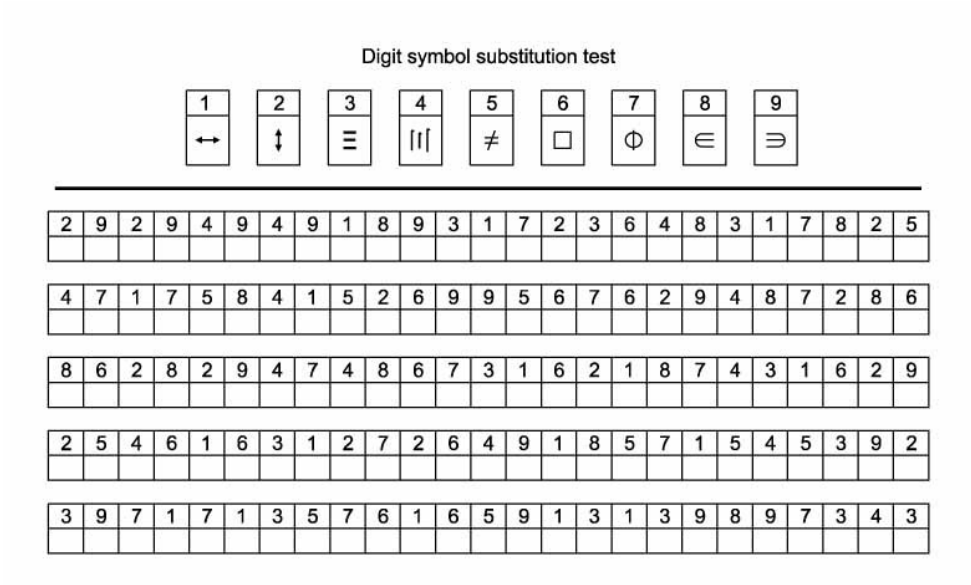
5. Are your orgasms satisfying?

1	2	3	4	5	6
extremely satisfying	very satisfying	somewhat satisfying	somewhat unsatisfying	very unsatisfying	can't reach orgasm

COMMENTS:

ATTACHMENT 10: DIGIT SYMBOL SUBSTITUTION TEST (DSST)

Sample Sheet



ATTACHMENT 11: COLUMBIA SUICIDE SEVERITY RATING SCALE (C-SSRS)

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.

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 thought about being dead or what it would be like to be dead?*** ***Have you wished you were dead or wished you could go to sleep and never wake up?*** ***Do you wish you weren't alive anymore?*** 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 thought about doing something to make yourself not alive anymore?*** ***Have you had any thoughts about 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 thought about how you would do that or how you would make yourself not alive anymore (kill yourself)? What did you think about?*** 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 <u>some intent to act on such thoughts</u>, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***When you thought about making yourself not alive anymore (or killing yourself), did you think that this was something you might actually do?*** ***This is different from (as opposed to) having the thoughts but knowing you wouldn't do anything about it.*** 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 decided how or when you would make yourself not alive anymore/kill yourself? Have you planned out (worked out the details of) how you would do it?*** ***What was your plan?*** ***When you made this plan (or worked out these details), was any part of you thinking about actually doing it?*** If yes, describe:	Yes ☐ No ☐
INTENSITY OF IDEATION	
The following feature 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?* *Write response*_____ (1) Only one time (2) A few times (3) A lot (4) All the time (0) Don't know/Not applicable	___

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. ***Did you do anything to try to kill yourself or make yourself not alive anymore? What did you do?*** ***Did you hurt yourself on purpose? Why did you do that?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to make yourself not alive anymore when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons, not at all to end your life or kill yourself (like to make yourself feel better, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?** **Has subject engaged in Self-Injurious Behavior, intent unknown?**	Yes No ☐ ☐ Total # of Attempts _____ 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 make yourself not alive anymore (end your life or kill yourself) but someone or something stopped you before you actually did anything? What did you do?*** If yes, describe:	Yes No ☐ ☐ Total # of interrupted _____
Aborted Attempt or Self-Interrupted 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 make yourself not alive anymore (end your life or kill yourself) but you changed your mind (stopped yourself) before you actually did anything? What did you do?*** If yes, describe:	Yes No ☐ ☐ Total # of aborted or self-interrupted _____
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 done anything to get ready to make yourself not alive anymore (to end your life or kill yourself)- like giving things away, writing a goodbye note, getting things you need to kill yourself?*** If yes, describe:	Yes No ☐ ☐ Total # of preparatory acts _____
Suicide: Death by suicide occurred since last assessment.	Yes No ☐ ☐
	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* _____

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed):

Institution and Address:

Signature: Date:

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed):

Institution and Address:

Telephone Number:

Signature: Date:

(Day Month Year)

Sponsor's Responsible Medical Officer:

[redacted]

Signature:

Date: 20 November 2018

Note If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.