Statistical Analysis Plan

A Randomized, Double-Blind Controlled Comparison of
NRX-101 to Lurasidone for Adults with
Bipolar Depression and Subacute Suicidal Ideation or Behavior

Protocol NRX101-003

Short title: NRX-101 Treatment for C-SSRS 3 Subjects

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1. CONTACT INFORMATION

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2. SIGNATURES

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3. SYNOPSIS

Name of Investigational Product:	NRX-101
Name of Active Ingredient:	NRX-101: Oral capsule containing a fixed-dose combination of D-cycloserine (DCS) + lurasidone HCl (NRX-101)
Reference Product(s):	Lurasidone HCl ("lurasidone") + placebo
Title of Study:	A Randomized, Double-Blind, Controlled Comparison of NRX-101 to lurasidone for Treatment of Bipolar Depression in Adults with Subacute Suicidal Ideation or Behavior
Phase of Development:	Phase 2b
Study Site(s):	10-20 sites located in the United States
Total Participant Number:	74 subjects
Study Duration:	Up to 10-weeks per patient: Screening 1 up to 10 days, Treatment from Day 1 to Day 42, and Follow-up on Day 70
Background and Rationale:	There is no currently-approved pharmacotherapy for patients with Severe Bipolar Depression and Suicidal Ideation or behavior. The purpose of this phase 2b trial is to determine whether patients with Severe Bipolar Depression and subacute Suicidal Ideation or Behavior (i.e. those not requiring inpatient care) can be treated effectively with NRX-101.
Objectives:	<u>Primary Efficacy Objective:</u> • To test the hypothesis that treatment with NRX-101 is superior to lurasidone (a standard of care medicine) in improving symptoms of depression as measured by the Montgomery Åsberg Depression Rating Scale (MADRS-10) total score in adults with severe bipolar depression and subacute suicidal ideation or behavior (SSIB). <u>Secondary Efficacy Objectives:</u> • To test the hypothesis that treatment with NRX-101 is superior to standard of care (lurasidone) in reducing suicidal ideation (MADRS item 10). • To test the hypothesis that treatment with NRX-101 is superior to lurasidone in the change from baseline to Day 14 in MADRS total score. • To test the hypothesis that treatment with NRX-101 is superior to lurasidone in reducing the frequency of suicidal thoughts, suicidality and risk (SIBAT Module 7). • To test the hypothesis that NRX-101 is superior to lurasidone in reducing suicidal ideation or behavior as measured by the Clinical Global Impression of Severity of Suicidality Scale (CGI-SS). • To test the hypothesis that NRX-101 is superior to lurasidone in time to treatment failure as defined as: study discontinuation due to adverse events; psychiatric hospitalization; or requiring a change in antidepressant treatment. • To test the hypothesis that treatment with NRX-101 is superior to treatment with lurasidone in the subgroup of participants recently (i.e. within two weeks of enrollment) treated with approved medications for bipolar depression (olanzapine/fluoxetine, quetiapine, cariprazine, lumateprone, or lurasidone).

	• To test the hypothesis that treatment with NRX-101 is superior to treatment with lurasidone in the subgroup of participants recently (i.e. within two weeks of enrollment) treated with approved medications for bipolar depression. • To further test the hypothesis that treatment with NRX-11 is superior to treatment with lurasidone in the subgroup of participants recently (i.e. within two weeks of enrollment) treated with any 5-HT2A agonist for bipolar depression. <u>Additional Efficacy Objective</u>: • To display NRX-101 vs Lurasidone change from baseline for each MADRS-10 factor as well as the three Borentain factors at each post-baseline evaluation including exit. <u>Safety Objectives:</u> • To test the hypothesis that treatment with NRX-101 is superior to lurasidone (a standard of care drug) in reducing suicidality in depressed bipolar patients with SSIB, as measured by the Columbia Suicide Severity Rating Scale (C-SSRS). • To test the hypothesis that remission from suicidality, measured as Week 6 percent with C-SSRS ≤ 3 will be superior for NRX-101 relative to lurasidone • To test the hypothesis that participants treated with NRX-101 are less likely to suffer from akathisia than those treated with lurasidone as measured by the Barnes Akathisia Rating Scale (BARS). • To test the hypothesis that fewer participants treated with NRX-101 will be discontinued for lack of efficacy or exacerbation of suicidality than participants treated with lurasidone.
Endpoint(s):	<u>Primary Efficacy Endpoint:</u> • Change from baseline over 42 days in MADRS total score. <u>Secondary Efficacy Endpoints:</u> • Change from baseline over 42 days in CGI-SS. • Time to treatment failure (TTF). • Change from baseline in Suicidal Thoughts on the MADRS (MADRS item 10). • Change from baseline to Day 14 in MADRS total score. • Change from baseline for each MADRS-10 factor at each post-baseline evaluation including exit. • Change from baseline for the three MADRS-10 factors defined by Borentain at each post-baseline evaluation including exit. • Change from baseline in each item of the Suicide Ideation and Behavior Assessment Tool (SIBAT) Module 7 (clinical global impressions of frequency of suicidal thinking, severity of suicidality, and imminent and long-term risks). • Change from baseline to endpoint (Day 42/exit) in MADRS total score in the subgroup of participants who were recently (within 2-weeks of enrollment) on approved medications for bipolar depression as well as the 5-HT2A subset. • Percent in remission from suicidality at Day 42/exit (exploratory endpoint).

Study Design:	A multicenter, randomized, stratified, double-blind, parallel-group, two-arm outpatient study of 74 participants comparing NRX-101 to lurasidone in a 1:1 ratio for the treatment of bipolar depression in participants with Subacute Suicidal Ideation or behavior and not requiring hospitalization, as reflected by a rating of 3 or 4 on the C-SSRS at screening. A priori sample size suggests > 90% power based on effect size of >1 seen in phase 2 STABIL-B trial. There is 80% power to detect a 0.66 effect size; a 0.462 effect size would reach two-sided p=0.05. Two interim analyses are planned. The first interim analysis (IA) assessing safety will be conducted six weeks after the first 30-35 participants have been followed for 6 weeks and the second IA assessing futility (primary efficacy endpoint) will be performed after the first 45-50 participants have been followed for 6 weeks. Each interim analysis has a different objective with neither interim analysis spending any Type 1 error. The study will be stopped at the first interim analysis if Serious Adverse Events are deemed statistically significantly more common in the NRX-101 group compared to the lurasidone group in a manner deemed by the DMC to pose a potential danger to human subjects. The study will be stopped at the second IA for futility if the conditional power (CP) is less than 10%. In the event that the study is not stopped for either safety or futility, then enrollment will continue until a total of 74 subjects are randomized. This preserves two-sided p=0.05 for the final analysis.
Inclusion Criteria:	A patient is eligible for inclusion in this study only if all of the following criteria apply: 1. 18 to 65 years of age, inclusive, at Screening. 2. Able to understand and provide written and dated informed consent prior to Screening. 3. Deemed likely to comply with the study protocol, including communication of adverse events (AEs) and other clinically important information, including adherence to the text messaging component of the trial. 4. Will follow medical directions for psychiatric care, as appropriate, per the standard of care. ~~5.~~ Resides in a stable living situation. A stable living situation will be defined as a minimum of 3 months at the same address with a reasonable expectation that the situation will continue such that the patient's ability to participate in the study will not be affected. Please note that housing in a shelter of any kind will not be deemed stable housing. 6. Previously diagnosed and treated for Bipolar Disorder (BD) I or II according to the criteria defined in the DSM-V. 7. Has an identified reliable informant/care partner that is willing to provide information and/or supportive care as necessary. 8. The diagnosis of BD will have been made by a psychiatrist or other qualified licensed psychiatric provider able to render a diagnosis and be supported by the MINI 7.0.2. 9. Treatment with a medication indicated for use in bipolar disorder in the past five years (See Appendix 2 for list). 10. Confirmed active suicidal ideation, (without the intention to act) as evidenced by an answer of 'Yes' on item 3 and/or item 4 and not requiring hospitalization at Screening and an answer of "No" on item 5 of the C-SSRS within 4-weeks of Screening. 11. A total score greater than or equal to 30 on the 10 items of the MADRS.

	12. No co-morbidities as ascertained by medical history, physical examination (including measurement of vital signs), clinical laboratory evaluations, and electrocardiogram (ECG) which might interfere with compliance or the ability to assess efficacy or safety. 13. If female, a status of non-childbearing potential or use of an acceptable form of birth control per the following criteria, and agrees to continue use of the same method of birth control for the duration of study participation: a. Non–childbearing potential: physiologically incapable of becoming pregnant (i.e., permanently sterilized [status post-hysterectomy, bilateral tubal ligation], or post-menopausal with last menses at least one year prior to Screening); or b. Childbearing potential, and meets the following criteria: i. Use of any form of hormonal birth control for at least 2 months prior to Screening, on hormone replacement therapy that started prior to 12 months of amenorrhea, using an intrauterine device (IUD) for at least 1 month prior to Screening, in a monogamous relationship with a partner who has had a vasectomy, or sexually abstinent. ii. Negative urinary pregnancy test at Screening, confirmed by a second negative urinary pregnancy test at Day 1, prior to receiving study treatment. 14. Body mass index (BMI) between 18-40 kg/m^2; BMI up to 45 kg/m^2 is allowed with Medical Monitor review and approval. 15. If receiving concurrent psychotherapy, the type and frequency of the therapy (e.g., weekly or monthly) has been stable for at least 3 months prior to Screening and is expected to remain stable for the duration of study participation. 16. Concurrent hypnotic therapy (e.g., with zolpidem, zaleplon, melatonin, benzodiazepines, maximum 2 mg daily, or trazodone) will be allowed if the therapy has been stable for at least 4-weeks prior to screening and if it is expected to remain stable during the course of the patient's participation in the study. 17. Concurrent treatment with benzodiazepines is allowed up to a maximum dose 2mg/daily used for anxiety if therapy has been stable relative to dose and schedule for at least four-weeks prior to screening and if it is expected to remain stable during the course of the patient's participation in the study. 18. If women are receiving hormone replacement therapy or estrogen replacement, the therapy has been stable for at least 3 months prior to screening and is expected to remain stable for the duration of the study participation.
Exclusion criteria:	A patient is ineligible for inclusion in this study if any of the following criteria apply: 1. Female of childbearing potential who is not willing to use one of the specified forms of birth control during the study. 2. Female who is pregnant or breastfeeding. 3. Female with a positive pregnancy test at Screening or prior to randomization. **4.** Current DSM-5 diagnosis of moderate or severe substance use disorder (except marijuana or tobacco use disorder) within the 12 months prior to

	Screening. (Note: Substance use disorder cannot be the precipitant for study entry). **5.** A lifetime history of: a. phencyclidine (PCP)/ketamine drug abuse, or b. failed use of ketamine for depression or suicidality. 6. History of schizophrenia or schizoaffective disorder, or any history of psychotic symptoms when not in an acute bipolar mood episode. 7. History of anorexia nervosa, bulimia nervosa, eating disorder not otherwise specified (NOS), or other specified feeding and eating disorders (OSFED) within 3 years of Screening. 8. Has dementia, delirium, amnestic, or any other cognitive disorder. 9. Current major psychiatric disorder, diagnosed at Screening with the MINI 7.0.2 which is the primary focus of treatment, with bipolar disorder as the secondary focus of treatment, within the past 6 months. 10. Estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m^2 using the Cockcroft-Gault formula. 11. A clinically significant abnormality on the Screening physical examination that may affect safety or study participation, or that may confound interpretation of study results according to the study clinician. 12. Current episode of: a. Myocardial infarction within 1 year of Screening. b. Diagnosis of angina pectoris. c. Prolonged QTc interval, as measured by Fridericia's correction formula (QTcF) ≥450 msec at Screening for males or ≥ 470 msec for females on 2 of 3 measurements at least 15 minutes apart prior to randomization on Day 1. 13. Diagnosis of chronic lung disease, excluding asthma. 14. Lifetime history of any of the following: surgical procedures involving the brain or meninges, encephalitis, meningitis, degenerative central nervous system (CNS) disorder (e.g., Alzheimer's Disease, Parkinson's Disease), epilepsy, mental retardation, or any other disease/procedure/accident/intervention that, according to the clinician, is deemed associated with significant injury to, or malfunction of, the CNS. 15. History of significant head trauma within the past two years. 16. Diabetes mellitus fulfilling any of the following criteria: a. Unstable diabetes mellitus defined as glycosylated hemoglobin (HbA1c) >8.0 percent at Screening. b. Admitted to the hospital for treatment of diabetes mellitus or diabetes mellitus–related illness in the past 12 weeks. c. Not under physician care for diabetes mellitus. d. Not on the same dose of oral hypoglycemic drug(s) and/or diet for the 4 weeks prior to Screening. e. Not on the same dose of oral thiazolidinediones (glitazones) for the 8 weeks prior to Screening. 17. Any current or past history of any physical condition which, in the opinion of the investigator, may put the patient at risk or interfere with study results interpretation. 18. Diagnosis of HIV/AIDS.

	19. Diagnosis of Hepatitis C. 20. On exclusionary concomitant psychotropic and non-psychotropic medications (see Appendix 1). 21. Prescribed more than one agent in each of the following categories at randomization: a. Approved SSRIs. b. Approved serotonin and norepinephrine reuptake inhibitors (SNRIs). c. Approved tetracyclic antidepressants (TeCAs). Note: Any/all 5hT2A medications will be discontinued at study entry. Participants currently on Lurasidone will be randomized to either standard of care or NRX-101 at the indicated starting dose. 22. Currently prescribed oxcarbazepine or carbamazepine. 23. Exclusionary laboratory values or any other clinically significant abnormal laboratory result at Screening. Within normal limits (WNL) will be determined based on lab values of the local lab used. 24. Known allergies to lurasidone or Latuda®, cycloserine or Seromycin®, or the following excipients: mannitol, croscarmellose sodium, magnesium stearate, silicon dioxide, and/or hydroxypropylmethylcellulose (HPMC). 25. Participation in any clinical trial with an investigational drug or device within the past month or planned concurrent study participation. 26. Study site personnel and/or persons employed by NRx Pharma, Inc., the Contract Research Organization (CRO), the investigator, or study site (i.e., permanent, temporary contract worker, or designee responsible for the conduct of the study), or an immediate family member (i.e., spouse, parent, child, or sibling [biological or legally adopted]) of such persons. 27. Positive urine toxicity screening for use of any cocaine, opiates, non-prescribed amphetamines, or non-prescribed barbiturates. (Note: cannabinoids or marijuana use is not exclusionary, unless patient meets the DSM-5 criteria for cannabis withdrawal). 28. Signs and symptoms of active or residual COVID-19, or unresolved symptoms of COVID-19 that impact health, e.g. requirements for oxygen supplementation, etc. Discharged from an inpatient hospitalization for more than 48 hours for COVID-19 within the past 28 days.
Analysis Sets:	For efficacy analyses, the intent-to-treat (ITT) population is defined as all participants who are randomized and treated. The mITT population will be the subset with evaluable data from at least one subsequent visit; the mITT population will be used for the primay efficacy analyses. The PP population will exclude any subjects with major protocol deviation. The Safety population will include data from all participants who are randomized and receive at least one dose of investigational product as treated.
Pharmacokinetic Assessments:	None
Safety Assessments:	The safety of NRX-101 will be assessed via: • Adverse Events • Vital signs (blood pressure, heart rate), weight • 12-lead ECGs

	• Clinical laboratory evaluations • Physical examination findings **Other Assessments:** • Mean change from baseline to endpoint (Day 42/exit) in C-SSRS score • Mean change from baseline to Day 14 in C-SSRS score • Mean change in BARS through Day 42 to assess akathisia • Rates of discontinuation between arms.
Dosage, Route of Administration, and Schedule:	On Day 1, eligible participants will be randomized to blinded NRX-101 or lurasidone and placebo capsules administered twice daily (BID). Investigational product will be titrated over 2 days. In the case of randomization to NRX-101, the blinded investigational product will consist of daily doses of 700 mg DCS and 33 mg lurasidone and increasing the dose to 950 mg DCS and 66 mg lurasidone on second day. The total daily NRX-101 maintenance dose for Day 3 through Day 42 is 950 mg DCS and 66 mg lurasidone. In the event a patient experiences agitation or psychosis, a blinded up-titration is permitted. Similarly, a blinded step-down titration is allowed for somnolence. In order to maintain the blind, lurasidone/placebo capsules will be administered to ensure participants take the same number of capsules with each dose administration. NRX-101 is supplied in capsules that contain 237.5 mg or 175 mg of DCS and a second capsule that contains 8.25 mg, 16.5 mg, or 33 mg of lurasidone. In order to maintain the blind, lurasidone/placebo capsules will be administered to ensure participants take the same number of capsules with each dose administration. In the case of randomization to lurasidone, the blinded investigational product will start with doses of 33 mg lurasidone and increasing the dose to 66 mg. The total daily lurasidone maintenance dose for Day 3 through Day 42 is 66 mg.
Endpoint Adjudication	All rating sessions for MADRS-10 and C-SSRS will be recorded as audio files and reviewed by central master-raters with >25 years' experience. Any MADRS-10 total score the differs by more than three points from the master-rater score will be deemed non-congruent. All non-congruent subject-visits from any site with >10% non-congruent scores will be sent to an independent adjudicator previously determined to have >90% concordance with study master raters on standardized training data. In the event of adjudication as above, the independent outside rater score shall be considered as the subject-visit primary study endpoint.
Statistical Methods:	All randomized participants will be evaluated for depression (MADRS), suicidality (C-SSRS), and other efficacy endpoints while on the study. Analyses will be conducted under ICH E9 (R1) guidelines. C-SSRS is a safety endpoint. Change from baseline in MADRS total scores through study exit to compare treatments will be analyzed using Mixed Model Repeated Measures analysis (SAS PROC MIXED) with Last Observation Carried Forward (LOCF) containing sex, baseline use of mood stabilizers, baseline use of anti-psychotics, BPRS rating scale (none, any) and evidence of a suicidal event in their lifetime (none, any) as stratification factors in the analysis. Additional analyses will alternatively rely on multiple imputation to assess the impact of dropouts. The NRX-101 and lurasidone treatment groups will be compared using stratified and unstratified log rank tests, as well as a proportional hazard model for time to relapse.

Sample Size Calculation:	Participants will be randomized in a 1:1 ratio (NRX-101:lurasidone). With 37 participants per group, there is an 80 percent power to detect a mean 8.85-unit advantage for NRX-101 vs lurasidone for the CFB to Day 42, assuming a SD of 13.4 for NRX-101 versus lurasidone at 6 weeks for a two-sided hypothesis test with two-sided 5 percent Type I error. This equates to a 0.66 effect size.
Interim Analysis	Two interim analyses are planned. The first interim analysis (IA) assessing safety will be conducted six weeks after the first 30-35 participants have been followed for 6 weeks and the second IA assessing futility (primary efficacy endpoint) will be performed after the first 45-50 participants have reached 42 days post-randomization. Each interim analysis has a different objective with neither interim analysis spending any Type 1 error. The study will be stopped at the first interim analysis if Serious Adverse Events are deemed statistically significantly more common in the NRX-101 group compared to the lurasidone group in a manner deemed by the DMC to pose a potential danger to human subjects. The study will be stopped at the second IA for futility if the conditional power (CP) is less than 10%. In the event that the study is not stopped for either safety or futility, then enrollment will continue until a total of 74 subjects are randomized. This preserves two-sided p=0.05 for the final analysis.

4. TABLE OF CONTENTS

List of Tables

List of Figures

5. LIST OF ABBREVIATIONS

Abbreviations	Full Terms
ACPC	Aminocyclopropanecarboxylic Acid
AE	Adverse Event
SSIB	Subacute Suicidal Ideation or Behavior
BARS	Barnes Akathisia Rating Scale
BDRM	Biostatistics Data Review Meeting
BID	Twice Daily
BMI	Body Mass Index
BPI	Bipolarity Index
BPRS(+)	Brief Psychiatric Rating Scale(+)
CFB	Change from Baseline
CFR	Code of Federal Regulations
CGI-SS	Clinical Global Impressions of Severity for Suicidality
CHF	Congestive Heart Failure
CHRT-C	Concise Health Risk Tracking-Clinician
CHRT-SR	Concise Health Risk Tracking-Self Report
CLIA	Clinical Laboratory Improvement Amendments
Cmax	Maximum Concentration
CNS	Central Nervous System
CP	Conditional Power
CRO	Contract Research Organization
C-SSRS	Columbia Suicide Severity Rating Scale
DCS	D-cycloserine
DSM-5	Diagnostic and Statistical Manual of Mental Disorders Fifth Edition
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
ECT	Electroconvulsive Therapy
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	Glycosylated Hemoglobin
HDPE	High Density Polyethylene
HIPAA	Health Insurance Portability and Accountability Act
HPMC	Hydroxymethylcellulose
ICH	International Conference on Harmonisation
ITT	Intent-to-Treat
IUD	Intrauterine Device
IWRS	Interactive Web Response System
Lurasidone	Lurasidone HCl
LOCF	Last Observation Carried Forward
MADRS	Montgomery Asberg Depression Rating Scale
MDD	Major Depressive Disorder
MMRM	Mixed Model Repeated Measures
NMDAR	N-methyl-D-aspartate Receptor

NOS	Not Otherwise Specified
OSFED	Other Specified Eating Disorder
PCP	Phencyclidine
PRISE	Patient Rated Inventory of Side Effects
QTcF	Fridericia's Correction Formula
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SIBAT	Suicide Ideation and Behavior Assessment Tool
SNRI	Serotonin and Norepinepherine Reuptake Inhibitors
SOP	Standard Operating Procedure
SSRI	Selective Serotonin Reuptake Inhibitor
TB	Tuberculosis
TeCA	Tetracyclic Antidepressant
TTF	Time to Treatment Failure

6. INTRODUCTION

6.1 Suicidal Ideation and Behavior in Bipolar Disorder

Bipolar Disorder (formerly known as manic depressive disorder) is a well-established psychiatric diagnosis, with a prevalence of about 2.6% in the United States (approximately 8.5 million people) (Kessler et al., 2005). The risk of subacute suicidal ideation or behavior (SSIB) is uniquely high in patients during bipolar depressive episodes, compared to those with major depressive disorder (MDD), thought disorders, and personality disorders. Lifetime suicide behavior occurs in 25% to 56% of people with bipolar disorder (Nierenberg et al., 2001). About 40% of the nearly 50,000 annual deaths from suicide in the United States are associated with bipolar disorder (Mahli et al., 2015). The overall rate of death by suicide among patients with bipolar disorder is 164 per 100,000 person years, compared to about 14 per 100,000 person years for the general population. Those who have attempted suicide are 2.3 times more likely to die by suicide compared to those without a suicide attempt (Coryell et al., 2016). Thus, bipolar depression with suicidal ideation has uniquely lethal clinical characteristics (Pompili, et al., 2013).

6.2 Current Treatment Options

Despite its lethal characteristics, there is no approved pharmacologic treatment for patients with bipolar depression and suicidal ideation. Electroconvulsive therapy (ECT), often combined with inpatient psychiatric care, remains the only Food and Drug Administration (FDA)-approved treatment for patients with acute suicidal ideation in bipolar depression, despite ECT's well-documented side effects that include memory loss and confusion, along with its high cost. However, the toxicity of ECT is such that it is less likely to be used in patients with subacute levels of suicidal ideation and no oral medication has been shown to reduce suicidal ideation in patients with depression in general or bipolar depression in specific. Physicians are increasingly cautious about the use of selective serotonin release inhibitors (SSRIs), particularly in patients with suicidal ideation because of evidence that SSRIs and other antidepressants may actually increase the risk of suicidal ideation, particularly in younger patients (Stone et al., 2009). This evidence has resulted in an FDA warning on the label of current antidepressants. Moreover, it seems clear that antidepressants do not decrease SSIB in proportion to their mitigating effect on symptoms of depression.

In recent years, several combined D2/5-HT2A antagonists have shown efficacy in treating bipolar depression (olanzapine/fluoxetine combination, quetiapine, and lurasidone) with treatment guidelines endorsing common use as first-line standard of care treatment in acute bipolar depression. While these medications are effective at reducing overall symptoms of depression, they do not specifically reduce suicidal ideation, as shown in recent clinical trials of lurasidone (Loebel et al., 2014a; Loebel et al., 2014b). Moreover, in these two studies, individuals with active suicidal ideation (Montgomery Asberg Depression Rating Scale [MADRS] item 10 $\geq$ 4) were specifically excluded because of concerns regarding the possibility of exacerbating suicidality with these medications. Similarly, acutely suicidal patients are routinely excluded from clinical trials of other experimental anti-depressive agents. Thus, bipolar depression with suicidal ideation

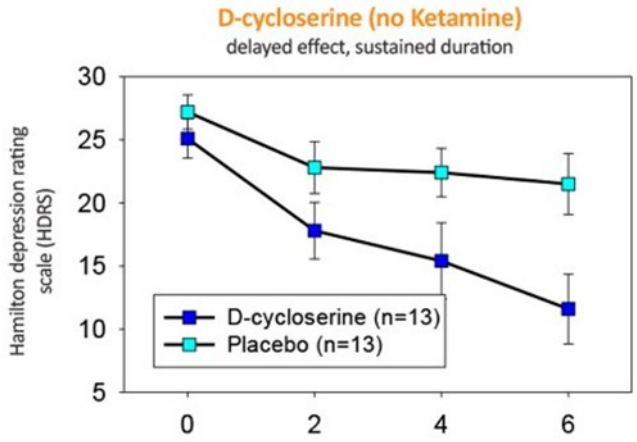
represents a major unmet medical need that must frequently be treated with voluntary or involuntary hospitalization under highly supervised conditions and ECT.

6.3 Clinical Experience with DCS

Antidepressant effects of high-dose DCS were first noted in the late 1950s, when it was introduced as a treatment for tuberculosis (TB). Several clinicians noted dramatic improvement in patients' depressive symptoms, leading to suggestions of DCS' potential psychotropic effects. These effects were subsequently confirmed in small-scale clinical studies (Crane, 1959 and 1961). The mechanism of action was unknown at the time, and the finding was not pursued. The interaction of DCS with the NMDAR was first demonstrated in 1989 (Hood et al., 1989), leading to some interest in NMDAR blockers as potential antidepressant treatments (Trullas and Skolnick, 1990; Skolnick et al., 1996). For example, both DCS and the related compound aminocyclopropanecarboxylic acid (ACPC) were shown to be active in mice, using the forced swim test for depression (Lopes et al., 1997). To the best of our knowledge, no clinical antidepressant research programs targeting the NMDA receptor were initiated at that time.

Interest in the potential clinical use of DCS as an antidepressant agent was renewed following Berman's fortuitous observation of ketamine's rapid antidepressant effect (Berman et al., 2000). An initial study performed with DCS at a dose of 250 mg/day did not show therapeutic effects, but it did demonstrate a relative lack of psychotomimetic side effect when DCS was combined with concurrent antidepressant treatment (Heresco-Levy et al., 2006). Based upon these safety data, a study using a higher dose of 1000 mg/day was initiated, with results reported in 2013 (Heresco-Levy et al., 2013). At the higher dose of 1000 mg/day, significant beneficial effects were observed in 13 subjects vs. placebo control with SSRI-nonresponsive depressive symptoms. The improvements were manifested within 2 weeks and persisted throughout the 6-week treatment period. These data suggest a >0.9 effect size. In that study, a slow DCS titration was used, with 250 mg/day for 3 days, followed by 500 mg/day for 18 days (i.e., until the end of week 3); followed by 750 mg/day for 1 week (i.e., until the end of week 4), followed by 1000 mg/day (i.e., until the end of study). A statistically significant improvement was observed in the DCS group compared to placebo by the end of week 4, i.e., within 1 week of initiation of a DCS dose >500 mg/day (see Figure 1).

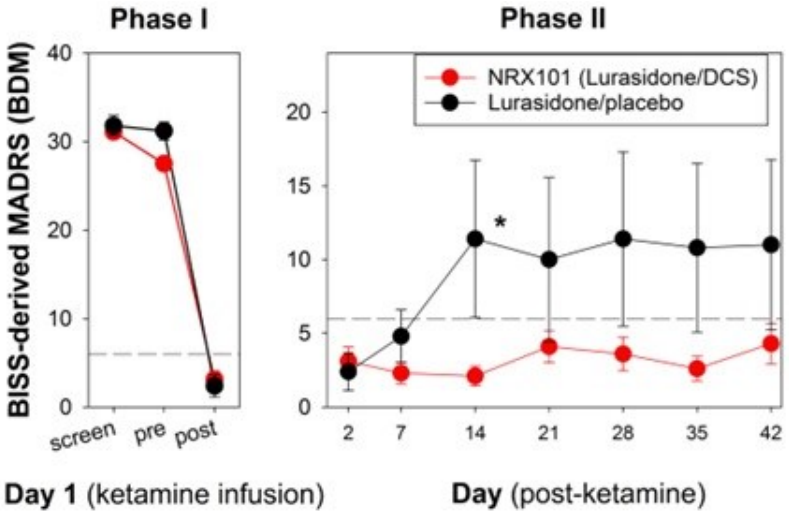
Figure 1 DCS vs. Placebo for Treatment of Depression



The data above provided initial evidence that DCS may be useful as an NMDAR-targeted antidepressant, but the time of onset for DCS alone was suboptimal for treating acutely depressed individuals (Figure 1).

The data below provides evidence of efficacy from a study of NRX-101 versus Lurasidone in patients with severe bipolar depression (MADRS ≥ 30) and Acute Suicidal Ideation or behavior (C-SSRS 4 or 5), after an initial stabilization with a single infusion of ketamine.

Figure 2 Randomization to NRX-101 vs. lurasidone following stabilization with ketamine



Source: Javitt et. al. 2018

6.4 Investigational Therapy

In accordance with FDA experience with lurasidone being used to successfully treat depression in bipolar disorder, participants will be randomized on Day 1 in a 1:1 ratio (NRX-101:lurasidone + placebo) and will receive maintenance treatment with matched twice-daily oral capsules. Participants will continue oral therapy through Day 42, according to treatment assignment.

It is anticipated that participants will also be receiving concurrent bipolar disorder–directed treatment with various predefined combinations of medications. This treatment regimen will be maintained upon entry into the study. However, any use of lurasidone, quetiapine, aripiprazole, risperidone, brexpiprazole, olanzapine, cariprazine, or lumateperone, will be discontinued at study entry. The treating psychiatrist should ensure that any medications to be discontinued can be done so safely. At entry, at the discretion of the investigators or the delegated treating physician subjects may continue their mood stabilizers which should not change over the course of the trial. In addition, participants receiving olanzapine/fluoxetine combination will continue to receive the fluoxetine component.

6.5 Dose Selection

Lurasidone is an FDA-approved medication for depressive episodes associated with Bipolar I Disorder (bipolar depression) as monotherapy and as adjunctive therapy with lithium or valproate at doses of 20 mg to 120 mg daily. The target dose of 66 mg/day is based on the mean daily dose of lurasidone observed during the fixed titration phase of the lurasidone registration trial for its indication in bipolar depression (Loebel et al., 2014b) and further validated in the STABIL-B trial (Javitt, et. al. 2018). Up-titrations are permitted if needed to doses of 99 or 132 mg/day, and down-titrations are permitted to 33 or 49.5 mg/day, which span the range of doses used in clinical studies of lurasidone (Loebel et al., 2014a; Loebel et al., 2014b).

DCS is well tolerated as a second-line treatment for TB at therapeutic split daily oral doses in the range of 500 to 1000 mg/day. Based on prior clinical results and animal studies, it is anticipated that therapeutic effects of DCS will be associated with plasma doses in excess of 25 µg/mL, which in turn are generally associated with daily oral doses in excess of 10 mg/kg (i.e., 700 mg/day for a 70 kg) individual. A starting daily dose at 700 mg DCS and 33 mg lurasidone will be used, and then titrated over 2 days to the target dose of 950 mg DCS and 66 mg lurasidone. Down-titrations of DCS to 825 or 700 mg/day are available in the case of side effects to permit reduced dosing within the anticipated therapeutic range (700 – 950 mg/day). The maximum dose of 950 mg/day is within FDA-approved dosing limits for DCS.

7. OBJECTIVES

7.1 Primary Efficacy Objective

The primary objective of the study is:

- To test the hypothesis that treatment with NRX-101 is superior to lurasidone (a standard of care medicine) in improving symptoms of depression as measured by the Montgomery Åsberg Depression Rating Scale (MADRS-10) total score in participants with severe bipolar depression and subacute suicidal ideation or behavior (SSIB).

7.2 Secondary Efficacy Objectives

- To test the hypothesis that treatment with NRX-101 is superior to standard of care (lurasidone) in reducing suicidal ideation (MADRS item 10).
- To test the hypothesis that treatment with NRX-101 is superior to lurasidone in the change from baseline to Day 14 in MADRS total score.
- To test the hypothesis that treatment with NRX-101 is superior to lurasidone in reducing the frequency of suicidal thoughts, suicidality and risk (SIBAT Module 7).
- To test the hypothesis that NRX-101 is superior to lurasidone in reducing suicidal ideation or behavior as measured by the Clinical Global Impression of Severity of Suicidality Scale (CGI-SS)
- To test the hypothesis that NRX-101 is superior to lurasidone in time to treatment failure as defined as: study discontinuation due to adverse events; psychiatric hospitalization; or requiring a change in antidepressant treatment.
- To test the hypothesis that treatment with NRX-101 is superior to treatment with lurasidone in the subgroup of participants recently (i.e. within two weeks of enrollment) treated with approved medications for bipolar depression (olanzapine/fluoxetine, quetiapine, cariprazine, lumateprone, or lurasidone).
- To test the hypothesis that treatment with NRX-101 is superior to treatment with lurasidone in the subgroup of participants recently (i.e. within two weeks of enrollment) treated with approved medications for bipolar depression.
- To further test the hypothesis that treatment with NRX-101 is superior to treatment with lurasidone in the subgroup of participants recently (i.e. within two weeks of enrollment) treated with any 5-HT2A agonist for the primary efficacy endpoint.

7.3 Additional Efficacy Objective

- To display NRX-101 vs Lurasidone change from baseline for each MADRS-10 question as well as the three Borentain factors at each post-baseline evaluation including exit.

7.4 Safety Objectives

- To test the hypothesis that treatment with NRX-101 is superior to lurasidone (a standard of care drug) in reducing suicidality in depressed bipolar participants with SSIB, as measured by the Columbia Suicide Severity Rating Scale (C-SSRS)
- To test the hypothesis that remission from suicidality, measured as Week 6 percent with C-SSRS ≤ 3 will be superior for NRX-101 relative to lurasidone

- To test the hypothesis that participants treated with NRX-101 are less likely to suffer from akathisia than those treated with lurasidone as measured by the Barnes Akathisia Rating Scale (BARS)
- To test the hypothesis that fewer participants treated with NRX-101 will be discontinued for lack of efficacy or exacerbation of suicidality than participants treated with lurasidone.

8. STUDY DESIGN

This is a group sequential, multicenter, randomized, double-blind, parallel-group, two-arm study comparing NRX-101 (n=37) to lurasidone (n=37) in a 1:1 ratio for the treatment of bipolar depression in participants with subacute levels of suicidal ideation, as reflected by the patient answering "yes" to item 3 and 4 on the C-SSRS within 4-weeks of screening, and do not require hospitalization.

Participants will be screened to ensure study eligibility prior to randomization on Day 1. Randomized participants will take either oral NRX-101 or lurasidone and placebo, in accordance with their treatment assignment, for 42 days. Participants will return to the investigational site on Day 70 for a follow-up visit (see Study Schema, Figure 3). During these visits, multiple psychometric scales will be completed, and participants will be assessed for safety, including the risk of increase in depression or suicidal ideation to the point where inpatient care or an alternative treatment is indicated.

Figure 3 Study Schema

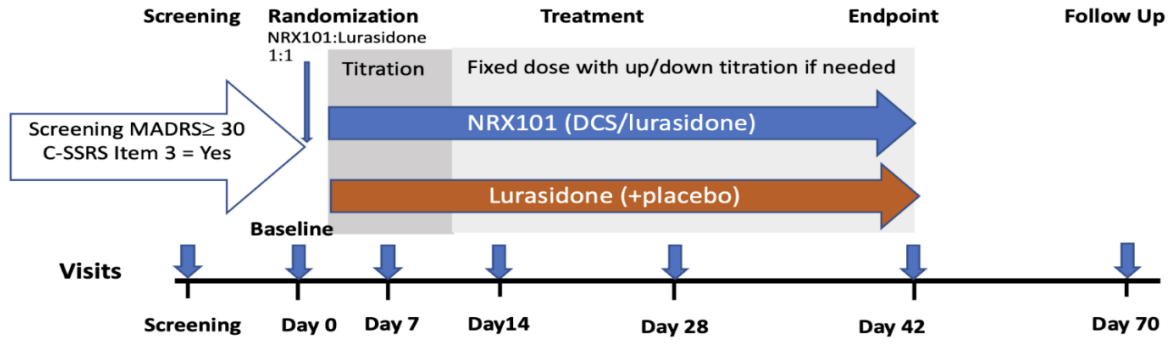


Table 1 Schedule of Assessments

	Screening	Treatment					Follow up[1]
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Study Day	**Day -10 to -1**	**Day 1[2] Baseline**	**Day 7**	**Day 14[3]**	**Day 28[3]**	**ET/Day 42[3]**	**Day 70**
Informed Consent	X						
Eligibility Review	X	X					
Randomization		X					
Demographics	X						
Medical History	X						
Psychiatric History	X						
MINI	X						
MINI Severity/Disability		X				X	
Subject Eligibility	X	X					
Physical Exam[4]	X					X	
Vital Signs, Weight[5]	X	X		X	X	X	
ECG[6]	X	X				X	
Pregnancy Test (Urine dipstick)	X	X					
Drugs of Abuse Screen (Urine dipstick) [7]	X	X	X	X	X	X	
Fasting Chemistry, Hematology	X					X	
C-SSRS[8]	X	X	X	X	X	X	
MADRS	X	X	X	X	X	X	
CGI-SS	X	X	X	X	X	X	
CHRT-C, -SR	X		X	X	X	X	
BPRS psychosis subscale	X	X	X	X	X	X	
BARS [12]	X	X	X	X	X	X	
PRISE	X	X	X	X	X	X	
Adverse Events		X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X
Adherence device training[9]		X					
Dispense investigational product and review adherence[10]		X	X	X	X		
Site monitoring of adherance[11]			X	X	X	X	

[1] Follow up visit will be a phone call; the study visit may occur within ± 7 days of the scheduled day (anchored to the Day 1 visit).

[2] Day 1 procedures need to meet eligibility criteria and will be performed prior to first dose.

[3] Study visits occurring after Day 7 may occur within ± 3 days of the scheduled day (anchored to the Day 1 visit). Study visits 3, 4, 5, 7 may be done virtually, preference is through videoconference.

[4] Full physical exam (including a neurological exam and height) at Screening and Visit 6 will be performed, and a brief exam (Blood Pressure, Respiration Rate, Heart Rate, and Temperature) will be performed at subsequent time points.

[5] After 5 min at rest, supine or sitting systolic and diastolic blood pressure and heart rate are recorded at each indicated visit. Weight is measured only at Screening and Visits 2,4,5, and 6.

[6] 12-lead ECG.

[7] Subjects who have 2 consecutive positive urine screens should be withdrawn from study, in case of a subject not being able to visit a site due to COVID-19 restrictions or impediments arrangements should be made for an outpatient test, or the investigators should note this and make an assessment during the tele visit, annotation should be included in the EDC why the drug screen text could not be done. In the case where the subject has 2 consecutive negative urine screens, the subject can skip

the next urine screen. Investigators can bring the subject in for a urine screen at any time if suspected drug use. Note: Since Cannabis use is not exclusionary, a positive UDS will not require that patient be withdrawn from the study.

[8] "Baseline" version should be administered at screening and "Since Last Visit" version should be administered at all other time points.

[9] Adherence device training should be performed pre-dose on Day 1 or with the first dose. Additional training will be provided as necessary. The subject's cellphone number will be input in a secure field of the EDC by the study site personnel, this field will only be accessible to designated study site personnel. The system will send a text message at designated hours to the subject as a reminder to take study the medication. The subject must respond affirmatively to enable compliance tracking. Absence of a response or a negative response will trigger a notification to the site.

[10] Medication adherence will be reviewed and returned pills recorded.

[11] Sites will monitor / review compliance for a target goal of 85 percent compliance of all doses taken. If more than 2 consecutive doses are missed they should contact the subject and counsel the subject on the need for compliance before the next scheduled dose.

[12] Rating akathisia using BARS needs to be a video call if completed remotely and will be documented.

9. EFFICACY ASSESSMENTS

Study procedures are described below. Assessment time points are included in the Schedule of Assessments (

Table 1).

9.1 Montgomery Asberg Depression Rating Scale (MADRS)

The Montgomery Åsberg Depression Rating Scale is a 10-item clinician-rated scale, with each item rated on a 0–6 severity scale (Montgomery, Åsberg 1979). The timeframe for the baseline MADRS-10 recorded at Screening and Day 1 is the past seven days; for the MADRS-10 recorded at all time points thereafter, the timeline measured will be since the last assessment.

9.2 Clinical Global Impression-Severity for Suicide

The three Clinical Global Impression scales represent the final three global ratings from the Suicidality Ideation Inventory and Behavior Assessment Tool (SIBAT Module 7), which is designed for the clinician to assess the relative risk and overall risk of suicide across different time scales (Alphs et al., 2016). The questions assess the clinician's global impression of immediate risk of suicide (that day), imminent risk of suicide (over the next 7 days), and long-term risk (i.e., likely to end their life by suicide sometime in the future). Each risk (immediate, imminent, long-term) is rated along a graded impressions scale starting at 0 ('normal', 'not suicidal' or 'no risk') and ranges to 6 ('among the most extremely suicidal' or 'extreme risk for imminent'/'long-term suicide').

9.3 Brief Psychiatric Rating Scale (BPRS psychosis subscale)

Overall the Brief Psychiatric Rating Scale (BPRS) is an 18-item clinician-rated scale that assesses a range of psychotic and affective symptoms, rated from both observation of the patient and the patient's own report (Overall and Gorham, 1962). Only the 4-item positive symptom subscale referred to in this document as the "BPRS psychosis subscale" (i.e., suspiciousness, hallucinations, unusual thought content, and conceptual disorganization) will be used.

9.4 Concise Health Risk Tracking – Self Report (CHRT-SR) and Clinician Rating (CHRT-C)

The Concise Health Risk Tracking – Self Report (CHRT-SR) and – Clinician (CHRT-C) are assessments of suicidality and related thoughts and behaviors (Trivedi et al., 2011). The CHRT-SR is a 16-item self-report suicidal ideation scale, and the CHRT-C is a 9-item clinician-rated behavioral module. Items are rated on a fully anchored five-point Likert scale with responses ranging from 1 (strongly disagree) to 5 (strongly agree). The time frame is the past seven days.

10. OTHER DIAGNOSTIC INSTRUMENTS

10.1 Mini International Neuropsychiatric Interview (MINI) 7.0.2

The MINI (Sheehan et al., 1998) is a short, structured diagnostic interview developed initially in 1990 by psychiatrists and clinicians in the United States and Europe for DSM-III-R and ICD-10 psychiatric disorders. The tool has been updated to map to DSM-5 diagnostic criteria in the MINI 7.0.2.

10.2 Bipolarity Index (BPI)

BPI was not collected in this study. The BPRS will be used instead of the BPI to rate the cardinal features of bipolar disorder across five domains: episode characteristics (signs and symptoms); age of onset (first episode); course of illness; response to treatment; and family history.

11. ASSESSMENT OF EFFICACY

11.1 Primary Efficacy Endpoint

The primary efficacy endpoint is:

- Mean change from baseline in total MADRS score

11.2 Secondary Efficacy Endpoints

The secondary efficacy endpoint are:

- Change from baseline over 42 days in CGI-SS
- Time to treatment failure

11.3 Additional Efficacy Endpoints

- Change from baseline in Suicidal Thoughts on the MADRS (MADRS item 10)
- Change from baseline to Day 14 in MADRS total score
- Change from baseline for each MADRS-10 factor as per Borentain at each post-baseline evaluation including exit
- Change from baseline in each item of the Suicide Ideation and Behavior Assessment Tool (SIBAT) Module 7 (clinical global impressions of frequency of suicidal thinking, severity of suicidality, and imminent and long-term risks)
- Change from baseline to endpoint (Day 42/exit) in MADRS total score in the subgroup of participants who were recently (within 2-weeks) on approved medications for bipolar depression
- Percent in remission at Day 42/exit.

12. ASSESSMENT OF SAFETY

Study procedures are described below. Assessment time points are included in the Schedule of Assessments (

Table 1).

12.1 Safety Scales

12.1.1 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a low-burden measure of the spectrum of suicidal ideation and behavior that was developed in the National Institute of Mental Health Treatment of Adolescent Suicide Attempters Study to assess severity and track suicidal events through any treatment (Posner et al., 2007). The timeframe for assessment is for both lifetime and the past 4-weeks for the Screening scale and since the last visit for all other ratings.

12.1.2 Patient Rated Inventory of Side Effects (PRISE)

The Patient Rated Inventory of Side Effects (PRISE) is a self-rated questionnaire (Rush and Asberg, 1999; Wisniewski et al., 2006) will be used to assess the specific symptoms considered by participants to be more or less tolerable drug side effects. The timeframe for assessment is at Screening for the Screening scale and in the past week for all other ratings.

12.1.3 Barnes Akathisia Scale (BARS)

The Barnes Akathisia (BARS) (Barnes, 1989) is a clinician-rated scale to assess drug-induced akathisia as absent, mild, moderate, or severe. It comprises items for rating the observable, restless movements which characterize the condition, the subjective awareness of restlessness, and any distress associated with the akathisia. In addition, there is an item for rating global severity. The timeframe for the scale is “at this time.”

12.2 Adverse Events and Serious Adverse Event

12.2.1 Definition of Adverse Events

An AE is any untoward medical occurrence in a clinical study patient administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship to the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product.

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

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Maximum intensity or changes in intensity
- Whether the AE is serious or not (see Section 12.2.4)
- Expectedness
- Investigator assessment of relationship to investigational product
- Action taken with regard to the investigational product (uptitration, downtitration, temporarily discontinued, permanently discontinued or no action taken)
- AE caused patient's withdrawal from the study (yes or no)
- Outcome

Adverse events will be collected from the time of signature on the informed consent form throughout the Follow-up visit or early termination. Whenever possible, diagnoses will be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion will be reported as "upper respiratory infection").

Worsening symptoms of the primary study condition (i.e., bipolar depression) will be recorded as a primary endpoint rating.

Any AE(s) that are unresolved at the follow-up visit (Day 70) will continue to be followed by the investigator for as long as medically indicated, but without further recording in the eCRF. The Contract Research Organization (CRO) and its representative retain the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if deemed medically necessary.

12.2.2 Adverse Event Intensity and Relationship

Intensities for each AE will be assessed by the investigator as:

- Mild: Awareness of sign or symptom, but easily tolerated;
- Moderate: Discomfort sufficient to cause interference with normal activities; or
- Severe: Incapacitating, with inability to perform normal activities.

Relationship to investigational product will be assessed by the investigator according to the following categories:

- Not Related: Clearly and incontrovertibly due only to extraneous causes and does not meet criteria listed under possible or probable.

- Unlikely Related: Does not follow a reasonable temporal sequence from administration. May have been produced by the patient's clinical state or by environmental factors or other therapies administered.
- Possibly Related: Follows a reasonable temporal sequence from administration but may have been also produced by the patient's clinical state, environmental factors, or other therapies administered.
- Related: Clear-cut temporal association with administration with improvement on cessation of investigational product or reduction in dose. Reappears upon re-challenge. Follows a known pattern of response to the investigational product.

12.2.3 Recording of Adverse Events

AE(s) spontaneously reported by the patient in response to an open-ended question from study personnel, such as, "Have you had any health problems since the previous visit?" or that are revealed by observation will be recorded at each visit. When reporting AE(s), the recording of diagnosis is preferred (when possible), rather than reporting the list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Participants should be encouraged to contact the investigator or a member of the clinical site staff at any time between visits concerning AE(s)or worsening of symptoms.

12.2.4 Definition of Serious Adverse Events

The following criteria define an SAE:

- Death
- Life-threatening event
- Inpatient hospitalization >24 hours or prolongation >24 hours of inpatient hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Medically important event, as defined in this protocol*

*Medical and scientific judgment will be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These will usually be considered serious.

In addition, the following variables will be collected, where applicable, for SAEs:

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- Description of SAE

- Explanation of seriousness of the AE
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to investigational product
- Causality assessment in relation to other medication

It is important to distinguish between serious and severe AE(s). Severity is a measure of intensity, whereas seriousness is defined by these criteria. An AE of severe intensity need not necessarily be considered serious. If inpatient hospitalization results from worsening psychiatric symptoms or suicidal ideation, the hospitalization will be reported as an SAE.

SAEs will be reported from the time of informed consent through the Follow-up visit or early termination. Unsolicited SAEs will be collected up to 30 days after the last study treatment.

12.2.5 Reporting Serious Adverse Events

When an SAE is discovered, it will be reported immediately (within 24 business hours of the site's knowledge of the event) to the Sponsor/CRO Medical Monitor. Reportable events which do not meet the criteria for an SAE will include (but will not be limited to): (a) pregnancy, and (b) clinically significant (in the judgment of the investigator) severe psychiatric complications.

The eCRF will provide a mechanism for sites to report SAEs, and for investigators and the Medical Monitor to sign off on the SAE reports.

Reportable SAEs will be sent to the FDA by the sponsor and sites will be notified. Sites are responsible for submission of SAE reports to their IRB(s), in accordance with IRB policies.

12.2.6 Anticipated Serious Adverse Events

Tan et al (2021) publication Identifying Anticipated Events of Future Clinical Trials by Leveraging Data from the Placebo Arms of Completed Trials looked at 18 Randomized, double-blind, controlled trials of Bipolar Depression that met similar inclusion and exclusion criteria to identify the most common Serious Adverse Events.

Based on this publication, the anticipated Serious Adverse Events are:

- Hospitalization, psychiatric symptoms
- Suicidal behavior, overdose
- Cholecystitis
- Fall
- Road traffic accident, injury

12.2.6.1 Overdose

Overdose of the investigational product will be considered an SAE, even when there are no symptoms or additional AEs, and will be reported according to the guidelines in Section 12.2.5. An overdose associated with symptoms must be reported as an AE.

12.2.6.2 Suicidal Ideation and Clinical Management

The documentation and proper management of suicidal ideation by sites will be documented with the use of the C-SSRS, completed by site clinicians during all visits. Safety will be evaluated throughout the course of the study.

Any patient who, based on the investigator's judgment, poses an imminent risk of suicide should be discontinued from the study. Suicide risk is assessed by the clinician at every visit.

Suicide, self-harm, and attempted suicide, irrespective of the method, will be reported as AEs (all suicides are SAEs; attempted suicides are considered to be SAEs). The event will be identified as suicide or attempted suicide, and the method of the suicide or attempt will be provided. If an attempted suicide meets the criteria for an SAE, the event must be reported according to the guidelines in Section 12.2.5. If a suicide attempt does not meet the criteria for an SAE, it will be considered a reportable AE, and a Suicidal Ideation or behavior Reportable Event Form will be completed by the investigator and submitted in accordance with the SAE reporting procedure in Section 12.2.5.

12.2.6.3 Pregnancy

If a patient (or patient's partner) becomes pregnant during the study, it must be reported within 24 business hours of the time the investigator becomes aware of the event and in accordance with the procedures described on the Pregnancy Report Form. Although pregnancy itself is not regarded as an SAE/AE, unless there is a suspicion that a study drug may have interfered with the effectiveness of a contraceptive medication, the pregnancy details will be captured in the AE/SAE module of the eCRF. Any pregnancy that occurs from Visit 1 to 30 days following the last dose given will be followed for gestational outcome, and the outcome will be reported to the sponsor. The female patient will be discontinued from investigational product, but will continue to attend study visits for the duration of her participation in the study.

12.3 Concomitant Medications, Therapies, and Alcohol Restrictions

12.3.1 Concomitant Medications

Lurasidone is contraindicated with the use of strong CYP3A4 inhibitors (e.g., ketoconazole) and strong CYP3A4 inducers (e.g., rifampin) (see Appendix 1). The lurasidone dose should not exceed 40 mg/day if co-administered with moderate CYP3A4 inhibitors. There are no known reported interactions between DCS and lurasidone.

It is anticipated that participants entering the study will be receiving concurrent disorder-directed treatment with various combinations of medications, including:

- Approved antidepressants (e.g., SSRIs, SNRIs, TeCAs, fluoxetine), but not 5-HT-2A antagonists (lurasidone, aripiprazole, olanzapine/fluoxetine, quetiapine, cariprazine, or lumateperone)
- Mood stabilizers (e.g., lithium, valproic acid, and lamotrigine)

Participants will be permitted into the study if they are treated with no more than one drug from each category of the indicated classes. Approved antidepressants and mood stabilizers will be maintained at stable dosages throughout the study. This is both to ensure continued treatment and to prevent withdrawal symptoms that may occur if such drugs are rapidly discontinued. Participants—taking aripiprazole, risperidone, brexpiprazole, lumateperone, olanzapine, cariprazine, or quetiapine will discontinue these medications prior to Randomization in order to avoid overlap with lurasidone.

Allowed concomitant medications include any prescription or over-the-counter medication not specifically excluded by the protocol (see Appendix 1), as well as stable, ongoing antidepressant or mood stabilizer therapy and stable allowed hypnotic therapy. Participants requiring excluded medications will be discontinued from the study and an Early Termination Visit will be performed in accordance with Protocol Section 9.1.3.

Prohibited concomitant medications that the patient and the investigator agree to discontinue for the purpose of study entry will be washed out for a period defined by the Investigator in consultation with the Medical Monitor. In the event concomitant medication washout is appropriate for a patient per investigator judgment, the patient must sign the informed consent form prior to beginning the washout period. Clinically appropriate tapering regimens should be used, if applicable. The Screening period may be extended, upon consultation with the Medical Monitor, to allow for a sufficient washout period.

All concomitant medications taken during the study and 4-weeks prior to study entry will be recorded in the electronic case report form (eCRF) for each patient, along with dosage information and start and stop dates.

12.3.2 Concomitant Therapy

Participants receiving concurrent psychotherapy that has been stable in type and frequency (e.g., weekly, monthly) for at least 3 months prior to Screening are eligible for study entry if the psychotherapy is expected to remain stable for the duration of the patient's participation in the study. Any changes in psychotherapy type and/or frequency during the study should be discussed with the Medical Monitor as soon as the investigator is aware of the proposed change.

12.3.3 Alcohol Restrictions

Participants should not use alcohol during the study. Ethyl alcohol may increase the possibility and risks of seizures in participants with a history of alcoholism receiving cycloserine.

12.3.4 Positive Drug Screen

Participants who have a positive urine drug screen two times in a row for use of any cocaine, opiates and non-prescribed amphetamine and non-prescribed barbiturates will be withdrawn from the study.

12.4 Laboratory/Diagnostic Procedures

Clinical laboratory safety testing will be performed locally at the study site using a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory. The frequency and type of procedures are detailed in the Schedule of Assessments (

Table 1). Local laboratory normal ranges must be reported according to gender.

Participants will have their blood drawn for clinical chemistry (ALT, AST, GGT, ALK phosphatase, Creatinine, T4, T3,TSH, Albumin, BUN, Calcium, Sodium, Potassium, Chloride, Glucose, Total Bilirubin, Direct Billirubin, Total Protein, Total Cholesterol, HDL/LDL, Triglycerides, Uric Acid, HbA1c) and hematology testing (Red blood cell count, White blood cell count, Platelet count, Hemoglobin, Hematocrit, Neutrophils Absolute or percent, Lymphocytes Absolute or percent, Monocytes Absolute or percent, Eosinophils Absolute or percent, Basophils Absolute or percent). Urine sample testing for pregnancy and drug screen will be by dipstick. In the event of clinically significant abnormal laboratory test result(s), follow-up laboratory testing may be conducted, at the discretion of the investigator. If applicable, clinically significant changes from baseline in laboratory results will be noted as AE(s), in accordance with Section 12.2.1.

12.5 Physical Examinations, Vital Signs, Height, and Weight

Physical examinations, vital signs, height, and weight will be obtained at the noted visits. Vital signs (blood pressure and heart rate) may be repeated 15 min apart, as needed, in order to obtain a resting reading. If applicable, clinically significant changes from baseline in physical examination parameters, vital signs, and weight will be noted as AE(s), in accordance with Section 12.2.1.

12.6 Electrocardiograms

Twelve-lead ECGs will be obtained after the patient has been resting in a semi-recumbent position for at least 5 minutes. All digital ECGs will include the date and time obtained, heart rate, QRS duration, PR interval, RR interval, QT interval, and QTcF interval using Fridericia formula (Puddu et al., 1988). If indicated, additional ECG assessments may be performed, at the discretion of the investigator. If applicable, clinically significant changes from baseline in ECG assessments will be noted as AE(s), in accordance with Section 12.2.1.

12.7 Study Monitoring by the Drug Safety Monitoring Board (DSMB)

The study will be monitored for safety, futility, and efficacy by a DSMB. Interim analysis for safety will be conducted six weeks after the first 30-35 participants complete Day 42 based on reported Adverse Events and Serious Adverse Events. The study may be stopped for safety concerns. A second DSMB assessment for safety and futility will be conducted when 45-50 participants have reached Day 42.

13. REGULATORY STANDARDS

The study analyses will be conducted in a GCP environment (ICH E6 and E9 [R1]). All analyses will be pre-specified and finalized prior to database lock. If the methods in this SAP do not agree with the protocol, the methods described in the SAP will govern the analysis.

14. RANDOMIZATION

Randomization will be stratified by evidence of a suicidal event in the prior 12 months (none, any). Investigational product for oral administration (NRX-101 or lurasidone) will be provided as blinded kits to sites for dispensing to subjects. Packaging will contain coded and blinded bottles with capsules of identical size, shape, and color irrespective of the study arm to which a subject is randomized. Storage

15. STUDY POPULATION

The study includes prospectively defined study populations.

The Intent-to-Treat (ITT) population will include all subjects who received the randomized study treatment. The modified ITT (mITT) population will include the ITT population with at least one post-randomization efficacy observation. The Per-Protocol (PP) population will also exclude mITT subjects with a major protocol deviation, e.g. ineligibility, unreliable MADRS-10 scoring, proscribed treatment. The Safety Population will include all subjects as treated.

The mITT population will be used for the primary efficacy analyses. If <5% are to be excluded from the mITT population, then the analysis will not be performed for the PP population.

Every effort will be made to encourage subjects to comply with the procedures and the assessments. Protocol violations will be reviewed in real time and prospective rules will be set for exclusions from the PP population. A Biostatistics Data Review Meeting (BDRM) will be held to identify all major protocol deviations prior to database lock inclusive of any case exclusions from the mITT and PP population as well as to manage any efficacy data following proscribed treatments.

16. HYPOTHESIS TESTS

16.1 Treatment Comparisons

In order to preserve the Type 1 error associated with multiple endpoints (per FDA guidance), all efficacy endpoints will be evaluated in this pre-defined order: (1) MADRS through Week 6. Each will be hypothesis testing driven.

16.2 Primary Hypothesis

MADRS

The primary study hypothesis is that treatment with NRX-101 is superior to lurasidone in improving symptoms of depression as measured by the MADRS over 6 weeks of treatment. The primary study hypothesis is that treatment with NRX-101 is superior to lurasidone in improving symptoms of depression as measured by the MADRS over 6 weeks of treatment. The null hypothesis for the primary endpoint is the mean change from baseline of MADRS-10 for NRX-101 is the same as lurasidone. Baseline is defined as MADRS-10 score at study entry.

The null hypothesis is no difference in the mean change in the MADRS-10 score from baseline to Day 42/exit between both treatment groups, while the alternative hypothesis is that there is a larger mean improvement in the NRX-101 group than the lurasidone group. The study is to have 80% power to detect a 0.66 effect size post-randomization for a two-sided test with 5% Type 1 error using mixed model repeated measures (MMRM).

16.3 Secondary Hypotheses

The secondary hypothesis are that:

- treatment with NRX-101 is superior to lurasidone in improving symptoms of suicidality as measured by the CGI-SS over 6 weeks of treatment. The null hypothesis is the mean change from baseline of CGI-SS for NRX-101 is greater than or equal to the mean change from baseline of CGI-SS for lurasidone while the alternative hypothesis is that the mean change from baseline of CGI-SS is less than the mean change from baseline of CGI-SS for lurasidone (improvement). Baseline is defined as CGI-SS score at this study entry.
- that NRX-101 is superior to lurasidone in time to treatment failure as defined as: study discontinuation due to Adverse Events; psychiatric hospitalization; or requiring a change in antidepressant treatment. Time to treatment failure may be ascertained as the treating physician's determination of a study discontinuation due to lack of efficacy; withdrawal due to a treatment related adverse event a psychiatric hospitalization; or the patient requiring any change in their baseline antidepressant, mood stabilizer, or antipsychotic medication. Titration or change in timing of administration of study medication will not be considered a failure of therapy. Lack of efficacy is defined as the need to implement a new treatment plan or an increase in suicidal ideation (a score of 4 or 5 on the C-SSRS, emergent suicidality requiring hospitalization), or increase in depressive symptoms (a score increase of ≥5 for two consecutive visits on the MADRS total score). The need to implement a new

treatment plan includes the addition of new antidepressant medication or somatic treatment (e.g. ECT or rTMS treatment) or an escalation of care such as hospitalization (i.e. moving the patient from outpatient care to initiating inpatient, partial or day hospitalization). Time to failure will be assessed using a Kaplan-Meier lifetable. The formal hypothesis test will be to detect a 0.421 hazard ratio (HR) with 80% power for a two-sided test using a proportional hazard model; a 0.545 hazard ratio reaches two-sided p=0.05.

17. ENDPOINTS

17.1 Efficacy

17.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline in the total MADRS score as measured by psychometric raters assessed over 42 days post randomization by mixed-model repeated measures analysis.

The primary endpoint will be based on adjudicated results. All rating sessions for MADRS-10 and C-SSRS will be recorded as audio files and reviewed by central master-raters with > 25 years of experience. Any MADRS-10 total score the differs by more than three points from the master-rater score will be deemed non-congruent. All non-congruent subject-visits from any site with >10% non-congruent scores will be sent to an independent adjudicator, previously determined to have >90% concordance with study master raters on standardized training data. In the event of adjudication as above, the independent outside rater score shall be considered as the subject-visit primary study endpoint.

17.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Change from baseline in CGI-SS score as measured by treating prescriber assessed over 42 days post randomization by mixed-model repeated measures analysis.
- **Time to Treatment Failure (TTF):** A Kaplan-Meier lifetable will be constructed for the time to failure of therapy. Failure of therapy will be defined as the treating physician's determination of a study discontinuation due to lack of efficacy; withdrawal due to a treatment related adverse event a psychiatric hospitalization; or the patient requiring any change in their baseline antidepressant, mood stabilizer, or antipsychotic medication. Titration or change in timing of administration of study medication will not be considered a failure of therapy.

The additional secondary efficacy endpoints are:

- Change from baseline in each item of the Suicide Ideation and Behavior Assessment Tool (SIBAT) Module 7 (clinical global impressions of frequency of suicidal thinking, severity of suicidality, and imminent and long-term risks).
- Change from baseline to endpoint in Suicidal Thoughts on the MADRS (MADRS item 10)

- Change from baseline to Day 14 in total MADRS score
- Change from baseline for each MADRS-10 factor at each post-baseline evaluation including exit.
- Change from baseline for the three MADRS-10 factors defined by Borentain at each post-baseline evaluation including exit.
- Change from baseline to endpoint (Day 42/exit) in MADRS total score in the subgroup of participants who were recently (within 2-weeks before enrollment) placed on approved medications for bipolar depression as well as the 5-HT2A subset.

17.1.3 Additional Efficacy Endpoints

The following other efficacy endpoints will be explored:

- **Remission from suicidality:** A Kaplan-Meier lifetable will be constructed for the remission duration from response onset where remission is defined as reaching CSSR-S ≤ 2 and remaining through the study. Remission rate is defined as percent remaining in remission.

Collectively, symptom improvement will be evaluated by assessing changes in the secondary outcome measures within and between treatment groups for each of the following at the times specified on the Schedule of Study Activities:

- Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery, Åsberg 1979)
- Clinical Global Impression of Severity of Suicidality Scale (CGI-SS)
- Concise Health Risk Tracking – Self Report (CHRT-SR) and Clinician Rating (CHRT-C) scales (Trivedi et al., 2011)
- Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962).

17.1.4 Other Efficacy Endpoints

The following additional endpoints will be recorded and analyzed by treatment group:

- Dose per treatment group
- Suicide rates (attempted and completed)
- Time to all-cause study discontinuation (and reason for discontinuation) due to any reason such as withdrawal due to an adverse event, or patient or investigator decision to withdraw
- Rate of participants who achieve a resolution of suicide risk by Clinical Global Judgement of Suicide Risk [CGI-SS] 0 or 1) or by MADRS (suicidal ideation item #10 of 0 or 1)
- Percent in remission at Day 42/exit, defined as having achieved a MADRS score of ≤ 10 during the last two visits (14 days)
- Proportion of participants who are treated with new SSRIs or have increased SSRI dosages
- Proportion of participants who discontinue SSRIs or have reduced SSRI dosages

- Efficacy for each MADRS question as well as the three Borentain factors.

17.1.5 Diagnostic Metric

The following metrics will be evaluated at baseline:

- MINI 7.0.2

17.2 Safety Assessments

- Change from baseline to endpoint (Day 42) in C-SSRS score
- Change from baseline to endpoint (Day 14) in C-SSRS score
- Mean change in BARS through Day 42 to assess akathisia
- Rates of discontinuation between the arms

17.2.1 Overall Adverse Events

Separate and combined safety analyses will be performed for the Safety population. All safety results will be presented separately for each treatment group. Safety endpoints will include adverse events (AEs), vital signs, ECGs, and laboratory parameters.

The principle of treatment emergence will be employed for the analysis of AE data. Treatment emergence is defined as any event that occurred following the initiation of therapy and was not present at baseline, or one which represents an exacerbation of a condition present prior to study entry (pre-existing).

Unresolved AE outcomes at the end of the study will be followed for an additional seven days or until resolution, whichever occurs earlier.

Adverse events will be classified by the Medical Dictionary for Regulatory Activities (MedDRA). For each study treatment, safety data will be collected and analyzed until treatment-emergent AEs are resolved. The type, incidence, timing (onset, duration), relationship, and severity of treatment-emergent AEs will be reported. Reasons for withdrawal due to AEs will also be reported.

Two-sided Fisher Exact tests will be performed to compare the two treatment groups with respect to incidence at the system order class level and for any preferred terms with >10 percent overall incidence.

17.2.2 Other Safety Measures

The timing and incidence of adverse findings will be compiled following planned surveillance of all study participants by a designated safety monitor.

Vital signs and ECGs will also be evaluated within and between study treatment groups. The overall ECG interpretation will be reported as normal or abnormal; if abnormal, then the percent clinically significant will be reported.

While symptom improvement will be evaluated by assessing changes in the secondary outcome measures (CHRT, MADRS, and CGI-SS), safety measures in the C-SSRS, PRISE, BPRS, and BARS (including the global severity rating) will be evaluated within and between study treatment

groups. The timeframe is for both lifetime and the past six months for the baseline Screening scale and since the last visit for the Since Last Visit scale.

18. SAMPLE SIZE CALCULATIONS

18.1 Background

For DCS treatment group in major depressive disorder Heresco-Levy identified a 0.91 effect size for Hamilton-D Total and a 0.95 effect size for BDI-II (Heresco-Levy, 2013) and an effect size of >1 was seen in the phase 2 STABIL-B study with a similar effect size observed by Chen and Heresco Levy.

A more modest 0.66 effect size is targeted in the sample size calculations assuming a 1:1 allocation for a two-sided hypothesis test with 5% Type I error.

18.2 Power and Significance

These sample size calculations are based on the alternative hypothesis corresponding to a 0.66 effect size which corresponds to a mean 8.85-unit MADRS-10 advantage change from baseline for NRX-101 vs control. A total of 74 subjects are to be randomized 1:1 to support the final analysis. As summarized below in Table 2, there is 80% power to detect a 0.66 effect size; a 0.462 effect size would reach two-sided p=0.05. A 0.462 (moderate) effect size reflects a 50 percent drop (based on lurasidone published data) in mean change from baseline for lurasidone with an assumed standard deviation of 13.4; this approximately corresponds to a -16 mean CFB for NRX-101 and a -10 mean CFB for lurasidone.

Table 2 MADRS-10 Change From Baseline Outcomes: T-tests

	Power	Significance
Test significance level, α	0.05	0.05
1 or 2 sided test	2	2
Effect size, d = $\lvert m_1 - m_2 \rvert$ / s	0.66	0.462
Power (%)	80	NA
N per group	37	37

18.3 Hierarchical Testing Strategy

The secondary efficacy hypotheses will also be evaluated using a hierarchical testing strategy where testing continues as long as two-sided p<0.05 is reached. The first such hypothesis to be tested will be for primary endpoint MADRS change from baseline to endpoint, then change from baseline in CGI-SS, followed by time to treatment failure in the NRX-101 and lurasidone groups.

18.4 Interim Analyses

Two interim analyses are planned. The first interim analysis (IA) assessing safety will be conducted six weeks after the first 30-35 participants have been followed for 6 weeks and the

second IA assessing futility (primary efficacy endpoint) will be performed after the first 45-50 participants have been followed for 6 weeks.

Each interim analysis has a different objective with neither interim analysis spending any Type 1 error. The study will be stopped at the first interim analysis if Serious Adverse Events are deemed statistically significantly more common in the NRX-101 group compared to the lurasidone group in a manner deemed by the DMC to pose a potential danger to human subjects. The study will be stopped at the second IA for futility if the conditional power (CP) is less than 10%. In the event that the study is not stopped for either safety or futility, then enrollment will continue until a total of 74 subjects are randomized. This preserves two-sided p=0.05 for the final analysis.

The unblinded Sponsor biostatistician will perform the interim analyses for the Data Safety Monitoring Board (DSMB). The blinded Sponsor biostatistician will then adjudicate cases with respect to intercurrent events which impact analysis inclusion.

19. ANALYSIS CONVENTIONS

19.1 Software

All calculations will be performed using SAS statistical software, version 9.3 or later, and StatXact, version 10 or later.

19.2 Display Formats

All efficacy and safety data will be displayed in tables and listings separately for each treatment group.

19.3 Conventions

Study visit dates will be analyzed using the nominal visit instead of the actual visit date.

Means, mean changes, standard deviations, and ranges will be presented separately for each treatment group. These endpoints will be evaluated using a paired t-test and between study treatment groups using an unpaired t-test at each time; these p-values will be presented as descriptive statistics.

For continuous variables, the mean, standard deviation, minimum, median and maximum will be presented, together with the total number of observations and the number of missing and non-missing values.

For ordinal and categorical variables, absolute and relative frequencies will be reported. Relative frequencies will be based on all observations and reported as percentages. Unless otherwise specified, percentages will be based on the number of participants with data and will not be calculated for missing categories.

Adverse events, medical histories, and concomitant medications will be reported on a patient and an event basis. Percentages will be calculated using the number of participants in the Safety population analysis set as the denominator.

All hypotheses will be tested at 5 percent (final analysis) level of significance using a two-sided test unless otherwise specified.

19.4 Estimand Structure

Analyses will be conducted in accordance with ICH E9 (R1) analysis principles as summarized below.

Primary scientific question of interest	The primary study hypothesis is that treatment with NRX-101 is superior to lurasidone in improving symptoms of depression as measured by the MADRS over 6 weeks of treatment. The null hypothesis for the primary endpoint is the mean change from baseline of MADRS-10 for NRX-101 is the same as lurasidone while the alternative hypothesis is that the mean change from baseline of MADRS-10 is larger than the mean change from baseline of MADRS-10 for lurasidone. Baseline is defined as MADRS-10 score at Visit 2 (randomization).
Target population	The mITT population will be the primary analysis population. The mITT population is defined through appropriate inclusion/exclusion criteria as specified in the protocol and blinded BDRM decisions.
Treatment of interest	NRX-101
Outcome Variables	MADRS-10 (and C-SSRS) will be recorded as audio files and reviewed by central master-raters with any non-congruent subject-visits from any site with >10% non-congruent scores sent to a qualified independent adjudicator to be considered as the subject-visit primary study endpoint.
Summary Measure	The contrast-estimated MADRS-10 Week 6 MMRM will use all post-randomization data with LOCF in the mITT population excluding all outcomes after BDRM-approved exclusions. The model will include treatment and the following four baseline covariates in addition to baseline MADRS-10: (1) sex, (2) mood stabilizer use, (3) anti-psychotic use, and (4) evidence of suicide event in their lifetime. The model will include treatment group, study visit, the interaction between study visit and treatment group, baseline MADRS-10, and the four baseline covariates as fixed effects. An unstructured error structure will be assumed.
Intercurrent Events	A BDRM will adjudicate all intercurrent events which may redact outcomes after disqualifying events; these intercurrent events may represent major protocol deviations.

20. STATISTICAL METHODOLOGY

20.1 General Methodology

The Mixed-Effect Model Repeated Measure (MMRM) will be the primary analysis for the primary efficacy endpoint (MADRS change from baseline); an unpaired t-test will be a secondary analysis. The proportional hazard model (PHREG) will be the primary analysis for time to event endpoints (time to remission, time to discontinuation); the unstratified log rank test will be a secondary analysis. The MMRM and PHREG models will all include treatment and the following four baseline covariates:

- sex
- mood stabilizer use
- anti-psychotic use
- evidence of suicide event in their lifetime.

All primary analyses will be in the mITT population as primary and repeated in the Per Protocol population if >5 percent are excluded.

All of the instruments used to measure SSIB or depression constitute serial continuous and ordinal outcomes that will be analyzed using MMRM with LOCF to account for missing data and early discontinuations. The models will include treatment group, study visit, the interaction between study visit and treatment group, the baseline level of the variable being analyzed, and the above four pre-defined baseline stratification factors as fixed effects. The primary endpoint change from baseline MADRS-10 will be analyzed using the MMRM model which will include baseline MADRS; treatment group; study visit; study visit*treatment; sex, mood stabilizer use, anti-psychotic use, and evidence of suicide event in their lifetime as defined above. An unstructured error structure will be assumed.

SAS PROC MIXED will be used for continuous endpoints.

In addition, supportive analyses will be performed using multiple imputation which will be performed to address any missing data. The method of Little and Rubin will be used. The presentation of the results for the primary efficacy endpoints using the ITT population will be based on the observed data with multiple imputation for missing endpoint data using SAS PROC MI. Missing data will be imputed using MCMC imputation under the assumption of a missing at random using the mITT population. The SAS® procedure PROC MI will be used for the MCMC imputation of 25 complete data sets.

20.2 Other Time to Event Efficacy Endpoints

Other time-to-event outcomes (all-cause discontinuation, and time to remission) further characterize this multi-component disorder. Time to event is a more sensitive measure than an assessment at a fixed time. Time to such events will be displayed using a Kaplan-Meier lifetable,

with the treatment groups compared using two-sided unstratified log rank tests (secondary) and a proportional hazard model (primary) to include the above cited baseline covariates.

Treatment Failure will be centrally judged blind in real time by the study physician using baseline measures of depression and suicidality as a guide. Treatment failure is defined above.

20.3 Secondary Efficacy Endpoints

All of the instruments used to measure SSIB or depression constitute serial continuous and ordinal outcomes that will be analyzed using MMRM with LOCF, which accounts for missing data and early discontinuations. Results will be presented separately for each treatment group.

The models will include treatment group, study visit, the interaction between study visit and treatment group, the randomization baseline of the variable being analyzed, and the four baseline stratification factors as fixed effects. The reason for missing data will be evaluated as a condition of MMRM analysis.

20.4 Other Efficacy Endpoints

The following additional endpoints will be recorded and analyzed by treatment group for both study phases:

- Dose per treatment group
- Suicide rates
- Proportion of participants who are treated with new SSRIs or have increased SSRI dosages
- Proportion of participants who discontinue SSRIs or have reduced SSRI dosages
- Efficacy for each BPRS factor.

Dose per treatment group will be displayed graphically over time per study treatment group. The percent decreasing and increasing over time relative to starting dose will be displayed per study treatment group.

Time to all-cause study dropout will be displayed using a Kaplan-Meier lifetable.

The following three measures will be separately evaluated using a two-sided Fisher Exact test to compare treatments:

- the need to implement a new treatment plan.
- an increase in suicidal ideation (a score of $\geq$4 on the C-SSRS, emergent suicidality requiring hospitalization).
- an increase in depressive symptoms (a score increase of $\geq$5 from the previous on-study visit for two consecutive visits on the MADRS total score).

The number of hospitalization and ER visits per subject will be evaluated using a Wilcoxon Rank Sum test to compare each study treatment group.

The proportions of participants discontinuing SSRIs or reducing SSRI dosages will be displayed graphically over time per study treatment group. The percent discontinuing SSRIs and reducing SSRI dosages relative to starting dose will be displayed per study treatment group.

20.5 Safety Endpoints

Adverse events will be classified by MedDRA. For each study treatment, safety data will be collected and analyzed while on treatment or until treatment-emergent adverse events are resolved. The type, incidence, timing (onset, duration), relationship, and severity of AEs will be reported for treatment-emergent and SAEs. Reasons for withdrawal due to AEs will also be reported. Narratives will be written for every AE classified as serious or associated with attempted suicide or death.

Safety and tolerability will be assessed using two-sided Fisher Exact tests to compare overall adverse event incidence for NRX-101 vs. lurasidone. Mean changes from randomization baseline will be displayed for each serum chemistry and hematology parameter as well as the shift; unpaired t-tests will be used to compare treatments. In addition, paired t-tests will be performed for the changes from randomization baseline for each study treatment group.

C-SSRS will also be considered as a safety endpoint but will be analyzed as a McNemar paired comparison test within treatment groups and as a Jonchkeere-Terpstra test to compare treatment groups.

Vital signs and ECGs (means and mean changes from baseline will also be evaluated within treatment groups using paired t-tests and between study treatment groups using unpaired t-tests. Percent with abnormal vital signs, heart rate, QRS duration, PR interval, RR interval, QT, and QTcF will be reported. McNemar paired comparison tests will be performed within study treatment groups for the abnormal discordant percent while two-sided Fisher Exact tests will be performed to compare incidences between treatment groups.

Blood draws for chemistries and hematologies will be evaluated within and between study treatment groups. Abnormality rates will be presented relative to established site-specific normal ranges and whether or not the abnormality is clinically significant. McNemar paired comparison tests will be performed within study treatment groups for the abnormal percents while two-sided Fisher Exact tests will be performed to compare incidences between treatment groups.

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22. APPENDICES

Appendix 1: Concomitant Medications

Medications Allowed (Y) and Not Allowed (N) as Concomitant Medications

Drug Name or Class	Episodic Use (PRN)	Chronic Use	Restrictions/Comments
Analgesics	Y	Y	Nonnarcotic analgesics are allowed. Medically appropriate episodic use of narcotic analgesics is allowed for acute medical indications but is limited to no more than three days for each episode. Chronic NSAID use is exclusionary; tramadol is also not allowed.
Anesthetics, general	Y (except for ketamine, which is excluded)	—	If procedures requiring general anesthesia are to occur/have occurred, please contact Medical Monitor to report the medical condition(s).
Anesthetics, local	Y	N	—
Anorexics	N	N	—
Antacids	Y	Y	—
Antiacne	Y	Y	Topical agents only, including topical antibiotics. Isotretinoin (Accutane) is not allowed.
Antianginal agents	N	N	—
Antiarrhythmics	N	N	Amiodarone is excluded.
Antiasthma agents	Y	Y	—
Antibiotics	Y	Y	Chronic use of topical antibiotics for acne is allowed, with the exception of the MAOI linezolid (Zyvox) and isoniazid, which are not allowed. Nafcillin, Erythromycin, clarithromycin, rifampin are excluded.
Anticoagulants	N	N	Warfarin (Coumadin) is not allowed. Antiplatelet agents are allowed (see “Antiplatelets”).
Anticholinergics	Y	Y	Except for scopolamine.

Drug Name or Class	Episodic Use (PRN)	Chronic Use	Restrictions/Comments
Anticonvulsants	N	Y	Gabapentin, lamotrigine and pregabalin are allowed. Other anticonvulsants are not allowed, including carbamazepine and oxcarbamazepine, phenytoin, phenobarbital, rufinamide (CYP3A4 inducers). Stable in dosing at least four weeks prior to randomization is required.
Antidepressants	N	Y	Stable (for at least 4 weeks prior to screening), ongoing antidepressant therapy is required during the course of the study. No dose changes are allowed during the study. Monoamine oxidase inhibitors (which may have unknown drug-drug interactions) are excluded. Concomitant use of trazodone (up to 200mg daily) is allowed. Nefazodone and St John's Wort are excluded (CYP3A4 inhibitor, inducer, respectively).
Antidiarrheal preparations	Y	N	Only loperamide HCl (Imodium), bismuth subsalicylate (Pepto-Bismol), and kaolin preparations are allowed.
Antifungals, systemic	N	Y	Ketoconazole, itraconazol, rifampin and rifabutin are excluded.
Antifungals, topical	Y	Y	Ketoconazole and itraconzole are excluded.
Antihistamines	Y	Y	The use of combinations containing pseudoephedrine or phenylephrine is not allowed. Combination products containing the word nighttime or are specifically marketed for before sleep routinely include an antihistamine and are not allowed. Combination products ending in "-D" routinely contain a stimulant such as phenylephrine, and the appropriate limits above apply to them. (See "Cough and Cold Preparations" for combination products.)
Antihypertensives	N	Y	Diltiazem, verapamil are excluded.
Anti-impotence medications	Y	Y	—
Anti-inflammatory drugs	Y	Y[a]	Indomethacin (Indocin) and systemic corticosteroids are not allowed. Chronic NSAID use is exclusionary.
Antimigraine	N	N	Triptans are not allowed.

Drug Name or Class	Episodic Use (PRN)	Chronic Use	Restrictions/Comments
Antinauseants/ Antiemetics	Y	N	Phosphoric acid preparations (Emetrol, Emecheck), bismuth subsalicylate (Pepto-Bismol), cola syrup, 5-HT_3 receptor antagonists (e.g., ondansetron), and prokinetic agents (metoclopramide) are allowed. Scopolamine is not allowed (see section on anticholinergic).
Antineoplastics/ Immunosuppressant agents	N	Y[c]	Interferons, methotrexate, and other immunosuppressant agents are not allowed. Call Medical Monitor for approval for certain cases in cancer remission maintaining therapy.
Antiobesity/Appetite suppressants	N	N	OTC Alli (Xenical), sibutramine (Meridia), and phentermine (Adipex-P and others) are not allowed.
Antiplatelet agents	N	Y[b]	Aspirin (maximum 325 mg/day) and clopidogrel (Plavix) are allowed. Note that use of an SSRI or of a triple uptake inhibitor may increase bleeding times and possibly prothrombin times.
Antipsoriatic treatments	Y	Y	Only topical agents are allowed. Acitretin (Soriatane) is not allowed.
Antipsychotics	N	Y	Stable in dosing at least four weeks prior to randomization is allowed. Lurasidone will be discontinued at study entry. Quetiapine, aripiprazole, risperidone, brexpiprazole, olanzapine, cariprazine, or lumateperone should be discontinued prior to randomization.
Antismoking medications	N	Y[c]	Varenicline (Chantix) is not allowed. Chronic nicotine replacement may be allowed in certain cases after review with Medical Monitor.
Antiviral agents	Y	Y	Only oral or topical agents are allowed. Only acyclovir, famciclovir, valacyclovir, penciclovir, docosanal, trifluridine, and vidarabine are allowed. Amantadine, rimantadine, and protease inhbitors (atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir) are not allowed. Tamiflu (oseltamivir phosphate), and Relenza (zanamivir) inhalants are permitted for influenza prophylaxis but use is limited to a 7- to 14-day course in accordance with prescribing information. Interferons are not allowed.
Anxiolytics	N	Y	Chronic, stable treatment with benzodiazepines is allowed. Stable in dosing at least four weeks prior to randomization is required.
Barbiturates	N	N	Barbiturates are not allowed.

Drug Name or Class	Episodic Use (PRN)	Chronic Use	Restrictions/Comments
Benign prostatic hyperplasia treatments	N	Y[b]	Male patients who have symptoms of obstructed voiding should not be included in the study. Surgically or medically treated patients must be asymptomatic and receiving a stable dosage of allowed medications (α-1 blockers, finasteride, or dutasteride) for one month before screening.
Buspirone	N	Y	Stable in dosing at least four weeks prior to randomization is allowed.
Cough/cold preparations	Y	N	Use of cough and cold preparations containing pseudoephedrine or dextromethorphan is not allowed, as are those containing phenylephrine Combination products ending in "-D" routinely contain a stimulant such as phenylephrine, and the appropriate limits apply to them. (See "Antihistamines".)
Diuretics	Y	Y[b]	Episodic use of diuretics is restricted to treatment of premenstrual symptoms. For chronic use, medication and dosage should be stable for 1 month before screening.
Dopaminergics	N	Y	Dopamine agonists for restless leg syndrome are allowed.
Ethyl alcohol	N	N	Participants should not use alcohol during the course of the trial because ethyl alcohol may increase the possibility and risks of seizures in participants receiving cycloserine.
Gastrointestinal: • H_2-blockers/ • proton pump inhibitors/ • prokinetic agents	Y	Y	Cimetidine (Tagamet) is not allowed. Metoclopramide is not allowed.
Hormonal (noncontraceptive) therapies	N	Y	See below.
Hormone suppressants	N	Y[b]	Only finasteride (Proscar) and dutasteride (Avodart) are allowed.
Hormones: reproductive	N	Y	Systemic hormonal contraceptives (oral contraceptives of estrogen and progestin combinations, depot injections such as Depo-Provera, the contraceptive implant Implanon, and/or transdermally delivered contraceptives such as Ortho Evra) are allowed.

Drug Name or Class	Episodic Use (PRN)	Chronic Use	Restrictions/Comments
Hormones: thyroid	N	Y	Thyroid hormone replacement is allowed (dosage of thyroid medication should be stable for three months before screening). Therapeutic use for psychiatric disorders (e.g., T3 augmentation) is not allowed.
Hypoglycemic agents	N	Y	Oral hypoglycemic agents are allowed. Insulin is allowed.
Hypolipidemics	N	Y[b]	Ezetimibe (Zetia) is allowed.
Hypolipidemics: bile acid sequestrants	N	N	—
Hypolipidemics: fibrates	N	Y[b]	Gemfibrozil and fenofibrate are allowed
Hypolipidemics: niacin	N	N	Niacin and niacinamide are not allowed.
Hypolipidemics: statins	N	Y[b]	Lovastatin, simvastatin, pravastatin, atorvastatin, fluvastatin, and rosuvastatin are allowed.
Laxatives	Y	Y[a]	Only fiber-based products and docusate sodium (Colace) are allowed.
Lithium	N	Y	Stable in dosing at least four weeks prior to randomization is allowed.
Medications that are primarily metabolized by CYP2C8 (e.g., cerivastatin, paclitaxel, repaglinide, sorafenib, and torsemide)	N	N	—
Muscle relaxants	N	N	—
NMDA receptor antagonist	N	N	Memantine is excluded.
Opioid agonists/analgesics (e.g., codeine, hydrocodone, methadone, morphine, maperidine, propoxyphene) and antagonists (e.g., naltrexone, naloxone, nalmefene)	N*	N*	See section on analgesics for exceptions.
Sedatives/hypnotics	N	Y	Ongoing, stable hypnotic therapy (e.g., zolpidem, zaleplon, benzodiazepine hypnotics, and low-dose trazodone 50-200mg) will be allowed during the course of the study. Eszopiclone is not allowed.

Drug Name or Class	Episodic Use (PRN)	Chronic Use	Restrictions/Comments
Steroids/systemic	Y	N	Systemic steroid treatment will be allowed only for medical emergencies, such as severe allergic reactions.
Steroids/topical and inhalant	Y	Y	—
Steroids/intra-articular	Y	NA	—
Stimulants	N	N	Oral or transdermal methylphenidate, amphetamine products or prodrugs, pseudoephedrine, modafinil (Provigil), and other medications of same category are not allowed.
Vaccines	Y	NA	—

a If being taken prior to enrolling in the study.

b If being taken for at least three months prior to enrolling in the study and the dose has been stable for at least 1 month.

c If approved by Medical Monitor5-HT_3 = 5-hydroxytryptomine receptor type 3; 5-HTP = 5-hydroxytryptophan; ACE = angiotensin-converting enzyme; CR = controlled release; DHEA = dehydroepiandrosterone; N = no; NA = not applicable; OTC = over the counter; PRN = as needed (prorenataT3prorenataT3=triiodothyronine; Y = yes.

Appendix 2: Medications Indicated for Use in Bipolar Disorder

Brand Name	Generic Name
☐ Abilify	☐ Aripiprazole
☐ Zyprexa	☐ Olanzapine
☐ Seroquel	☐ Quetiapine
☐ Risperdal	☐ Risperidone
☐ Rexulti	☐ Brexpiprazole
☐ Vraylar	☐ Cariprazine
☐ Caplyta	☐ Lumaterperone
☐ Lurasidone	☐ Latuda
☐ Ziprasidone	☐ Geodon
☐ Saphris	☐ Asenapine
☐ Eskalith, Lithobid	☐ Lithium
☐ Lamotrigine	☐ Lamictal
☐ Eprontia, Qudexy XR Sprinkle, Topamax, Topamax Sprinkle, Trokendi XR, Topiragen, Topiramate ER (Eqv-Qudexy XR)	☐ Topiramate
☐ Depakote	☐ Divalproex sodium
☐ Tegretol	☐ Carbamazepine
☐ Trileptal	☐ Oxcarbazepine