PROTOCOL TITLE	A Randomized, Double-Blind, Placebo-Controlled, Proof-of-Concept Study to Evaluate the Efficacy and Safety of Once-Weekly Oral NBI-1065846 in the Treatment of Anhedonia in Major Depressive Disorder (TERPSIS STUDY)
Protocol Identifier:	NBI-1065846-MDD2020
Phase:	Phase 2
Sponsor:	Neurocrine Biosciences, Inc. 12780 El Camino Real San Diego, CA 92130 United States
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Protocol Amendment	3.0 – 21 March 2023

PROTOCOL AMENDMENTS

Protocol/Amendments	Date
Original Protocol	09 August 2021
Amendment 1.0	01 July 2022
Amendment 2.0	18 November 2022
Amendment 3.0	21 March 2023

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Ab	Antibody
AE	Adverse event
AIDS	Acquired Immune Deficiency Syndrome
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
BA	Behavioral activation
β-hCG	β-human chorionic gonadotropin
BMI	Body mass index
CBT	Cognitive behavioral therapy
CFR	Code of Federal Regulations
[redacted]	[redacted]
CGI-S	Clinical Global Impression – Severity Scale
CK	Creatine kinase
CMH	Cochran-Mantel-Haenszel
CRO	Contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	Cytochrome
DARS	Dimensional Anhedonia Rating Scale
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
DSPV	Drug Safety and Pharmacovigilance
ECG	Electrocardiogram
eCRF	Electronic case report form
ECT	Electroconvulsive therapy
EDC	Electronic data capture
EDTA K_2	Dipotassium ethylenediaminetetraacetic acid
ET	Early termination
FDA	Food and Drug Administration
FIH	First in human
FSH	Follicle-stimulating hormone
F/U	Follow-up
GCP	Good Clinical Practice

GGT	Gamma-glutamyl transferase
GPR139	G-protein-coupled receptor 139
HAM-D17	Hamilton Depression Rating Scale-17 Item
HDPE	High density polyethylene
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th Revision
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IWRS	Interactive web response system
MADRS	Montgomery Åsberg Depression Rating Scale
MAOI	Monoamine oxidase inhibitor
MAR	Missing-at-random
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDD	Major depression disorder
MedDRA	Medical Dictionary for Regulatory Activities
MGH-ATRQ	Massachusetts General Hospital - Antidepressant Treatment Response Questionnaire
MGH-CTNI	Massachusetts General Hospital Clinical Trials Network and Institute
MINI	Mini-International Neuropsychiatric Interview
MMRM	Mixed effects repeated measures
MPV	Mean platelet volume
MRI	Magnetic resonance imaging
NBI	Neurocrine Biosciences, Inc.
NOAEL	No observed adverse effect level
PCRS	Placebo-Control Reminder Script
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]	[redacted]
PK	Pharmacokinetic(s)
[redacted]	[redacted]
PT	Prothrombin time
QTcF	QT interval corrected for heart rate using Fridericia's correction
RBC	Red blood cell count
RDW	Red cell distribution width
SAE	Serious adverse event
SAFER	State versus Trait, Assessability, Face Validity, Ecological Validity, Rule of Three P's
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SHAPS	Snaith-Hamilton Pleasure Scale
TBILI	Total bilirubin
TCA	Tricyclic antidepressant
TEAE	Treatment-emergent adverse event
[redacted]	[redacted]
TMS	Transcranial magnetic stimulation
uCMS	Unpredictable chronic mild stress
UDS	Urine drug screen
ULN	Upper limit of normal
US	United States
WBC	White blood cell

1. SYNOPSIS

Title of study: A Randomized, Double-Blind, Placebo-Controlled, Proof-of-Concept Study to Evaluate the Efficacy and Safety of Once-Weekly Oral NBI-1065846 in the Treatment of Anhedonia in Major Depressive Disorder (TERPSIS STUDY)

Protocol number: NBI-1065846-MDD2020

Phase of development: 2

Study centers: Approximately 20 study centers in the United States

Objectives

Primary:

- To evaluate the efficacy of NBI-1065846 compared with placebo on improving symptoms of anhedonia in subjects with major depressive disorder (MDD).

Secondary:

- To evaluate the efficacy of NBI-1065846 compared with placebo on symptoms of depression in subjects with MDD.
- To evaluate the safety, tolerability, and pharmacokinetics of NBI-1065846 in subjects with MDD.

Study design:

This is a Phase 2, randomized, double-blind, parallel-group, proof-of-concept study comparing use of NBI-1065846 with placebo for improvement of anhedonia in patients with MDD. The study consists of a Screening Period of up to 28 days (Days -28 to -1), an 8-week Treatment Period (Days 1 to 57), and an 8-week Safety Follow-up Period (with visits at 4 and 8 weeks [Days 78 and 106] after last dose of study treatment).

Approximately 88 subjects are planned to be enrolled in the study. Eligible subjects include patients with MDD who have been treated with antidepressant medication(s) and who continue to have anhedonia (Snaith-Hamilton Pleasure Scale [SHAPS] ≥30). Subjects currently receiving antidepressant medication(s) must be receiving them for ≥8 weeks prior to screening at or above the therapeutic dose based on the Massachusetts General Hospital - Antidepressant Treatment Response Questionnaire (MGH-ATRQ). Subjects not currently receiving pharmacological treatment for depression must have received ≥1 antidepressant medication(s) at a therapeutic dose per MGH-ATRQ for ≥8 weeks in the current or most recent episode of depression. To ensure adequate representation of subjects across ranges of depression severity, the Sponsor may add limits to prevent further enrollment in specific subgroups based on Hamilton Depression Rating Scale-17 Item (HAM-D17) scores at baseline.

Study treatment will be administered as monotherapy or as adjunctive treatment to the subject's current oral antidepressant medication(s); subjects receiving antidepressant medication(s) at screening are expected to continue using them at the same dose throughout the study.

Subjects will be randomized in a 1:1 ratio in a double-blinded fashion to receive either NBI-1065846 or placebo, administered on a weekly basis, for a period of 8 weeks. The randomization will be stratified based on the HAM-D17 score at baseline: remission (HAM-D17 ≤7), mild illness (HAM-D17 from 8 to 18), and moderate to severe illness (HAM-D17 ≥19).

The data generated in this study will be used to support a separate effort to evaluate the psychometric properties of the Dimensional Anhedonia Rating Scale (DARS), included as the primary efficacy assessment in this study. Additionally, at the final study visit (Day 57 or Early Termination [ET] Visit), 20 subjects, regardless of whether they complete the study, will participate in exit interviews with the

objective of understanding perceptions of meaningful change and treatment experience. The psychometric analysis plan and results from the exit interviews will be reported separately.

The end-of-study will be the date of the last visit of the last subject or last scheduled procedure shown in the schedule of assessments for the last subject in the study.

Study population:

Subjects 18 to 65 years of age (inclusive) with MDD and who have been treated with antidepressant medication(s) but continue to have clinically significant anhedonia.

Duration of study treatment and study participation: The expected duration of treatment for each subject is approximately 8 weeks. Total study participation is approximately 20 weeks, which includes a 4-week Screening Period and an 8-week Safety Follow-Up Period.

Investigational product, dosage, and mode of administration:

NBI-1065846 will be supplied as 40 mg tablets for oral administration. Subjects will be administered a loading dose of 160 mg on Day 1, followed by a once-weekly dose of 80 mg in Weeks 2 to 8.

Reference therapy, dose, and mode of administration:

Placebo tablets identical in appearance to the test product will be administered on an identical schedule as NBI-1065846.

Endpoints

Primary:

- Change in anhedonia severity, as measured by change in DARS score from baseline to Day 57.

Secondary:

- Change in total Montgomery Åsberg Depression Rating Scale (MADRS) score from baseline to Day 57 in subjects with moderate or higher severity depression.
- Change in Clinical Global Impression – Severity (CGI-S) score from baseline to Day 57.

Other:

- [redacted]

Safety:

- Safety endpoints include the occurrence of treatment-emergent adverse events (TEAEs), observed and changes from baseline in clinical laboratory tests (hematology and clinical chemistry), vital sign measurements (including orthostatic blood pressure and pulse rate), 12-lead electrocardiogram (ECG) parameters, and scores from the Columbia-Suicide Severity Rating Scale (C-SSRS).

Statistical methods:

Efficacy analysis:

The primary endpoint will be analyzed using an analysis of covariance (ANCOVA) model with the outcome being the change in DARS score from baseline to Day 57. The model will include treatment group, illness severity (stratification factor), use of concomitant antidepressant medication(s) at time of randomization ([ie, yes vs no], covariate), and baseline DARS score (covariate).

Continuous secondary efficacy endpoints will be analyzed using a similar ANCOVA model as described for the primary endpoint; categorical and ordinal secondary endpoints will be analyzed using the Cochran-Mantel-Haenszel Chi-square test. Psychometric properties of the DARS will be assessed and reported separately.

2. INTRODUCTION

2.1. Background

Anhedonia, defined as the loss of interest in the usually pleasurable activities, is a characteristic of depression and several other neuropsychiatric disorders. The original definition of anhedonia as the loss of capacity to experience pleasure applies in particular to major depression disorder (MDD), in which anhedonia is recognized as a core feature of the disorder (Hasler et al., 2004). Clinically, in addition to being associated with greater depression severity, greater social impairment, worse quality of life (Buckner et al., 2008; Yee et al., 2015), and higher risk of suicide (Fawcett et al., 1990), anhedonia is also predictive of poor clinical outcome (Uher et al, 2012; Vrieze et al., 2013), including in adolescents (McMakin et al., 2012). Moreover, anhedonia reportedly does not respond well to serotonergic antidepressants (Shelton and Tomarken, 2001; Nutt et al., 2007). Thus, MDD with anhedonia represents an important unmet therapeutic need. Recent advances in affective neuroscience have revealed an association of anhedonia with deficits in the appetitive reward system, specifically the anticipation, consumption, and learning of reward, and it has been hypothesized that a differential deficit in the components of pleasure could have important implications for therapy development (Edwards et al., 2015; Favrod et al., 2015).

NBI-1065846 is a selective and potent agonist of the orphan G-protein-coupled receptor 139 (GPR139) being developed for the treatment of symptoms of anhedonia in subjects with MDD. GPR139 has its highest levels of expression in the medial habenula, a subdivision of a brain nucleus controlling dopaminergic and serotonergic effector systems, which modulate reward, emotion, and cognition (Boulos et al., 2017).

NBI-1065846, single-dose and repeat-dose, showed in vivo efficacy to reverse anhedonia caused by 4 weeks of unpredictable chronic mild stress (uCMS) in rats. The sweet drive test and sucrose consumption test were used as measures of anhedonic behavior in this rat model. NBI-1065846 also reversed anxiety-related behavior in the novelty suppressed feeding test and depressive state-related behavior in the forced swim test in the uCMS rat model. Chronic dosing of NBI-1065846 for up to 20 days in the uCMS model did not result in diminished efficacy, indicating a low risk of tachyphylaxis or tolerance to its effects.

Functional MRI was used in combination with the monetary incentive delay task in patients with schizophrenia to assess the effects of NBI-1065846 on activity in the ventral striatum, a brain region closely related to anhedonia. Relative to healthy controls, decreased ventral striatal activity during reward anticipation, which is associated with anhedonia, is observed in schizophrenia and MDD. NBI-1065846 increased ventral striatal activation in schizophrenic patients during reward anticipation, demonstrating that NBI-1065846 modulates key neurocircuitry that underlies anhedonia, and shifts activity in the normative direction. These data support further clinical development of NBI-1065846 for the treatment of anhedonia in MDD.

NBI-1065846 was safe and well-tolerated across the dose ranges studied in clinical trials to date (5 to 160 mg in single- and multiple-ascending doses) in healthy subjects and subjects with schizophrenia.

This Phase 2 study is being conducted to evaluate the efficacy and safety of NBI-1065846 compared with placebo (used as monotherapy or as adjunctive treatment to oral antidepressant medication[s]) in the treatment of symptoms of anhedonia in subjects with MDD.

2.2. Benefit/Risk Assessment for NBI-1065846

NBI-1065846 is a potential first-in-class drug; therefore, there are no known class effects. The GPR139 receptor is present in other species, including rats, dogs, and monkeys (NHRPR.org). Cholestatic liver injury was species-specific and observed in the 13-week no observed adverse effect level (NOAEL) toxicity study in dogs, but not in rats or monkeys. The NOAEL was 30 mg/kg/day for both male and female dogs and attributed to hepatic cholestasis and renal tubule degeneration considered secondary to hepatic changes at 60 mg/kg/day, including elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), bile acids, blood urea nitrogen, creatinine, gamma-glutamyl transferase (GGT), phosphorus, and total bilirubin (TBILI). These findings were monitorable and partially reversible. In this study, monitoring for hepatobiliary injury includes elevation of liver enzymes (eg, ALT, AST, alkaline phosphatase [ALP], GGT, 5'-nucleotidase, and TBILI), physical examinations, and monitoring of treatment-emergent adverse events (TEAEs). Additional assessments may be completed as clinically indicated.

In clinical studies, including the first in human (FIH) Study TAK-041-1001 and Study TAK-041-1002, there were no reported deaths, serious adverse events (SAEs), adverse events (AEs) leading to study treatment or study visit discontinuations, other significant AEs, clinically meaningful safety laboratory results (including ALP, ALT, AST, GGT, 5'-nucleotidase, TBILI), clinically significant physical examination results, vital signs, and/or electrocardiogram (ECG) results.

Although suicidality was not reported in subjects administered NBI-1065846 in the clinical development program, subjects at an imminent risk of suicide per the Columbia-Suicide Severity Rating Scale (C-SSRS) or according to the investigator's clinical judgment will be excluded from this study. Subjects will be assessed for any signs of suicidal ideation or behaviors, and appropriate psychiatric interventions or other precautions will be instituted, if warranted.

Additional information about the benefits and risks of NBI-1065846 is provided in the Investigator's Brochure.

3. OBJECTIVES

3.1. Primary

The primary objective for this study is:

- To evaluate the efficacy of NBI-1065846 compared with placebo on improving symptoms of anhedonia in subjects with MDD.

3.2. Secondary

The secondary objectives for this study are the following:

- To evaluate the efficacy of NBI-1065846 compared with placebo on symptoms of depression in subjects with MDD.
- To evaluate the safety, tolerability, and pharmacokinetics (PK) of NBI-1065846 in subjects with MDD.

4. STUDY DESIGN

4.1. Overall Study Design

This is a Phase 2, randomized, double-blind, parallel-group, proof-of-concept study comparing use of NBI-1065846 with placebo for improvement of anhedonia in patients with MDD.

The study consists of a Screening Period of up to 28 days (Days -28 to -1), an 8-week Treatment Period (Days 1 to 57), and an 8-week Safety Follow-up Period (with visits at 4 and 8 weeks [Days 78 and 106] after last dose of study treatment).

Approximately 88 subjects are planned to be enrolled in the study. Eligible subjects include patients with MDD who have been treated with antidepressant medication(s) and who continue to have anhedonia (Snaith-Hamilton Pleasure Scale [SHAPS] ≥30 [Krystal et al., 2020; Trostheim et al., 2020]). Subjects currently receiving antidepressant medication(s) must be receiving them for ≥8 weeks prior to screening at or above the therapeutic dose based on the Massachusetts General Hospital - Antidepressant Treatment Response Questionnaire (MGH-ATRQ). Subjects not currently receiving pharmacological treatment for depression must have received ≥1 antidepressant medication(s) at a therapeutic dose per MGH-ATRQ for ≥8 weeks in the current or most recent episode of depression. To ensure adequate representation of subjects across ranges of depression severity, the Sponsor may add limits to prevent further enrollment in specific subgroups based on Hamilton Depression Rating Scale-17 Item (HAM-D17) scores at baseline.

Study treatment will be administered as monotherapy or as an adjunctive treatment to the subject's current oral antidepressant medication(s); subjects receiving antidepressant medication(s) at screening are expected to continue using them at the same dose throughout the study.

Subjects will be randomized in a 1:1 ratio in a double-blinded fashion to receive either NBI-1065846 or placebo, administered on a weekly basis, for a period of 8 weeks. The randomization will be stratified based on the Hamilton Depression Rating Scale-17 Item (HAM-D17) score at baseline: remission (HAM-D17 ≤7), mild illness (HAM-D17 from 8 to 18), and moderate to severe illness (HAM-D17 ≥19) (Zimmerman et al., 2013).

The end-of-study will be the last scheduled visit assessments of the last subject or last scheduled procedure shown in the schedule of assessments (Table 8) for the last subject in the study.

After providing informed consent, subjects will be screened for eligibility within 28 days prior to Day 1 (first day of dosing). Subjects may be rescreened once based on the clinical judgment of the investigator in collaboration with the sponsor or designee. The screening period may be extended by up to 14 days in extenuating circumstances in consultation with the Sponsor or designee.

Eligible subjects will return to the study site on Day 1 for baseline assessments. Randomized subjects will receive a loading dose of 160 mg (consisting of four 40 mg tablets) in the clinic on Day 1 and subsequently 80 mg (consisting of two 40 mg tablets) once weekly (Weeks 2 to 8) thereafter or matching placebo. Subjects will also receive their second (Day 8), and fifth (Day 29) doses of study treatment at the study site in order to obtain ECG and PK pre- and post-dose assessments. Subjects will be instructed to take study treatment orally on the same day

each week (with or without food) and will be released from the study site after completion of all study assessments with sufficient study treatment supply between study visits. Compliance with study treatment will be assessed throughout the study. Subjects will have onsite and virtual study visits during the Treatment Period and complete study assessments as shown in the schedule of assessments (Table 8).

Subjects who discontinue study treatment should not be automatically withdrawn from the study prior to completion of Day 57 assessments, regardless of study treatment compliance, unless consent for study participation has been withdrawn (Section 8.1).

Subjects who withdraw from the study early will be asked to return to the study site for an Early Termination (ET) Visit and, unless consent has been withdrawn, will be asked to come back approximately 4 and 8 weeks after their last study treatment for Safety Follow-Up visits.

The data generated in this study will be used to support a separate effort to evaluate the psychometric properties of the Dimensional Anhedonia Rating Scale (DARS), which is the primary efficacy assessment in this study. The psychometric analysis plan and results will be reported separately. Additionally, at the final study visit (Day 57 or ET Visit), 20 subjects, regardless of whether they complete the study, will participate in exit interviews with the objective of understanding perceptions of meaningful change and treatment experience. The protocol, interview guide, and results from the exit interview study will be reported separately.

A schematic of the study design is shown in Figure 1.

4.2. Rationale for Dose Selection

The dose regimen planned for this study is a single loading dose of NBI-1065846 160 mg on Day 1, followed by once-weekly doses of 80 mg from Week 2 through Week 8. In the FIH study in healthy subjects (Study TAK-041-1001), NBI-1065846 was found to be safe and well-tolerated at single doses of up to 160 mg and in the multiple dose cohorts consisting of 4 weekly doses, 1 loading dose ranging from 40 to 160 mg followed by weekly maintenance doses ranging from 20 to 80 mg for 3 weeks. No SAEs, no clinically meaningful abnormalities in safety laboratory results (including ALP, AST, ALT, GGT, 5'-nucleotidase, and TBILI), and no clinically significant abnormalities in physical examination, vital signs, or ECG results were reported from Study TAK-041-1001. In another study in subjects with stable schizophrenia (Study TAK-041-2001), subjects received 40 or 160 mg doses of NBI-1065846 and demonstrated an increase in ventral striatal activation at both dose levels on Day 14 following a single dose administration.

Overall, the proposed dose regimen for this study is anticipated to achieve exposures that are expected to show pharmacodynamic activity while not exceeding doses demonstrated to be safe and well-tolerated in prior clinical studies.

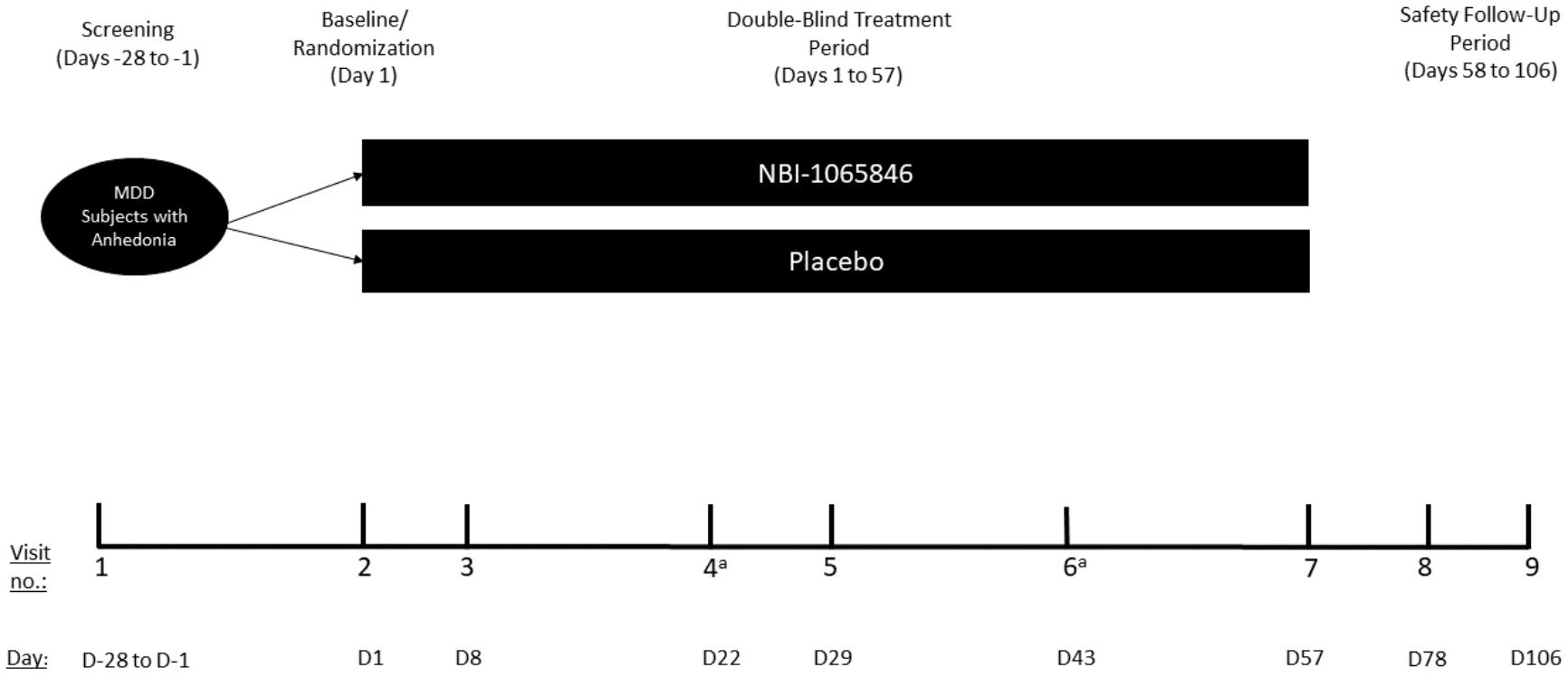
4.3. End of Study Definition

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data used for the primary endpoint, whether the study concluded as planned or was terminated early. The planned primary completion date for this study is the date when the last subject has completed the assessments for

Day 57. If the study is terminated early, then the primary completion date will be the date of the last visit for the last subject in the study.

End of Study: The end of study is defined as the date of the last visit of the last subject or last scheduled procedure shown in the schedule of assessments (Table 8) for the last subject in the study.

Figure 1: Study Design Schematic



D=Day; MDD=major depressive disorder; no.=number
[a] These are virtual visits.

5. STUDY POPULATION

Subjects must fulfill all inclusion and exclusion criteria to participate in the study.

5.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria:

1. Completed written informed consent.
2. Aged 18 to 65 years, inclusive, at the time of informed consent.
3. The subject has a primary diagnosis of recurrent MDD (mild to severe, or in partial remission), persistent depressive disorder, or single episode MDD in remission meeting the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) and International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) criteria codes 296.31 (F33.0), 296.3 (F33.40), 296.26 (F33.42), 296.32 (F33.1), 296.35 (F33.41), 300.4 (F34.1). The diagnosis must be confirmed using the Mini-International Neuropsychiatric Interview (MINI) in a face-to-face evaluation. If the current episode of MDD is in remission, Criteria A1a and A2a on the MINI must be a "YES" and must meet criteria for MDD = Past.
4. Subjects must meet one of the following criteria:

   - Subjects currently receiving pharmacological treatment for depression must have been taking ≥1 of the oral antidepressant medication(s) at or above the therapeutic dose per MGH-ATRQ (with the exception of the antidepressant medications excluded in Table 2) for ≥8 weeks prior to screening as confirmed by records/documentation (eg, medical, prescription, or pharmacy records; or a letter from a treating physician). Subjects must be willing and able to continue with current antidepressant medication(s) with no dose changes. All antidepressant medications for the previous 2 months prior to baseline must be confirmed by records/documentation (as defined above) and be documented on the concomitant therapies electronic case report form (eCRF).
   - Subjects not currently receiving pharmacological treatment for depression must have received ≥1 antidepressant medication(s) at a therapeutic dose per MGH-ATRQ for ≥8 weeks in the current or most recent episode of depression as confirmed by records/documentation (eg, medical, prescription, or pharmacy records; or a letter from a treating physician). Alternatively, this criterion may be satisfied based on the investigator's assessment and with approval from the study Medical Monitor (or designee).

   Subjects receiving psychotherapy (including cognitive behavioral therapy [CBT]) or behavioral activation (BA) can continue receiving psychotherapy; however, CBT or BA must have been ongoing for the last 3 months prior to the start of the screening. No new therapy of any kind, including transcranial magnetic stimulation (TMS) or electroconvulsive therapy (ECT), is allowed to initiate during this study.

5. SHAPS score is ≥30 at screening and Day 1. The anhedonia should be associated with the subject's current or most recent episode of depression based on investigator assessment.
6. The subject's current or most recent major depressive episode, depression symptom severity, and, if the subject is taking pharmacological treatment for depression, antidepressant treatment response in the current depressive episode must be confirmed by the "State versus Trait, Assessability, Face Validity, Ecological Validity, Rule of Three P's" (SAFER) Interview and final agreement with the Sponsor or Sponsor designee.
7. The subject is judged by the investigator to be in good health or have stable medical conditions, based on clinical evaluations, including laboratory safety tests (Screening Visit only), medical history, physical examination, 12-lead ECG, and vital sign measurements performed at the Screening Visit and Baseline (Day 1).
8. A body mass index (BMI) of 17 to 39 kg/m^2, inclusive (BMI is defined as the subject's weight in kilograms divided by the square of the subject's height in meters).
9. Negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test at screening and urine pregnancy test at Day 1, for females of childbearing potential. If a female of childbearing potential has an indeterminant β-hCG pregnancy test result, the test should be repeated during the screening period and the subject discussed with the medical monitor.
10. Female subjects of childbearing potential must agree to use an acceptable method of contraception listed below consistently from screening until 55 days after the last dose of study treatment. Women are considered to not be of childbearing potential if they are either:

    - Postmenopausal, defined as no menses for 12 months without an alternative medical cause and confirmed by elevated follicle-stimulating hormone (FSH) consistent with a postmenopausal range, OR
    - Permanent sterilization procedure, such as hysterectomy, bilateral salpingectomy, or bilateral oophorectomy.

    Acceptable methods of contraception are required for women of childbearing potential and include the following:

    - Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS).
    - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (which may be oral, intravaginal, or transdermal) beginning at least 3 months prior to screening and must be used in combination with a barrier method of contraception (preferably male condom). Use of combined hormonal contraception alone is not considered an acceptable method as NBI-1065846 may decrease the efficacy of hormonal contraceptives due to a potential drug interaction.
    - Progestogen-only hormonal contraception associated with inhibition of ovulation (which may be oral, injected, or implanted) beginning at least 3 months prior to screening and must be used in combination with a barrier method of contraception

(preferably male condom). Use of progestogen-only hormonal contraception alone is not considered an acceptable method as NBI-1065846 may decrease the efficacy of hormonal contraceptives due to a potential drug interaction.

- Bilateral tubal ligation.
- Total abstinence from sexual intercourse (periodic abstinence is not acceptable). Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment.
- Sexual partner(s) who has been vasectomized at least 3 months prior to screening with medically confirmed successful procedure.
- Male or female condom with or without spermicide.
- Cap, diaphragm, or sponge with spermicide.

Male subjects are not required to use barrier contraception in this study.

11. Willing and able to comply with all study procedures and restrictions.

5.2. Exclusion Criteria

Subjects will be excluded from the study if they meet any of the following criteria:

1. Pregnant or breastfeeding or plan to become pregnant during the study.
2. Other than MDD (primary focus of treatment), having a current psychiatric disorder, such as personality disorder, schizophrenia, schizoaffective disorder, other psychotic disorder, bipolar disorder, eating disorder, dementia, fibromyalgia, intellectual disability, or mental disorder due to a general medical condition, as defined by DSM-5, or has been treated with ECT within 6 months prior to screening. Comorbid anxiety disorders are not exclusionary.

3. With the exception of caffeine dependence and mild to moderate nicotine dependence, have a positive urine drug screen (UDS) at screening or Day 1 for disallowed substances, including barbiturates, phencyclidine, cocaine, amphetamines, or a history of illicit drug or alcohol abuse within 1 year prior to screening judged by the investigator to be excessive or compulsive, or currently using drugs of abuse or any prescribed or over the-counter medication in a manner that the investigator considers indicative of abuse or dependence.

   Note: Subjects testing positive for cannabinoids at screening may be eligible for participation in the study if all of the following criteria are met:

   - The subject does not meet the diagnostic criteria for moderate or severe substance use disorder within the 6 months before screening based on the MINI
   - Based on the investigator's clinical assessment, the subject's marijuana use is limited to ≤3 times per week and is not expected to interfere with their ability to adhere to study procedures
   - Marijuana is legal per local law

4. Have a significant risk of suicidal or violent behavior. Subjects with any 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) or any suicidal behavior in the past 12 months before screening based on the C-SSRS or according to the investigator's clinical judgment should be excluded.
5. A history of seizure disorder, stroke, Alzheimer disease, Parkinson disease, multiple sclerosis, head injury associated with loss of consciousness for more than 15 minutes, or other neurodegenerative disorder.
6. Have a known or suspected diagnosis of Acquired Immune Deficiency Syndrome (AIDS).
7. Other clinically significant laboratory or vital sign abnormalities that are not attributed to a stable, well-controlled medical condition.
8. A clinically significant ECG abnormality confirmed by central rater at screening or prior to randomization confirmed by the site investigator.
9. An unstable medical condition or chronic disease (including history of neurological [including cognitive impairment, myasthenia gravis], hepatic, renal, cardiovascular, gastrointestinal, pulmonary, autoimmune, or endocrine disease that may affect study participation or results) within 3 months before Day 1, or malignancy within 6 months before Day 1, or any history of gallstones, endoscopic retrograde cholangio pancreatography or cholestasis.
10. QT interval corrected for heart rate using Fridericia's correction (QTcF) >450 msec (males) or >470 msec (females) either at screening (per central rater) or Day 1 (per investigator), confirmed with 1 repeat test; or the subject has long QT syndrome or is under the treatment with Class 1A (eg, quinidine, procainamide) or Class 3 (eg, amiodarone, sotalol) antiarrhythmic drugs.

11. Evidence of chronic renal or liver disease based on any of these screening laboratory test abnormalities:
    - Serum creatinine >1.5×upper limit of normal (ULN) for males and >1.2×ULN for females.
    - AST >2×ULN.
    - ALT >2×ULN.
    - ALP >1.5×ULN.
    - GGT >2×ULN.
    - TBILI >1.5×ULN unless due to a documented diagnosis of Gilbert syndrome.
12. Have any of the following laboratory abnormalities at screening:
    - Prothrombin time (PT) expressed as international normalized ratio (INR) >1.3, unless the subject is on anticoagulant treatment that affects INR.
    - Hemoglobin <10 g/dL.
    - White blood cell (WBC) count $<3.0 \times 10^3/mm^3$.
    - Platelet count $<100,000/mm^3$.
    - Absolute neutrophil count $<1.0 \times 10^3/mm^3$.
13. Are currently taking any of the prohibited medications listed in Section 7.1 Table 2. Subjects who have received these medications in the past must have been off them for at least 30 days prior to Day 1.
14. Have ingested grapefruit juice, grapefruit products, Seville oranges, or Seville orange products within 7 days before Day 1.
15. Used any active investigational drug in the context of a clinical study within 3 months before baseline or plans to use such an investigational drug (other than the study treatment) during the study.
16. Blood loss ≥550 mL within 8 weeks before Day 1.
17. Has previously participated in this study, has participated in more than 2 investigational drug studies in the previous 12 months, is currently participating in another clinical study per subject registry database query, or has participated in a clinical study for a psychiatric condition that is exclusionary per this protocol. This criterion does not pertain to participation in an investigational vaccine clinical study, which is allowed if completed more than 30 days before screening. This criterion must be reconfirmed prior to the first dose of study treatment on Day 1.
18. In the investigator's opinion, the subject is not capable of adhering to the protocol requirements, or has a history of poor or suspected poor compliance in clinical research studies, or the subject has a history of poor or suspected poor compliance to antidepressant medication.

6. STUDY TREATMENT

6.1. General Information

Study treatments are summarized in Table 1.

Table 1: Study Treatments

Treatment Group	Active (NBI-1065846)	Placebo
Treatment administration	NBI-1065846 will be administered orally once weekly, at a loading dose of 160 mg on Day 1 followed by a once weekly 80 mg dose on Weeks 2 to 8.	Placebo tablets identical in appearance to the active product will be administered in the same manner and on an identical schedule as NBI-1065846
Unit dose strength	40 mg per tablet	Not applicable
Dose formulation	Tablet	Tablet
Route of administration	Oral	Oral
Sourcing	Provided centrally by Sponsor	Provided centrally by Sponsor
Packaging and labeling	Provided in HDPE bottles labeled in accordance with applicable regulatory requirements.	Provided in HDPE bottles labeled in accordance with applicable regulatory requirements.

HDPE=high density polyethylene

6.2. Study Treatment Administration

Study treatment will be administered orally once weekly (every 7 days ± 2 days), with each dose taken at least 5 days apart. Subjects receive a loading dose of 160 mg (consisting of four 40 mg tablets) in the clinic on Day 1 (Week 1) and subsequently 80 mg (consisting of two 40 mg tablets) once weekly (Weeks 2 to 8) thereafter. Subjects will also receive their second (Day 8), and fifth (Day 29) doses of study treatment in the clinic. Subjects will take study treatment at home on Days 15, 22, 36, 43, and 50. Study treatment will be administered with 240 mL of water and may be administered with or without food.

If a subject forgets or is unable to take the study treatment, the dose can be taken ± 2 days from the scheduled weekly dose (with each dose taken at least 5 days apart); otherwise the study treatment should be taken at the next dosing time.

6.3. Study Treatment Compliance

At each onsite or virtual study visit (except the Day 1 visit), the investigator or designee will remind subjects to take their study medication on the next scheduled day as specified in Section 6.2. For weeks with no study visit scheduled, this reminder should occur via telephone. The subject should also be reminded that if they forget or are unable to take the study treatment,

the dose can be taken ± 2 days from the scheduled weekly dose (with each dose taken at least 5 days apart); otherwise the study treatment should be taken at the next dosing time.

A compliance check will be performed by counting the tablets of study treatment returned at each specified study visit; details are provided in Section 6.4. Assessment of study treatment compliance will be determined by the investigator at each visit based on all available information.

6.4. Study Treatment Storage/Compliance

The designated personnel are responsible for maintaining records of the quantity and dates of all study treatment supplies received, dispensed, returned, lost, and destroyed, according to applicable regulations and study procedures. Study treatment should be stored in a locked area accessible only to the designated pharmacist or qualified personnel. A detailed description of how study treatment should be dispensed, stored, and any stability changes will be provided in the Pharmacy Manual.

6.5. Study Treatment Accountability and Return

Subjects will bring all unused study treatment and empty packaging material to the center at specified study visits for study treatment accountability and reconciliation by study center personnel. A compliance check will be performed by counting the tablets returned at each on-site study visit.

The quantity of study treatment dispensed, used, and returned will be recorded on a dispensing log or otherwise documented. The quantity of study treatment lost or destroyed must also be accounted for and documented. The designated pharmacist or qualified personnel will be responsible for maintaining accurate records of the quantity and dates of all study treatment supplies received, dispensed, and returned.

If unused study treatment is not returned to the Sponsor or its designee, alternative disposition of study treatment must be documented and follow local laws and regulations.

6.6. Direct-to-Subject Shipments of Study Treatment

To ensure continued access to study treatment, if a subject is unable to go to the site when study treatment is to be dispensed, study treatment may be delivered to the subject's residence by a distributor independent from the Sponsor. The subject's name, address, and other contact details will not be accessible to the Sponsor, and the distributor will not have access to the subject's health information.

6.7. Blinding

This is a double-blind, placebo-controlled study during which the subject, investigator, all study center personnel, pharmacist, and the Sponsor, with the exception of clinical study material supply chain personnel who are not involved in decisions regarding subject's study treatment, will be blinded to the subject's study treatment assignment (NBI-1065846 or placebo).

The randomization code will be broken for an individual subject only if the subject is pregnant, experiences an SAE that the investigator feels cannot be adequately treated without knowing the subject's study treatment assignment, or for regulatory reporting requirements. In the case of a medical emergency in which knowledge of the identity of the study treatment is important for subject management, the investigator has the responsibility to decide whether to break the blind; study treatment assignments would be unblinded using interactive web response system (IWRS). It is recommended that the investigator contact the Study Medical Monitor (or designee) before unblinding if it would not result in unnecessary delay to the immediate medical management of the subject. The investigator must document the date, time, and the reason the blind was broken.

6.8. Procedures for Overdose

Any dose of study treatment administered in excess of the protocol-specified dose will be considered an overdose.

In the event of a suspected overdose, the investigator and/or treating physician should:

1. Closely monitor the subject for any AE/SAE and laboratory abnormalities and follow the AE reporting process. The Study Medical Monitor should be contacted for AEs related to an overdose.
2. Document the total quantity of the excess dose(s) as well as the date(s) on which additional dose(s) were taken, if this information is available.

Subjects who overdose will be counseled on correct dosing and administration of study treatment, as necessary. Decisions regarding study discontinuation, dose interruptions, or dose modifications will be made by the investigator in consultation with the Study Medical Monitor based on the clinical evaluation of the subject.

7. SUBJECT RESTRICTIONS

7.1. Prior and Concomitant Medications

All prescription and over-the-counter medications, dietary supplements (including vitamins), and herbal supplements taken by the subject within 30 days (6 months for antidepressant therapy) before Day 1 (Visit 2) will be recorded on the Prior and Concomitant Medications page of the eCRF.

No antidepressant medication or dose changes are permitted from Day 1 through Day 57 (or ET visit) unless approved by the Study Medical Monitor (or designee).

The following medications listed in Table 2 are prohibited for all subjects beginning 30 days before Day 1 (Visit 2) until the end of the Study Treatment Period (Day 57 or ET visit). If a subject is prescribed treatment with a prohibited medication during the conduct of the study, the investigator should contact the Sponsor or designee to review the relevant clinical information and medication treatment to determine subject disposition.

Table 2: Prohibited Concomitant Medications

Prohibited Concomitant Medication
Glutamate modulators, eg, esketamine or ketamine, memantine, riluzole
Salvinorin A (Sal A) or salvia divinorum (street names include Maria Pastora, Sally-D, and Salvia)
Other antidepressant medications including tricyclic (eg, clomipramine) or tetracyclic (eg, maprotiline) antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs)
Antipsychotics, including injectable/depot antipsychotics (lifetime)
Stimulants (eg, amphetamines, dextroamphetamine, methylphenidate, methamphetamine, modafinil, armodafinil)
Kappa opioid antagonists (eg, buprenorphine)
Dopamine agonists such as pramipexole
Strong and moderate CYP3A4 inhibitors, including but not limited to, clarithromycin, itraconazole, ketoconazole[a], nefazodone, saquinavir, suboxone, and telithromycin
Strong and moderate CYP3A4 inducers, including but not limited to avasimibe, phenytoin, rifampin, St John's wort, bosentan, efavirenz, etravirine, modafinil, and nafcillin
Antiepileptics
Investigational drugs[b]

CYP=cytochrome P450

[a] Topical ketoconazole is permitted.

[b] Any active investigational drug in the context of a clinical study within the 3 months before baseline or plans to use such an investigational drug (other than the study treatment) during the study.

Benzodiazepines and non-benzodiazepine hypnotics are permitted to be used within specific restricted parameters during the study beginning from screening (Visit 1) until the end of the study treatment period (Day 57 or ET visit) as detailed in Table 3. Restrictions include maximum dosage allowed and the timing of use around assessments, ie, restricted medications should not be administered within 6 hours before any efficacy assessments (SHAPS, DARS, HAM-D17, Montgomery Åsberg Depression Rating Scale [MADRS], Clinical Global Impression – Severity [CGI-S], [redacted] Any usage of restricted medications should be documented, including the date and the time of last dose taken, prior to the visits specified in the table. If the subject has taken any restricted concomitant medications within 6 hours of these scheduled assessments, then the site should reschedule these assessments to the next day (or within 2 to 3 calendar days).

Benzodiazepines must be at a stable dose equal to or less than the equivalent of 6 mg/day of lorazepam for 2 weeks before screening (Visit 1). As needed (prn) use of benzodiazepines is restricted; benzodiazepines should not be administered 6 hours prior to the subject's clinic visit (Table 3).

Table 3: Restricted Concomitant Medications

Medication Class	Dosage Allowed	Timing Restrictions
Benzodiazepines	Maximum of 6 mg/day of lorazepam or equivalent dose of another benzodiazepine for chronic use	Not permitted within 6 hours before any efficacy assessments (SHAPS, DARS, HAM-D17, MADRS, CGI-S, [redacted], and [if applicable] [redacted] performed on any study visit they are administered; refer to the schedule of assessments (see Table 8).
	Maximum of 2 mg/day of lorazepam or equivalent dose of another benzodiazepine for episodic use; up to 3 days per week	
Non-Benzodiazepine Hypnotics	Zolpidem up to 10 mg/day; zaleplon up to 20 mg/day; eszopiclone up to 3 mg/day; zopiclone 7.5 mg/day; or doxepin up to 6 mg/day for sleep	
Narcotic Analgesics	Only episodic use is allowed with Sponsor and/or Study Medical Monitor approval.	

[redacted]; CGI-S=Clinical Global Impression – Severity; DARS=Dimensional Anhedonia Rating Scale; HAM-D17=Hamilton Depression Rating Scale-17 Item; MADRS=Montgomery Åsberg Depression Rating Scale; [redacted] SHAPS=Snaith-Hamilton Pleasure Scale; [redacted]

7.2. Dietary and Other Restrictions

Grapefruit juice, grapefruit products, Seville oranges, and Seville orange products are prohibited from 7 days before Day 1 until the end of the study.

Any positive UDSs for disallowed substances (as specified in exclusion criterion #3) during conduct of the study must be discussed with the Sponsor or designee to determine the subject's disposition.

On the day of study visits, subjects may not use marijuana or alcohol until all assessments have been completed If a subject appears intoxicated at a study visit, efficacy assessments should not be performed that day and the site should reschedule these assessments to the next day (or within the window defined in the Schedule of Assessments (Table 8).

Subjects receiving psychotherapy (including CBT or BA) can continue receiving psychotherapy; however, CBT or BA must have been ongoing for the last 3 months prior to the start of the screening. With the exception of new CBT or BA, which is prohibited, no new psychotherapy is allowed during this study. Furthermore, the use of TMS and/or ECT is also prohibited during this study. Any change in existing therapy or new therapy must be documented on the concomitant therapies form.

8. DISCONTINUATION OF STUDY TREATMENT AND SUBJECT WITHDRAWAL

At any time during the study subjects can discontinue study treatment or withdraw their consent to participate in the study. The investigator must discontinue study treatment or withdraw any subject from the study at their request.

8.1. Discontinuation of Study Treatment

If a subject prematurely discontinues study treatment, the investigator will record the reason for discontinuation on the relevant eCRF. Data for any outcome measures, particularly the primary and secondary endpoints, as well as safety follow-up, are important to collect. Subjects will not be automatically withdrawn from the study and should continue participation in the study, regardless of study treatment compliance, unless consent for study participation has been withdrawn. For any subsequent study visits after study treatment is prematurely discontinued, subjects should have 1 final PK sample collected (ie, subsequent PK samples are not required); however, subjects should continue with study assessments at the study site or with virtual visits.

If medically indicated, treatment with medication listed under Section 7.1 is no longer prohibited after study treatment discontinuation.

Reasons for discontinuation from study treatment include but are not limited to:

- Withdrawal by subject
- Death
- Lost to follow-up

- Site termination by the Sponsor
- Study termination by the Sponsor
- AE
- Pregnancy
- Lack of efficacy
- Protocol deviation
- Investigator decision
- Sponsor decision

The investigator must discontinue study treatment if the subject experiences any of the following:

- If the type, frequency, or severity of any AE becomes unacceptable/intolerable
- If the subject is unable to tolerate the lowest allowable dose (80 mg or placebo)
- QTcF of >500 msec (cardiologist verified) on any ECG tracing
- If the subject is confirmed to be pregnant
- Withdrawal of consent for study treatment administration by subject
- If the subject exhibits 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 or according to the investigator's clinical judgement
- Study treatment should be discontinued with appropriate clinical follow-up (including repeat laboratory tests) until a subject's laboratory profile has returned to normal/baseline status), if any of the following occur (see Appendix D for additional detail):
  - ALT or AST >8×ULN, or
  - ALT or AST >5×ULN and persists for more than 2 weeks, or
  - ALT or AST >3×ULN in conjunction with elevated total bilirubin >2×ULN or INR >1.5
  - ALT or AST >3×ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%)
  - ALP elevations >1.5×ULN in conjunction with elevated TBLI >1.5×ULN, or
  - 5'nucleotidase >2×ULN, or GGT >5×ULN, or AST/ALT >3×ULN.

Every effort should be taken to obtain follow-up data for any subject who discontinues study treatment because of an AE, abnormal laboratory test, vital sign measurement, physical examination, or ECG finding.

8.2. Withdrawal from Study

If a subject prematurely withdraws from the study, the investigator will record the reason for withdrawal on the relevant eCRF. All subjects who withdraw from the study prematurely will be asked to have all ET assessments performed and, unless consent has been withdrawn, will be asked to come back for 2 safety follow-up visits at 4 and 8 weeks after last dose of study treatment. If a subject's last dose of study treatment was >8 weeks before the ET visit, the Safety Follow-Up visits are not needed. If a subject's last dose of study treatment was >3 weeks but <8 weeks before the ET visit, only the Week 16 Safety Follow-Up visit is needed (ie, only one Safety Follow-Up visit approximately 8 weeks after the last dose of study treatment is needed).

Reasons for withdrawal from study include, but are not limited to:

- Withdrawal by the subject
- AE
- Death
- Lost to follow-up
- Site terminated by Sponsor
- Study terminated by Sponsor
- Protocol deviation
- Investigator decision
- Sponsor decision

8.3. Sponsor's Termination or Temporary Halt of Study or Study Site

The Sponsor or designee reserves the right to close a study site, terminate, or temporarily halt the entire study, or terminate or temporarily halt the study at individual sites, at any time for any reason. If the study is prematurely terminated or temporarily halted, the Sponsor shall promptly inform the investigators, the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), the regulatory authorities, and any contract research organizations (CROs) used in the study of the reason for termination or temporary halt, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate therapy and/or follow-up.

9. STUDY ASSESSMENTS AND PROCEDURES

A schedule of assessments is provided in Table 8 (Appendix A). No study procedures should be performed until after the subject has signed the informed consent form (ICF). Subject-related events and activities including specific instructions, procedures, concomitant medications, dispensing of study treatment, and descriptions of AEs should be recorded in the appropriate source documents and eCRFs.

When the following assessments are scheduled to be performed at the same timepoint, the order of priority will be as follows: vital signs, physical and neurological examination, questionnaires, ECG, and blood sampling for safety and PK.

9.1. Screening Assessments and Procedures

9.1.1. Subject Registry Database Review Consent

Clinical study subject registries seek to reduce subjects from enrolling into multiple clinical studies by identifying potential duplicates before enrollment. This study will utilize 1 or more subject registry database(s) at sites where they are available. At the time of providing informed consent for the study, the investigator or designee will explain the subject registry database review process to the subject and witness the signature.

During screening, site staff who have received training and login information to access the registry will enter the subject identification number and authorized subject identifiers on the registry website. An immediate report based on matches to exclusion criterion #17 in Section 5.2 will be generated and should be printed for source documentation. The report will specify either (1) no matches found, (2) a potential match was found to 1 or more specified criteria, and/or (3) the subject matches 1 or more specified criteria. The registry database check should be performed as early as possible at the screening visit to avoid unnecessary procedures.

9.1.2. Mini-International Neuropsychiatric Interview

The MINI is a structured diagnostic interview that was originally developed for DSM-IV and ICD-10 disorders, for multicenter clinical studies and epidemiology studies (Lecrubier et al., 1997; Sheehan et al., 1997; Sheehan et al., 1998). The MINI has been validated against the Structured Clinical Interview for DSM Patients and Composite International Diagnostic Interview for ICD-10. The MINI has been translated and validated in over 70 languages and has been updated to match DSM-5 (MINI 7.0.2).

The MINI may be administered by a healthcare professional with a clinically relevant qualification (eg, psychiatrist, psychiatric nurse or psychologist) and documented experience assessing patients with MDD. Raters must be trained and certified for administration of MINI in this study.

Specific timepoints for collection are provided in Table 8.

9.1.3. Massachusetts General Hospital Antidepressant Treatment Response Questionnaire

The MGH-ATRQ is a clinician-rated scale used to determine treatment resistance in MDD. The MGH-ATRQ defines 8 weeks on an adequate dose of antidepressant medication as an adequate duration of treatment. The MGH-ATRQ has been validated in the ADAPT-A study by independent clinician raters (Chandler et al., 2010).

Specific timepoints for collection are provided in Table 8.

9.1.4. Hamilton Depression Rating Scale-17 Item

The HAM-D17 is administered via a clinician-rated interview with the subject. HAM-D17 ratings must be performed by qualified study personnel who have been trained and certified for the purpose of performing ratings in this study.

The HAM-D17 is a 17-item clinician-rated scale that assesses the range of symptoms that are commonly seen in patients with MDD (Hamilton, 1960). With well-known psychometric properties, it is widely accepted as a standard measure of symptom change in studies of psychopharmacological agents.

Specific timepoints for collection are provided in Table 8.

9.1.5. Snaith-Hamilton Pleasure Scale

The SHAPS (Snaith et al., 1995) is a well-validated 14-item questionnaire used to assess anhedonia. The SHAPS is a self-rated scale that asks participants to agree or disagree with statements of hedonic response in usually pleasurable situations (eg, “I would enjoy my favorite television or radio program”). Four responses are possible: Strongly disagree, Disagree, Agree, or Strongly agree. A total score can be derived by summing the responses to each item. Items answered with “strongly agree” are coded as “1”, while a “strongly disagree” response was assigned a score of “4.” Therefore, scores on the SHAPS can range from 14 to 56, with higher scores corresponding to higher levels of anhedonia. The SHAPS covers four domains of hedonic experience: interest/pastimes, social interaction, sensory experience, and food/drink.

Specific timepoints for collection are provided in Table 8.

9.1.6. SAFER Interview

The subject’s current or most recent major depressive episode, depression symptom severity, and, if the subject is taking pharmacological treatment for depression, antidepressant treatment response in their current depressive episode must be deemed valid for participation in the clinical study based on the SAFER Interview, which is a site-independent qualification assessment. The SAFER Interview for subject eligibility verification will be performed by the Massachusetts General Hospital Clinical Trials Network and Institute (MGH-CTNI). This interview is performed remotely (Freeman et al., 2017; Desseilles et al., 2013).

Specific timepoints for collection are provided in Table 8.

9.2. Efficacy Assessments and Procedures

9.2.1. Placebo-Control Reminder Script

To mitigate expectation bias leading to increased placebo response, the Placebo-Control Reminder Script (PCRS) will be utilized in this study (Cohen et al, 2021). The PCRS is a script which carefully reviews placebo response factors with research subjects with the goal of reducing placebo effect through increased awareness of its impact. A trained rater will read the PCRS script to each subject prior to the administration of efficacy assessments. It is followed by a discussion between the rater and subject about the key points, including understanding of double-blind clinical studies, recognition of the rater's neutral position regarding subject responses, and the importance of providing honest feedback. Specific timepoints for administered are provided in Table 8.

9.2.2. Dimensional Anhedonia Rating Scale

The DARS (Rizvi et al., 2015) is a dynamic scale that measures desire, motivation, effort and consummatory pleasure across hedonic domains. The DARS is a self-report questionnaire that measures anhedonia across 4 domains: hobbies/past-times, food/drinks, social activities, and sensory experiences.

The data generated in this study will be used to support a separate effort to evaluate the psychometric properties of the DARS. Additionally, at the final study visit (Day 57 or ET visit), 20 subjects, regardless of whether they complete the study, will participate in exit interviews with the objective of understanding perceptions of meaningful change and treatment experience (Section 9.2.2.1). The psychometric analysis plan and results from the exit interviews will be reported separately.

Specific timepoints for collection are provided in Table 8.

9.2.2.1. Subject Exit Interview

The purpose of the exit interview is to explore meaningful change in anhedonia in subjects with MDD, as measured by the DARS and related questionnaires. Specific aims of the exit interview include understanding changes in subjects' responses to the DARS, [redacted] and [redacted] and whether the changes/responses were meaningful, and understanding subjects' overall expectations and experience with the clinical study.

At the final study visit, subjects will be asked to participate in an exit interview until 20 subjects have completed the exit interview. The objective of the subject exit interview is to understand perceptions of meaningful change and treatment experience; additional details are provided below. The exit interview enrollment and scheduling process will begin after the subject has completed study treatment at Day 57 (or ET visit in subjects who discontinue study treatment). The exit interview will be conducted within a 14-day window following Day 57 (or ET visit in subjects who discontinue study treatment). The exit interview will be audio recorded by the interviewer and subsequently transcribed, but data will not be collected in the electronic data capture (EDC) system.

The exit interview is not designed to assess the subjects' experience with aspects of the clinical study engagement, such as enrollment, compliance requirements, or interactions with sites. Subjects will need to sign a separate consent to agree to participate in this optional assessment.

9.2.3. Montgomery Åsberg Depression Rating Scale

The MADRS is a validated rating scale designed to measure changes in the severity of depressive symptoms (Montgomery and Åsberg, 1979). The MADRS consists of 10 items scored on a 7-point scale (0 to 6) with increasing number value indicating increasing severity for each item with anchor points provided at 2-point intervals.

Specific timepoints for collection are provided in Table 8.

9.2.4. Clinical Global Impression – Severity Scale

The CGI-S scale, which is based on a 7-point scale (range: 1=normal, not all ill to 7=among the most extremely ill patients), will be used to rate the severity of the subject's illness at the time of assessment, relative to the clinician's past experience with subject's who have the same diagnosis (Guy, 1976).

The investigator or qualified clinician designee will rate the scale at the scheduled times. Every effort should be made to have the same person rate the CGI-S at all timepoints.

Specific timepoints for collection are provided in Table 8.

9.2.5. [redacted]

[redacted]

9.2.6. [redacted]

[redacted]

9.2.7. [redacted]

9.2.8. [redacted]

9.2.9. [redacted]

9.2.10. [redacted]

9.3. Safety Assessments

For any abnormal safety assessment deemed clinically significant, the investigator will perform appropriate follow-up assessments, until the cause of the abnormality is determined and/or until the value returns to baseline (or within normal limits) or the investigator deems the abnormality to be of no clinical significance.

Appropriate psychiatric evaluation and intervention will be provided for any study treatment-emergent suicidal behavior or clinically significant suicidal ideation.

9.3.1. Vital Sign Measurements, Height, and Weight

Vital signs will be measured for the following: orthostatic systolic and diastolic blood pressure, orthostatic pulse rate, respiratory rate, and body temperature.

The same method should be used to take body temperature throughout the study. Body temperature may be measured orally or at the forehead, ear, or rectum.

Blood pressure and pulse rate will be measured using a calibrated non-invasive blood pressure cuff after the subject has been supine for at least 5 minutes and after approximately 2 minutes standing, if possible.

Vital sign measurements will be obtained before any scheduled blood sample collection at screening and then at the time points specified in the schedule of assessments (Table 8).

Height will be measured at screening only. Height and weight will be measured with subjects not wearing shoes; and weight will be measured with subjects not wearing outerwear (eg, jackets or coats).

9.3.2. Medical History

A medical history will be taken at the screening visit and updated on Day 1 (baseline) and as needed throughout the study.

9.3.3. Physical Examination

The complete physical examination will consist of an assessment of general appearance, skin and mucosae, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest/lungs, cardiovascular, abdomen, extremities, musculoskeletal, and neurological system.

The physical examination schedule is provided in Table 8.

9.3.4. Electrocardiogram

Triplicate 12-lead ECG will be recorded (at least 1 minute apart and within 15 minutes) after the subject has rested supine for at least 5 minutes. The ECG parameters that will be assessed include heart rate, PR interval, QRS duration, QT interval, and QTcF (machine readings or calculated). Additionally, the occurrence of de- and re-polarization, ectopic cardiac activity and rhythm disorders or other abnormalities will be assessed. Based on the review of these parameters, the investigator will note if the ECG is Normal, Abnormal not Clinically Significant, or Abnormal Clinically Significant. If the ECG is Abnormal Clinically Significant, the

investigator will provide a description of the abnormality recorded on the AE eCRF. The ECG schedule is provided in Table 8.

9.3.5. Clinical Laboratory Assessments

All clinical laboratory assessments will be performed by a central laboratory. The central laboratory will provide instructions and supplies to the study staff before study initiation and instructions will be included in a laboratory manual. The following clinical safety laboratory assays will be performed:

Hematology: complete blood count including WBC count with differential, red blood cell (RBC) count, hemoglobin, hematocrit, and platelet count, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), red cell distribution width (RDW), mean platelet volume (MPV).

Clinical Chemistry: sodium, potassium, calcium, magnesium, phosphorus, chloride, blood urea nitrogen, bicarbonate, creatinine, uric acid, albumin, ALP, 5' nucleotidase, lactate dehydrogenase, AST, ALT, GGT, creatine kinase (CK), TBILI, direct bilirubin, total protein, and glucose. See Appendix D for further detail on liver function test monitoring.

Coagulation: PT and INR.

Urinalysis: casts, crystals, specific gravity, nitrite, ketones, protein, urobilinogen, glucose, bilirubin, leukocyte esterase, occult blood, and pH; microscopic examination of sediment will be performed only if the results of the urinalysis dipstick evaluation are positive for nitrite, protein, leukocyte esterase, or blood.

The following additional laboratory tests will be performed:

Drug Screen: The UDS will test for amphetamines, barbiturates, benzodiazepines, cocaine, phencyclidine, cannabinoids, and opiates. The UDS will be performed at screening by the central laboratory. A UDS kit provided by the central laboratory will be used at the site to confirm eligibility on Day 1. Drug/alcohol screening may be repeated at any time per the investigator's clinical judgment. Any positive UDSs during conduct of the study must be discussed with the Sponsor or designee to determine the subject's disposition.

Pregnancy Test: Pregnancy tests will be performed throughout the study for female subjects of childbearing potential. A serum β-hCG pregnancy test will be performed at screening and a urine pregnancy test (using a urine pregnancy kit provided by the central laboratory) will be performed at the time points indicated in Table 8.

FSH: An FSH level will be tested at screening (Visit 1) only in postmenopausal woman.

9.3.6. Columbia-Suicide Severity Rating Scale

The C-SSRS is a validated instrument to prospectively assess suicidal ideation and behavior (http://www.cssrs.columbia.edu). There are versions of the questionnaire designed for use at screening (Baseline/Screening version) and at baseline and visits throughout the study (Since Last Visit version). All versions of the C-SSRS include a series of screening questions related to suicidal ideation and suicidal behavior. Subject responses of "yes" to one or more screening

questions will prompt additional questions that evaluate frequency and intensity of suicidal ideation and/or behavior.

The C-SSRS will be administered and scored by the investigator or qualified study center personnel when conducted at the study center. When the study visit is conducted at the subject's home the site will administer the C-SSRS virtually. The C-SSRS will be assessed at the time points indicated in Table 8.

Suicidal ideation type 4, suicidal ideation type 5, and all reports of suicidal behavior must be documented as an AE or SAE (if SAE criterion is met). Suicidal ideation type 1, 2, or 3 must be documented as AEs or SAEs (if SAE criterion is met) if considered clinically significant by the investigator. For reporting instructions and definitions of AE and SAE, please refer to Section 10.

9.4. Pharmacokinetic Assessments

Blood samples for determination of plasma concentrations of NBI-1065846 will be collected at the timepoints identified in the schedule of assessments (Table 8). If the subject discontinues study treatment early, a blood sample for PK is needed at any time during the ET visit (Table 8).

For each sample, blood will be collected in tubes containing dipotassium ethylenediaminetetraacetic acid (EDTA K_2). The exact time of sampling in hours and minutes will be recorded for all PK blood samples. The blood samples will be processed and stored according to the procedure as specified in the laboratory manual. Samples will be shipped on dry ice to the central laboratory for analysis.

9.5. Other Procedures

9.5.1. Blood Sample for Pharmacogenomics (Optional)

It is recognized that genetic variation can be an important contributory factor to interindividual differences in drug distribution and response and can also serve as a marker for disease susceptibility and prognosis. Pharmacogenomic research may help to explain interindividual variability in clinical outcomes and may help to identify population subgroups that respond differently to a drug. The goal of the pharmacogenomic component is to collect DNA to allow the identification of genetic and/or epigenetic factors that may influence the PK, pharmacodynamics, efficacy, safety, or tolerability of NBI-1065846 in subjects with MDD and anhedonia and to identify genetic factors associated with MDD and anhedonia.

Participation of study subjects in pharmacogenomic sample collection is optional and requires additional consent from the subject (see ICF in Section 12.9.2). A blood sample for DNA isolation will be collected from participating subjects at the timepoints indicated in the schedule of assessments (Table 8). Subjects who do not wish to participate in the pharmacogenomic research may still participate in the study.

Analyses may be conducted if it is hypothesized that this may help resolve issues with the clinical data. DNA samples will be used for research related to NBI-1065846 or MDD with anhedonia. For example, in the event of an unusual response or observation of unexplained AEs, DNA samples may be used to determine if there are any pharmacogenetic associations with drug

response. They may also be used to develop tests/assays related to NBI-1065846 and MDD with anhedonia.

DNA samples may be used for research related to MDD with anhedonia for the assessment of genetic and epigenetic changes in genes known to be in pathways relevant to depression (eg, ion channels, monoamine transporters, growth factors, inflammation) and NBI-1065846. Pharmacogenomic research may consist of the analysis of one or more candidate genes, the analysis of genetic markers throughout the genome, or analysis of the entire genome (as appropriate) in relation to NBI-1065846 or MDD with anhedonia clinical endpoints, including, but not limited to, candidate gene, single nucleotide polymorphism analysis, genome-wide association study, next generation sequencing, and whole genome sequencing. In the future, as the understanding of a disease increases, additional genetic analyses may be warranted to refine the knowledge of the molecular basis of the disease and the drug response and to advance the development of novel therapeutics.

The DNA samples will be coded with the subject's identification number and stored for 15 years or a duration dictated by local, national, or regional laws or regulations. No genotyping or genetic data will be provided to the subject. Subjects may withdraw consent and request to have their sample destroyed at any time, and no further genetic data will be generated; any data already generated will not be destroyed.

In addition, where local regulations and ethics committee approval allow, an optional genetic consent will be offered to subjects to allow samples to be stored for future unspecified genetic research related to other diseases and traits of interest to sponsor.

Details on processes for collection and shipment and destruction of these samples can be found in the laboratory manual.

9.6. Specific Study Period Information

9.6.1. Screening Period (Day -28 to Day -1)

After consent is obtained, the subject registry database review should be performed as early as possible at the Screening Visit to avoid unnecessary procedures.

Subjects will undergo screening procedures that may be completed in 1 or more visits during the Screening Period of up to 4 weeks. Subjects may be rescreened once based on the clinical judgment of the investigator in collaboration with the sponsor or designee. The screening period may be extended by up to 14 days in extenuating circumstances in consultation with the Sponsor or designee.

Vital signs should be collected prior to the collection of blood for clinical laboratory tests.

The SAFER Interview will be conducted by interview remotely during the Screening Period and is a site-independent qualification assessment (see Section 9.1.6 for further details).

Training should be provided on the use of concomitant medications (Section 7.1).

Eligible subjects will return to the study site on Day 1 for baseline assessments.

9.6.2. Baseline Visit and Study Treatment Period (Day 1 to Day 57)

If the subject has taken any restricted concomitant medications (Table 3) within 6 hours before any efficacy assessments (SHAPS, DARS, HAM-D17, MADRS, CGI-S, [redacted], and [redacted] then the site should reschedule these study visit assessments to the next day (or within 2 to 3 calendar days).

Subjects should not use marijuana or alcohol on the day of study visits. If a subject appears intoxicated at a study visit, efficacy assessments should not be performed that day and the site should reschedule these assessments to the next day (or within the window defined in the Schedule of Assessments (Table 8).

After completing baseline assessments on Day 1, subjects will be randomized 1:1 to receive NBI-1065846 or placebo. The first dose of study treatment will be administered in the clinic at the end of Day 1; the date and time of first dose should be recorded in the eCRF. Subjects will be instructed to take study treatment as described in Section 6.2. Subjects will have onsite and virtual study visits as specified in the schedule of assessments (Table 8).

After administering the PCRS, the efficacy assessments applicable to each study visit should be performed in the following order throughout the study:

Subject-Reported Outcomes:

1. SHAPS
2. DARS
3. [redacted]
4. [redacted]
5. [redacted]
6. [redacted]
7. [redacted]

Clinician-Reported Outcomes:

1. MADRS
2. HAM-D17
3. CGI-S
4. [redacted]

At each onsite or virtual study visit (except the Day 1 visit), the investigator or designee will remind subjects to take their study medication on the next scheduled day as specified in Section 6.2. For weeks with no study visit scheduled, this reminder should occur via telephone. The subject should also be reminded that if they forget or are unable to take the study treatment, the dose can be taken ± 2 days from the scheduled weekly dose (with each dose taken at least 5 days apart); otherwise the study treatment should be taken at the next dosing time.

Schedule the exit interview in approximately 20 subjects at Day 57 (or ET visit in subjects who discontinue study treatment).

9.6.3. Follow-Up Period (Day 58 to Day 106)

The follow-up visits (±3 days) will be conducted at the study site.

10. ADVERSE EVENTS

All AEs, whether observed by the investigator, reported by the subject, noted from laboratory findings, or identified by other means, will be recorded from the time the subject has signed the ICF until the subject's final study visit/contact (or upon ET).

10.1. Definition

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that occurs after enrollment into the study and which does not necessarily have a causal relationship with the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

AEs include, but are not limited to, any of the following:

- Worsening or change in nature, severity, or frequency of conditions present at the start of the study
- Subject deterioration beyond what would be expected due to the primary illness
- Intercurrent illness
- Drug interaction

C-SSRS suicidal ideation type 4, C-SSRS suicidal ideation type 5, and all reports of suicidal behavior and clinically significant suicidal ideation must be documented as an AE or SAE (if SAE criterion is met). C-SSRS suicidal ideation types 1, 2, or 3 must be documented as AEs or SAEs (if SAE criterion is met) if considered clinically significant by the investigator.

Subjects should be questioned in a general way, without asking about the occurrence of any specific symptom. The investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and not the individual signs/symptoms. Following questioning and evaluation, all AEs, whether believed by the investigator to be related or unrelated to the study treatment, must be documented in the subject's medical records, in accordance with the investigator's normal clinical practice and on the AE eCRF. Each AE is to be evaluated for duration, intensity, frequency, seriousness, outcome, other actions taken, and relationship to the study treatment.

The following are not considered AEs:

- Continuous persistent disease/symptom present before study treatment administration, unless it unexpectedly progresses, or increases in severity following study treatment administration
- Study treatment failure or lack of efficacy
- Pregnancy

- Overdose of either study treatment or concomitant medication without any clinical signs or symptoms

10.1.1. Intensity of Adverse Events

Adverse events must be graded for intensity. An intensity category of mild, moderate, or severe, as defined in Table 4, must be entered on the AE eCRF. It should be noted that the term "severe" used to grade intensity is not synonymous with the term "serious."

Table 4: Intensity of Adverse Events

Grade	Intensity
Mild	An AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	An AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.
Severe	An AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

AE=adverse event

10.1.2. Relationship to Study Treatment

The investigator will document his/her opinion of the relationship of the AE to treatment with study treatment using the criteria outlined in Table 5. An AE is deemed associated with the use of the study treatment "if there is a reasonable possibility that the treatment caused the AE" (otherwise referred to as a suspected adverse reaction). Reasonable possibility means there is evidence to suggest a causal relationship between the study treatment and the AE (Title 21 Code of Federal Regulations [CFR] 312.32 [a]).

Table 5: Relationship of Adverse Events to Study Treatment

Relationship	Description
Definite	The AE follows a reasonable temporal sequence from administration of the study treatment, abates upon discontinuation of the study treatment, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the study treatment is reintroduced.
Possible	The AE follows a reasonable temporal sequence from administration of the study treatment and cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental, or toxic factors, or other modes of therapy administered to the subject. There should be some evidence to support a causal relationship between the study treatment and the AE.
Unlikely	The temporal sequence between the AE and the study treatment is such that the study treatment is not likely to have any reasonable association with the AE or other plausible explanations exist for the AE (eg, disease, other drugs).
Not related	The AE does not follow a reasonable temporal sequence from administration of the study treatment, may not abate upon discontinuation of the study treatment, does not follow a known or hypothesized cause-effect relationship, and (if applicable) may not reappear when the treatment is reintroduced, furthermore, there may exist a clear alternative medical explanation (eg, underlying disease state) or association with study procedure or study conduct.

AE=adverse event

10.2. Recording Adverse Events

For randomized subjects, each AE will be listed as a separate entry on an AE eCRF. Screen failure subjects who experience an AE will have the information noted only in the source document (not in the EDC system). The investigator (or designee) will provide information on dates of onset and resolution, intensity, seriousness, frequency, action(s) taken, changes in study treatment usage, relationship to study treatment, and outcome.

10.3. Poststudy Follow-Up of Adverse Events

All AEs, including clinically significant changes in ECGs, physical examination findings, or isolated clinically significant laboratory findings must be followed until the event resolves, the condition stabilizes, the event is otherwise explained, or the subject is lost to follow-up.

Adverse events ongoing at the final visit or at ET will be followed for as long as necessary to adequately evaluate the subject's safety or until the event stabilizes, resolves, or the subject is lost to follow-up. The investigator is responsible for ensuring that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals, as is practical.

10.4. Serious Adverse Events

All SAEs will be recorded from the time the subject has signed the ICF until the final study visit. Investigators are not obligated to actively seek SAEs after a subject has withdrawn from or completed the study. However, if the investigator learns of any SAE, including a death, at any time after a subject has been withdrawn from or has completed the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor as described in Section 10.4.3.

10.4.1. Definition of a Serious Adverse Event

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

- Death
- A life-threatening AE. Life-threatening means that the subject was, in the view of the investigator or Sponsor, at immediate risk of death from the reaction as it occurred. It does not mean that hypothetically the event might have caused death if it occurred in a more serious form.
- Inpatient hospitalization or prolongation of existing hospitalization. Hospitalization for elective treatment or a preexisting condition that did not worsen during the clinical investigation is not considered an AE. Hospitalization or nursing home admission for the purpose of caregiver respite is not considered an AE. Complications that occur during hospitalization are AEs, and if a complication prolongs hospitalization, the event is considered serious. Treatment in a hospital emergency room is not a hospitalization.
- A persistent or significant incapacity or substantial disruption of a person's ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization. These events may be considered serious when, based on appropriate medical judgment, they may jeopardize the health of the subject and may require medical or surgical intervention to prevent one of the outcomes listed. Any other event thought by the investigator to be serious should also be reported, following the reporting requirements detailed in this section. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

10.4.2. Managing Serious Adverse Events

Subjects experiencing an SAE or an emergency situation will be examined by a physician as soon as possible. The physician in attendance will do whatever is medically needed for the safety and well-being of the subject. The subject will remain under observation as long as medically indicated. Appropriate laboratory studies will be conducted until all parameters return to normal

or are otherwise explained or stable. The subject will be followed until the SAE resolves or until the subject is medically stabilized.

10.4.3. Reporting Serious Adverse Events and Other Immediately Reportable Events

SAEs and pregnancies must be reported immediately and no later than 24 hours of first knowledge of the event by study personnel to NBI Drug Safety and Pharmacovigilance (DSPV). Reports of SAEs and pregnancies must be followed by a fax or email of the SAE or Pregnancy Form (Table 6). It is important that the investigator provides his or her assessment of relationship to study treatment at the time of the initial SAE report. The investigator (or designee) will also notify the IRB/IEC, if necessary) of the SAE and the outcome of the SAE, as required by the IRB/IEC.

Additionally, the following categories of medical events that could occur during participation in a clinical study must be reported within 24 hours to the Study Medical Monitor and must be followed by a fax or email of the Other Immediately Reportable Events Form (Table 6).

- Treatment unblinding for any reason
- Events of suicidal behavior or suicidal ideation 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.

Table 6: Contact Information for Drug Safety and Pharmacovigilance

Drug Safety and Pharmacovigilance Facsimile Email	 +1 (888) 617-7551 or +1 (858) 617-7561 cds@neurocrine.com
Study Medical Monitor	+1 (858) 617-7387

10.4.4. Expedited Safety Reports

The Sponsor or its representatives will submit an Expedited Safety Report for any suspected adverse reaction (Section 10.1.2) that is considered both serious and unexpected within 15 calendar days and for any unexpected fatal or life-threatening experience within 7 calendar days to the applicable regulatory authority(ies); or according to country-specific regulations.

The Sponsor or its representatives will send copies of each safety report submitted to regulatory authorities to the investigators. The safety report must be submitted to the appropriate IRB/IEC as soon as possible. Documentation of the submission to the IRB/IEC and receipt by the IRB/IEC (if applicable) must be retained for each safety report.

10.5. Urgent Safety Measures

If an event occurs that is related to the conduct of the study or the development of the study treatment, and this new event is likely to affect the safety of subjects, the Sponsor and the investigator will take appropriate urgent safety measures to protect subjects against any immediate hazard. The Sponsor will work with the investigator to ensure the IRB/IEC and local regulatory authority is notified within 3 days or in accordance with applicable local laws and regulations.

10.6. Pregnancy

Pregnancy is neither an AE nor an SAE unless the criteria for an SAE are met. However, all pregnancies in subjects who received NBI-1065846 will be followed to assess for pregnancy outcome. Subjects of childbearing potential must be counseled at all visits to continue using contraception until 55 days (females) (Section 5.1, inclusion criterion #10 after the last dose of study treatment. If a female subject believes she is pregnant at any time between signing the ICF and the last study visit, she should return to the study center within 24 hours and undergo a serum pregnancy test. Female subjects confirmed to be pregnant will be discontinued from study treatment, unblinded, and withdrawn from the study.

All confirmed pregnancies in female subjects who received study treatment must be immediately reported to NBI (contact information is provided in Section 10.4.3), followed by fax or email of the pregnancy form to NBI DSPV. A first trimester ultrasound may be requested for all confirmed pregnancies. Pregnancies in subjects who received NBI-1065846 will be followed until resolution (ie, termination [voluntary or spontaneous] or birth).

11. STATISTICAL METHODS

This section represents a brief description of the planned primary analysis of the primary and secondary objectives. A comprehensive and detailed statistical analysis plan (SAP) will be generated and finalized prior to study database lock and treatment unblinding. The SAP will provide additional details regarding the methods of analysis summarized in this protocol, will describe analysis methods for other endpoints, will describe analyses to characterize the study conduct and population, and may describe sensitivity and supplementary analyses for selected endpoints.

11.1. Statistical Hypothesis

The null hypothesis for the primary endpoint is that the mean change in DARS from baseline to Day 57 in the placebo group is greater than or equal to that in the NBI-1065846 group. The alternative hypothesis is that the mean change in DARS from baseline to Day 57 in the placebo group is less than that in the NBI-1065846 group.

The null hypothesis to be tested is:

$$H_0: \mu_1 \geq \mu_2$$

The alternative hypothesis is:

$$H_1: \mu_1 < \mu_2$$

where μ_1 is the mean change in DARS from baseline to Day 57 in the placebo group, and μ_2 is the mean change in DARS from baseline to Day 57 in the NBI-1065846 group.

11.2. Sample Size Determination

Assuming that 85% of the 88 subjects (randomized in a 1:1 ratio to NBI-1065846 and placebo groups) complete the Day 57 assessment, the study has approximately 80% power to detect an effect size of 0.5 for the primary endpoint at 1-sided significance level of 0.1.

11.3. Analysis Sets

Statistical analysis sets used in this study are defined in Table 7. Additional analysis sets may be specified in the SAP.

Table 7: Analysis Sets

Population	Description
Full analysis set	The Full Analysis Set includes all randomized subjects. Subjects will be analyzed according to their randomized treatment group, regardless of compliance with study treatment administration and availability of postbaseline data.
Safety analysis set	The Safety Analysis Set will include all randomized subjects who take at least 1 dose of study treatment. Subjects will be analyzed according to their randomized treatment group, unless they receive the incorrect study treatment for the entire treatment duration.
PK Analysis Set	The PK Analysis Set will include all randomized subjects who received at least 1 dose of study treatment and who have any measurable NBI-1065846 plasma concentration data.

PK=pharmacokinetic

11.4. Endpoints

11.4.1. Primary

- Change in anhedonia severity, as measured by change in DARS score from baseline to Day 57.

11.4.2. Secondary

- Change in total MADRS score from baseline to Day 57 in subjects with moderate or higher severity depression.
- Change in CGI-S score from baseline to Day 57.

11.4.3. Other

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

11.4.4. Safety

- Safety endpoints include the occurrence of TEAEs, observed and changes from baseline in clinical laboratory tests (hematology and clinical chemistry), vital sign measurements (including orthostatic blood pressure and pulse rate), 12-lead ECG parameters, and scores from the C-SSRS.

11.5. Statistical Analyses

Descriptive and inferential statistical methods will be used to evaluate and summarize the data from this study. Descriptive statistics typically include the number of subjects (n), mean, standard deviation (SD) or standard error (SE), median, first (Q1) and third (Q3) quartile, minimum, maximum, and confidence intervals for continuous variables; and refers to the number and percentage of subjects for categorical variables. The term "inferential statistics" refers to the analysis results from hypothesis tests, which will be performed to assess differences between treatment groups. The overall level of significance (Type I error) for this study is 0.1.

11.5.1. Efficacy Analyses

This section is a summary of the planned statistical methods for the primary analysis of the primary and secondary endpoints. Additional details of the analyses will be described in the SAP. Unless otherwise specified, efficacy analyses will be conducted using the Full Analysis Set.

11.5.1.1. Procedure to Control for Multiple Comparisons

P-values will not be adjusted for multiplicity and should be interpreted as nominal p-values.

11.5.1.2. Primary Endpoint

The primary endpoint will be analyzed using an analysis of covariance (ANCOVA) model with outcome being the change in DARS score from baseline to Day 57. The model will include treatment group, illness severity (stratification factor), use of concomitant antidepressant medication(s) at time of randomization ([ie, yes vs. no], covariate), and baseline DARS score (covariate). Subjects who are missing the DARS score at Day 57 will have their data imputed through a multiple imputation procedure. Missing data will be imputed for subjects in the NBI-1065846 treatment group using retrieved data (ie, observed data from subjects who discontinued study treatment) in the same treatment group, provided there is sufficient retrieved data. Otherwise, missing data will be imputed using observed data from subjects in the placebo treatment group. For subjects in the placebo treatment group, missing data will be imputed using observed data from subjects in the placebo treatment group. Additional analyses to address sensitivity to missing data will be specified in the SAP.

11.5.1.3. Secondary endpoints

Continuous secondary efficacy endpoints will be analyzed using a similar ANCOVA model as described for the primary endpoint; categorical and ordinal secondary endpoints will be analyzed using the Cochran-Mantel-Haenszel Chi-square test. Psychometric properties of the DARS will be assessed and reported separately.

11.5.2. Safety Analyses

Safety data from this study will be analyzed using the safety analysis set. The subject incidence of TEAEs will be tabulated by treatment group for AEs, SAEs, fatal AEs, and AEs leading to discontinuation of study treatment. TEAEs are those AEs with onset dates on or after the date of the first dose of study treatment and on or before 55 days after the date of the last dose of study treatment. Descriptive statistics by treatment group will be generated for additional safety data, including selected laboratory analytes, vital signs, ECG parameters, C-SSRS, which will be further described in the SAP.

11.5.3. Pharmacokinetic Analyses

The plasma concentration data for NBI-1065846 and metabolites, if appropriate, will be summarized by sampling time point using the PK Analysis Set. The number and percentage of subjects with data, with quantifiable results, and with values below the limit of quantification will be provided.

11.6. Interim Analyses

Other than the ongoing monitoring of the study as described in Section 9.3, there is no planned interim analysis in this study.

12. SUPPORTING DOCUMENTATION

12.1. Case Report Forms

The eCRF data for this study are being collected with an EDC system (Rave®) provided by Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific eCRFs will comply with US Food and Drug Administration (FDA) Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study specific eCRFs will be conducted by the Sponsor and the required documentation will be maintained in the Trial Master File.

The investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by authorized study personnel in the EDC system, with the exception of data captured in an electronic format, which will be loaded electronically into the appropriate eCRFs. All data entered into the eCRF will be supported by source documentation. The investigator should review the eCRFs as soon as possible after the subject visit has occurred and electronically sign the eCRFs as soon as possible after the subject completes or discontinues from the study.

The investigator or an authorized member of the investigator's staff will make any necessary additions/corrections to the eCRF. All change information, including the date, person performing the corrections, and reason for the change will be available via the electronic audit trail, which is part of the EDC system. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by the Sponsor (or designee). The Sponsor will also be allowed access to all source documents and medical records pertinent to the study in order to verify eCRF entries. The Principal Investigator will review the eCRFs for completeness and accuracy and enter his or her electronic signature on the eCRFs as evidence thereof.

Medidata will provide access to the NBI portal of the EDC system for the duration of the study through a password-protected method of internet access. Such access will be removed from study centers at the end of the center's participation in the study. Data from the EDC system will be archived on appropriate data media or uploaded to a secure location with restricted access, in order to provide the investigator with a durable record of the center's eCRF data.

All clinical work conducted under this protocol is subject to Good Clinical Practice (GCP) regulations. This includes an inspection by the Sponsor and/or health authority representatives at any time. The Principal Investigator will agree to the inspection of study-related records by health authority representatives and/or the Sponsor.

12.2. Data Capture, Review, and Validation

Data entered in the EDC system will be verified against the source data by the Sponsor (or designee); the percentage of source data verification will be determined by risk assessment. Any discrepancies will be corrected on-line by authorized study center personnel. After data are entered into EDC, automated (computer-generated) logic checks will run in order to identify items such as inconsistent study dates. In addition, manual review/checks may be performed by the Sponsor on the data. Any inconsistencies/errors/omissions identified will be sent to the study center (via an electronic query) for the necessary corrections to be made to the eCRF. Once

entered and saved in an eCRF, data immediately become part of the study database and are available to the Sponsor.

12.3. Coding Dictionaries

AEs and medical history will be coded using the chosen version of the Medical Dictionary for Regulatory Activities (MedDRA), per the Sponsor. Prior and concomitant medications will be coded using the chosen version of the World Health Organization Drug Dictionary, per the Sponsor.

12.4. Ethics

The Sponsor personnel and the investigators will ensure that the study is conducted in full compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) GCP guidelines, and with the laws and regulations of the country in which the study is conducted.

The investigator and/or Sponsor/CRO will submit this protocol and any related document(s) to be provided to the subject to an IRB/IEC and to the national competent (health) authority (as applicable). Approval documentation (as applicable) from both the IRB/IEC and the national competent (health) authority must be obtained before starting the study.

12.5. General Legal References

The study will be carried out according to provisions of the US CFR, the US FDA, the laws and regulations of the country in which the study is conducted, and the ICH Guidelines for GCP. All clinical work conducted under this protocol is subject to GCP regulations. This includes an inspection by the Sponsor or its representative, health authority, or IRB/IEC representatives at any time. The investigator must agree to the inspection of study related records by health authority representatives and/or the Sponsor or its designee.

12.6. Institutional Review Board/Independent Ethics Committee

The final approved protocol and the ICF will be reviewed by the IRB/IEC at the study center. The committee’s decision concerning conduct of the study will be sent in writing to the investigator and a copy will be forwarded to the Sponsor. The investigator must agree to make any required progress reports to the IRB/IEC, as well as reports of SAEs, life threatening problems, or death.

A list of members participating in the IRB/IEC meetings must be provided, including the names, qualifications, and functions of these members. If that is not possible, the attempts made to obtain this information along with an explanation as to why it cannot be obtained or disclosed must be documented in the study documentation.

If a member of the site study personnel was present during an IRB/IEC meeting, it must be clear that this person did not vote.

12.7. Protocol Adherence – Amendments

The protocol must be read thoroughly, and the instructions must be followed exactly. Any changes in the protocol will require a formal amendment. Such amendments will be agreed upon and approved in writing by the investigator and the Sponsor. The IRB/IEC and local health authorities will be notified of all amendments to the protocol in accordance with local regulations.

Modifications made to the protocol or the ICF after receipt of the approval must also be submitted as amendments by the investigator and/or Sponsor/CRO to the IRB/IEC and to the national competent (health) authority in accordance with local procedures and regulations.

12.8. Required Documents

The investigator must provide the Sponsor or its designee with the following documents before the enrollment of any subject (originals should be kept by the investigator in the investigator's study regulatory document binder):

- Signed copy of the protocol signature page
- Investigator's Brochure acknowledgement page
- Completed and signed statement of investigator qualifications, as applicable
- Financial disclosure documentation as required
- Curriculum vitae and current medical license of the investigator and subinvestigators
- Letter of approval from the IRB/IEC for protocol and ICF
- Copy of the IRB/IEC approved written ICF to be used
- Laboratory documents (certifications/accreditations, normal ranges) if not provided by a central laboratory

12.9. Informed Consent

Subjects must provide written informed consent.

Each subject's chart will include the signed ICF for study participation. When the study treatment is completed and the eCRF has been monitored, the ICF will be kept in the investigator's central study file. Regulatory authorities may check the existence of the signed ICF in this central study folder if not having done so during the study.

12.9.1. Subject Registry Database Review Informed Consent

At the time of providing informed consent for the study, the investigator or designee will explain the subject registry database review process to the subject and witness signature.

12.9.2. Pharmacogenomic Informed Consent

Informed consent pertaining to collection, usage and storage of any sample which may be used for pharmacogenomic analysis must be obtained prior to collecting for pharmacogenomic

research for this study. The provision of consent to collect and analyze the pharmacogenomic sample is independent of consent to the other aspects of the study.

12.10. Study Monitoring

Throughout the course of the study, the study monitor will make frequent contacts with the investigator. This will include telephone calls and on-site visits. During the on-site visits, the eCRFs will be reviewed for completeness and adherence to the protocol. As part of the data audit, source documents will be made available for review by the study monitor. The study monitor will also perform treatment accountability checks and may periodically request review of the investigator study file to ensure completeness of documentation in all respects of clinical study conduct.

Upon completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period. The investigator or appointed delegate will receive the study monitor during these on-site visits, will cooperate in providing the documents for inspection, and will respond to inquiries. In addition, the investigator will permit inspection of the study files by authorized representatives of the regulatory agencies.

12.11. Quality Assurance

The study will be conducted in accordance with the Sponsor's standard operating procedures designed to ensure that all procedures are in compliance with GCP and the laws and regulations of the country in which the study is conducted. Quality assurance audits may be performed at the discretion of the Sponsor.

12.12. Record Retention

Study records should be retained in compliance with federal, national, and/or local regulations of the clinical site.

The Sponsor may request these records to be retained for a longer period if required by applicable regulatory requirements or Sponsor contractual obligations. If the investigator is unable to retain the study documents for the required amount of time, the Sponsor must be informed of the individual who will be assuming this responsibility.

12.13. Confidentiality and Data Protection

The Sponsor or its designee, and the study center affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, all data will be identified only by an identification number. Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

All information concerning this study and which was not previously published is considered confidential information. This confidential information shall remain the sole property of the

Sponsor; it shall not be disclosed to others without written consent of the Sponsor; and shall not be used except in the performance of this study.

The information compiled during the conduct of this clinical study is also considered confidential and may be disclosed and/or used only by the Sponsor as deemed necessary. To allow the use of the information derived from this clinical study and to ensure compliance with the laws and regulations of the country in which the study is conducted, the investigator is obliged to provide the Sponsor with the complete test results and all data compiled in this study.

12.14. Publication and Disclosure Policy

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

The Sponsor will submit study results for posting on public registry(ies) as required for compliance with applicable laws and/or regulations in the region(s) where the study is being conducted. For the purposes of study results disclosure, study completion is defined as the date of the last visit or procedure for the last subject in the study globally.

13. STUDY COMMENCEMENT AND DISCONTINUATION

Upon satisfactory receipt of all required regulatory documents, the Sponsor (or designee) will arrange that all study materials be delivered to the study site. Subject entry should not begin until after the required regulatory documents are confirmed as received and the Investigator Meeting/Initiation Meeting has occurred. All personnel expected to be involved in the conduct of the study will undergo orientation to include review of the study protocol, instructions for eCRF completion, AE reporting, and overall responsibilities including those for treatment accountability and study file maintenance.

If the study is discontinued, all subjects should undergo a complete follow-up examination. Any clinically relevant finding, including laboratory values of potential clinical concern, and adverse experiences will be followed until they resolve or return to a clinically acceptable level.

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APPENDIX A. SCHEDULE OF ASSESSMENTS

Table 8: Schedule of Assessments

	Screening Period[a]	Treatment Period						Safety Follow-Up Period	
Study Day (Study Week)	**Day -28 to Day -1 (W-4 to D-1)**	**Day 1[b] Baseline (W1)**	**Day 8 (±2) (W2)**	**Day 22 (±2) (W4)**	**Day 29 (±2) (W5)**	**Day 43 (±2) (W7)**	**Day 57 (±2) *OR* ET Visit**	**Day 78[c] (±3) (W12)**	**Day 106[c] (±3) (W16)**
Visit No.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Onsite Visit	**X**	**X**	**X**		**X**		**X**	**X**	**X**
Virtual Visit				**X**		**X**			
Informed consent	X								
Subject registry database review informed consent	X								
Pharmacogenomic informed consent	X								
Subject registry database review[d]	X								
Inclusion/exclusion criteria	X	update							
Medical history	X	update							
Medication history	X	update							
Physical examination (including height and weight)[e]	X						X	X	X
Triplicate 12-Lead ECG[f]	X	X			X		X		
Vital signs[g]	X	X	X		X		X	X	X
Pregnancy test: Urine (u) Serum (s)	X (s)[h]	X (u)			X (u)		X (u)	X (u)	X (u)
FSH[i]	X								
Clinical laboratory tests	X	X	X		X		X	X	X
Drug/alcohol screen[j]	X	X			X				
Pharmacogenomics sample (optional)		X							
MINI	X								
SAFER Interview	X								
MGH-ATRQ	X								
HAM-D17[k]	X	X							
PCRS[k]		X			X		X		

	Screening Period[a]	Treatment Period						Safety Follow-Up Period	
Study Day (Study Week)	**Day -28 to Day -1 (W-4 to D-1)**	**Day 1[b] Baseline (W1)**	**Day 8 (±2) (W2)**	**Day 22 (±2) (W4)**	**Day 29 (±2) (W5)**	**Day 43 (±2) (W7)**	**Day 57 (±2) *OR* ET Visit**	**Day 78[c] (±3) (W12)**	**Day 106[c] (±3) (W16)**
Visit No.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Onsite Visit	**X**	**X**	**X**		**X**		**X**	**X**	**X**
Virtual Visit				**X**		**X**			
SHAPS[k]	X	X							
DARS[k]	X	X			X		X		X
[redacted]		X			X		X		
[redacted]		X			X		X		
[redacted]					X		X		
[redacted]		X			X		X		
[redacted][,l]		X					X[c]		
MADRS[k]		X			X		X		
CGI-S[k]		X			X		X		
[redacted]					X		X		
C-SSRS Baseline/Screening Version	X								
C-SSRS Since Last Visit Version		X	X	X	X	X	X	X	X
PK blood sample up to 2 hours predose		X	X		X				
PK blood samples at 0.5-2 hours and 2-36 hours postdose (samples must be obtained ≥30 minutes apart)		X			X				
PK blood sample at any time[m]							X		
Dispense[n]/Collect[o] study treatment		X[n]	X[n]				X[o]		
Dose study treatment[p]		X (once weekly)[p]							
Remind subjects to take study treatment[p]		X (once weekly)[p]							
Compliance check[q]		X	X	X	X	X			

	Screening Period[a]	Treatment Period						Safety Follow-Up Period	
Study Day (Study Week)	**Day -28 to Day -1 (W-4 to D-1)**	**Day 1[b] Baseline (W1)**	**Day 8 (±2) (W2)**	**Day 22 (±2) (W4)**	**Day 29 (±2) (W5)**	**Day 43 (±2) (W7)**	**Day 57 (±2) *OR* ET Visit**	**Day 78[c] (±3) (W12)**	**Day 106[c] (±3) (W16)**
Visit No.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Onsite Visit	**X**	**X**	**X**		**X**		**X**	**X**	**X**
Virtual Visit				**X**		**X**			
AE assessment	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X
Schedule exit interview							X		

AE=adverse event; [redacted]; CGI-S= Clinical Global Impression – Severity; C-SSRS=Columbia-Suicide Severity Rating Scale; DARS=Dimensional Anhedonia Rating Scale; ECG=electrocardiogram; ET=early termination; FSH=follicle-stimulating hormone; HAM-D17=Hamilton Depression Rating Scale-17; MADRS=Montgomery-Åsberg Depression Rating Scale; MGH-ATRQ=Massachusetts General Hospital - Antidepressant Treatment Response Questionnaire; MINI=Mini-International Neuropsychiatric Interview; PCRS=Placebo-Control Reminder Script; [redacted] PK=pharmacokinetics; [redacted]; SAFER= State versus Trait, Assessability, Face Validity, Ecological Validity, Rule of Three P's; SHAPS=Snaith-Hamilton Pleasure Scale; [redacted]
W=week

[a] Subjects will undergo screening procedures that may be completed in 1 or more visits during the Screening Period of up to 4 weeks. Subjects may be rescreened once based on the clinical judgment of the investigator in collaboration with the sponsor or designee. The screening period may be extended by up to 14 days in extenuating circumstances in consultation with the Sponsor or designee.

[b] Assessments on Day 1 should be performed prior to study treatment administration.

[c] Subjects will return to the clinic approximately 4 and 8 weeks following their final dose for safety follow-up or 7 days (±2) for the ET visit assessments if the subject discontinues study treatment or withdraws consent to participate in the study.

[d] After consent is obtained, the registry database check should be performed as early as possible at the screening visit to avoid unnecessary procedures.

[e] Height will be collected at screening only.

[f] Triplicate 12-lead ECGs will be performed (at least 1 minute apart and within 15 minutes) after the subject has rested supine for at least 5 minutes on screening, Day 1, Day 29, and Day 57 or ET visit. On Day 1 and Day 29, ECGs will be performed at predose and 2 hours postdose. ECGs are also needed on Day 78 and Day 106 if ECG(s) during the Treatment Period were abnormal.

[g] Vital signs will be measured for the following: orthostatic systolic and diastolic blood pressure, orthostatic pulse rate, respiratory rate, and body temperature. The same method should be used to take body temperature throughout the study.

[h] If a female of childbearing potential has an indeterminant β-hCG pregnancy test result, the test should be repeated during the screening period and the subject discussed with the medical monitor.

[i] Only for postmenopausal women.

[j] Urine drug screen (UDS) will be analyzed at screening by the central lab. A UDS kit provided by the central laboratory will be used at the site to confirm eligibility on Day 1. Drug/alcohol screening may be repeated at any

time per the investigator's clinical judgment. Any positive UDSs during conduct of the study must be discussed with the Sponsor or designee to determine the subject's disposition.

[k] A trained rater will read the PCRS to the subject prior to administration of the efficacy rating assessments. After administering the PCRS, the efficacy assessments should be performed in the following order throughout the study: SHAPS (at screening and baseline only), DARS, [redacted] MADRS, HAM-D17 (at screening and baseline only), CGI-S, [redacted].

[l] [redacted]

[m] If the subject discontinues study treatment, a blood sample for PK is needed at any time during early ET visit.

[n] One bottle will be dispensed to the site at Baseline/Day 1 and will remain in the clinic for onsite subject dosing (ie, on Days 1, 8, and 29). A second bottle will be dispensed to the subject at Day 8 to take home for at-home dosing (ie, on Days 15, 22, 36, 43, and 50).

[o] Collect any remaining study treatment from the subject at Day 57 or ET visit if the subject discontinues study treatment.

[p] Each dose of study treatment should be taken at least 5 days apart. Onsite dosing in the clinic will occur on Day 1, Day 8, and Day 29. Subjects should hold morning study treatment dose until instructed to take at the study site in order to collect predose PK blood samples. Subjects will take study treatment at home on Days 15, 22, 36, 43, and 50. At each onsite or virtual study visit (except the Day 1 visit), the investigator or designee will remind subjects to take their study medication on the next scheduled day. For weeks with no study visit scheduled, this reminder should occur via telephone. The subject should also be reminded that if they forget or are unable to take the study treatment, the dose can be taken ± 2 days from the scheduled weekly dose (with each dose taken at least 5 days apart); otherwise the study treatment should be taken at the next dosing time.

[q] A compliance check will be performed by counting the tablets returned at each on-site study visit.

APPENDIX B. INVESTIGATOR SIGNATURE

CLINICAL STUDY TITLE: A Randomized, Double-Blind, Placebo-Controlled, Proof-of-Concept Study to Evaluate the Efficacy and Safety of Once-Weekly Oral NBI-1065846 in the Treatment of Anhedonia in Major Depressive Disorder (TERPSIS STUDY)

PROTOCOL No.: NBI-1065846-MDD2020

As Agreed:

_____ _____

Principal Investigator Signature Date

PRINCIPAL INVESTIGATOR:

_____

(Print Principal Investigator Name)

STUDY CENTER:

_____

(Print Study Center Name)

APPENDIX C. SPONSOR APPROVAL SIGNATURE

The undersigned has reviewed and approves the content of this document.

[redacted] Electronically signed and dated

[redacted]

Signature	Date

Neurocrine Biosciences, Inc.
12780 El Camino Real
San Diego, CA 92130

APPENDIX D. LIVER FUNCTION TEST MONITORING

If a subject is noted to have ALT or AST elevated >3×ULN, the investigator will take the following actions:

- Obtain follow-up laboratory tests: ALT, AST, ALP, GGT, and total bilirubin, direct bilirubin, PT, and INR within 48 to 72 hours after the abnormality was noted.
- Assess whether the subject has experienced any clinical manifestations such as fatigue, low-grade fever, anorexia, nausea/vomiting, right upper quadrant pain, jaundice, or pruritus.
- Inform the Study Medical Monitor.

If symptoms persist or repeat testing shows ALT or AST >3×ULN, repeat ALT, AST, ALP, GGT, total bilirubin, direct bilirubin, and INR two or three times weekly. The frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study treatment has been discontinued and the subject is asymptomatic. Serial testing should continue until the liver function tests return to baseline values. Further assessment will be conducted as clinically indicated, in consultation with the Study Medical Monitor. The study treatment may be discontinued by the investigator in consultation with the Study Medical Monitor, or at the request of the Study Medical Monitor

The Study Medical Monitor should also be promptly notified if any of the following criteria are met:

- ALP >1.5×ULN in conjunction with elevated TBILI >1.5×ULN, or
- 5’nucleotidase >1.5×ULN, or GGT >2×ULN, or AST/ALT:>1.5×ULN
- ALP >2×ULN persisting for longer than 3 days;
- ALP >3×ULN;
- Total bilirubin >2.0×ULN;
- Creatinine >2 mg/dL;
- Baseline elevations in liver enzymes <3×ULN, yet worsen by 2-fold increases above Baseline values after study drug exposure.

Additionally, the study treatment should be discontinued immediately if any of the following criteria has been meet:

- ALT or AST >8×ULN, or
- ALT or AST >5×ULN and persists for more than 2 weeks, or
- ALT or AST >3×ULN in conjunction with elevated total bilirubin >2×ULN or INR >1.5.
- ALT or AST >3×ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%)
- ALP elevations >1.5×ULN in conjunction with elevated TBLI >1.5×ULN or
- 5’nucleotidase >2×ULN or GGT >5×ULN or AST/ALT >3×ULN

Signature Page for VV-CLIN-002587 v1.0

Approval Task	[redacted] Clinical 25-Mar-2023 05:55:50 GMT+0000

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