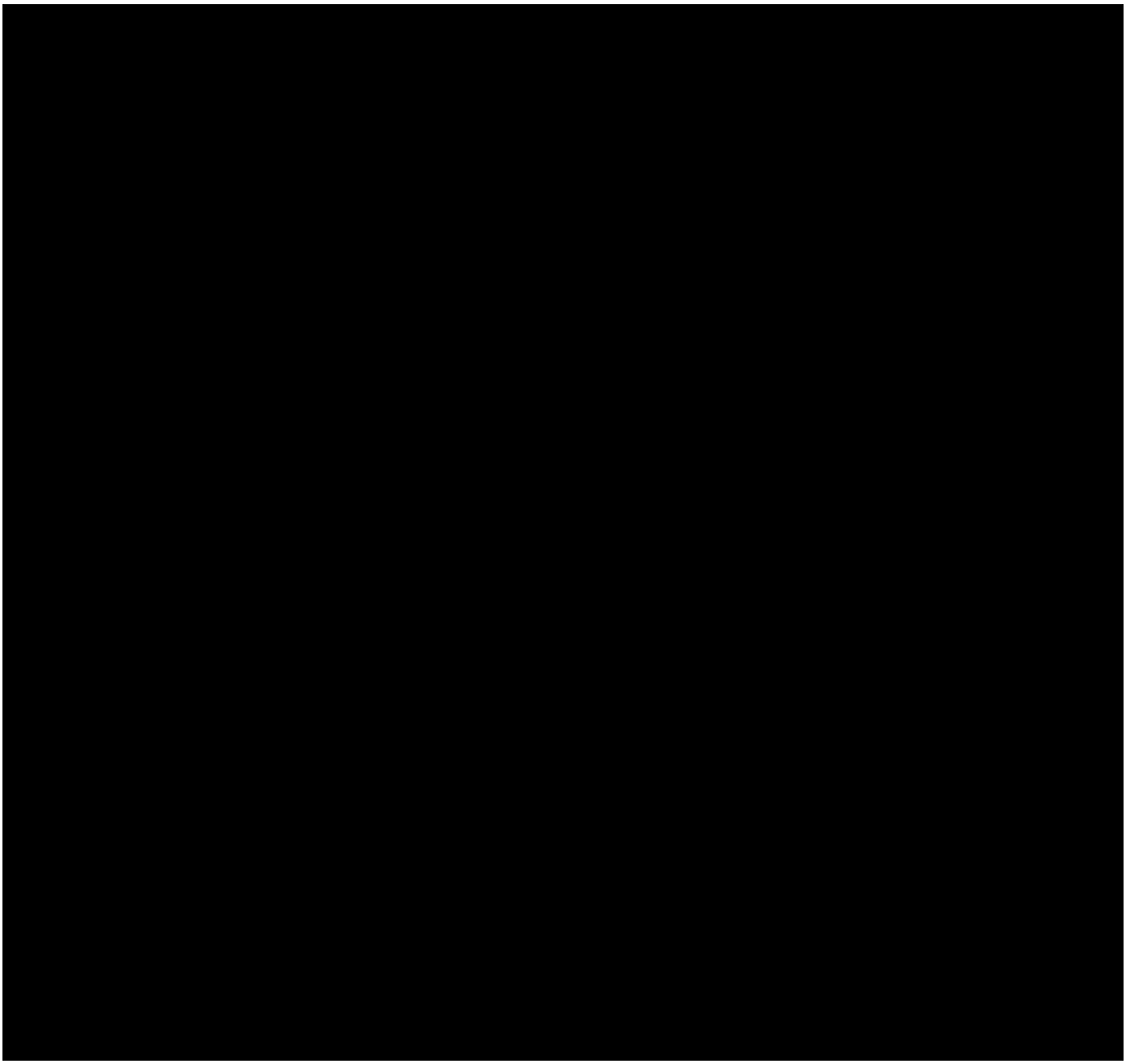
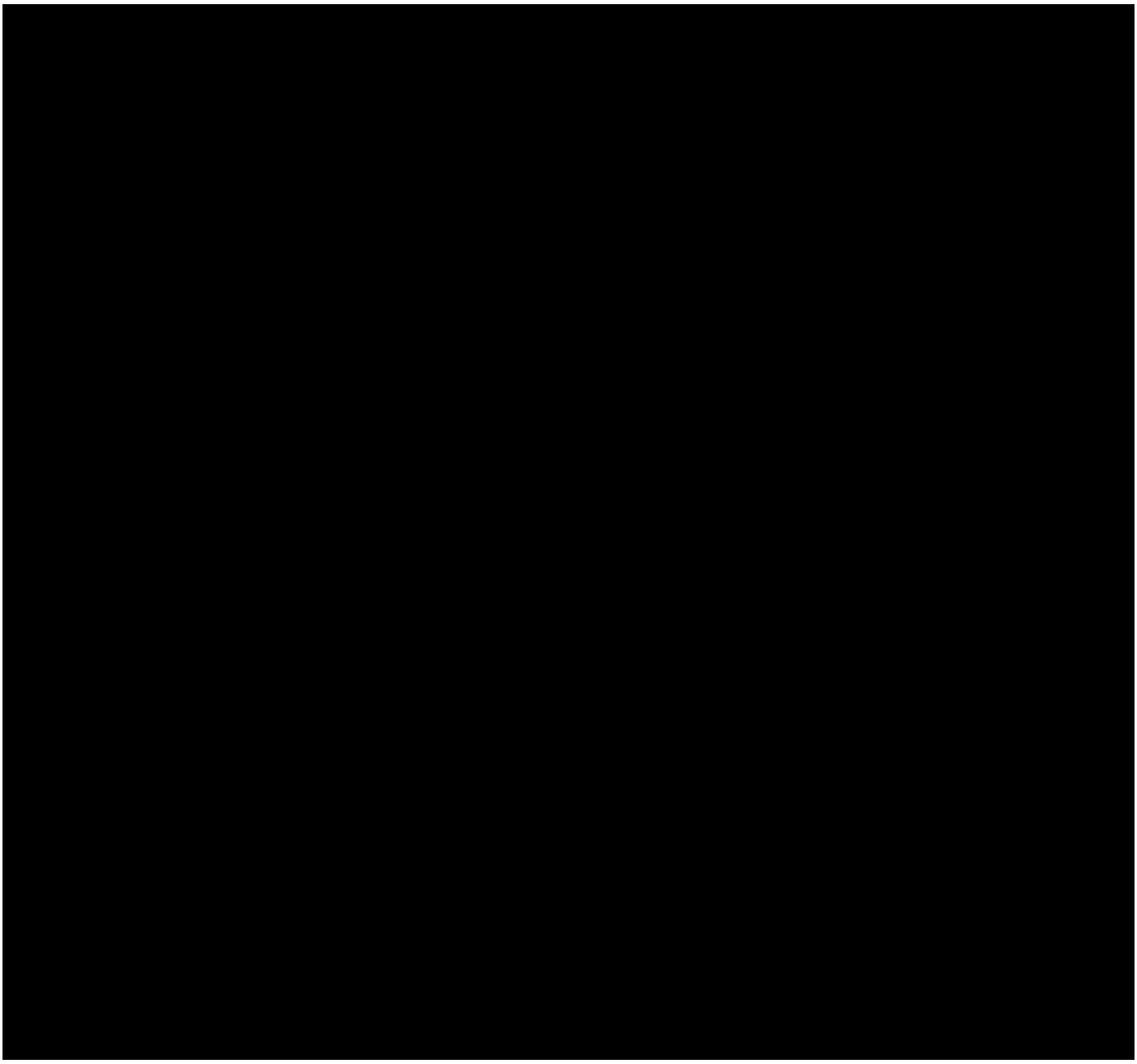
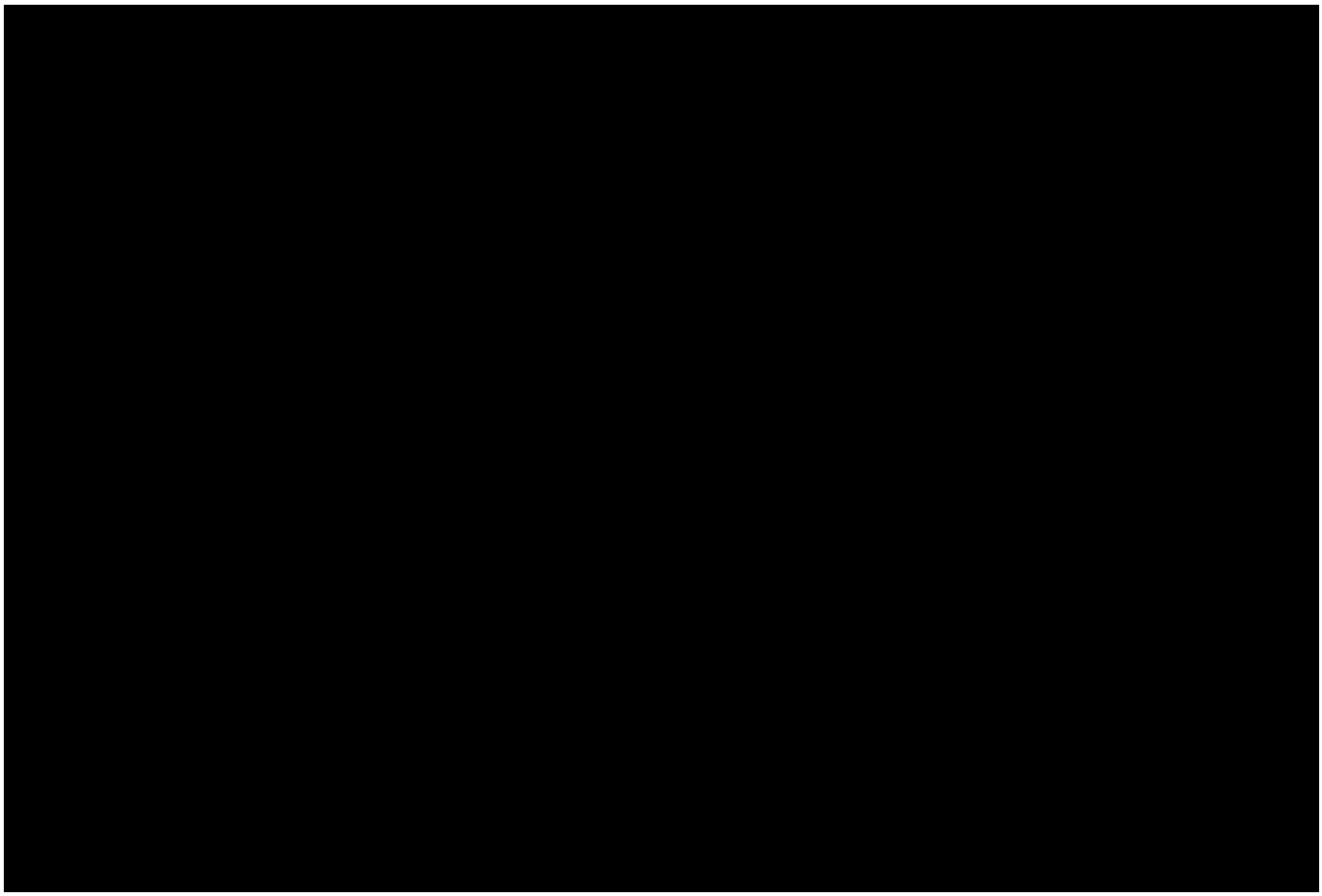
TITLE PAGE

Protocol Number:	NAV-17A-008
Title:	An Open-Label, Single-Group Study to Evaluate the Efficacy and Safety of SPN-820 in Adults With Major Depressive Disorder
Sponsor:	Navitor Pharmaceuticals, Inc. 6 Liberty Square PMB #284 Boston, Massachusetts 02109 USA Office: 857-285-4328 Fax: 857-998-6313
IND Number:	155072
Investigational Medicinal Product:	NV-5138 SPN-820 (Supernus Pharmaceuticals, Inc. product alternative identification number)
Indication:	Major Depressive Disorder
[redacted]	
[redacted]	
[redacted]	
Phase:	2
Protocol Version:	3.0
Amendment:	Not applicable
Date:	14 February 2024
Good Clinical Practice Statement:	This study is to be performed in full compliance with the International Council for Harmonisation Good Clinical Practices and all applicable local regulations. All required study documentation will be archived as required by regulatory authorities.







CLINICAL PROTOCOL SYNOPSIS

Sponsor: Navitor Pharmaceuticals, Inc.	
Investigational Medicinal Product: NV-5138 SPN-820 (Supernus Pharmaceuticals, Inc. alternative product identification number)	**Name of Active Ingredient:** (S)-2-amino-5,5-difluoro-4,4-dimethylpentanoic acid
Protocol Number: NAV-17A-008	**Phase of Development:** 2
Study Title: An Open-Label, Single-Group Study to Evaluate the Efficacy and Safety of SPN-820 in Adults With Major Depressive Disorder	
Number of Study Sites: Up to 6 investigational sites are planned in the United States (US)	
Number of Subjects: Approximately 50 subjects will be enrolled to achieve approximately 40 subjects completed.	
Indication: Major Depressive Disorder (MDD)	

Objectives:

Primary Objective:

- To evaluate the efficacy of SPN-820 administered once every 3 days for a 7-day treatment period in adults with MDD.

Secondary Objectives:

- To evaluate the safety and tolerability of SPN-820 administered once every 3 days for a 7-day treatment period in adults with MDD.

[redacted]

Exploratory Objective:

- To characterize the effect of SPN-820 on brain-derived neurotrophic factor (BDNF) concentrations.

Endpoints:

Primary Endpoint:

- Change from baseline to each time point in the Hamilton Depression Rating Scale-6 Items ($HAM\text{-}D_6$) total score.

Secondary Efficacy Endpoints:

- Change from baseline to each time point in the Montgomery–Åsberg Depression Rating Scale (MADRS) total score.
- Change from baseline to each time point in the Clinical Global Impression – Severity of Illness (CGI-S) total score.
- Proportion of subjects achieving a ≥50% reduction from baseline in the MADRS total score.
- Proportion of subjects in remission (MADRS total score ≤10) at each time point.

- Percentage of subjects with a CGI-S score of 1 or 2 at each time point.

[redacted]

Safety Endpoints:

- Treatment-emergent adverse events (TEAEs).
- Clinical safety laboratory test results.
- Vital sign measurements including orthostatic blood pressure and pulse rate.
- Body weight.
- Electrocardiography (ECG) findings.
- Physical examination findings.
- Suicidal ideation and behavior as measured by the Columbia Suicide Severity Rating Scale (C-SSRS) score.
- Dissociative symptomatology as measured by Clinician-Administered Dissociative State Scale (CADSS) score.
- Psychopathology severity as measured by Brief Psychiatric Rating Scale Positive Subscale (BPRS+) score.

Exploratory Endpoint:

- Change from baseline to each time point for BDNF concentrations.

Study Design:

This is an open-label study of SPN-820 administered orally every 3 days for a 7-day treatment period in adult subjects with MDD. The study consists of a 28-day screening period, a 10-day evaluation period (clinic and home), and a safety follow-up phone call approximately 5 (+2) days after the last administration of study medication (SM).

To be eligible, subjects must be taking 1 approved antidepressant medication (i.e., an approved therapy for depression; Appendix 11.2) at a stable dosage for a minimum of 6 weeks before the screening visit. If a subject is taking a second antidepressant or an augmentation therapy, the investigator will decide the appropriate medication that should be discontinued. The second medication should be discontinued for at least 5 half-lives before baseline. In addition, subjects must maintain a MADRS total score ≥22, a CGI-S score ≥4, and a detectable level of antidepressant therapy (ADT) during the screening period to be eligible. If the MADRS total scores vary ≥25% between the highest and lowest score from screening to baseline (Day 1), subjects will be excluded. All subjects who meet the eligibility criteria will take 2400 mg (six 400 mg capsules) of SPN-820 orally and continue their ADT at a stable and therapeutic dose while in the study.

The evaluation period includes 4 clinic visits (on days 1, 4, 7 and 10). Subjects will receive SM at the clinic on days 1, 4 and 7. Subjects will not receive SM on days 2, 3, 5, 6, 8, 9 and 10. Subjects will continue their ADT throughout the study. All safety, efficacy, [redacted], and pharmacodynamic (PD) assessments and procedures will be performed as outlined in Table 1 and Table 2.

At the end of study (EOS; Day 10) or early termination (ET), if applicable, subjects will return to the clinic for the EOS visit. Approximately 5 days (+2 days) after the last administration of SM (Day 7) and once all study visits are completed; subjects will receive a safety follow-up phone call. Subjects who discontinue the study due to adverse events (AEs) will be followed for at least 30 days following the date of last administration of SM or until resolution, or until, in the medical judgment of the investigator, the event has stabilized or is assessed as chronic.

Duration of Subjects' Participation:

The total study duration for each subject's participation is up to 40 days (screening period [up to 28 days], evaluation period [10 days], and safety follow-up phone call [5 days from Day 7]).

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

Study Medication: SPN-820 400 mg capsules

Dosage: 2400 mg (six 400-mg capsules) administered once a day every 3 days

Mode of Administration: Oral, as intact capsules, in the morning approximately 3 hours after breakfast

Sampling for [redacted] Pharmacodynamic Assessments:

[redacted].

Seven total blood samples will be collected for measurement of BDNF concentrations: 3 pre-dose collections on days 1, 4, and 7; 3 post-dose collections 4 hours after SM administration on days 1, 4, and 7; and 1 collection on Day 10.

Statistical Methodology:

Sample Size: Approximately 50 subjects will be enrolled to achieve approximately 40 subjects completed. This sample size is based on clinical judgment without a power calculation.

Analysis Populations:

The full analysis set (FAS) includes all subjects who receive at least one dose of SM and have a baseline and at least one post-baseline measurement of HAM-D_6.

The safety population includes all subjects who receive at least one dose of SM.

[redacted].

The PD population includes subjects who receive at least one dose of SM and have a baseline and at least one post-baseline BDNF concentration.

Statistical Methods: Continuous variables will be summarized using descriptive statistics (i.e., number of subjects, mean, standard deviation, median, interquartile range [Q1and Q3], minimum and maximum values). Categorical variables will be summarized with counts and percentages.

The efficacy, safety, [redacted] and PD endpoints will be analyzed descriptively using the FAS, safety, [redacted] and PD populations, respectively. Unless otherwise specified, no missing data will be imputed. Details of data analyses will be described in the statistical analysis plan.

Inclusion Criteria:

1. Is a male or female subject, aged 18 to 65 years (inclusive) at screening.
2. Capable of giving signed informed consent, able to understand and comply with protocol requirements, instructions, and protocol-related restrictions, and likely to complete the study as planned.
3. Has a body mass index 19.0 to 40.0 kg/m^2 (inclusive).
4. Is able to swallow each capsule whole, without crushing, chewing, or opening.
5. Has a current diagnosis of MDD according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) for either recurrent or single episode MDD without psychotic features that is confirmed by the Mini International Neuropsychiatric Interview (MINI) at screening.
6. Has a MADRS total score of ≥22 for the current major depressive episode (MDE) at screening and baseline (Day 1) before SM administration.
7. Has a CGI-S score of ≥4 (moderately ill or worse) at screening and baseline (Day 1) before SM administration.
8. Has been on a stable, therapeutic dose of one of the following study-approved ADTs for the current MDE for ≥6 weeks prior to screening: citalopram, escitalopram, paroxetine, fluoxetine, sertraline, duloxetine, venlafaxine (immediate release or extended release), desvenlafaxine, vilazodone, levomilnacipran, vortioxetine, bupropion, or dextromethorphan/bupropion. Subject must be on antidepressant monotherapy before baseline.

   Note: If a subject is taking a second ADT or augmentation therapy at screening, the investigator should decide if it is medically appropriate to discontinue the second drug before baseline. If so, the second drug should be discontinued for at least 5 half-lives prior to baseline. If not, the subject should be excluded from the study.
9. Agrees to maintain a stable therapeutic dose of the approved ADT throughout the study.
10. Non-pregnant female subjects of childbearing potential (FOCP) who are exclusively in a same-sex relationship are included without the need of acceptable birth control methods.

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

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

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

    All FOCP must have a negative serum pregnancy test result before administration of SM.
11. Male subjects
    a. Who have been surgically sterilized (6 months minimum) prior to Screening visit are eligible to participate without any contraception.
    b. Who are biologically capable of having children and have female partners of childbearing potential must use one or more methods of contraception as stated in IC #10 which must be used from the time of signing the ICF until 90 days after the last dose of SM.

c. Who are exclusively in a same-sex relationship or have female partners considered not to be of childbearing potential are required to use a condom from the first administration of SM through 7 days after the last administration of SM.

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

Exclusion Criteria:

1) Has a MADRS total score improvement of ≥25% from the highest to the lowest score from screening to baseline.
2) Has been treated with electroconvulsive therapy, transcranial magnetic stimulation, or vagal nerve stimulation for the current MDE within 6 months prior to screening.
3) Has received treatment with long-acting injectable antipsychotics within 3 months prior to screening.
4) Has demonstrated a non-response to esketamine or off-label use of ketamine; or has taken esketamine or ketamine <6 months prior to screening.
5) If treated with trazodone, is unable to discontinue treatment with doses >150 mg daily for a minimum of 5 half-lives before baseline.
   Note: trazodone ≤150 mg/day for sleep is permitted as needed if the subject has been taking the same low dose of trazodone for insomnia for at least 3 months.
6) Has unstable hypothyroidism. If the thyroid-stimulating hormone value is out of range (>4.0 mIU/L), regardless of thyroid history, a free thyroxine (FT4) will be measured. If the FT4 value is abnormal (levels <0.8 mIU/L) and considered to be clinically significant (after discussion with the Medical Monitor), the subject will not be eligible.
   Note: treatment with thyroid hormones is allowed if taken at a stable dose for ≥ 3 months and the subject's thyroid levels are normal.
7) Has clinically significant abnormal laboratory profiles (alanine aminotransferase or aspartate aminotransferase values ≥3 × the upper limit of normal [ULN] or total bilirubin ≥1.5 × ULN), vital sign measurements, or ECGs prior to baseline, per investigator judgment (see **Note** below). If there are any abnormalities that are not specified in the inclusion and exclusion criteria, the investigator must determine their clinical significance and record it in the subject's source documents.
8) Has abnormal renal function as demonstrated by an estimated glomerular filtration rate ≤60 mL/min according to the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) equation at screening and baseline.
9) Has a history of substance use disorder within 6 months prior to screening or is currently using or has a positive result (urine drug screen) at screening or baseline for drugs of abuse (except for cannabis, see exclusion 11).
10) Has a history of alcohol use disorder within 6 months prior to screening. A subject who has a positive alcohol test result at screening and, if based on the investigator's opinion the subject does not have a history of alcohol use disorder, the subject may continue to the baseline visit. Subjects who have a positive alcohol test result at baseline will be excluded. Subjects should refrain from using alcohol during the study. Subjects who have a positive alcohol test result on days 1, 4, or 7 will be withdrawn from the study.
11) Has a diagnosis of cannabis use disorder within 6 months before screening and has a positive urine drug screen for cannabis at screening.
    a. At the discretion of the Sponsor, recreational use (not daily) is allowed and should be kept consistent during the study. Subjects must agree to refrain from using cannabis 48 hours prior to the clinic visits.
    b. Medical cannabis prescribed for a medical condition (e.g., muscle spasms, nausea, vomiting, pain) other than depression and seizures is allowed if taken at a stable regimen for at least 3

months prior to screening (Appendix 11.1.1). Newly prescribed cannabis treatment and/or a change to the existing regimen are/is prohibited. When applicable, subjects should show proof of their prescription for medical cannabis.

12) Has had any suicidal behavior or suicidal ideation of type 4 (active suicidal ideation with some intent to act, without specific plan) or type 5 (active suicidal ideation with specific plan and intent) based on the C-SSRS in the 1 year before screening; a history of suicide attempt in the last 2 years; or more than 2 lifetime suicide attempts.
13) Has a lifetime history of psychotic disorder, including but not limited to schizophrenia, MDD with psychotic features, or bipolar I/II disorder with and without psychotic features.
14) Has a diagnosis within the last 12 months before screening or current diagnosis of post-traumatic stress disorder, obsessive-compulsive disorder, panic disorder, acute stress disorder, or has a history of intellectual disability, autism, or cluster A or B personality disorder (per DSM-5 criteria).
    a. Current diagnosis of co-morbid generalized anxiety disorder is allowed but is subject to medication restrictions (anticonvulsants and beta-blockers are allowed if the subject is on a stable regimen for 2 months prior to screening).
    b. Established attention-deficit/hyperactivity disorder (ADHD) diagnosis is allowed. Subjects must provide confirmation of ADHD diagnosis (i.e., provide medical records for prescribed ADHD medications) and be on a stable dose of ADHD medication for at least 3 months prior to screening.
15) Has a history of a psychiatric or neurologic condition or symptoms that could impose undue risk or compromise the study including but not limited to:
    a. History of seizure disorder or history of epilepsy (except history of absence or uncomplicated childhood febrile seizures).
    b. History of clinically significant or moderate head trauma that, in the investigator's opinion, is likely to affect central nervous system functioning.
    c. Has current evidence of delirium or dementia.
16) Has a history of cardiovascular, respiratory, gastrointestinal, renal, hepatic, hematologic, or other medical disorder that could impose undue risk or compromise the study, in the investigator's opinion, including but not limited to:
    a. Cardiovascular:
        i. Clinically significant symptomatic orthostatic hypotension.
        ii. Uncontrolled hypertension despite diet, exercise, and antihypertensive medications.
        iii. Acute coronary syndrome.
        iv. History of unexplained loss of consciousness, unexplained syncope, unexplained irregular heartbeats.
        v. QT interval corrected using Fridericia's method ≥450 msec (for men) or ≥470 msec (for women) at screening (see **Note** below).
        vi. Subject or family history of congenital long QT syndrome.
    b. Oncological:
        i. Malignant tumors within 5 years prior, with the exception of benign skin tumors.
        ii. Diagnosis or family history of tuberous sclerosis complex.
    c. Positive result for human immunodeficiency virus 1/2 antigen/antibody (HIV 1/2 Ag/Ab), hepatitis B surface antigen (HBsAg) or hepatitis C antibody (HCV Ab) at screening, unless:
        i. HIV 1/2 Ag/Ab positive: subjects must have an HIV confirmation test. If the confirmatory test is positive, subjects are eligible if they are on chronic suppressive antiviral medication for >6 months with an undetectable viral load at screening.

ii. HBsAg positive: subjects should be tested for immunoglobulin M antibody to hepatitis B core antigen and hepatitis B surface antibody to detect acute or chronic infection (ineligible). Subjects whose results indicate immunity (either by natural infection or vaccination) with no active infection are eligible.

iii. HCV Ab positive: subjects must have undetectable HCV ribonucleic acid to be eligible.

d. Unintended recent clinically significant weight loss in the investigator's opinion.

e. Has chronic urinary tract infections.

f. Blood donation or loss of blood of ≥500 mL within 56 days prior to screening.

g. Is on any medication that could, in the investigator's opinion, interfere with the assessments of safety, tolerability, or efficacy, or interfere with the conduct or interpretation of the study.

17) Requires treatment with a medication or other substance that is prohibited by the protocol (see Section 5.7.2).
18) Has history of severe drug allergy or hypersensitivity, or hypersensitivity to the SM or excipients.
19) Female subjects who are pregnant or lactating or planning to become pregnant while enrolled in the study.
20) In the investigator's opinion, is unlikely to comply with the protocol or is unsuitable for any other reason.
21) Has previously enrolled in a NV-5138 study.
22) Is currently participating in another clinical trial or has received an investigational product in another clinical trial within 30 days of screening.
23) Is a member of study personnel or of their immediate families or is a subordinate (or immediate family member of a subordinate) to any of the study personnel.

Note: Repeat testing for clinical laboratory parameters, vital signs, and ECG is permitted one time for each test, at the discretion of the investigator, as long as the repeat test result is available within the 28-day screening period to determine eligibility. Repeat testing is not allowed without justification from the study site and agreement from the Medical Monitor and the Sponsor on a case-by-case basis.

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1 LIST OF ABBREVIATIONS

Abbreviation	Definition of Term
ACE	angiotensin-converting enzyme
ADHD	attention-deficit/hyperactivity disorder
ADR	adverse drug reaction
ADT	antidepressant therapy
AE	adverse event
AUC	area under the concentration-time curve
BDNF	brain-derived neurotrophic factor
BPRS+	Brief Psychiatric Rating Scale Positive Subscale
CADSS	Clinician-Administered Dissociative State Scale
CFR	Code of Federal Regulations
CGI-S	Clinical Global Impression – Severity of Illness
ClinRO	clinician-reported outcome
C_{max}	maximum observed concentration
CRA	Clinical Research Associate
CRO	Contract Research Organization
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
C_{trough}	trough concentration
DSM-5	Diagnostic and Statistical Manual of Mental Disorders – 5th Edition
ECG	electrocardiography
eCRF	electronic case report form
EOS	end of study
ES	effect size
ET	early termination
FAS	full analysis set
FDA	Food and Drug Administration
FOCP	female subjects of childbearing potential
FPC	follow-up phone call
FSH	follicle-stimulating hormone
FT4	free thyroxine
GCP	Good Clinical Practice
HAM-D_6	Hamilton Depression Rating Scale – 6 Items
HBsAg	hepatitis B surface antigen
HCV Ab	hepatitis C antibody
HIV 1/2 Ag/Ab	human immunodeficiency virus 1/2 antigen/antibody
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IND	Investigational New Drug Application
IRB	Institutional Review Board
MADRS	Montgomery–Åsberg Depression Rating Scale
MDD	major depressive disorder
MDE	major depressive episode
MINI	Mini International Neuropsychiatric Review
mTORC1	mechanistic target of rapamycin complex 1
NMDAR	N-methyl-D-aspartate receptor
PD	pharmacodynamics

Abbreviation	Definition of Term
PK	pharmacokinetics
POC	point-of-care
PT	Preferred Term
QTcF	QT corrected using Fridericia's method
SADR	suspected adverse drug reaction
SAE	serious adverse event
SAP	statistical analysis plan
SM	study medication
SOC	System Organ Class
TDD	total daily dose
TEAE	treatment-emergent adverse event
T_{max}	time to maximum observed concentration
TRD	treatment-resistant depression
ULN	upper limit of normal
US	United States

2 INTRODUCTION

2.1 Background

SPN-820 (Supernus Pharmaceuticals, Inc. product alternative identification number) is being developed to provide rapid-onset antidepressant response via oral administration for the treatment of adult patients with treatment-resistant depression (TRD). Major depressive disorder (MDD) is a common psychiatric disorder, with a lifetime prevalence of approximately 13 to 17% in the United States (US) (Hasin 2005; Kessler 2005; Otte 2016). Although options for pharmacologic treatment have expanded significantly in the past 25 years, patients with MDD typically require 6 to 12 weeks to respond to pharmacotherapy. Up to two-thirds of patients with MDD will not respond to the first antidepressant prescribed, and up to one-third will not respond to multiple interventions; the latter is commonly defined as TRD (Berlim 2008; Cain 2007; Karasu 2000).

There are several novel antidepressants either in clinical development or approved for the treatment of TRD that modulate the N-methyl-D-aspartate and its receptor, N-methyl-D-aspartate receptor (NMDAR), leading to rapid and sustained symptom relief in patients with TRD (Abdallah 2015; Zarate 2017). However, acute modulation of the NMDAR has been associated with dissociative and other undesirable neurological effects. Thus, alternative therapeutic options for TRD not involving NMDAR modulation could be of great value in treating patients with TRD (Pennybaker 2017). There is substantial evidence from animal models that rapid-acting antidepressants such as ketamine require post-synaptic activation of mechanistic target of rapamycin complex 1 (mTORC1) signaling following NMDAR modulation for their antidepressant effects (Harmer 2017). The central role of mTORC1 signaling in the rapid-acting antidepressant effects of several agents suggests that a direct activator of mTORC1 signaling may provide rapid antidepressant efficacy without the potential neurological side effects associated with some NMDAR-modulating compounds.

2.2 SPN-820

SPN-820 (also called NV-5138 [in a joint development agreement with Navitor Pharmaceuticals, Inc.]) is a first-in-class, orally bioavailable, selective activator of the mTORC1 signaling pathway. The proposed mechanism of SPN-820, via the direct activation of mTORC1 signaling, involves the compound binding to sestrin protein isoforms 1 and 2 leading to the direct activation of mTORC1 signaling without binding to, or modulating, other synaptic receptors or other signaling proteins (e.g., NMDAR).

2.3 Nonclinical Studies

In multiple preclinical rodent models of stress-induced depressive behavior, including the female urine sniffing test, the novelty-suppressed feeding test, chronic unpredictable stress test, the forced swimming test, and the non-human primate human threat test, oral administration of SPN-820 was shown to be comparable to injectable ketamine in terms of efficacy and duration of antidepressant effect (Section 4.1.3 of the Investigator's Brochure [IB]; Supernus Pharmaceuticals 2022). Like ketamine (Li 2011), the antidepressant effects of SPN-820 were shown to be dependent on the activation of mTORC1 signaling and brain-derived neurotrophic factor (BDNF) and were associated with an increase in synaptic protein expression (e.g.,

glutamate ionic receptor AMPA type subunit 1, synapsin1) and the induction of dendritic spine formation in layer V pyramidal neurons in the medial prefrontal cortex. In addition to demonstrating efficacy in several models of stress-induced depressive behavior, SPN-820 was also shown to significantly increase relative power in the delta band frequency of the electroencephalography profile following a second and third sequential dose in conscious rats, suggesting a potential translational approach to measuring the effects of the compound clinically.

Detailed information from the SPN-820 clinical development program (e.g., nonclinical pharmacology, pharmacokinetics [PK] and drug metabolism in animals, and toxicology) are provided in the IB (Supernus Pharmaceuticals 2022).

2.4 Clinical Studies

The PK, pharmacodynamics (PD), preliminary efficacy, and safety of SPN-820 have been evaluated in 6 completed Phase 1 clinical studies.

Completed Studies

A total of 145 adult subjects have been exposed to SPN-820 in the Phase 1 studies, including 129 healthy subjects and 16 subjects with TRD. Single doses up to 2400 mg and multiple doses up to 3000 mg for 7 days have been administered in the Phase 1 clinical studies.

- Study NAV-17A-001 was a Phase 1a/1b, randomized, two-part, double-blind, placebo-controlled, on-site study of single ascending dosage levels of SPN-820 or placebo in 48 healthy subjects (Part A) and a single dose of SPN-820 2400 mg or placebo in 32 subjects with TRD (Part B).
- Study NAV-17A-002 was a Phase 1, randomized, double-blind, placebo-controlled, on-site, single-dose study to evaluate the safety, PK, metabolomic and proteomic profiles of SPN-820 in plasma and cerebrospinal fluid (CSF) in healthy male subjects between the ages of 18 and 55 years.
- Study NAV-17A-003 was a randomized, double-blind, placebo-controlled, on-site study of the effects on quantitative electroencephalography and event-related potential of 2 sequential doses of SPN-820 or placebo administered 48 hours apart, to healthy adult male subjects.
- Study NAV-17A-004 was a Phase 1, randomized, double-blind, placebo-controlled, single-center study of the safety, tolerability, and PK of multiple ascending doses of SPN-820 in healthy subjects.
- Study NAV-17A-005 was a Phase 1, 4-period, 4-treatment, 4-sequence crossover study in which subjects received a single dose of SPN-820 400 mg oral solution, 400 mg capsule, 1600 mg oral solution, and 1600 mg capsule under fasted conditions.
- Study NAV-17A-006 was a Phase 1, open-label, singe-dose, mass balance study to assess the disposition of [14C]-SPN-820 in healthy male subjects.

Completed Study Results

[redacted]

Safety

The majority of treatment-emergent adverse events (TEAEs) reported by healthy subjects were reported as mild, none were severe, and all resolved. The most frequently reported TEAEs by healthy subjects included dizziness (postural dizziness and orthostatic hypotension) nausea, headache, and somnolence. Two subjects who received single doses of SPN-820 400 mg discontinued due to adverse events (AEs): muscle strain, nausea, and vomiting (n=1); vomiting (n=1).

The most frequently reported TEAEs by subjects with TRD (n=32) included somnolence, dizziness, and headache. The majority of TEAEs did not require treatment and resolved without sequelae.

Preliminary Assessments of Efficacy

[redacted]

[redacted]

Ongoing Study

- Study NAV-17A-007 is an ongoing Phase 2, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy of flexible doses of SPN-820 800 to 1600 mg or placebo in subjects with TRD.

2.5 Study Rationale

SPN-820, the investigational medicinal product for this study, is being developed to provide a rapid-onset antidepressant response via oral administration and is currently being investigated in a Phase 2 study (Study NAV-17A-007) for the treatment of depression in adult subjects with TRD. This study (Study NAV-17A-008) is designed to characterize the antidepressant response and early onset of response of SPN-820 when administered every 3 days for a 7-day treatment period in adult subjects with MDD. The exposure-response relationship at the efficacious dose of SPN-820 and the engagement of mTORC1 activation will also be explored.

Rationale for Dose Regimen

[redacted]

Rationale for Primary and Secondary Endpoints

The appropriately selected scales as the primary and secondary efficacy endpoints are the HAM-D_6, MADRS, and CGI-S.

The Hamilton Depression Rating Scale is one of the most widely used clinician-administered depression scales (Hamilton 1960; Williams 1988). Because the HAM-D_6 is sensitive to short-term changes in depression symptoms, change in HAM-D_6 total score was selected as the primary outcome measure for this study.

The MADRS is a validated tool that measures the severity of depressive episodes in patients and is designed to be sensitive to changes brought on by treatment (Montgomery 1979). Change in MADRS total score was selected as a secondary outcome measure because MADRS is a clinician/investigator structured interview assessing the severity of MDD symptoms per the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria. MDD severity is also addressed by the inclusion criteria related to severity score of several MADRS items.

The CGI-S is a 7-point scale of the clinician's assessment of the severity of symptoms in relation to the clinician's total experience with the patient population. The CGI-S was selected as a secondary outcome measure because it is commonly used as a reliable measure of severity of a disease/disorder in clinical research, as well as a measure of change in severity over time during an experimental treatment.

2.6 Summary of Benefits and Risks

Detailed information about the known and expected benefits and risks and reasonably expected AEs of SPN-820 is provided in the current SPN-820 IB (Supernus Pharmaceuticals 2022).

Single dose SPN-820 2400 mg produced rapid and sustained efficacy signals on the core symptoms of depression as measured by the HAM-D_6, including statistically significant improvement at 4- and 12-hours post-dose compared to placebo.

Subjects in the study will contribute to the process of developing a novel, oral, adjunctive antidepressant.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

3.1.1 Primary Objective

- To evaluate the efficacy of SPN-820 administered once every 3 days for a 7-day treatment period in adults with MDD.

3.1.2 Secondary Objectives

- To evaluate the safety and tolerability of SPN-820 administered once every 3 days for a 7-day treatment period in adults with MDD.

- [redacted]

3.1.3 Exploratory Objective

- To characterize the effect of SPN-820 on BDNF concentrations.

3.2 Endpoints

3.2.1 Primary Endpoint

- Change from baseline to each time point in the HAM-D_6 total score.

3.2.2 Secondary Efficacy Endpoints

- Change from baseline to each time point in the MADRS total score.
- Change from baseline to each time point in the CGI-S total score.
- Proportion of subjects achieving a ≥50% reduction from baseline in the MADRS total score.
- Proportion of subject in remission (MADRS total score ≤10) at each time point.
- Percentage of subjects with a CGI-S score of 1 or 2 at each time point.

[redacted]

- [redacted].

3.2.4 Safety Endpoints

- TEAEs.
- Clinical safety laboratory test results.
- Vital sign measurements including orthostatic blood pressure and pulse rate.

- Body weight.
- Electrocardiography (ECG) findings.
- Physical examination findings.
- Suicidal ideation and behavior as measured by the Columbia Suicide Severity Rating Scale (C-SSRS) score.
- Dissociative symptomatology as measured by the Clinician-Administered Dissociative State Scale (CADSS) score.
- Psychopathology severity as measured by the Brief Psychiatric Rating Scale Positive Subscale (BPRS+) score.

3.2.5 Exploratory Endpoint

- Change from baseline to each time point for BDNF concentrations.

4 INVESTIGATIONAL STUDY PLAN

4.1 Overall Study Design and Plan

This is an open-label study of SPN-820 administered orally once every 3 days for a 7-day treatment period in adult subjects with MDD. Approximately 50 subjects will be enrolled into the study. The study consists of a 28-day screening period, a 10-day evaluation period (clinic and home), and a safety follow-up phone call approximately 5 (+2) days after the last administration of study medication (SM). The total study duration from the screening visit to completion of the safety follow-up phone call is up to 40 days.

The Schedule of Events and Assessments is provided in Table 1, and a detailed Schedule of Timed Assessments with windows is provided in Table 2.

Screening Period (up to 28 days, Day -28 to Day -1): The screening period is up to 28 days, and after informed consent is obtained, subjects will undergo initial screening evaluations as outlined in Table 1. Subjects will have their diagnosis of MDD confirmed by the Mini International Neuropsychiatric Interview (MINI). To be eligible, subjects must be taking 1 study-approved antidepressant medication (i.e., an approved therapy for depression; Appendix 11.2) at a stable dosage for a minimum of 6 weeks before the screening visit. If a subject is taking a second antidepressant or an augmentation therapy, the investigator will decide the appropriate medication that should be discontinued. The second medication should be discontinued for at least 5 half-lives before baseline.

Subjects should maintain their current, stable antidepressant therapeutic dose for their study-approved antidepressant therapy (ADT) through the screening period. Dose adjustment of ADT will not be allowed at any time during the study. ADTs approved for use in this study will not be supplied by the Sponsor.

In addition, subjects must maintain a MADRS total score ≥22, a CGI-S score ≥4, and a detectable level of ADT during the screening period to be eligible. If the MADRS total scores vary ≥25% between the highest and the lowest score from screening to baseline (Day 1), subjects will be excluded.

Subjects who do not meet eligibility criteria at any time during the screening period will be excluded. Re-screening is not permitted. Protocol waivers in the study will be granted on a case-by-case basis after approval from the Sponsor.

Evaluation Period (Day 1 [baseline] to Day 10): All eligible subjects will receive SPN-820 orally at 2400 mg (six 400 mg capsules) once every 3 days for a 7-day treatment period (on days 1, 4, and 7). The 10-day evaluation period consists of 4 clinic visits (on days 1, 4, 7, and 10) and 6 at-home phone call assessments (on days 2, 3, 5, 6, 8, and 9). All safety, efficacy, [redacted] and PD assessments will be performed as outlined in Table 1 (Schedule of Events and Assessments) and Table 2 (Detailed Schedule of Timed Assessments).

Subjects should maintain their current, stable antidepressant therapeutic dose for the study-approved ADT through the evaluation period. Subjects will take their ADT at home and record the administration in a paper ADT adherence diary. Dose adjustments of ADTs will not be allowed at any time during the study. ADTs approved for use in this study will not be supplied by the Sponsor.

Clinic Visits

On days 1 (baseline), 4, and 7, during their in-clinic visits, subjects will receive a single, oral dose of SPN-820 2400 mg (six 400 mg capsules). After Day 7, SM will be discontinued, and subjects should continue with their ADT.

At-Home Phone Call Assessments

On days 2, 3, 5, 6, 8, and 9, subjects will continue taking their ADT at home. Subjects will receive a telephone call for remote efficacy (i.e., HAM-D_6 and MADRS) and safety (i.e., review of AEs, review of concomitant medications, C-SSRS [Since Last Visit Version], CADSS, and BPRS+) assessments.

End of Study/Early Termination

Subjects will have completed the study after completing the safety follow-up phone call at Day 12 (±2). After completion of the end of study (EOS) study procedures, subjects should continue with their ADT. If the subject withdraws or is terminated early, he/she will complete, at the earliest convenience, early termination (ET) assessments as outlined in Table 1 (Day 10).

Unscheduled visits may be conducted at the discretion of the investigator throughout the study. AEs and concomitant medications will be assessed at all scheduled and unscheduled visits. (Section 6.4).

Safety Follow-Up Phone Call (Day 12 [+2]): Subjects will receive a safety follow-up phone call approximately 5 (+2) days after the last administration of SM on Day 7 (Section 6.3).

4.2 Study Population

4.2.1 Number of Subjects

Approximately 50 subjects will be enrolled to complete approximately 40 subjects.

4.2.2 Inclusion Criteria

1. Is male or female, aged 18 to 65 years (inclusive) at screening.
2. Capable of giving signed informed consent, able to understand and comply with protocol requirements, instructions, and protocol-related restrictions, and likely to complete the study as planned.
3. Has a body mass index 19.0 to 40.0 kg/m^2 (inclusive).

4. Is able to swallow capsules whole, without crushing, chewing, or opening.
5. Has a current diagnosis of MDD according to the DSM-5 for either recurrent or single episode MDD without psychotic features that is confirmed by the MINI at screening.
6. Has a MADRS score of ≥22 for the current major depressive episode (MDE) at screening and baseline (Day 1) before SM administration.
7. Has a CGI-S score of ≥4 (moderately ill or worse) at screening and baseline (Day 1) before SM administration.
8. Has been on a stable therapeutic dose of one of the following study-approved ADTs for the current MDE for ≥6 weeks prior to screening: citalopram, escitalopram, paroxetine, fluoxetine, sertraline, duloxetine, venlafaxine (immediate release or extended release), desvenlafaxine, vilazodone, levomilnacipran, vortioxetine, bupropion, or dextromethorphan/bupropion. Subject must be on antidepressant monotherapy before baseline.

   Note: If a subject is taking a second ADT or augmentation therapy at screening, the investigator should decide if it is medically appropriate to discontinue the second drug before baseline. If so, the second drug should be discontinued for at least 5 half-lives prior to baseline. If not, the subject should be excluded from the study.
9. Agrees to maintain a stable therapeutic dose of the approved ADT throughout the study.
10. Non-pregnant female subjects of childbearing potential (FOCP) who are exclusively in a same-sex relationship are included without the need of acceptable birth control methods.

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

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

    Females are considered not to be of childbearing potential if they are either postmenopausal (amenorrhea for at least 2 years and serum follicle-stimulating hormone [FSH] level of >40 IU/L) or permanently sterilized

(e.g., bilateral tubal ligation, bilateral oophorectomy, or bilateral salpingectomy, etc.) for a minimum of 6 months prior to screening.

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

11. Male subjects:
    a. Who have been surgically sterilized (6 months minimum) prior to Screening visit are eligible to participate without any contraception.
    b. Who are biologically capable of having children and have female partners of childbearing potential must use one or more methods of contraception as stated in IC #10 which must be used from the time of signing the ICF until 90 days after the last dose of SM.
    c. Who are exclusively in a same-sex relationship or have female partners considered not to be of childbearing potential are required to use a condom from the first administration of SM through 7 days after the last administration of SM.

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

4.2.3 Exclusion Criteria

1. Has a MADRS total score improvement of ≥25% from the highest to the lowest score from screening to baseline.
2. Has been treated with electroconvulsive therapy, transcranial magnetic stimulation, or vagal nerve stimulation for the current MDE within 6 months prior to screening.
3. Has received treatment with long-acting injectable antipsychotics within 3 months prior to screening.
4. Has demonstrated a non-response to esketamine or off-label use of ketamine; or has taken esketamine or ketamine <6 months prior to screening.
5. If treated with trazodone, is unable to discontinue treatment with doses >150 mg daily for a minimum of 5 half-lives before baseline.

   Note: trazodone ≤150 mg/day for sleep is permitted as needed if the subject has been taking the same low dose of trazodone for insomnia for at least 3 months.
6. Has unstable hypothyroidism. If the thyroid-stimulating hormone value is out of range (>4.0 mIU/L), regardless of thyroid history, a free thyroxine (FT4) will be measured. If the FT4 value is abnormal (levels <0.8 mIU/L) and considered to be clinically significant (after discussion with the Medical Monitor), the subject will not be eligible.

   Note: treatment with thyroid hormones is allowed if taken at a stable dose for

≥3 months and the subject's thyroid levels are normal.

7. Has clinically significant abnormal laboratory profiles (alanine aminotransferase or aspartate aminotransferase values ≥3 × upper limit of normal [ULN] or total bilirubin ≥1.5 × ULN), vital sign measurements, or ECGs at screening, per investigator judgment (see **Note** below). If there are any abnormalities that are not specified in the inclusion and exclusion criteria, the investigator must determine their clinical significance and record it in the subject's source documents.
8. Has abnormal renal function as demonstrated by an estimated glomerular filtration rate ≤60 mL/min according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation at screening and baseline.
9. Has a history of substance use disorder within 6 months prior to screening or is currently using or has a positive result (urine drug screen) at screening or baseline for drugs of abuse (except for cannabis, see exclusion 11).
10. Has a history of alcohol use disorder within 6 months prior to screening. A subject who has a positive alcohol test result at screening and, if based on the investigator's opinion, the subject does not have a history of alcohol use disorder, the subject may continue to the baseline visit. Subjects who have a positive alcohol test result at baseline will be excluded. Subjects should refrain from using alcohol during the study. Subjects who have a positive alcohol test result on days 1, 4, or 7 will be withdrawn from the study.
11. Has a diagnosis of cannabis use disorder within 6 months before screening and has a positive urine drug screen for cannabis at screening.
    a. At the discretion of the Sponsor, recreational use (not daily) is allowed and should be kept consistent during the study. Subjects must agree to refrain from using cannabis 48 hours prior to the clinic visits.
    b. Medical cannabis prescribed for a medical condition (e.g., muscle spasms, nausea, vomiting, pain) other than depression and seizures is allowed if taken at a stable regimen for at least 3 months prior to screening (Appendix 11.1.1). Newly prescribed cannabis treatment and/or change to the existing regimen are/is prohibited. When applicable, subjects should show proof of their prescription for medical cannabis.
12. Has had any suicidal behavior or suicidal ideation of type 4 (active suicidal ideation with some intent to act, without specific plan) or type 5 (active suicidal ideation with specific plan and intent) based on the C-SSRS in the 1 year before screening; a history of suicide attempt in the last 2 years; or more than 2 lifetime suicide attempts.

13. Has a lifetime history of psychotic disorder, including but not limited to schizophrenia, MDD with psychotic features, or bipolar I/II disorder with and without psychotic features.
14. Has a diagnosis within the last 12 months before screening or current diagnosis of post-traumatic stress disorder, obsessive-compulsive disorder, panic disorder, acute stress disorder or has history of intellectual disability, autism, or cluster A or B personality disorder (per DSM-5 criteria).
    a. Current diagnosis of co-morbid generalized anxiety disorder is allowed but is subject to medication restrictions (anticonvulsants and beta-blockers are allowed if the subject is on a stable regimen for 2 months prior to screening).
    b. Established attention-deficit/hyperactivity disorder (ADHD) diagnosis is allowed. Subjects must provide confirmation of ADHD diagnosis (i.e., provide medical records for prescribed ADHD medications) and be on a stable dose of ADHD medication for at least 3 months prior to screening.
15. Has a history of a psychiatric or neurologic conditions or symptoms that could impose undue risk or compromise the study including but not limited to:
    a. History of seizure disorder or history of epilepsy (except history of absence or uncomplicated childhood febrile seizures).
    b. History of clinically significant or moderate head trauma that, in the investigator's opinion, is likely to affect central nervous system functioning.
    c. Has current evidence of delirium or dementia.
16. Has a history of cardiovascular, respiratory, gastrointestinal, renal, hepatic, hematologic, or other medical disorder that could impose undue risk or compromise the study, in the investigator's opinion, including but not limited to:
    a. Cardiovascular:
        i. Clinically significant symptomatic orthostatic hypotension.
        ii. Uncontrolled hypertension despite diet, exercise, and antihypertensive medications.
        iii. Acute coronary syndrome.
        iv. History of unexplained loss of consciousness, unexplained syncope, unexplained irregular heartbeats.
        v. QT interval corrected using Fridericia's method ≥450 msec (for men) or ≥470 msec (for women) at screening (see **Note** below).
        vi. Subject or family history of congenital long QT syndrome.

b. Oncological:

   i. Malignant tumors within 5 years prior, with the exception of benign skin tumors.

   ii. Diagnosis or family history of tuberous sclerosis complex.

c. Positive result for human immunodeficiency virus 1/2 antigen/antibody (HIV 1/2 Ag/Ab), hepatitis B surface antigen (HBsAg), or hepatitis C antibody (HCV Ab) at screening, unless:

   i. HIV 1/2 Ag/Ab positive: subjects must have an HIV confirmation test. If the confirmatory test is positive, subjects are eligible if they are on chronic suppressive antiviral medication for >6 months with an undetectable viral load at screening.

   ii. HBsAg positive: subjects should be tested for immunoglobulin M antibody to hepatitis B core antigen and hepatitis B surface antibody to detect acute or chronic infection (ineligible). Subjects whose results indicate immunity (either by natural infection or vaccination) with no active infection are eligible.

   iii. HCV Ab positive: subjects must have undetectable HCV ribonucleic acid to be eligible.

d. Unintended recent clinically significant weight loss in the investigator's opinion.

e. Has chronic urinary tract infections.

f. Blood donation or loss of ≥500 mL within 56 days prior to screening.

g. Is on any medication that could, in the investigator's opinion, interfere with the assessments of safety, tolerability, or efficacy, or interfere with the conduct or interpretation of the study.

17. Requires treatment with a medication or other substance that is prohibited by the protocol (see Section 5.7.2).

18. Has history of severe drug allergy or hypersensitivity, or hypersensitivity to the SM or excipients.

19. Female subjects who are pregnant or lactating or planning to become pregnant while enrolled in the study.

20. In the investigator's opinion, is unlikely to comply with the protocol or is unsuitable for any other reason.

21. Has previously enrolled in a NV-5138 study.

22. Is currently participating in another clinical trial or has received an investigational product in another clinical trial within 30 days of screening.

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

Note: Repeat testing for clinical laboratory parameters, vital signs, and ECG is permitted one time for each test, at the discretion of the investigator, as long as the repeat test result is available within the 28-day screening period to determine eligibility. Repeat testing is not allowed without justification from the study site and agreement from the Medical Monitor and the Sponsor on a case-by-case basis.

4.3 Completion of Study

Subjects will be considered to have completed the study if they complete the safety follow-up phone call at Day 12 (±2).

All reasons for screening failure will be recorded in the electronic case report form (eCRF).

4.4 Discontinuation or Early Termination of Subjects

Subjects who receive SM but withdraw or are withdrawn from participation in the study by the investigator before completion of the study (i.e., after SM administration on Day 1 but prior Day 10), should complete at the earliest time an ET visit. Procedures and assessments listed for Day 10 (see Table 1) should be completed at the ET visit.

If subject's ET visit occurs ≥72 h after the date of subject's last dose, efficacy assessments should not be performed/collected at the ET visit.

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

Reasons for a subject's early discontinuation may include:

- Withdrawal of consent
- Noncompliance of study procedures
- Occurrence of unmanageable AEs
- Lost to follow-up
- Lack of efficacy
- The investigator or the Sponsor believes it is in the best interest of the subject to discontinue the study (i.e., for safety or tolerability reasons)
- Other

If the subject withdraws consent or the investigator discontinues the subjects from the study, the primary reason for the subject's withdrawal, or the investigator's discontinuation

of the subject should be documented and captured in the eCRF. If a subject is withdrawn for more than one reason, each reason should be documented in the source document and the primary reason should be entered in the eCRF.

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

Subjects who withdraw will not be replaced.

5 STUDY TREATMENT

5.1 Study Medication Identity, Packaging, and Labeling

SM is supplied by the Sponsor as capsules packaged in bottles. Each capsule will contain 400 mg of SPN-820 (Supernus Pharmaceuticals, Inc. product alternative identification number). The capsule is Size 00 elongated (00 EL), white opaque cap and body. Each bottle will contain 40 capsules of 400 mg SPN-820. Each bottle will be labeled with the protocol number.

5.2 Study Medication Administration

SM will be administered orally in the clinic once every 3 days for a 7-day treatment period. SM should be administered in the morning, approximately 3 hours after breakfast.

Subjects will receive a single dose of SPN-820 2400 mg as six 400 mg capsules on days 1, 4, and 7. The capsules will be consumed intact, and splitting the daily dose (e.g., taking part of the daily dose in the morning and the remainder of the daily dose in the evening) is not permitted.

Subjects who cannot tolerate SPN-820 2400 mg should be discontinued from the study at the discretion of the investigator.

Subject will not receive SM on days 2, 3, 5, 6, 8, 9, or 10.

5.3 Missed Study Medication Administrations or At-Home Phone Calls

Subjects may be discontinued from the study at the discretion of the investigator and in consultation with the Medical Monitor and the Sponsor if:

1) the subject misses 1 of the 3 SM administrations, or

2) the subject misses >1 of the at-home phone calls.

All discontinuation procedures will be followed as listed on Day 10 of Table 1.

5.4 Subjects' Antidepressant Therapy

All subjects must be on stable (for ≥6 weeks before screening) therapeutic doses of one of the study-approved ADTs for treatment of their current MDE. The following are the antidepressants approved for the study: citalopram, escitalopram, paroxetine, fluoxetine, sertraline, duloxetine, venlafaxine (immediate release or extended release), desvenlafaxine, vilazodone, levomilnacipran, vortioxetine, bupropion, or dextromethorphan/bupriopion (see Appendix 11.2 for study-approved ADTs). If a subject is taking a second ADT or augmentation therapy at screening, the investigator should decide if it is medically appropriate to discontinue the second drug before baseline. If so, the second drug should be discontinued at least 5 half-lives prior to baseline.

Subjects will continue to take their ADT for their current MDE throughout the study and after completion of the study. Subjects will bring their daily supply of ADT at each clinic

visit and continue to take their ADT at home (on days 2,3,5, 6, 8 and 9). Dose adjustments or changes of subjects' ADTs will not be allowed at any time during the study. ADTs approved for use in this study will not be supplied by the Sponsor.

Subjects will receive a paper ADT adherence diary at screening and document the day of each dose of their ADT throughout the study. Subjects must bring their diaries to each clinic visit for review of subject's compliance. This should be reinforced at each clinic visit.

5.5 Method of Assigning Subjects to Treatment

All eligible subjects will receive SPN-820 2400 mg (six 400 mg capsules) on each dosing day.

5.5.1 Blinding

Not applicable.

5.6 Study Medication Handling and Accountability

All SM will be supplied by the Sponsor to the investigator. SM supplies must be stored at 20 to 25°C in an appropriate, secure area (e.g., locked cabinet) and stored according to the conditions specified on the SM label.

Following Sponsor instructions and in compliance with International Council for Harmonisation (ICH) E6 as well as local, state, and federal regulations, the investigator and study staff will be responsible for the accountability of all clinical supplies (receiving, shipment, dispensing, inventory, and record keeping) in a SM accountability log, a copy of which will be collected by the Sponsor at the end of the study.

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

An accurate and timely record of the receipt of all clinical supplies; collection of unused clinical supplies must be maintained with dates. This SM accountability log includes but may not be limited to: 1) documentation of receipt of SM, 2) SM inventory log, and 3) all shipping service receipts. Forms may be provided by the Sponsor. Any comparable forms that the study site wishes to use must be approved by the Sponsor.

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

site personnel and documentation procedures by Sponsor personnel, SM is to be returned to the Sponsor with a copy of the completed SM disposition form.

5.7 Concomitant and Prohibited Medications

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

Lists of permitted and prohibited medications are provided in Appendix 11.1.

5.7.1 Permitted Concomitant Medications

A comprehensive list of permitted medications is shown in Appendix 11.1.1. The list is not all inclusive. Contact the Medical Monitor for any questions related to the subject's current concomitant medication(s). Most of the concomitant medications are allowed if on a stable dose for at least 3 months prior to screening or otherwise specified in Appendix 11.1.1.

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

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

As needed, the following treatments will also be permitted:

- For sleeping, the following medications are permitted if on a stable dose (dose incrementation is prohibited) for ≥4 weeks prior to screening (Appendix 11.1.1):
  - Hypnotics (e.g., zaleplon and zolpidem).
  - Benzodiazepines: lorazepam (2 mg total daily dose [TDD]), clonazepam (0.5 mg TDD), and flurazepam (30 mg TDD). Benzodiazepines should be taken >12 hours prior to any study visits.

  - Trazodone (≤150 mg/day) as needed if the subject has been taking the same low dose of trazodone for insomnia for ≥3 months.
- Nutritional supplements (e.g., multivitamins, fish oil, melatonin).
- EMLA® or other numbing cream for venipuncture.
- Common over-the-counter therapies for minor, transient ailments (e.g., acetaminophen or ibuprofen for headaches, fever, etc.).

All concomitant medications will be recorded in the eCRF.

Subjects must be on a stable dose of 1 study-approved antidepressant medication; a list of these ADTs is provided in Appendix 11.2.

5.7.2 Prohibited Concomitant Medications

A comprehensive list of prohibited medications is provided in Appendix 11.1.2. The list is not all inclusive. Contact the Medical Monitor for any questions related to a subject's current concomitant medication(s).

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

6 STUDY METHODS

The Schedule of Events and Assessments is provided in Table 1, and a detailed schedule of timed assessments (Window) is provided in Table 2.

All subjects who are enrolled and receive the initial administration of SM on Day 1 will be followed according to the protocol regardless of the number of doses of SM taken, unless consent for follow-up is withdrawn. The Sponsor or Sponsor's designee must be notified of all deviations from the protocol clinic visits or procedures, except as noted, and these procedures, if applicable, will be rescheduled or performed at the nearest possible time to the original schedule. AEs should be reported during clinic visits and during at-home contacts. Subjects will also be instructed to call study personnel to report any AEs during the intervals outside the established study contacts and to come to the clinic/or seek medical care if medical evaluation is needed and as the urgency of the situation indicates. For emergencies and other unscheduled visits to a medical facility other than the clinic, medical records will be obtained by the investigator or qualified designee as source data for study follow-up.

Table 1: Schedule of Events and Assessments

Study Period	Screening	Evaluation Period							Safety/ Follow-Up (FPC[a])
		Seven-Day Treatment Period						EOS/ ET	
	Clinic	Clinic (Baseline)	Home	Clinic	Home	Clinic	Home	Clinic	Home
Visit Number	1	2	-	3	-	4	-	5	
Study Day	-28 to -1	1	2-3	4	5-6	7	8-9	10	12
Window Visit (days)									+2
Sign informed consent	X								
Review eligibility criteria	X	X							
Demographics	X								
Medical history[b]	X								
Confirm MDD diagnosis	X								
Record prior medications	X								
Confirm stable, therapeutic dose of one study-approved ADT	X								
MINI	X								
Physical examination[c]	X	X						X	
Height	X								
Body weight	X	X		X		X		X	
Calculation of body mass index	X								
Vital signs with orthostatic blood pressure and pulse rate[d]	X	X		X		X		X	
12-Lead ECG[e]	X	X		X		X		X	
Blood sample for hematology	X	X				X		X	
Blood sample for chemistry	X	X				X		X	

Study Period	Screening	Evaluation Period							Safety/ Follow-Up (FPC[a])
		Seven-Day Treatment Period						EOS/ ET	
	Clinic	Clinic (Baseline)	Home	Clinic	Home	Clinic	Home	Clinic	Home
Visit Number	1	2	-	3	-	4	-	5	
Study Day	-28 to -1	1	2-3	4	5-6	7	8-9	10	12
Window Visit (days)									+2
Blood sample for serology[f]	X								
Blood sample for FSH (postmenopausal females only)	X								
Serum pregnancy test (FOCP only)	X								
Urine sample for urinalysis	X	X				X		X	
Urine sample for urine drug screen and alcohol screen[g]	X	X		X		X		X	
Urine sample for pregnancy test (FOCP only)		X		X		X		X	
HAM-D_6	X	X	X[h]	X	X[h]	X	X[h]	X	
MADRS	X	X		X		X		X	
CGI-S	X	X		X		X		X	
C-SSRS (Screening/Baseline Version)	X								
C-SSRS (Since Last Visit Version)		X		X		X		X	X
CADSS	X	X				X		X	X
BPRS+	X	X				X		X	X
Review AEs[i]		X	X	X	X	X	X	X	X
Review concomitant medications	X	X	X	X	X	X	X	X	X

Study Period	Screening	Evaluation Period							Safety/ Follow-Up (FPC[a])
		Seven-Day Treatment Period						EOS/ ET	
	Clinic	Clinic (Baseline)	Home	Clinic	Home	Clinic	Home	Clinic	Home
Visit Number	1	2	-	3	-	4	-	5	
Study Day	-28 to -1	1	2-3	4	5-6	7	8-9	10	12
Window Visit (days)									+2
[redacted]									
Blood sample for BDNF[j]		X		X		X		X	
SM administered[k]		X[i]		X[i]		X[i]			
Medication adherence diary[l]	X	X	X	X	X	X	X	X	
ADT[m]	◄								►

ADT = antidepressant therapy; AE = adverse event; BDNF = brain-derived neurotrophic factor; BPRS+ = Brief Psychiatric Rating Scale Positive Subscale; CADSS = Clinician- Administered Dissociative State Scale; CGI-S = Clinical Global Impression – Severity of Illness; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiography; EOS = End of Study; ET = Early Termination; FOCP = females of childbearing potential; FPC = Follow-Up Phone Call; FSH = follicle-stimulating hormone; HAM-D_6 = Hamilton Depression Rating Scale-6 Items; MADRS = Montgomery–Åsberg Depression Rating Scale; MDD = major depressive disorder; MINI = Mini International Neuropsychiatric Review; [redacted]; SM = study medication

Note: An attempt will be made to have the same qualified rater administer the same scales (efficacy) throughout the study for each subject. Administration of the HAM-D_6 and MADRS will be performed by 2 different raters.

a. The follow-up assessments will be performed through a safety follow-up phone call. The safety follow-up phone call will occur approximately 5 days after the last administration of SM.

b. AEs reported during screening will be recorded as part of the subject's medical history.

c. A complete physical examination will be performed at screening and baseline visits; a brief physical examination will be performed at EOS/ET.

d. Vital signs measurements include orthostatic blood pressure/pulse rate, respiratory rate, and oral temperature. Orthostatic blood pressure and pulse rate should be measured after the subject has been sitting for 5 minutes and again within 3 minutes of subject standing.

e. ECGs should be performed prior to blood draws.

f. Serology tests include human immunodeficiency 1/2 antigen/antibody, hepatitis B surface antigen, and hepatitis C virus antibody.

g. A standard urine drug screen will be performed at screening and point-of-care urine drug screen together with the breathalyzer will be performed at baseline (Day 1) and all post-baseline clinic visits (days 4, 7, and 10).

h. On days 2, 3, 5, 6, 8, and 9, the HAM-D_6 questionnaire will be administered remotely by telephone.

i. SAEs will be captured from the time of ICF signing, and AEs will be captured following the first administration of SM and continue through the FPC.

j. Seven total blood samples will be collected for measurement of BDNF concentrations: 3 pre-dose collections on days 1, 4 and 7; 3 post-dose collections 4 hours after SM administration on days 1, 4, and 7; and 1 collection on Day 10.

k. Subjects will take their SM in the clinic.

l. Subjects will receive a paper ADT adherence diary at screening and document the day of each dose of their ADT throughout the study. Subjects will bring their ADT adherence

diaries to each clinic visit for review of subject compliance.
m. ADT will not be provided by the Sponsor. Subject's ADT will have started and have been stable for at least 6 weeks prior to screening and will continue through the safety follow-up phone call.

Table 2: Detailed Schedule of Timed Assessments (Window)

Study Day	Clinic Visit Number	Location	Time[a]	[redacted]	HAM-D_6[b]	MADRS[b]	CGI-S	BDNF[c]
1	2	Clinic	Pre-dose		X (-60 min)	X (-60 min)	X (-60 min)	X (-60 min)
			1 hour					
			2 hours		X (±30 min)			
			4 hours		X (±30 min)	X (±30 min)		X (±30 min)
			8 hours		X (±30 min)			
2	–	Home	24 hours		X (±2 h)[e]			
3	–	Home	48 hours		X (±2 h)[f]			
4	3	Clinic	Pre-dose		X[e] (-60 min)	X (-60 min)	X (-60 min)	X (-60 min)
			1 hour					
			2 hours		X (±30 min)			
			4 hours		X (±30 min)	X (±30 min)		X (±30 min)
			8 hours		X (±30 min)			
5	–	Home	24 hours		X (±2 h)[e]			
6	–	Home	48 hours		X (±2h)[f]			
7	4	Clinic	Pre-dose		X[f] (-60 min)	X (-60 min)	X (-60 min)	X (-60 min)
			1 hour					
			2 hours		X (±30 min)			
			4 hours		X (±30 min)	X (±30 min)		X (±30 min)
			8 hours		X (±30 min)			
8	–	Home	24 hours		X (±2 h)[e]			
9	–	Home	48 hours		X (±2 h)[f]			
10	5	Clinic	72 hours		X (±2 h)[g]	X (±2 h)	X (±2 h)	X (±60 min)

BDNF = brain-derived neurotrophic factor; CGI-S = Clinical Global Impression – Severity of Illness; h = hours; HAM-D_6 = Hamilton Depression Rating Scale-6 Items; MADRS = Montgomery–Åsberg Depression Rating Scale; min = minutes; [redacted]

a. Time either before (pre-dose) or after SM administration.

b. Administration of the HAM-D_6 and MADRS will be performed preferably by 2 different raters.

c. Seven total blood samples will be collected for measurement of BDNF concentrations: 3 pre-dose collections on days 1, 4 and 7; 3 post-dose collections 4 hours after SM

administration on days 1, 4 and 7; and 1 collection on Day 10.

[redacted]

e. The HAM-D_6 will be administered remotely on days 2, 5, and 8, approximately 24 hours (±2 hours) after SM was administered in the clinic on days 1, 4, and 7, respectively.
f. The HAM-D_6 will be administered remotely on days 3, 6, and 9, approximately 48 hours (±2 hours) after SM was administered in the clinic on days 1, 4, and 7, respectively.
g. The HAM-D_6, MADRS, and CGI-S will be administered on Day 10, approximately 72 hours (±2 hours) after SM was administered in the clinic on Day 7. The HAM-D_6, MADRS, and CGI-S will be administered prior to any safety assessments.

6.1 Clinic Study Visits and Procedures

6.1.1 Visit 1 – Screening (Day -28 to Day -1)

The following assessments will be conducted:

- Obtain written informed consent
- Confirm MDD diagnosis and conduct the MINI
- Review Inclusion/Exclusion Criteria
- Confirm stable, therapeutic dose of one study-approved ADT
- Record relevant history (social [including alcohol and cannabis consumption], medical, psychiatric, family psychiatric, and neurological)
- Record demographics, height, and body weight
- Record prior and concomitant medications
- Perform a complete physical examination, including the calculation of body mass index
- Record vital signs (orthostatic blood pressure and pulse rate, respiratory rate, and oral temperature)
- Perform 12-lead ECG
- Collect blood sample for:
  - FSH (postmenopausal females only)
  - Serum pregnancy test (FOCP only)
  - Hematology and serum chemistry (non-fasted sample allowed)
  - Serology (i.e., HIV 1/2 Ag/Ab, HBsAg, and HCV Ab)
- Collect urine sample for:
  - Urinalysis
  - Drug and alcohol screen (Table 3)
- Administer efficacy assessments (HAM-D_6, MADRS, and CGI-S)
- Administer safety assessments (C-SSRS [Screening/Baseline Version], CADSS, and BPRS+ scales)
- Provide the subject a paper ADT adherence diary

6.1.2 Visit 2 – Baseline (Day 1)

The assessments listed below will be conducted. See Table 2 for details for efficacy assessments and blood collections for [redacted] BDNF.

- Review eligibility criteria
- Record body weight
- Record vital signs (orthostatic blood pressure and pulse rate, respiratory rate, and oral temperature)
- Perform complete physical examination

- Perform 12-lead ECG
- Collect blood samples for:
  - Hematology and serum chemistry (non-fasted sample allowed)
  - BDNF pre-dose
  - [redacted]
- Collect urine sample for:
  - Urine pregnancy test (FOCP only)
  - Urinalysis
  - Drug and alcohol screen
- Administer efficacy assessments (pre-dose HAM-D_6, MADRS, and CGI-S)
- Administer safety assessments (C-SSRS [Since Last Visit Version], CADSS, and BPRS+ scales)
- Review concomitant medications
- Administer SM
- Review AEs
- Administer efficacy assessments following SM administration (HAM-D_6 and MADRS)
- [redacted]
- Collect blood sample for BDNF concentration following SM administration (after efficacy assessments)
- Review ADT adherence diary

6.1.3 Visit 3 (Day 4)

The assessments listed below will be conducted. See Table 2 for details for efficacy assessments and blood collections for [redacted] BDNF.

- Record body weight
- Record vital signs (orthostatic blood pressure and pulse rate, respiratory rate, and oral temperature)
- Perform 12-lead ECG
- Collect blood samples for:
  - BDNF pre-dose
  - [redacted]
- Collect urine sample for:
  - Urine pregnancy test (FOCP only)
  - Drug and alcohol screen
- Administer efficacy assessments (pre-dose HAM-D_6, MADRS, and CGI-S)

- Administer safety assessments (C-SSRS [Since Last Visit Version])
- Review AEs
- Review concomitant medications
- Administer SM
- Administer efficacy assessments following SM administration (HAM-D_6 and MADRS)
- [redacted]
- Collect blood sample for BDNF concentration following SM administration (after efficacy assessments)
- Review ADT adherence diary

6.1.4 Visit 4 (Day 7)

The assessments listed below will be conducted. See Table 2 for details for efficacy assessments and blood collections for [redacted] BDNF.

- Record body weight
- Record vital signs (orthostatic blood pressure and pulse rate, respiratory rate, and oral temperature)
- Perform 12-lead ECG
- Collect blood samples for:
  - Hematology and serum chemistry (non-fasted sample allowed)
  - BDNF pre-dose
  - [redacted]
- Collect urine sample for:
  - Urine pregnancy test (FOCP only)
  - Urinalysis
  - Drug and alcohol screen
- Administer efficacy assessments (pre-dose HAM-D_6, MADRS, and CGI-S)
- Administer safety assessments (C-SSRS [Since Last Visit Version], CADSS, and BPRS+ scales)
- Review AEs
- Review concomitant medications
- Administer SM
- Administer efficacy assessments following SM administration (HAM-D_6 and MADRS)
- [redacted]
- Collect blood sample for BDNF concentration following SM administration (after

efficacy assessments)

- Review ADT adherence diary

6.1.5 Visit 5 – End of Study (Day 10)

The assessments listed below will be conducted. See Table 2 for details of efficacy assessments.

- Administer HAM-D_6, MADRS, and CGI-S (approximately 72 hours after the SM administration on Day 7)
- Perform a brief physical examination
- Record body weight
- Record vital signs (orthostatic blood pressure and pulse rate, respiratory rate, and oral temperature)
- Perform 12-lead ECG
- Collect blood samples for:
  - Hematology and serum chemistry (non-fasted sample allowed)
  - BDNF
- Collect urine sample for:
  - Urine pregnancy test (FOCP only)
  - Urinalysis
  - Drug and alcohol screen
- Administer safety assessments (C-SSRS [Since Last Visit Version], CADSS, and BPRS+ scales)
- Review AEs
- Review concomitant medications
- Review and collect ADT adherence diary

6.2 Home Evaluations

On days 2, 3, 5, 6, 8, and 9, subjects will receive a telephone call for safety and efficacy assessments. Subjects will continue to take their ADT.

6.2.1 Days 2, 3, 5, 6, 8 and 9

The following assessments will be conducted remotely by telephone:

- Review AEs
- Review concomitant medications
- Confirm compliance and remind subject to complete the ADT adherence diary
- Administer HAM-D_6 remotely approximately 24 and 48 hours (±2 hours) after each administration of SM on days 1, 4, and 7 as detailed in Table 2

6.3 Safety Follow-Up Phone Call (Day 12)

Subjects who complete EOS/Study Day 10 will receive a safety follow-up phone call approximately 5 days (+2 days) after the administration of SM on Day 7.

The following assessments will be conducted:

- Administer safety assessments (C-SSRS [Since Last Visit Version], CADSS, and BPRS+ scales)
- Review AEs
- Review concomitant medications

6.4 Unscheduled Visits

At the discretion of the investigator throughout the study, unscheduled visits may be conducted to perform or repeat assessments, including to record an ECG, measure vital signs (orthostatic blood pressure/pulse rate) or body weight, draw a blood sample for hematology and/or serum chemistry or serum pregnancy test (FOCP) or alcohol drug screen, obtain urine sample for urine pregnancy test and/or drug screen, administer the C-SSRS, and/or perform a physical examination. AEs and concomitant medications should be reviewed and recorded at all unscheduled visits.

6.5 Urine Drug and Alcohol Screen

The urine drug screen should be completed, and results known before any efficacy assessments are conducted at baseline and all post-baseline clinic visits. Subjects should refrain from taking alcohol during the study after the first administration of SM. The urine drug screen will be performed as point-of-care (POC) testing with POC kits provided to study site(s).

If a subject has a positive drug screen or tests positive for ethanol at baseline or any post-baseline clinic visits (days 1, 4, and 7), then the subject should be withdrawn from the study and no efficacy assessments (HAM-D_6, MADRS, and CGI-S) should be performed at that visit. All safety assessments should still be performed. The subject should receive a follow-up phone call approximately 1 week following discontinuation from the study.

6.7 Pharmacodynamic Blood Sampling

Separate, additional blood draws will be collected to measure BDNF concentrations. Six blood samples (2.0 mL each) will be collected at clinic visits on days 1, 4, and 7, as follows:

- Pre-dose (within 60 minutes of SM administration)
- 4 hours (±30 minutes) following SM administration

One blood sample (2.0 mL) will be collected at the clinic visit on Day 10 approximately 72 hours after SM administration on Day 7.

- 72 hours (±60 minutes) following SM administration

7 STUDY VARIABLES AND ASSESSMENTS

All clinical outcome assessments will be collected using paper scales/questionnaires.

7.1 Rater Qualification Process

Identified raters from each study site will be asked to provide information regarding their highest degree of education, field of study, study indication and scale administration experience, and previous certifications using a rater qualification form provided by the Sponsor. Based on the information entered on the qualification form and accompanying certificates, the Sponsor or Sponsor's designee will determine if raters are qualified to administer scales or require Sponsor provided training. Raters can appeal their qualification status; final determination will be made by the Sponsor. All qualified study coordinators, investigators, and designees must complete the Sponsor rater trainings.

A site will be considered activated once at least one rater per scale training is completed. Investigators from recent previous Supernus Pharmaceutical Inc. studies will be considered as qualified raters.

An attempt will be made to have the same qualified rater administer the same scales (efficacy) throughout the study for each subject.

7.1.1 Hamilton Depression Rating Scale – 6 Items

The Hamilton Depression Rating Scale is one of the most widely used clinician-administered depression scales (Hamilton 1960; Williams 1988). The original version contains 17 items related to symptoms of depression over the past week developed for hospital inpatients. The HAM-D_6 derived from the original 17-item version of the scale offers sensitivity for measuring severity of detecting improvement of depression comparable to other more complex versions (O'Sullivan 1997).

Five of the 6 items (Depressed Mood, Low Self-Esteem and Guilt, Social Life Activities/Interests, General Psychomotor Retardation, and Psychic Anxiety) are scored on a scale of 0 to 4, and 1 item (Tiredness and Pains) is scored on a scale of 0 to 2, for a possible total score of 0 to 22.

The scale is a clinician-reported outcome (ClinRO) administered by a qualified rater at all clinic visits, and it will be administered remotely on days 2, 3 5, 6, 8, and 9 to subjects while at home.

7.1.2 Montgomery-Åsberg Depression Rating Scale

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

Successful therapy is indicated by a lower total score in subsequent testing (Montgomery-Åsberg Depression Rating Scale Past Week [Follow-Up Evaluation]).

There are 10 subtests based on each item:

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

The rater will use a structured interview that standardizes the administration of the 10 MADRS items known as structured interview guide for the MADRS, a structured interview was developed by Dr. Janet Williams and Dr. Kenneth Kobak in order to increase inter-rater reliability, thus improving signal detection (Williams 2008).

The Standard (including comparison to euthymic baseline for 3 items) and Past Week versions will be administered, with the Standard Version administered at screening and the Past Week Version administered on days 1, 4, 7, and 10. Euthymic baseline is auto populated based on the information captured at the first administration.

The scale is a ClinRO administered by a qualified rater at all clinic visits.

7.1.3 Clinical Global Impression – Severity of Illness

The CGI scale was developed to provide a brief, stand-alone assessment of the clinician's view of a subject's global functioning prior to and after administration of SM (Guy 1976). The CGI-S is a single-item, clinician rating of the clinician's assessment of the severity of symptoms in relation to the clinician's total experience with patients with MDD. The CGI-S is evaluated on a 7-point scale, where:

- 1=Normal, not at all ill, asymptomatic
- 2=Borderline ill
- 3=Mildly ill
- 4=Moderately ill
- 5=Markedly ill
- 6=Severely ill
- 7=Extremely ill

Successful therapy is indicated by a lower overall score in subsequent testing.

The scale is a ClinRO administered by a qualified rater at all clinic visits.

7.2 Safety Variables and Assessments

Safety assessments include monitoring, evaluation, and recording of all concomitant medications and AEs, and the evaluation of clinical laboratory test results, vital sign measurements, body weight, 12-lead ECGs, C-SSRS, CADSS, BPRS+, and the performance of physical examinations as detailed in the Schedule of Events and Assessments (Table 1).

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

7.2.1 Adverse Events

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

An AE can be, for example:

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

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

7.2.2 Adverse Events of Special Interest

At the current time, no adverse events of special interest have been identified. This section will be updated when new information becomes available.

7.2.3 Overdose

No data are available. Should an overdose of SPN-820 be administered or ingested, the subject should be closely monitored for adverse signs and symptoms and appropriate supportive medical care administered.

7.2.4 Causality

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

SADRs are a subset of AEs for which there is evidence to suggest a causal relationship between the SM and the AE (i.e., there is a reasonable possibility that the SM caused the AE).

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

7.2.5 Recording and Evaluation of Adverse Events

All subjects who are screened will be questioned regarding any current and prior medical health status or diagnoses and any medical records will be documented as medical history. At each contact with the subject following the first administration SM on Day 1, The investigator must seek information on AEs by specific questioning and, as appropriate, by examination. Information on all AEs should be recorded immediately in the source document, and also in the appropriate AE module of the eCRF. All clearly related signs, symptoms, and abnormal diagnostic procedure results should be recorded in the source document, though they may be grouped under one diagnosis. For example, fever, elevated white blood cell count, cough, abnormal chest X-ray, etc., can all be reported as "pneumonia."

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

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

- Serious versus non-serious: Is the event a serious adverse event (SAE)?
- Causality: Was the AE related or not related to the SM?
- Severity: How pronounced is the incapacity/discomfort caused by an AE?

7.2.6 Criteria for Assessing Severity

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

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

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

7.2.7 Criteria for Assessing Causality

The investigator is responsible for determining the relationship between the administration of SM and the occurrence of an AE as not suspected or as a suspected reaction to SM, as defined below:

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

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

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

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

7.2.8 Serious Adverse Events

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

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

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

7.2.9 Investigator Responsibilities for Reporting Serious Adverse Events

The investigator must immediately report to the Sponsor all SAEs, regardless of whether the investigator believes they are related to SM.

All SAEs must be reported to the Drug Safety Team within 24 hours of first becoming aware of the SAE. The investigator must complete an SAE form and include a detailed description of the SAE, as well as other available information pertinent to the case (e.g., hospital records, autopsy reports, and other relevant documents). The investigator will keep a copy of this SAE report form on file at the study site.

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

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

The drug safety contact for SAE reporting is:

If the email was not successfully transmitted and a second attempt is unsuccessful, contact the study site CRA.

7.2.10 Other Events Requiring Immediate Reporting

The investigator must report a pregnancy that occurs in a subject during the study to the Drug Safety Team within 24 hours of first becoming aware of the event.

Subjects who become pregnant during the study should be discontinued from SM immediately. A pregnancy should be reported on a pregnancy report form. The investigator should discuss the case with the Medical Monitor, and the investigator must follow any pregnant subject until 3 months after the child is born. Any AEs concerning the pregnancy of the subject during pregnancy or the child after birth must be documented and reported to the Sponsor or designee.

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

7.2.11 Sponsor Responsibilities for Reporting Serious Adverse Events

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

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

It is the responsibility of the Sponsor to notify the investigator, in a written Investigational New Drug Safety Report, of any SADR that is both serious and unexpected. The Sponsor will also notify the investigator of any findings from other sources (other studies, animal, and in vitro testing, etc.) that suggest a significant risk for human subjects. Such findings will typically lead to safety-related changes in the study protocol, ICF, and/or IB.

7.2.12 Clinician-Administered Dissociative States Scale

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

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

The scale is a ClinRO administered by a qualified rater at screening, days 1, 7, and 10 of the evaluation period, and during the safety follow-up phone call.

7.2.13 Brief Psychiatric Rating Scale

The BPRS is one of the most widely used instruments enabling the clinician to quickly gather information about the possible presence and severity of various psychiatric symptoms (Zanello 2013). Varying in the number and type of symptoms assessed, clarity of anchor point definitions and administration and rating instructions, the BPRS exists in various forms. Originally in the early 1960s, the BPRS was developed as a 16-item instrument (Overall 1962), that was later extended to 18 items and was used for many years (Overall 1967). In order to increase its sensitivity to psychotic and affective disorders as well as to be used with patients living in the community, the BPRS was expanded to 24 items (Version 2, Lukoff 1986). In its latest version (Version 4.0), the manual of administration of the 24-item BPRS+ (Ventura 1993) not only offers a more detailed semi-structured interview containing more probe questions for each symptom but also provides supplementary rules for the rating (e.g., delusions) with better-defined anchor points.

The version used for this study is adapted from the original BPRS+. The scale is comprised of 4 items assessing a subject's experience of psychosis, often referred to as positive symptoms of Suspiciousness, Hallucinatory Behavior, Unusual Thought Content, and Conceptual Disorganization. Of the 4 items assessed, the first 3 items are based on questions asked by the clinician to the subject. Conceptual Disorganization is a clinician-rated item based on observation of a subject's behavior and speech during the assessment.

The scale is a ClinRO administered by a qualified rater at screening, days 1, 7, and 10 of the evaluation period, and during the safety follow-up phone call.

7.3 Treatment-Emergent Suicidal Ideation

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

subsequent clinic visit as well as during the safety follow-up phone call to monitor the occurrence of new suicidal and self-injurious tendencies.

7.3.1 Columbia Suicide Severity Rating Scale

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

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

The scale is a ClinRO administered by a qualified rater at screening, days 1, 4, 7, and 10 of the evaluation period, and during the safety follow-up phone call.

7.3.2 Suicide Risk Management Plan

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

7.3.2.1 Assessment of Suicide Risk

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

Acute Suicidal Crisis

A person evaluated as being at high risk for suicide should be transferred to an immediate care facility. The investigator will guide intervention as clinically indicated and follow-up with the subject within 1 week and/or refer him/her to a qualified mental health professional.

Non-Acute Suicidal Risk

The investigator will conduct safety planning with a subject evaluated as being a non-acute risk for suicide and will follow up within 1 week.

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

7.4 Clinical Measurements

7.4.1 Screening and Clinical Safety Laboratory Assessments

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

Details for collecting, handling, and shipping samples (including shipment addresses) will be detailed in a separate clinical laboratory manual. The Schedule of Events and Assessments (Table 1) shows the time points at which blood and urine samples will be collected. Table 3 lists the clinical laboratory tests to be performed.

Table 3: Clinical Laboratory Tests

Category	Parameter
Hematology	Red blood cell count, hemoglobin, hematocrit, platelet count, white blood cell count with differential
Chemistry	**Electrolytes**: chloride, phosphate, potassium, sodium
	Liver function tests: alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, direct bilirubin
	Renal function parameters: blood urea nitrogen, serum creatinine[a]
	Other: glucose, calcium, albumin, total protein, bicarbonate, thyroid-stimulating hormone, free triiodothyronine (T3), free thyroxine (T4), follicle-stimulating hormone (postmenopausal females only)
Serology[b]	HBsAg, HCV Ab, HIV 1/2 Ag/Ab
Urinalysis	Microscopic examination[c], pH, specific gravity, protein, glucose, ketone, occult blood, white blood cell count, nitrites, bilirubin, urobilinogen
Standard Urine Drug Screen[d]	Amphetamines[e], barbiturates, benzodiazepines[e], buprenorphine, cocaine, ecstasy, ethanol, methadone, methamphetamine[e], methylphenidate[e], opiates, oxycodone, phencyclidine, propoxyphene, tricyclic antidepressants, tetrahydrocannabinol (cannabinoids)
POC[f] Urine Drug Screen	Amphetamines[e], barbiturates, benzodiazepines[e], buprenorphine, cocaine, ecstasy, methadone, methamphetamine[e], opiates, oxycodone, phencyclidine, propoxyphene, tricyclic antidepressants, tetrahydrocannabinol (cannabinoids)
Breathalyzer[f]	Ethanol
Pregnancy test (FOCP only)[g]	Human chorionic gonadotropin

ADHD = attention-deficit/hyperactivity disorder; FOCP = females of childbearing potential; HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C antibody; HIV = human immunodeficiency virus 1/2 antigen/antibody; POC = point-of-care
a. Glomerular filtration rate will be calculated using the Chronic Kidney Disease Epidemiology Collaboration equation at screening only.
b. Confirmatory serology testing for positive HIV, hepatitis B and HCV at screening will be performed.
c. A microscopic examination will be performed on abnormal findings unless otherwise specified.
d. Standard urine drug screen will be performed at screening. A positive test must be confirmed against medical history and concomitant medications.

e. Amphetamine, methamphetamine, and methylphenidate (methylphenidate will not be tested during the treatment period) positive tests are allowed only for subjects diagnosed with ADHD confirmed by a prescription record. Benzodiazepine positive test is allowed if used for insomnia.
f. POC urine drug screen together with the breathalyzer will be performed at baseline (Day 1) and all post-baseline visits (days 4, 7, and 10).
g. A serum pregnancy test will be performed at screening; a urine pregnancy test will be performed on days 1, 4, 7, and 10.

7.4.2 Vital Signs and Weight

Vital signs measurements (includes orthostatic blood pressure/pulse rate, respiratory rate, and oral temperature) and body weight will be obtained at the time points shown in the Schedule of Events and Assessments (Table 1). Orthostatic blood pressure and pulse rate should be measured after the subject has been sitting for 5 minutes and again within 3 minutes of subject standing. Vital sign measurements may be taken at any other time, as deemed necessary by the investigator.

7.4.3 Physical Examinations and Height

Physical examinations and measurement of height will be obtained at the time points shown in the Schedule of Events and Assessments (Table 1). The complete physical examination conducted at screening and baseline visits will include assessments of all body systems except genitourinary. Any abnormal findings during screening will be recorded as medical history and any clinically significant abnormal findings following the first administration of SM on Day 1 will be recorded as TEAEs. Only changes from baseline observations will be noted during the brief physical examination at the EOS.

7.4.4 Electrocardiography

A 12-lead ECG will be obtained at the time points shown in the Schedule of Events and Assessments (Table 1). Additional ECGs may be performed at other times if deemed necessary by the investigator.

The ECG will be recorded while the subject is resting in a supine position for at least 5 minutes. The ECG will electronically measure the PR, QRS, QT, QTc intervals, and heart rate. All ECG tracings will be reviewed within 24 hours by the investigator or qualified sub-investigator. PR intervals will be determined for each of these ECGs from a single reading. Invalid measurements will be repeated. QTc will be reported as QT interval corrected using Fridericia's method (QTcF).

[redacted]

7.6 Pharmacodynamic Variables and Assessments

Concentrations of BDNF will be measured from blood samples collected as outlined in Table 2.

7.7 Screening Scales and Assessment Tools

7.7.1 Mini International Neuropsychiatric Interview

The diagnosis of MDD will be made by the investigator and supported by the MINI. The MINI is a short, structured diagnostic interview developed by psychiatrics and clinicians in the US and Europe for Diagnostic and Statistical Manual of Mental Disorders and has been updated to map to the DSM-5 (Hergueta 2013; Sheehan 1998). With an administration time of approximately 15 minutes, the MINI is often used for psychiatric evaluation in clinical studies and is the most widely used psychiatric structured diagnostic interview instrument in the world.

7.7.2 Montgomery-Åsberg Depression Rating Scale

The MADRS is described in Section 7.1.2. Subjects must have a MADRS total score of ≥22 for their current MDE at screening and baseline (Day 1) before SM administration. The MADRS total score cannot vary ≥25% between the highest and the lowest score from screening to baseline (Day 1).

7.7.3 Clinical Global Impression – Severity of Illness

The CGI-S is described in Section 7.1.3. Subjects must have a CGI-S score of ≥4 (moderately ill or worse) at screening and baseline (Day 1) before SM administration.

8 STATISTICAL METHODS

8.1 General Considerations

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

The data summaries will be accompanied by individual subject data listings, as specified in Sections 16.2 and 16.4 of ICH Guidance E3, sorted by unique subject identifier. All data available from the eCRFs will be listed.

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

8.2 Sample Size and Power Considerations

Approximately 50 subjects will be enrolled to achieve approximately 40 subjects completed. This sample size is based on clinical judgment without a power calculation.

8.3 Handling of Dropout or Missing Data

For safety analyses, a missing date for an AE and non-study medication use will be imputed as described in the SAP. Missing data for all other safety endpoints will not be imputed.

8.4 Analysis Populations

The full analysis set (FAS) includes all subjects who receive at least one dose of SM and have a baseline and at least one post-baseline measurement of HAM-D_6.

The safety population includes all subjects who receive at least one dose of SM.

[redacted].

The PD population includes all subjects who receive at least one dose of SM and have a baseline and at least one post-baseline BDNF concentration.

8.5 Demographics and Baseline Analysis

Demographic variables including age, sex, ethnicity, race, height, body weight, body mass index, and other baseline efficacy measurements will be summarized descriptively using the safety population and the FAS.

8.6 Population Disposition

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

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

- Withdrawal of consent
- Noncompliance with study procedures

- Occurrence of unmanageable AEs
- Lost to follow-up
- Lack of efficacy
- The investigator or the Sponsor believes it is in the best interest of the subject to discontinue the study (i.e., for safety or tolerability reasons)
- Other

8.7 Study Medication Exposure

Duration of exposure is defined as the total number of days a subject is exposed to any SM. This will be calculated for each subject by taking the difference between the date of last administration of SM minus the date of the first administration of SM + 1 (date of last dose – date of first dose + 1). Duration of treatment exposure will be summarized using descriptive statistics. The amount of the dosage will be summarized descriptively by visit and overall.

8.8 Medical History

Medical histories will be tabulated and listed by subject.

8.9 Prior and Concomitant Medications

Prior and concomitant medications will be assigned an 11-digit code using the World Health Organization Drug Dictionary drug codes. Concomitant medications will be further coded to the appropriate Anatomical-Therapeutic-Chemical code indicating therapeutic classification. A tabular summary of concomitant medications by drug class will be presented for the safety population.

8.10 Efficacy Analyses

All efficacy data will be summarized descriptively and listed.

8.10.1 Primary

The change from baseline to each time point in the HAM-D_6 total score will be analyzed using descriptive statistics. The primary efficacy analysis will be performed with the FAS.

8.10.2 Secondary

The change from baseline at each time point in the MADRS and CGI-S total scores will be analyzed using descriptive statistics. Analyses for responders (proportion of subjects achieving a ≥50% reduction from baseline in the MADR total score), remission (proportion of subjects achieving MADRS ≤10 total score), and percentage of subjects with a CGI-S score of 1 or 2 will be summarized. The secondary efficacy analyses will be performed using the FAS population.

[redacted]

[redacted]

8.12 Pharmacodynamic Analysis

The PD analysis is an exploratory analysis and will be performed using the PD population. The change from baseline to each time point for BDNF concentration will be analyzed descriptively.

8.13 Safety Analysis

Safety analysis is a secondary analysis and will be performed using the safety population. Summaries will be presented for TEAEs and data from the clinical laboratory tests, vital sign measurements, body weight, ECGs, C-SSRS, CADSS, and BPRS+. Physical examination results will be listed by subject.

TEAEs: The incidence rate for all TEAEs will be summarized for each System Organ Class (SOC) and Preferred Term (PT). The severity of the TEAEs, the relationship to SM, SAEs, AEs leading to SM withdrawn, and deaths will be summarized for each SOC and PT. Common TEAEs (≥5%) will be summarized by PT. The verbatim descriptions with Medical Dictionary for Regulatory Activities coded SOCs and PTs for all AEs will be contained in the subject data listings.

Clinical Laboratory Values, Vital Sign Measurements, and Body Weight: Both actual values and change from baseline and shift from baseline will be summarized for clinical laboratory values, vital sign measurements, and body weight.

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

C-SSRS outcomes will be summarized using number and percentage of subjects by categories for suicidal ideation only, suicidal behavior only, and suicidality (ideation and behavior combined).

CADSS outcomes will be summarized using descriptive statistics.

BPRS+ outcomes will be summarized using descriptive statistics.

8.14 Interim Analysis

No interim analysis will be performed.

9 DOCUMENTATION

9.1 Adherence to the Protocol

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

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

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

9.2 Changes to the Protocol

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

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

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

9.3 Data Quality Assurance

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

9.3.1 Data Collection

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

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

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

9.3.2 Clinical Data Management

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

9.3.3 Database Quality Assurance

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

9.3.4 Bioanalytical Sample Handling

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

[redacted]

Blood samples for determination of BDNF concentrations will be shipped to a Sponsor-designated analytical laboratory. BDNF concentrations will be determined using a validated enzyme-linked immunosorbent assay method as specified in the laboratory manual.

9.4 Retention of Records

The investigator has the responsibility to retain all essential documents from this study, as described in ICH E6 for at least 2 years after approval of a marketing application or after formal discontinuation of the clinical program. Essential documents include but are not limited to the protocol, eCRFs, source documents, laboratory test results, SM inventory records, IB, and regulatory agency registration documents (e.g., FDA form 1572, ICFs, and IRB correspondence). The investigator must obtain written permission from the Sponsor prior to the destruction of any study document.

9.5 Auditing Procedures

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

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

9.6 Publication of Results

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

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

9.7 Financing and Insurance

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

9.8 Disclosure and Confidentiality

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

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

9.9 Discontinuation of Study

The Sponsor reserves the right to discontinue the study for medical or administrative reasons at any time. The investigator will be reimbursed for reasonable expenses covering subjects,

laboratory tests, and other professional fees. The investigator will refund the excess of payments made in advance.

The investigator reserves the right to discontinue the study should his/her judgment so dictate. The investigator will notify the IRB in case of study discontinuation. Study records must be retained as noted above.

10 ETHICS

10.1 Institutional Review Boards

The IRB that approves this study and the approval letters will be included in the appendices of the clinical study report for this protocol.

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

10.2 Ethical Conduct of the Study

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

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

10.3 Investigator and Study Personnel

This study will be conducted by a qualified investigator(s) under the sponsorship of Navitor Pharmaceuticals, Inc. and its partner Supernus Pharmaceuticals, Inc.

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

The study will be monitored by qualified personnel from the CRO and Sponsor. Data management and statistical analyses will be the responsibility of the CRO data management and biostatistics groups.

10.4 Subject Information and Consent

The investigator (or designee) will inform the subject of all aspects pertaining to the subject's participation in the study and will provide oral and written information describing the nature and duration of the study, the procedures involved, the expected duration, the potential risks and benefits involved, and any potential discomfort. The process for obtaining informed consent will be in accordance with all applicable regulatory requirements. The investigator (or designee) and subject must sign and date the ICF before the subject can participate in the study.

The subject will be given a copy of the signed and dated ICF, and the original will be retained in the investigational site study records.

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

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

11 APPENDIX

11.1 Prohibited and Permitted Concomitant Medications

These lists of medications are not all inclusive; please contact the Medical Monitor for any questions related to the subject's current concomitant medication(s). Additional concomitant medications may be permitted on a case-by-case basis at the discretion of the investigator, the Medical Monitor, and the Sponsor.

Medications on the prohibited medications list should be discontinued for 5 half-lives prior to the first administration of SM (Day 1, baseline).

Where discontinuation of prohibited medications is required prior to Day 1 (baseline), tapering rates are at the discretion of the investigator and are to be determined on an individual basis, with consideration to subject state, dose, and known PK of the medication being discontinued. The subject must be consented prior to any tapering of medication is started or any discontinuation of medication occurs.

Note: If a medication is part of the study-approved ADT regimen (FDA approved and at a stable dose) initiated prior to screening, it must be continued until the end of the study.

11.1.1 Permitted Concomitant Medications

Permitted concomitant medications for pre-existing medical conditions should be taken at a stable dose for at least 3 months prior to screening or as otherwise specified in the list below:

Drug Class/Medications	PRN Use	Comments
Antimigraine medications (e.g., calcium channel blockers, and amitriptyline)		Allowed, if on a stable regimen for at least 3 months prior to screening and as long as it is not used for a mood disorder, such as bipolar disorder.
Antidepressants (refer to Appendix 11.2) for the FDA approved antidepressants allowed in this study		Only **1** of the predefined oral antidepressant treatment options is permitted. Note: a second antidepressant or an augmentation therapy at screening, must be discontinued at least 5 half-lives prior to baseline per the investigator's decision.
Antidiabetic medication(s) (e.g., metformin and sulfonylureas) except insulin		Allowed, if on a stable regimen for at least 3 months prior to screening.
Antihypertensive medication(s) (ACE inhibitors, beta-blockers, angiotensin receptor blockers, and calcium channel blockers [alone or in combination with diuretics])		Allowed, if on a stable regimen for at least 2 weeks before screening.

Drug Class/Medications	PRN Use	Comments
Antimigraine medication(s) unless used for mood disorders (including bipolar disorder) and combinations: NSAIDs, antihistamines, antiemetics, corticosteroids muscle relaxants, and beta-blockers		Allowed, if used for migraine prevention and on a stable regimen for at least 3 months before screening. Antimigraine medications for bipolar disorders are excluded. Rescue or prn use is not allowed.
Anti-convulsant medication(s) unless used for mood disorders (including bipolar disorder)		Allowed, if used for migraine prevention and on a stable regimen for at least 3 months before screening. Rescue or prn use is not allowed.
Aspirin (81mg) for cardiovascular protection		
Bisphosphonates (e.g., alendronate)		
Benzodiazepines for insomnia: • 2 mg/day lorazepam • 0.5 mg/day clonazepam • 30 mg/day flurazepam	Yes	Allowed, if on a stable regimen 4 weeks before screening. Benzodiazepines should be taken more than 12 hours prior to any clinic visits. Newly prescribed benzodiazepines and/or an increment of the existing dose are prohibited during the study.
Cholesterol-lowering agents (e.g., statins, gemfibrozil)		Allowed, if on a stable regimen for at least 3 months prior to screening.
Corticosteroids (oral, IV or IM, inhaled, intranasal, topical, and ophthalmic steroids)	Yes	Inhalers for asthma are allowed if the subject has stable asthma control and no changes for the last 6 months prior to screening. Intermittent IM/IV corticosteroids are allowed.
Cough/cold remedies (i.e., acetaminophen and ibuprofen)	Yes	Intranasal decongestants are allowed.
Antihistamines (e.g., Loratadine, Cetirizine)	Yes	Allowed for seasonal allergies.
Diphenhydramine	Yes	Allowed if taken more than 12 hours prior to any clinic visit.
Diuretics		Allowed, if on a stable regimen for at least 2 weeks before screening.

Drug Class/Medications	PRN Use	Comments
EMLA® or other numbing cream for venipuncture	Yes	
Esketamine and off-label ketamine		Allowed for prior esketamine and ketamine responders if used and discontinued more than 6 months prior to screening.
Gabapentin		Allowed, if on a stable regimen for at least 3 months prior to screening. Gabapentin should be taken in the evening.
Medical cannabis prescribed for medical conditions other than depression and seizures		Medical cannabis is allowed if taken on a stable regimen for at least 3 months prior to screening.
Non-benzodiazepine sleep medications: zolpidem, zaleplon, ramelteon, and tasimelteon	Yes	Allowed, if the medication has been taken at the same dose for at least 4 weeks prior to screening. Dose increment is prohibited during the study.
Non-stimulants (atomoxetine, clonidine, and guanfacine)		Allowed only in subjects with an established ADHD diagnosis. Treatment must be confirmed with prescription records.
Nutritional supplements (e.g., multivitamins, fish oil, and melatonin)	Yes	
Over-the-counter NSAIDs	Yes	
Paxlovid		
Psychostimulants (e.g., amphetamine, methylphenidate, and modafinil)		Allowed only in subjects with an established ADHD diagnosis. Treatment must be confirmed with prescription records.
Pregabalin		Allowed, if on a stable regimen for at least 3 months prior to screening. Pregabalin should be taken in the evening.
Proton-pump inhibitors and H2 blockers		Allowed, if on a stable regimen for at least 3 months prior to screening.
Thyroid hormone supplement for treatment of thyroid condition only (not for depression)		Note: during the study, TSH levels will be monitored.

Drug Class/Medications	PRN Use	Comments
Trazodone for insomnia only (≤150 mg/day)	Yes	Allowed, if on the same low dose for at least 3 months prior to screening.

ACE = angiotensin-converting enzyme; ADHD = attention-deficit/hyperactivity disorder; IM = intramuscular; IV = intravascular; NSAID = nonsteroidal anti-inflammatory drug; PRN = pro re nata (as needed); TSH = thyroid-stimulating hormone

11.1.2 Prohibited Concomitant Medications

Drug Class/Medications	Comments
Amantadine	
Anorexiants (e.g., phentermine, phendimetrazine)	
Antibiotics (i.e., cefaclor, ceftizoxime, cephaloridine, and penicillin G). Antivirals (i.e., acyclovir, valacyclovir, ganciclovir, oseltamivir, and carboxylate)	Note: efficacy of these antibiotics will be minimally affected by SM, we recommend using a different class.
Anticholinesterase inhibitors	
Antipsychotics and long-acting injectable	
Anti-Parkinson medications (e.g., apomorphine, L-dopa, carbidopa-levodopa, COMT inhibitors, and MAO-B inhibitors)	
Baclofen	
Barbiturates	
Chloral hydrate, valerian	
Dextromethorphan	
Esketamine and off-label ketamine	Allowed in responders who have taken >6 months prior to screening and discontinued. Use of esketamine and off-label ketamine for treatment of depression <6 months prior to screening is not allowed. Other uses of ketamine should be discussed with the Medical Monitor for approval.
Eszopiclone	
Famotidine	Note: efficacy of famotidine can be minimally affected by SM, we recommend a different class of antiacid.
Furosemide	Note: efficacy of furosemide can be minimally affected by SM, we recommend a different diuretic.

Drug Class/Medications	Comments
Ketanserin	
Insulin	
Lithium, lamotrigine	
Memantine	
Methotrexate	Note: efficacy of methotrexate can be minimally affected by SM, when possible, we recommend using a different class of medication.
Viloxazine	
Opioids, tramadol	
Induced-QTc prolongation medications such as (not limited to): quinidine, disopyramide, chlorpromazine, haloperidol, risperidone, thioridazine, azithromycin, erythromycin, fluoroquinolones, levofloxacin, moxifloxacin, ketoconazole, terfenadine, and astemizole	
Reserpine	
Scopolamine	
St. John's Wort	
Tricyclic antidepressants, atypical antidepressants	Atypical antidepressants, e.g., mirtazapine, maprotiline, nefazodone, etc. Any off-label antidepressant medication use needs to be discussed and confirmed by the Medical Monitor prior to enrollment.
Thyroxine/T3, thyroid hormone prescribed for depression	
Trazodone (>150 mg/day)	Trazodone treatment before screening should be discontinued for a minimum of 5 half-lives before baseline.
Warfarin, anticoagulants medications, coumarins and indandiones, factor Xa inhibitors, heparins, antiplatelets, and direct thrombin inhibitors	

CGRP = calcitonin gene-related peptide; COMT = catechol-O-methyltransferase; IM = intramuscular; MAO-B = monoamine oxidase B; QTc = corrected QT interval; SM = study medication; T3 = triiodothyronine

11.2 Approved Antidepressant Treatment

This list includes all FDA approved antidepressants treatments allowed in the study.

Note: Subjects should be on 1 of the medications listed at a stable, therapeutic dose for at least 6 weeks before screening. If a subject is taking a second antidepressant or augmentation therapy at screening, the investigator should decide if it is medically appropriate to discontinue the second drug before randomization. In that case, the second drug should be discontinued at least 5 half-lives prior to baseline. If not, the subject should be excluded from the study.

Selective Serotonin Reuptake Inhibitors

Drug Name	Commercial Name	Minimally Adequate Dose	Minimal Dose at Optimal Level
Paroxetine	PAXIL, PAXIL CR, PEXEVA	20/25/25 mg/day	60/62.5/75 mg/day
Fluoxetine	PROZAC, SARAFEM, SYMBYAX	20 mg/day	60 mg/day
Sertraline	ZOLOFT	50 mg/day	150 mg/day
Citalopram	CELEXA	20 mg/day	60 mg/day
Escitalopram	LEXAPRO	10 mg/day	30 mg/day
Vortioxetine	BRINTELLIX/ TRINTELLIX	10 mg/day	20 mg/day
Vilazodone	VIIBRYD	40 mg/day	80 mg/day

Serotonin-Norepinephrine Reuptake Inhibitors

Drug Name	Commercial Name	Minimally Adequate Dose	Minimal Dose at Optimal Level
Venlafaxine / Venlafaxine XR	EFFEXOR, EFFEXOR XR	150/75 mg/day	250/225 mg/day
Duloxetine	CYMBALTA	60 mg/day	120 mg/day
Desvenlafaxine	PRISTIQ, KHEDEZIA	50 mg/day	100 mg/day
Levomilnacipran	FETZIMA	40 mg/day	120 mg/day

Other Antidepressants

Drug Name	Commercial Name	Minimally Adequate Dose	Minimal Dose at Optimal Level
Bupropion	WELLBUTRIN	300 mg/day	450 mg/day
Dextromethorphan/ Bupropion	AUVELITY	45/105 mg/day	90/110 mg/day

12 SUMMARY OF AMENDMENT CHANGES

Document History	
Document	**Date**
Version 3.0	14FEB2024
Version 2.0	01DEC2023
Version 1.0	09OCT2023

Amendment 3.0 (14 February 2024)

Supersedes previous version; date	Version 2.0; 01DEC2023
Current version; date	Version 3.0; 14FEB2024

Substantial changes to the protocol and their location within the protocol are summarized below. In addition, corrections of typographical errors that have been made throughout the protocol are not explained here.

Primary Reason for the Substantial Modification of the Protocol:

Revised select Inclusion Criteria to align with current clinical and regulatory definitions or guidance.

Summary of Changes

Section # Section Title	Description of Changes in Protocol Version Amendment Version 3.0; 14 February 2024	Brief Rationale for Change
Inclusion Criterion 8, Synopsis and Section 4.2.2; Global	Revised inclusion criterion #8 to include subjects that have received a stable dose of study-approved antidepressant for at least 6 weeks instead of 4.	To align with current clinical and regulatory definitions for adequate duration of treatment.
Exclusion Criterion 12, Synopsis and Section 4.2.2	Revised exclusion criterion #12 to update accepted timeframes for type 5 suicidal ideations based on C-SSRS and history of suicide attempt.	To better align with understanding of targeted study population
Inclusion Criterion 10 and 11, Synopsis and Section 4.2.2	Revised inclusion criterion #10 to remove sexual abstinence as an acceptable form of contraception in both sexes.	To align with current regulatory guidance for contraception in clinical studies.
Sections 4.1, 4.3, 6.3	Revised definition of study completers to include follow-up phone call on Day 12 (±2).	Administrative clarification.
Section 7.4.1; Table 3: Clinical Laboratory Tests	Revised "Other" clinical laboratory tests to specify that "free" triiodothyronine (T3) and "free" thyroxine (T4) testing will be conducted.	Administrative clarification: T3 and T4 testing will not include bound T3 and T4 testing.
Section 11.1	Revised permitted and prohibited concomitant medication lists; removal of antiseizure medications as permitted medication.	Exclusion criterion #15 excludes subjects with history of seizure disorder.

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