Clinical Study Protocol

NRX-101 for the Treatment of Acute Suicidal Ideation and Behavior in Bipolar Depression
IND 129194

Principal Investigator	Andrew Nierenberg, MD
Study Sponsor	NeuroRx, Inc. 913 North Market St., Suite 200 Wilmington, DE 19801
Phase	2b/3
Document Status	Final
Version, Date	Version 1.0 17 November 2016

Contact Information

Role in Study	Name	Address and Telephone
Principal Investigator	Andrew Nierenberg	617-724-0837

1. SYNOPSIS

Name of Investigational Product:	NRX-101 (administered to subjects who respond to an intravenous infusion of ketamine - 0.5 mg/kg administered over 40 min; on Day 0)
Name of Active Ingredient:	Fixed dose combination of d-cycloserine + lurasidone
Reference Product(s):	Lurasidone/placebo
Title of Study:	NRX-101 for the Treatment of Acute Suicidal Ideation and Behavior (ASIB) in Bipolar Depression
Phase of Development:	Phase 2b/3
Study Site(s):	Approximately 12 study sites which may be either inpatient psychiatric hospitals or community mental health centers/bipolar clinics with immediate access to inpatient care facilities. All sites will have a minimum of 12 months prior experience in the use of ketamine for stabilization of patients with ASIB in Bipolar Depression as part of their practice of medicine.
Study Duration:	Screening: up to 48 hours; IV ketamine Day 0; 6-week treatment; 4 week follow up
Background and Rationale:	DCS and Lurasidone, taken together, have been shown to maintain a 50% reduction in depression and a 75% reduction in suicidality following a single infusion of ketamine in patients with suicidal ideation and bipolar depression. Ketamine is increasingly used in medical practice to achieve rapid stabilization of patients with ASIB. However, the duration of ketamine effect is limited and its repeated use for maintenance of stabilization is not proven.
Objectives:	The objectives of the study are as follows: <u>Primary Objective:</u> • The primary objective of the study is to test the hypothesis that following stabilization of depression and ASIB in response to initial ketamine infusion, NRX-101 is superior to lurasidone alone and also superior to placebo as oral-therapy for delaying time to relapse (resulting in a new treatment plan or the subject relapsing to baseline levels of depression or suicidality) in subjects with documented bipolar depression presenting with symptoms of depression and suicidal ideation. <u>Secondary Objectives:</u> • To demonstrate superiority over placebo and over lurasidone alone in maintaining remission from depression in bipolar disorder. • To demonstrate efficacy can be sustained with NRX-101 dosing regimens • To demonstrate NRX-101 safety

Endpoint(s)	Primary Endpoint: • The primary outcome measure will be time to relapse, defined as the need to implement a new treatment plan or a return to baseline levels on the Columbia-Suicide Severity Rating Scale (C-SSRS), or the Montgomery Asberg Depression Rating Scale (MADRS) subset on the Bipolar Inventory of Symptom Severity (BISS).
Study Design	IV Ketamine infusion followed by a double blind, placebo – controlled, parallel arm trial
Inclusion Criteria:	A subject will be eligible for inclusion in this study only if all of the following criteria apply: 1. Male or female, 18 to 65 years of age, inclusive, at screening. 2. Able to read, understand, and provide written, dated informed consent prior to screening. Participants will be deemed likely to comply with study protocol and communicate with study personnel about AEs and other clinically important information. 3. Diagnosed with Bipolar Disorder (BD) according to the criteria defined in the DSM-5. The diagnosis of BD will be made by a site psychiatrist and supported by the MINI 7.0.2. The diagnosis will be confirmed by remote, independent raters, via teleconference between the screen visit and the baseline visit. 4. Suicidal ideation or behavior of sufficient severity to meet the requirements for a score of 4, or 5 on the C-SSRS (suicide attempt, interrupted attempt, aborted attempt, preparatory actions toward imminent suicidal behaviors, active method, intent +/- plan). 5. A score equal to or greater than 20 on the MADRS items of the BISS. 6. In good general health, in the opinion of the investigator, as ascertained by medical history, physical examination (PE) (including measurement of seated vital signs), clinical laboratory evaluations, and electrocardiogram (ECG). 7. If female, a status of non-childbearing potential or use of an acceptable form of birth control per the following specific criteria: a. Non-childbearing potential (e.g., physiologically incapable of becoming pregnant, i.e., permanently sterilized [status post hysterectomy, bilateral tubal

ligation], or is post-menopausal with her last menses at least one year prior to screening); or

b. Childbearing potential, and meets the following criteria:

i. Childbearing potential, including women using any form of hormonal birth control, on hormone replacement therapy started prior to 12 months of amenorrhea, using an intrauterine device (IUD), having a monogamous relationship with a partner who has had a vasectomy, or is sexually abstinent.

ii. Negative urinary pregnancy test at screening, confirmed by a negative urinary pregnancy test at randomization prior to receiving study treatment.

iii. Willing and able to continuously use one of the following methods of birth control during the course of the study, defined as those which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly: implants, injectable or patch hormonal contraception, oral contraceptives, IUD, double-barrier contraception, sexual abstinence. The form of birth control will be documented at screening and baseline.

8. Body mass index between 18-35 kg/m^2.

9. Concurrent psychotherapy will be allowed if the type (e.g., supportive, cognitive behavioral, insight-oriented) and frequency (e.g., weekly or monthly) of the therapy has been stable for at least three months prior to screening and if the type and frequency of the therapy is expected to remain stable during the course of the subject's participation in the study.

10. Concurrent hypnotic therapy (e.g., with zolpidem, zaleplon, melatonin, benzodiazepines 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 subject's participation in the study. Subjects can also continue treatment with benzodiazepines used for sleep or anxiety if 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 subject's participation in the study.

Exclusion criteria:	A subject will not be eligible 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 that is pregnant or breastfeeding. 3. Female with a positive pregnancy test at screening or baseline. 4. Current diagnosis of a substance use disorder (abuse or dependence, as defined by DSM-5, with the exception of nicotine dependence), at screening or within 6 months prior to screening. 5. Current Axis I disorder, diagnosed at screening with the use of the MINI 7.0.2, that is the primary focus of treatment and BD the secondary focus of treatment for the past 6 months or more. 6. History of schizophrenia or schizoaffective disorders, or any history of psychotic symptoms. 7. History of anorexia nervosa, bulimia nervosa, or eating disorder not otherwise specified, within 5 years of screening. 8. Any Axis I or Axis II Disorder, which at screening is clinically predominant to their BD or has been predominant to their BD at any time within 6 months prior to screening. 9. Has dementia, delirium, amnestic, or any other cognitive disorder. 10. Has a clinically significant abnormality on the screening physical examination that might affect safety, study participation, or confound interpretation of study results according to the study clinician. 11. Participation in any clinical trial with an investigational drug or device within the past month or concurrent to study participation. 12. Current episode of: a. Hypertension, Stage 1 as defined by a systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg at screening on two of three measurements at least 15 minutes apart.

b. Hypertension, Stage 1 as defined by a systolic blood pressure ≥155 mmHg or diastolic blood pressure ≥99 mmHg at the Baseline Visit (Visit 1) within 1.5 hours prior to ketamine infusion on two of three measurements at least 15 minutes apart.

c. Recent myocardial infarction (within one year) or a history of myocardial infarction.

d. Syncopal event within the past year.

e. Congestive heart failure (CHF) New York Heart Association Criteria >Stage 2

f. Angina pectoris.

g. Heart rate <50 or >105 beats per minute at screening or randomization (Baseline Visit).

h. QTcF (Fridericia-corrected) ≥450 msec at screening or randomization (Baseline Visit).

13. Current history of hypertension, or on antihypertensives for the purpose of lowering blood pressure, with either an increase in antihypertensive dose or increase in the number of antihypertensive drugs used to treat hypertension over the last 2 months.

14. Chronic lung disease excluding asthma.

15. Lifetime history of surgical procedures involving the brain or meninges, encephalitis, meningitis, degenerative central nervous system (CNS) disorder (e.g., Alzheimer's or Parkinson's Disease), epilepsy, mental retardation, or any other disease/procedure/accident/intervention which, according to the screening clinician, is deemed associated with significant injury to or malfunction of the CNS, or history of significant head trauma within the past 2 years.

16. Presents with any of the following lab abnormalities:

    a. Subjects with diabetes mellitus fulfilling any of the following criteria:

        i. Unstable diabetes mellitus defined as glycosylated hemoglobin (HbA1c) >8.5% at screening.

        ii. Admitted to hospital for treatment of diabetes mellitus or diabetes mellitus-related illness in the past 12 weeks.

        iii. Not under physician care for diabetes mellitus.

	iv. Has not been on the same dose of oral hypoglycemic drug(s) and/or diet for the 4 weeks prior to screening. For thiazolidinediones (glitazones) this period should not be less than 8 weeks. b. Any other clinically significant abnormal laboratory result (determined as such by the investigator and medical monitor) at the time of the screening. 17. Any current or past history of any physical condition which in the investigator's opinion might put the subject at risk or interfere with study results interpretation. 18. Positive screening urine test for drugs of abuse at screening: cocaine, amphetamines, barbiturates, opiates. 19. Subjects with exclusionary laboratory values, or requiring treatment with exclusionary concomitant medications as defined in the study manual 20. Subjects on exclusionary concomitant psychotropic medications. 21. Subjects with a lifetime history of illicit PCP/ketamine drug use or previous failed use of ketamine for depression. 22. Liver Function Tests higher than 2.5 times upper limit of normal as defined in the study manual. 23. Known allergies to Lurasidone or Latuda, Cycloserine or Seromycin, Mannitol, Croscarmellose Sodium, Magnesium Stearate, Silicon Dioxide, and/or HPMC (hydroxypropylmethylcellulose)
Analysis Sets:	
Pharmacokinetic Assessments:	A single sample of blood will be collected at the following time points: Blood draws for NRX-101 analyses 2 hours after the initial dose, prior to administration of NRX-101 on day 14 and pre-dose plus 2-hours post-dose on day 42
Safety Assessments:	• The safety and tolerability of NRX-101 will be assessed via: o Adverse events (AEs) o Vital signs (blood pressure, heart rate), weight o 12-Lead electrocardiograms (ECGs) o Clinical laboratory evaluations

	○ Physical examination (PE) findings ○ Suicidality assessment (C-SSRS) ○ Suicidal Ideation and Behavior Questionnaire (SIBQ) ○ Clinician-Administered Dissociative States Scale (CADSS) ○ Brief Psychiatric Rating Scale (BPRS) ○ Concise Health Risk Tracking – Self Report (CHRT-SR) and Clinician Rating (CHRT-C) scales Barnes Akathesia Scale (BARS)
Dosage, Route of Administration and Schedule:	All eligible subjects will receive an intravenous infusion of ketamine (0.5 mg/kg administered over 40 min; on Day 0) Ketamine responders will be randomised to the 6-week treatment period and will receive oral medication. Subjects will be instructed to take two capsules, one each morning and evening.
Statistical Methods:	Fisher exact test and t-test for determination of primary study endpoint. See protocol for detailed explanation
Sample Size Calculation:	Randomization of 124 subjects will yield a type I error of less than 0.05 at a study power of 90%. See protocol

2. TABLE OF CONTENTS

Table of Tables

Table of Figures

3. LIST OF ABBREVIATIONS

Abbreviations	Full Terms
ACPC	Aminocyclopropanecarboxylic acid
APA	American Psychiatric Association
ASIB	Acute Suicidal Ideation and Behavior
BARS	Barnes Akathesia Scale
BISS	Bipolar Inventory of Symptoms Scale
BPD	Bipolar Depression
BPRS	Brief Psychiatric Rating Scale
CADSS	Clinician Administered Dissociative State Scale
CHRT	Concise Health Risk Tracking
CYP3A4	Cytochrome P450 3A4
C-SSRS	Columbia Suicide Severity Rating Scale
DCS	D-cycloserine
ECG	Electrocardiogram
FDC	Fixed Dose Combination
HAM-D	Hamilton Depression Scale
IV	Intravenous
MADRS	Montgomery Asberg Depression Rating Scale
MGH CTNI	Massachusetts General Hospital Clinical Network and Institute
MDD	Major Depressive Disorder
MMRM	Mixed Effect Model Repeated Measure
NMDA	N-methyl-D-aspartate
NMDAR	N-methyl-D-aspartate Receptor
PI	Package Insert
POC	Proof of Concept
PRISE	Patient Rated Inventory of Side Effects
RAAD	Rapid Acting Anti-depressants
RCT	Randomized Clinical Trial
rh	Relative humidity
SIBQ	Suicidal Ideation and Behavior Questionnaire
SSRI	Selective Serotonin Reuptake Inhibitor
TB	Tuberculosis

4. INTRODUCTION

4.1 Acute Suicidal Ideation and Behavior in Bipolar Disorder

Bipolar disorder (i.e., formerly known as manic depressive disorder) is a well-established psychiatric diagnosis, with a prevalence in about 2.6% in the United States (approximately 8.5 million people) (Kessler et al., 2005). The risk of acute suicidal ideation and behavior (ASIB) 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 BD (Nierenberg et al., 2001). About 3% to 14% of the total 30,000 annual deaths from suicide in the United States are associated with bipolar depression (Mahli et al., 2015). The overall rate of death by suicide among bipolar patients is 164 per 100,000 person years, compared to about 14 per 100,000 person years for the general population. Those who have a suicide attempt are 2.3 times more likely to die by suicide compared to those without a suicide attempt (Coryell et al., 2016). Thus, ASIB in bipolar depression has uniquely lethal clinical characteristics (Pompili, Gonda, &Serafini, 2013).

4.2 Current Treatment Options

Despite its lethal characteristics, there is no approved pharmacologic treatment for patients with ASIB in bipolar depression. As a result, electroconvulsive therapy, often combined with inpatient psychiatric care remains the treatment of last resort for patients with ASIB in bipolar depression, despite its well-documented side effects that include memory loss and confusion, along with its high cost. No antidepressants have Federal Drug Administration (FDA) approval for use in patients with bipolar depression and acute suicidality. Physicians are increasingly cautious about the use of selective serotonin release inhibitors (SSRI's), particularly in patients with ASIB because of evidence that SSRI's 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 suicidal ideation and behavior in proportion to their effect on symptoms of depression.

In recent years, 5-HT2a antagonists have been shown to have efficacy in treating bipolar depression (olanzapine fluoxetine combination, quetiapine, and lurasidone). 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 (MADRS item $10 \geq 4$) were specifically excluded because of concerns regarding exacerbating suicidality. Similarly, acutely suicidal patients are routinely excluded from clinical trials of other experimental anti-depressive agents. Thus, ASIB in bipolar depression represents a major unmet medical need that must frequently be treated with voluntary or involuntary hospitalization under highly supervised conditions and electroconvulsive therapy (ECT).

Whereas all approved drugs for depression act primarily through monoaminergic mechanisms, the serendipitous discovery that ketamine has a rapid and profound effect on depression and suicidality

(Berman, et. al., 2000) led to the realization that the glutamate system and the Nmethyl-D-aspartate receptor (NMDAR) may play an important role in depression and suicidality.

4.3 Rationale for Clinical Development Plan

To meet the unmet need for the treatment of ASIB in adults with BD, NeuroRx, Inc. is developing NRX-101, a fixed-dose combination oral capsule composed of d-cycloserine (DCS) and lurasidone, intended as a component of a sequential therapy, which takes advantage of a unique synergistic confluence of three FDA-approved drugs with long histories of safety.

The combination of the drugs for the proposed sequential therapy (DCS, lurasidone, ketamine) has been tested in an acute toxicity study under a protocol reviewed in advance by FDA and found to have no evidence of neurotoxicity, even at otherwise toxic doses (i.e. 2000 mg/kg) of lurasidone. Each of the proposed drugs has a long history of safe use in humans and their AE profiles are well characterized. The safety of the three drugs, given in combination has been tested in a human phase 2 study that was deemed IND-exempt by FDA.

DCS is a broad spectrum antibiotic approved for the treatment of tuberculosis (TB). DCS has been used in millions of individuals without report of significant safety concerns.

Lurasidone is an atypical antipsychotic with approval for the treatment of depressive episodes associated with bipolar depression. Of the other drugs in its class, lurasidone requires the lowest treatment dose and demonstrates the fewest side effects.

Ketamine is a nonbarbiturate, rapid-acting general anesthetic for intravenous (IV) or intramuscular injection, approved for surgical anesthesia. Ketamine has a wide margin of safety. Its use for more than 12,000 types of operative and diagnostic procedures was studied in over 10,000 subjects participating in 105 separate clinical studies.

Ketamine has been shown in multiple randomized clinical trials to induce nearly immediate remission from acute suicidality and depression, however the clinical effect has been demonstrated to diminish at 3 days post-dose. Whereas Ketamine is a direct NMDA channel blocker which binds to the PCP binding site, DCS in high doses has an NMDA antagonist effect by binding to the glycine site. This effect is apparently unrelated to its properties as an anti-infective By combining the potential of DCS to extend the anti-depressant effects of ketamine with the antipsychotic properties of lurasidone (Stone et al., 2009), NRX-10 has potential to stabilize individuals with bipolar depression during acute crisis and address a serious medical need.

For details regarding the physical, chemical, and pharmaceutical properties of the three drug product components of the proposed sequential therapy, please see the Investigator's Brochure (IB), which also provides a review of relevant non-clinical and clinical experience for each. Safety information is also provided in the product safety labeling for each of the drugs in the Investigator's Brochure.

4.4 Preclinical Experience

Although the mechanisms mediating anti-depressant-related increases in suicide are not totally established, leading theories suggest that increases in anxiety/akathisia may play a critical role. (Harada et al., 2014; Popovic et al., 2015) Serotonin-related anxiety/akathisia may be modeled in rodents using several well-established assay systems such as the elevated plus maze and are known to be sensitive to serotonergic agents. (Sachdev, Brune, 2000) In this assay, increased percent time spent in the open arms of the maze is believed to be associated with increased akathisia and anxiety. In contrast, increased total distance traveled in the maze is thought to be a signal related to psychosis. As shown by Javitt (2014) and in

Table 1 (below), DCS significantly reduces the anxiogenic effects of lurasidone and quetiapine as measured by % time spent in open arm, suggesting that this treatment might reduce medication-induced suicidality as well as suicidality associated with BD itself. These findings are consistent with the documented anti-suicidal effectiveness of acute ketamine treatment (DiazGranados et al., 2010; Ballard et. al., 2014), including theories that ketamine's reductions in suicidality are associated with reductions not only in depression but also in anxiety.

Table 1 Effect of NMDA and 5-HT2a Antagonists in Rodent Akathisia Model

							% time spent in open arm		Distance travelled	
DOI/Control	Dose DOI	5-HT2A antagonist	Dose	NMDA antagonist	Dose	N	Mean	Std. Dev.	Mean	Std. Dev.
Control	0	—		—		10	22.438	14.8418	786.30	68.631
DOI	1 mpk	—		—		10	46.859	22.3661	687.10	108.721
DOI	2 mpk	—		—		30	37.241	17.7616	678.20	96.958
DOI/D-cycloserine	2 mpk	—		D-cycloserine	30 mpk	10	44.598	10.6373	781.50	96.345
DOI/D-cycloserine	2 mpk	—		D-cycloserine	300 mpk	10	48.086	14.9833	733.70	76.202
DOI (2 mpk) + MDL100907	1	MDL100907	0.3 mpk	—		10	26.760	17.8137	693.20	69.089
MDL100907	2 mpk	MDL100907	0.3 mpk	—		40	21.938	21.4108	741.70	85.718
MDL100907/D-cycloserine	2 mpk	MDL100907	0.3 mpk	D-cycloserine	30 mpk	10	20.807	24.1793	735.10	131.341
MDL100907/D-cycloserine	2 mpk	MDL100907	0.3 mpk	D-cycloserine	300 mpk	10	35.826	29.2316	887.10	105.288
MDL100907/CGS19755	2 mpk	MDL100907	0.3 mpk	CGS-19755		10	21.749	19.2252	527.00	139.276
MDL100907/CPPene	2 mpk	MDL100907	0.3 mpk	D-CPPene		10	31.813	22.6649	727.90	66.527
MDL100907/CP101806	2 mpk	MDL100907	0.3 mpk	CP101806		9	25.122	18.9580	775.00	157.463
MDL100907/GV150526A	2 mpk	MDL100907	0.3 mpk	GV150526A		11	20.818	16.8459	863.55	93.861
MDL100907/L701324	2 mpk	MDL100907	0.3 mpk	L701324		10	25.980	31.5739	622.90	189.097
MDL100907/PCP	2 mpk	MDL100907	0.3 mpk	PCP	1 mpk	10	14.916	13.8546	792.60	155.336
Ketanserin	2 mpk	Ketanserin	2 mpk	—		10	10.400	11.0660	648.90	161.515
Ketanserin/D-cycloserine	2 mpk	Ketanserin	2 mpk	D-cycloserine	300 mpk	10	21.390	18.2661	640.60	96.388
EMD281014	2 mpk	EMD281014	30 mpk	—		10	23.050	20.7267	628.20	110.375
EMD281014/D-cycloserine	2 mpk	EMD281014	30 mpk	D-cycloserine	300 mpk	10	27.380	26.7496	541.10	148.076
Antipsychotics										
Lurasidone	2 mpk	Lurasidone	1 mpk	—		10	36.020	16.2589	715.50	116.712
Lurasidone/D-cycloserine	2 mpk	Lurasidone	1 mpk	D-cycloserine	300 mpk	10	53.230	17.6298	739.10	91.594
Quetiapine	2 mpk	Quetiapine	30 mpk	—		10	8.950	10.6937	676.50	116.319
Quetiapine/D-cycloserine	2 mpk	Quetiapine	30 mpk	D-cycloserine	300 mpk	10	26.004	28.9504	630.20	140.271
Antidepressants										
Duloxetine	2 mpk	Duloxetine	10 mpk	D-cycloserine	300 mpk	10	22.290	30.4841	979.50	181.190
Mirtazapine	2 mpk	Mirtazapine	5 mpk	D-cycloserine	300 mpk	10	25.282	22.3245	764.20	97.790
Vaniafaxine	2 mpk	Vaniafaxine	16 mpk	D-cycloserine	300 mpk	10	21.144	12.0805	928.50	78.921

Source: Javitt, 2014

Our preclinical research, using the Rat Akathisia model, suggests an additional synergistic interaction between DCS and lurasidone. On one hand, as described above, DCS appears to block the anxiogenic effects of lurasidone. Conversely, lurasidone may in turn have the ability to reverse low-level psychotomimetic effects of DCS and ketamine. This signal may be appreciated from the decrease in distance traveled when lurasidone is added to DCS. Lurasidone mediates its antipsychotic effects at both D2 and 5-HT2A receptors. As opposed to pure serotonergic agents used in the treatment of major depressive disorders (e.g., SSRIs), the additional D2 blockade of lurasidone makes it a clinically effective antipsychotic and, thus, also potentially effective in treatment of psychotic symptoms that may be induced by NMDA antagonists.

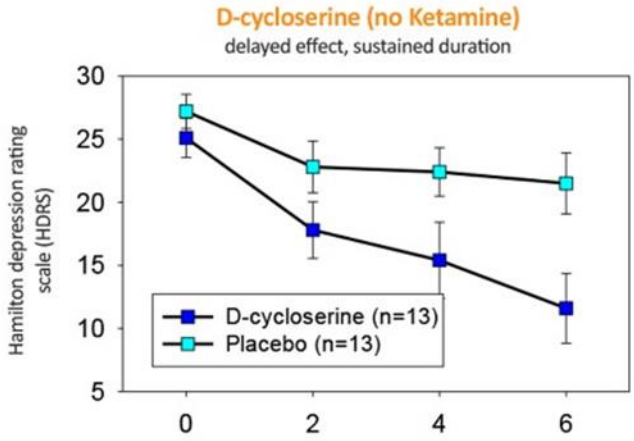
Clearly the phenomena observed in rodents should not be viewed as isomorphic with drug- induced akathisia and/or jitteriness/anxiety syndrome in humans. However, we believe that these findings provide a rationale for combining glycine site-binding NMDAR antagonists with 5-HT2a antagonists in phase 2 and 3 studies of otherwise-safe drugs for the treatment of bipolar depression. This is particularly true in situations where akathisia is believed to predispose to suicide in vulnerable patients.

4.5 Clinical Experience

Antidepressant effects of high dose DCS were first noted in the late 1950's when it was first introduced as a treatment for tuberculosis (TB). Several clinicians noted dramatic improvement in patients' depressive symptoms, leading to suggestions of 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 NMDA receptor was first demonstrated in 1989, (Hood et al., 1989), leading to some interest in NMDAR blockers as potential antidepressant treatments. (Trullas, Skolnick 1990; Skolnick et al., 1996). For example, both DCS and the related compound 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 in 2000. An initial study performed with DCS at a dose of 250 mg/d did not show therapeutic effect, but did demonstrate relative lack of psychotomimetic side effect when DCS was combined with concurrent antidepressant treatment (Heresco-Levy, Javitt et al., 2006). Based upon these safety data, a study using a higher dose of 1000 mg/d) was initiated with results reported in 2013 (Heresco-Levy et al., 2013) (see Figure 1). At the higher, 1000 mg dose, significant beneficial effects were observed in 13 subjects vs placebo control with SSRI-nonresponsive depressive symptoms. The improvements were manifest within 2 weeks and persisted throughout the 6-week treatment period.

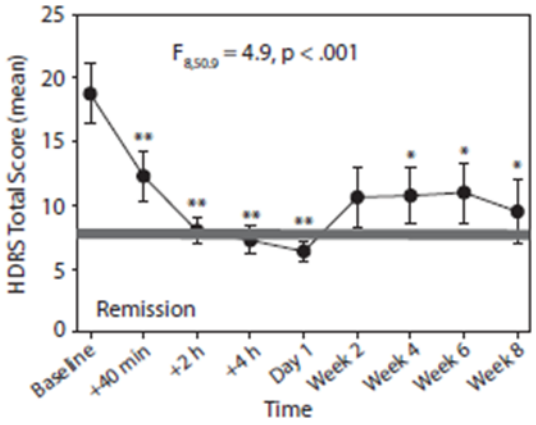
Figure 1 DCS vs. Placebo for Treatment of Depression



Source: Kantrowitz, 2015

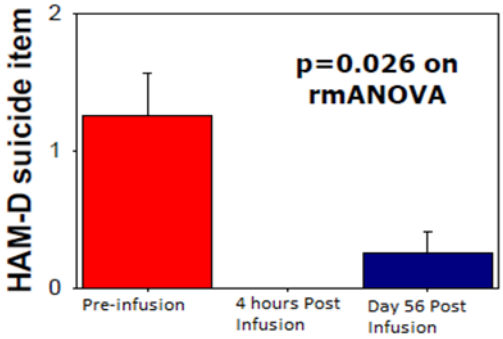
The 2013 Heresco-Levy study provided initial evidence that DCS might be useful as an NMDAR- targeted antidepressant, but the time of onset for DCS alone was suboptimal for treating acutely depressed individuals. Therefore, an open-label study was performed in which subjects with bipolar depression received an infusion of ketamine on Day 1, followed by oral administration of DCS, titrated to a dose of 1000mg/day combined with lurasidone 66mg/day as individual commercially-supplied medications. Seven of 8 subjects completed the study and no adverse effects were noted. Over a period of 8 weeks, a > 75% reduction in suicidal ideation and a 50% reduction in depression was noted, using the Hamilton Depression Scale (HAM-D). (Figure 2; Kantrowitz, 2015). Note that suicidal ideation was eliminated entirely at 4 hours post-infusion of ketamine (Figure 3; Kantrowitz, 2014).

Figure 2 Depression Score after Ketamine followed by DCS + 5-HTZA



Source: Kantrowitz, 2015

Figure 3 Suicidal Ideation after Ketamine followed by DCS + 5-HTZA



Source: Kantrowitz, 2014

4.6 Investigational Therapy

The investigational therapy to be evaluated in this study consists of sequential treatment consisting of the following components:

1. an initial, one-time intravenous infusion of ketamine (0.5 mg/kg administered over 40 min) on Day 0, followed by
2. twice daily oral capsules of NRX 101 (d-cycloserine [DCS] + lurasidone), which is initiated on Day 1 (in subjects who respond to ketamine) and continued for up to 6 weeks. It is anticipated that subjects entering the study will be receiving concurrent disorder-directed treatment with various predefined combinations of medications. This treatment regime will be maintained upon entry into the study. However, any use of lurasidone, quetiapine, or olanzapine will be stopped at study entry.This regimen may be supplemented with mood stabilizers at the discretion of the treating physician.

Our clinical objective is to offer patients the clinical benefit of rapid reduction in symptoms of depression and suicidal ideation that has been observed with intravenous ketamine, while maintaining that benefit with a daily oral agent that does not have ketamine's potential for abuse and psychosis.

4.7 Dosing Rationale

The doses chosen for the three components of the sequential therapy are based on current dosing recommendations for each. In Stage1, the one-time IV infusion of ketamine on Day 0 at 0.5 mg/kg over 40 minutes is below the lowest recommended IV concentration (1 mg/kg) to induce anesthesia, and is consistent with studies of ketamine for use in depression.

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. The recommended oral dose of lurasidone for the treatment of acute depressive BD is 20 to 120 mg/day for up to 6 weeks. Therefore, dosing of the fixed-dose combination NRX 101 during Stage 2 will be twice daily over 6 weeks. The starting doses at 350 mg DCS and 16.5 mg lurasidone, and the titration over 5 days to a maximum of 950 mg DCS and 66 mg lurasidone are planned accordingly. Up-titration is built in to the dosing strategy in the case of subject agitation and a stepdown is allowed for somnolence.

For complete details regarding dosing recommendations, please see the product safety labeling for each of the drugs, which are included in the Investigator Brochure (IB).

5. OBJECTIVES

5.1 Primary Objective

The primary objective of the study is to test the hypothesis that following response to initial ketamine infusion, experimental drug NRX-101 (DCS + lurasidone) is superior to lurasidone alone and placebo as oral-therapy for delaying time to relapse (resulting in a new treatment plan or the subject relapsing to baseline levels of depression or suicidality) in subjects with documented bipolar depression presenting with symptoms of depression and suicidal ideation.

The primary study hypothesis (alternative hypothesis) is that ketamine and experimental drug NRX-101 (K/N) delays the time to documented relapse as compared to both lurasidone (L) and placebo (P) as measured by the hazard ratio (h) versus the null hypothesis of no delay in time to relapse for either comparator treatment (ketamine/lurasidone [K/L] and ketamine/placebo [K/P]) as follows:

H_0: $h_{NRX\text{-}101} < h_L$ and h_P

H_a: $h_{NRX\text{-}101} \geq h_L$ and h_P.

The primary outcome measure will be time to relapse, defined as the need to implement a new treatment plan or a return to baseline levels on the Columbia-Suicide Severity Rating Scale (C-SSRS), or the Montgomery Asberg Depression Rating Scale (MADRS) subset on the Bipolar Inventory of Symptom Severity (BISS).

All relapses will be documented by the site physician and reviewed on a monthly basis by a Relapse Adjudication Committee. The Relapse Adjudication Committee (RAC) will determine whether the relapse met the primary endpoint criteria.

5.2 Secondary Objective

The secondary objectives of the study are the following:

- To demonstrate bipolar depression efficacy
- To demonstrate efficacy can be sustained with NRX-101 dosing regimens
- To demonstrate NRX-101 safety

The secondary study hypotheses (alternative hypotheses favoring K/N vs. K/L and K/P) are the following:

1. K/N will favorably separate from both K/L and K/P by 72 hours, with sustained difference between groups thereafter.
2. All cause discontinuation (including discontinuation for continued suicidal ideation) will be lower for K/N than both K/L and K/P.
3. K/N will favorably separate from K/L and K/P starting at day 7, with sustained difference thereafter.
4. Improvements within the K/N group observed at Week 2 will remain stable to end of study.

5. C-SSRS scores will remain <4 for 4 weeks following treatment discontinuation (i.e., “crisis” will resolve within the 6 week time period with more favorable outcomes in the K/N group as compared to K/L and K/P.

Additionally, symptom improvement will be evaluated by assessing changes in the secondary outcome measures: C-SSRS, CHRT, and the BISS (including its subscales). These measures will be assessed at the times specified on the Study Activity Schedule, Table 3.

6. STUDY DESIGN

6.1 Overview

The multi-center study will consist of a 6-week, parallel group, double-blind, randomized, adaptive, superiority trial designed to test the hypothesis that following response to ketamine infusion, experimental drug NRX-101 (DCS + lurasidone) is superior to both lurasidone alone and placebo as oral-therapy for delaying time to relapse (resulting in a new treatment plan or the subject relapsing to baseline levels of depression or suicidality) in subjects with documented bipolar depression presenting with symptoms of depression and suicidal ideation.

6.2 Methods

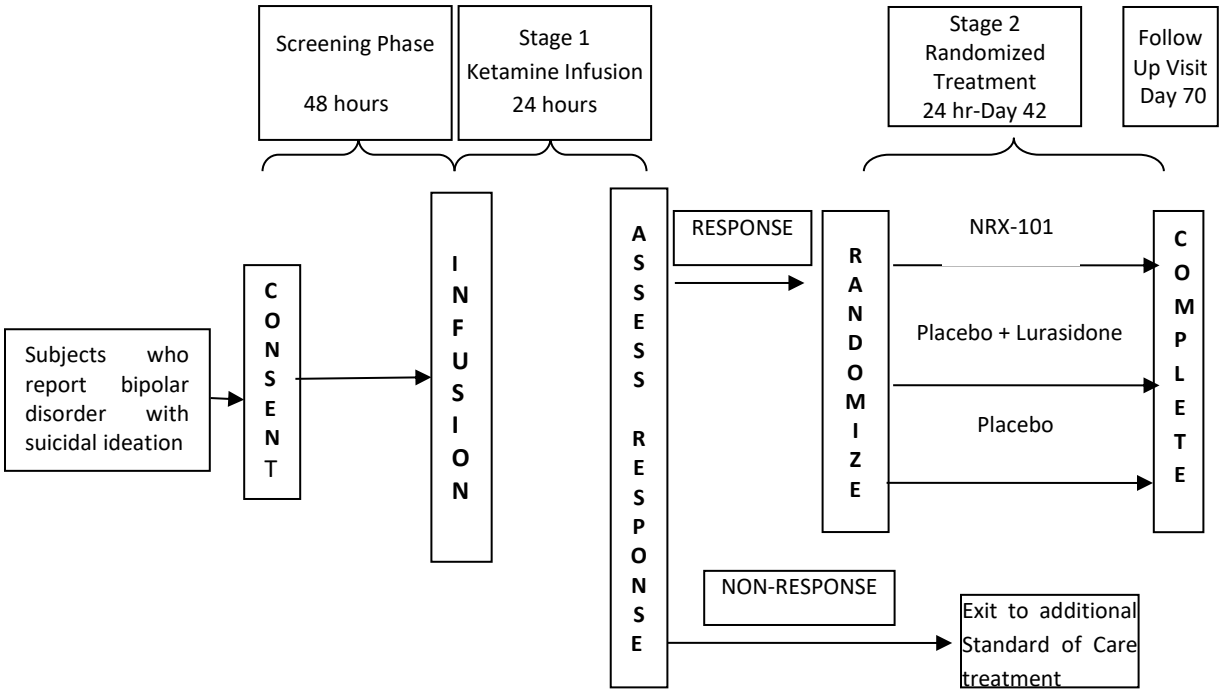
In Stage 1 eligible subjects will initially receive an infusion of open-label ketamine 0.5mg/Kg. Those who do not respond to ketamine infusion as measured by a ≥25% improvement in the MADRS subset on the BISS and a reduction in C-SSRS suicidal ideation to ≤ 3 at 24 hours post infusion will be withdrawn from the study and treated according to standard of care for subjects with suicidal ideation or behaviors.

Subjects who respond successfully to ketamine infusion, as defined above (≥25% improvement in the MADRS subset of the BISS and C-SSRS ≤3) at 24 hours post infusion will proceed to Stage 2 and be randomized to either experimental drug NRX-101 (DCS + lurasidone), lurasidone alone, or placebo. Efficacy data will be collected for the subjects responding to ketamine through 6 weeks or until earlier rescue.

Subjects may be terminated from the study and rescued with alternative therapy at any time if, in the opinion of the investigator, subjects have a significant safety risk for clinical deterioration or suicide.

6.3 Study Schema

Figure 4. NRX-101 for the Treatment of Suicidality in Bipolar Disorder



6.4 Study Population

The study analyses will be conducted in a GCP environment (ICH E6). All analyses will be pre-specified in a Statistical Analysis Plan (SAP) prior to beginning subject enrollment. The study will have prospectively defined study populations including separate evaluability rules for the ketamine treatment (Stage 1) and randomized treatment (Stage 2).

For Stage 1, the Intent-to-Treat (ITT) population will include all subjects who received the ketamine infusion and have the 24-hour post-infusion efficacy assessments. The Per-Protocol Population will include the subset of ITT subjects who were eligible, who had the 24-hour post-infusion efficacy assessments within 18 to 30 hours post the start of the initial infusion, and who had no major protocol violations. The Safety Population will include all subjects treated with ketamine who have any post-baseline safety data.

For Stage 2, the ITT population will include all subjects who received the randomized study treatment and have any post-baseline efficacy assessments. The Per-Protocol population will include the subset of ITT subjects who were eligible, who have any post-baseline efficacy assessments within 1 day of scheduled visits through Day 7 and within 2 days of scheduled visits through Day 42, and who had no major protocol violations. The Safety Population will include all subjects as treated with study treatment who have any post-baseline safety data through Day 70.

The ITT population will be used for the primary analyses. If <5% are to be excluded from the ITT 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 involved in study. Non-compliance will be tracked. Protocol violations will be reviewed in real time; rules will be set for exclusions from the PP population.

A sufficient number (estimated to be 192 subjects) will be entered into Stage 1 in order to have 124 randomized subjects to complete Stage 2. IRB-approved written informed consent will be obtained from all subjects before any protocol-specified procedures are carried out. The subjects will be drawn from a sample of subjects with BD with suicidal ideation, diagnosed with the use of the MINI 7.0.2 for DSM 5. For entry into the study, all inclusion criteria must be met, and none of the exclusion criteria can be met.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

Subjects must meet all of the inclusion and none of the exclusion criteria to be qualified to participate in this study.

7.1 Inclusion Criteria

1. Male or female, 18 to 65 years of age, inclusive, at screening.
2. Able to read, understand, and provide written, dated, informed consent prior to screening. Participants will be deemed likely to comply with study protocol and communicate with study personnel about AEs and other clinically important information.
3. Diagnosed with BD according to the criteria defined in the DSM-5. The diagnosis of BD will be made by a site psychiatrist and supported by the MINI 7.0.2. The diagnosis will be confirmed by remote, independent raters via teleconference between the screen visit and the baseline visit.
4. Suicidal ideation or behavior of sufficient severity to meet the requirements for a score of 4 or 5 on the C-SSRS.
5. A score equal to or greater than 20 on the MADRS items of the BISS.
6. In good general health, as ascertained by medical history, physical examination (PE) (including measurement of seated vital signs), clinical laboratory evaluations, and electrocardiogram (ECG).
7. If female, a status of non-childbearing potential or use of an acceptable form of birth control per the following specific criteria:

    c. Non-childbearing potential (e.g., physiologically incapable of becoming pregnant, i.e., permanently sterilized [status post hysterectomy, bilateral tubal ligation], or is post-menopausal with her last menses at least one year prior to screening); or

    d. Childbearing potential, and meets the following criteria:

        iv. Childbearing potential, including women using any form of hormonal birth control, on hormone replacement therapy started prior to 12 months of amenorrhea, using an intrauterine device (IUD), having a monogamous relationship with a partner who has had a vasectomy, or is sexually abstinent.

        v. Negative urinary pregnancy test at screening, confirmed by a negative urinary pregnancy test at randomization prior to receiving study treatment.

        vi. Willing and able to continuously use one of the following methods of birth control during the course of the study, defined as those which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly: implants, injectable or patch hormonal contraception, oral contraceptives, IUD, double-barrier contraception, sexual abstinence. The form of birth control will be documented at screening and baseline.

8. Body mass index between 18-35 kg/m^2.

9. Concurrent psychotherapy will be allowed if the type (e.g., supportive, cognitive behavioral, insight-oriented) and frequency (e.g., weekly or monthly) of the therapy has been stable for at least three months prior to screening and if the type and frequency of the therapy is expected to remain stable during the course of the subject's participation in the study.
10. Concurrent hypnotic therapy (e.g., with zolpidem, zaleplon, melatonin, benzodiazepines 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 subject's participation in the study. Subjects can also continue treatment with benzodiazepines used for anxiety if 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 subject's participation in the study.

7.2 Exclusion Criteria

1. Female of childbearing potential who is not willing to use one of the specified forms of birth control during the study.
2. Female that is pregnant or breastfeeding.
3. Female with a positive pregnancy test at screening or baseline.
4. Current diagnosis of a substance use disorder (abuse or dependence, as defined by DSM-5, with the exception of nicotine dependence), at screening or within 6 months prior to screening.
5. Current Axis I disorder, diagnosed at screening with the use of the MINI 7.0.2, that is the primary focus of treatment and BD the secondary focus of treatment for the past 6 months or more.
6. History of schizophrenia or schizoaffective disorders, or any history of psychotic symptoms when not in acute bipolar mood episode.
7. History of anorexia nervosa, bulimia nervosa, or eating disorder not otherwise specified, within 5 years of screening.
8. Any Axis I or Axis II Disorder, which at screening is clinically predominant to their BD or has been predominant to their BD at any time within 6 months prior to screening.
9. Has dementia, delirium, amnestic, or any other cognitive disorder.
10. Has a clinically significant abnormality on the screening physical examination that might affect safety, study participation, or confound interpretation of study results according to the study clinician.
11. Participation in any clinical trial with an investigational drug or device within the past month or concurrent to study participation.
12. Current episode of:
    i. Hypertension, Stage 1 as defined by a systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg at screening on two of three measurements at least 15 minutes apart.

j. Hypertension, Stage 1 as defined by a systolic blood pressure ≥155 mmHg or diastolic blood pressure ≥99 mmHg at the Baseline Visit (Visit 1) within 1.5 hours prior to ketamine infusion on two of three measurements at least 15 minutes apart.

k. Recent myocardial infarction (within one year) or a history of myocardial infarction.

l. Syncopal event within the past year.

m. Congestive heart failure (CHF) New York Heart Association Criteria >Stage 2

n. Angina pectoris.

o. Heart rate <50 or >105 beats per minute at screening or randomization (Baseline Visit).

p. QTcF (Fridericia-corrected) ≥450 msec at screening or randomization (Baseline Visit).

13. Current history of hypertension, or on antihypertensives for the purpose of lowering blood pressure, with either an increase in antihypertensive dose or increase in the number of antihypertensive drugs used to treat hypertension over the last 2 months.

14. Chronic lung disease excluding asthma.

15. Lifetime history of surgical procedures involving the brain or meninges, encephalitis, meningitis, degenerative central nervous system (CNS) disorder (e.g., Alzheimer's or Parkinson's Disease), epilepsy, mental retardation, or any other disease/procedure/accident/intervention which, according to the screening clinician, is deemed associated with significant injury to or malfunction of the CNS, or history of significant head trauma within the past 2 years.

16. Presents with any of the following lab abnormalities:

    c. Subjects with diabetes mellitus fulfilling any of the following criteria:

        v. Unstable diabetes mellitus defined as glycosylated hemoglobin (HbA1c) >8.5% at screening.

        vi. Admitted to hospital for treatment of diabetes mellitus or diabetes mellitus-related illness in the past 12 weeks.

        vii. Not under physician care for diabetes mellitus.

        viii. Has not been on the same dose of oral hypoglycemic drug(s) and/or diet for the 4 weeks prior to screening. For thiazolidinediones (glitazones) this period should not be less than 8 weeks.

    d. Any other clinically significant abnormal laboratory result (determined as such by the investigator and medical monitor) at the time of the screening.

17. Any current or past history of any physical condition which in the investigator's opinion might put the subject at risk or interfere with study results interpretation.

18. Positive screening urine test for drugs of abuse at screening: cocaine, amphetamines, barbiturates, opiates.

19. Subjects with exclusionary laboratory values (see Table 2), or requiring treatment with exclusionary concomitant medications (see Appendix 1).
20. Subjects on exclusionary concomitant psychotropic medications.
21. Subjects with a lifetime history of PCP/ketamine drug use.
22. Liver Function Tests higher than 2.5 times upper limit of normal.
23. Known allergies to Lurasidone or Latuda, Cycloserine or Seromycin, Mannitol, Croscarmellose Sodium, Magnesium Stearate, Silicon Dioxide, and/or HPMC (hydroxypropylmethylcellulose).

Table 2 Exclusionary Safety Values of Potential Clinical Concern

Hematology	
Leukocytes	<2 or >17.5 x $10^3/mm^3$
Platelets	<75 or >700 x $10^3/mm^3$
Chemistry	
Total bilirubin	>2.5 times the upper limit of the reference range
AST	>2.5 times upper limit of the reference range
ALT	>3 times upper limit of the reference range
GGT	>3 times upper limit of the reference range
Alk Phosphatase	>3 times upper limit of the reference range
Creatinine	>1.3 times upper limit of the reference range
BUN/Urea	>1.3 times upper limit of the reference range
Glucose	<70 mg/dl or >2 times the limits of the reference range
HbA1c	>7.0%
Uric acid	>1.5 times upper limit of the reference range

7.3 Selection and Withdrawal of Subjects

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to ensure that the results of the study are meaningful in relation to the research hypotheses. It is imperative that subjects fully meet all eligibility criteria.

7.4 Replacement of Subjects

Subjects who withdraw will not be replaced.

8. STUDY ASSESSMENTS – PLAN AND METHODS

8.1 Site of Care and Study Conduct

Subjects may be recruited upon presentation in an outpatient psychiatric practice, emergency department, community mental health setting, or psychiatric hospital. The site of care will be either (1) a community mental health/bipolar clinic setting with overnight observation capability and with immediate access to a psychiatric inpatient facility or (2) an inpatient setting. Only sites that have been using ketamine for stabilization of patients with bipolar depression as part of their practice of medicine for at least 12 months will be included as study sites in the trial. Eligible study sites will already have written policies and procedures around the use of ketamine, will be properly licensed by the Drug Enforcement Administration for the storage and use of ketamine, and will have written criteria for ensuring the safety of patients under their care who receive ketamine.

It should be emphasized that dedicated (typically for-profit) psychiatric research facilities whose physicians do not otherwise provide ongoing care to patients with suicidal bipolar depression are not eligible to participate as study sites because of concerns that such facilities may not have adequate clinical experience or resources to ensure patient safety over the course of the study.

The study protocol does not dictate the site of care (inpatient vs. outpatient). That is determined by the treating physician in consultation with the patient and family, based upon assessment of the patient's acuity, the patient's home environment, and other factors that psychiatrists expert in the management of this patient population use in determining the appropriate site of care. It is anticipated that subjects enrolled at C-SSRS level 4 are likely to be managed in the outpatient setting, whereas those enrolled at C-SSRS level 5 will be maintained under continuous professional observation until they have stabilized at a C-SSRS level 3 or lower. Just as site of care is determined by the treating physician, the decision to discharge those subjects who begin in the inpatient setting is entirely up to the study physician, based upon the same protocols and criteria already in place to determine discharge for patients with suicidal bipolar depression. The study sponsor and the study protocol will not influence this decision in any way. The sponsor does require, however, that subjects with C-SSRS level 5 ideation or behavior be under continual professional observation from the time of enrollment and ketamine infusion to the point at which the patient is deemed to have stabilized and is randomly assigned to one of the study arms.

All eligible subjects will receive ketamine infusion according to the procedures in this protocol. All infusions will be conducted in a clinic-like or hospital setting with a licensed anesthetist, standard monitoring equipment, and full emergency backup available. Subjects who experience sufficient improvement and are stable after the ketamine infusion may be hospitalized or discharged at the discretion of the treating physician. Discharge will only be allowed if there is an established support structure and agreement to follow the safety plan whereby sites will contact subjects twice daily for the next week either in person or through a video connection provided by sponsor and then at least weekly through the end of the study to collect study data to support efficacy and safety. The election to follow subjects who respond to initial ketamine on an inpatient or outpatient basis will be made by the treating study physician with the consent of the subject.

Subjects who meet study criteria for relapse at any point during the study will be withdrawn from the study and offered clinically-appropriate treatment as determined by the treating study physician, which may

include inpatient hospitalization, repeated administration of ketamine, electroconvulsive therapy (ECT), or other treatments determined by professional judgment. Subjects who demonstrate therapeutic benefit from experimental drug NRX-101 (DCS+ lurasidone) at study completion may be offered prescribed DCS by their treating psychiatrist.

The Schedule of Study Activities (Table 3) summarizes the frequency and timing of efficacy, PK, and safety measurements applicable to this study. With the exception of post-dose assessments, visit-specific subject-reported outcomes assessments should be conducted or completed before any tests, procedures, or other consultations for that clinic visit to prevent influencing subject perceptions. A recommended order of study procedures will be provided to sites as a separate document.

Actual dates and times of assessments will be recorded in the source documentation and electronic Case Report Form (eCRF).

8.1.1 Study Visits and Assessments

A schedule of study visits and assessments is provided in Table 3 Schedule of Study ActivitiesTable 3

Table 3 Schedule of Study Activities

			Stage 1			Stage 2									Follow Up /ET
	Study Day	Screening Period	Day 0			Day 1	Day 6	Day 7	Day 10	Day 14	Day 21	Day 28	Day 35	Day 42	Day 70
		48 hrs	Ket. Dosing	4 hr	10 hr +2 hours	24 hr post dose	+/- 1 day								
Assessment/Activity	Visit Name/No.	Screen	Baseline			1	2	3	4	5	6	7	8	9	10
Informed Consent		X													
MINI 7.0.2 DSM 5		X													
Demographics		X													
Medical History		X													
Psychiatric History		X													
Physical Exam		X								X					X
Vital Signs		X	X	X		X		X	X	X	X	X	X	X	X
ECG		X				X				X					X
Concomitant Medications		X	X				X	X	X	X	X	X	X	X	
C-SSRS		X	X	X	X	X	X	X	X	X	X	X	X	X	
Phone Visit*					X		X								
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X
CHRT—C, SR		X						X		X	X	X	X	X	
Remote Independent Rater Interview		X**													
CADSS			X	X											
BISS		X	X	X		X		X	X	X	X	X	X	X	
SIBQ			X	X		X		X	X	X	X	X	X	X	
Blood Draw for drug analyses		X				X***				X***				X***	
BARS			X					X	X	X	X	X	X	X	
BPRS			X	X											
PRISE			X	X		X		X	X	X	X	X	X	X	
Chemistry, CBC		X								X				X	
Urine Tox Screen		X								X				X	
Pregnancy Test (Urine)		X								X				X	
Ketamine Infusion			X												
Randomization						X									
Drug Dispensation & Pill Count						X		X		X	X	X	X	X	

*This phone visit should be performed by the site Principal Investigator, or Sub-Investigator. **The independent interview is performed remotely by telephone by independent raters.
***Blood draws for drug analyses 2 hours after the initial dose, prior to administration of NRX-101 on days 14 and 42, and 2 hours after administration of NRX-101 on day 42.

8.1.2 Screening Period

Once subjects agree to participate in the study by signing the informed consent document, a full medical and psychiatric history will be taken and a physical and laboratory examination will be performed, as outlined in the Schedule of Study Activities (Table 3). The screening period may extend for up to 48 hours following the signing of the informed consent in order to allow time for the independent third party raters' interview to be conducted and the ketamine infusion to be scheduled. Upon determination by the site investigator(s) that the subject meets the inclusion and exclusion criteria for the study, a remote interview will be scheduled with an independent rater.

8.1.3 Remote Interview

To ensure that appropriate subjects are entered into the trial, remote diagnostic assessments (for Bipolar Disorder, C-SSRS and BISS) will be performed by remote, independent third party raters'. The interview will be performed remotely by the independent, third party rater, via telephone during the 24 hour screening period. Depending on level of suicidal ideation and behavior, the subject may be contacted while at home or while being managed in an ED, hospital, or other acute care facility. Sites will be notified of the results within 2 business hours of the interview completion.

8.1.4 Stage 1: Ketamine Infusion

For entry into Stage 1 of the study (ketamine infusion), all eligibility criteria MUST continue to be met (i.e., all inclusion criteria and no exclusion criteria).

All subjects will receive ketamine by continuous infusion for 40 minutes by use of an electronic pump. The start and stop times of the ketamine infusions will be documented in the eCRF.

Detailed instructions for dose preparation will be provided to site research pharmacists in an additional guidance document. Storage conditions should be followed according to the package insert. Dosing procedures will be provided to the clinical unit in a separate infusion document.

Assessments: During the infusion, the Clinician Administered Dissociative Symptom Scale (CADSS) and the Brief Psychiatric Rating Scale (BPRS) are administered at 0 (-5 minutes), 40 minutes (completion of infusion) and 4 hours. Both are administered by a clinician.

Physiological Monitoring: Each participant will be allowed to rest in a semi-recumbent position. Each subject will receive an intravenous (IV) line. The monitoring will include a non-invasive blood pressure cuff, a 3- or 5-lead ECG, a pulse oximeter and oxygen by face mask or nasal cannula at 4 to 6 liters per minute, as needed. Vital signs will be monitored continuously and recorded every 20 minutes. Each subject will receive an infusion for 40 minutes.

The IV line will be left in place for at least 1 hour following the infusion to allow for additional medications to control emergent side effects. Medical staff monitoring the infusion will be prepared to treat increases in blood pressure greater than 180/100 mmHg or heart rate greater than 110 bpm, or follow their institutional guidelines if more conservative. If these elevations resolve spontaneously within a short time period, they will generally not be treated. The study

infusion will be discontinued in the event that three consecutive measurements remain above protocol-defined limits for 20 minutes or more, or according to institutional guidelines if more conservative, despite antihypertensive administration. The psychiatry research staff member will administer rating scales at -5, 40 minutes and 4 hours. All side effects and vital parameters will be recorded during the infusion and for the 4 hours following at 1 hour intervals. Clinically relevant vital sign changes will be recorded as AEs. The subject may be released after the 4 hour measurements are complete as long as they have achieved pre-treatment vital signs measurements or are deemed to be clinically stable" or something along those lines.. Subjects will be required to have an adult escort them home post-administration of ketamine, or may be transported home by a medical transport company provided that presence of a responsible adult at the home location has been verified. Participants who cannot ensure a reliable adult transport or home observer will not be allowed to enroll in the study. Subjects will be instructed not to drive or operate heavy machinery for at least 24 hours post-administration.

8.1.5 Post Discharge Phone Visit

At 10 hours post the start of the ketamine infusion (plus/minus 2 hours) the patient will be assessed by a study investigator (in-person or called at home if subject were to be discharged). During this phone visit, the procedures listed in Table 3 (C-SSRS (since last visit), and an assessment of AEs) will be completed.

8.1.6 Randomization

Subjects will be assessed in person 24 hours post-infusion for response to ketamine. Those who do not respond will be provided standard of care for ongoing suicidal ideation. Following the documented observance of a therapeutic response to intravenous ketamine as defined by a 25% or greater reduction in the on the MADRS subset of the BISS score and a score of ≤3 on the C-SSRS at 24 hours post infusion, subjects will be randomized 2:1:1 to either a fixed dose combination of experimental drug NRX-101 (DCS + lurasidone), or to an identical capsule containing placebo + lurasidone, or to an identical capsule containing placebo. Randomization blocks will be allocated at the site level to ensure that treatment and control groups are balanced per site. An Interactive Web Response System will be used.

8.1.7 Early Termination Visit

If a subject withdraws consent, or is otherwise terminated from the study, every effort should be made by the site to perform the procedures listed for Day 70.

8.1.8 Post Ketamine Infusion Follow-Up

Subjects who are non-responders at 24 hours following the start of the ketamine infusion will be withdrawn from the study and treated according to the site's standard treatment procedure. Non-response is defined as less than a 25% reduction on the MADRS subset of the BISS score and a score of ≥4 on the C-SSRS.

8.1.9 Concomitant Medications

All concomitant medications taken during the study will be recorded in the Concomitant Medication Log for each subject, along with dosage information and start and stop dates. 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 antipsychotic therapy and stable allowed hypnotic therapy. Subjects requiring excluded drugs will be discontinued from the study.

Prohibited concomitant medications which the patient and the study investigator agree may be discontinued, will be washed out for a period of 5 half lives or one week, whichever is longer. Clinically appropriate tapering regimens may be used if necessary. The screen period may be extended, upon consultation with the medical monitor, to allow for a sufficient washout period. A list of prohibited concomitant medications is included in Appendix 1.

8.1.10 Subject Recruitment

Subjects will be recruited through study clinicians from patients who present at the site with bipolar depression and suicidal ideation. Those deemed eligible will be scheduled for a screening visit with one of the study physicians at the site. Appropriate recruitment strategies such as advertising, primary care physician referrals and internet based outreach may be used as well. Any patient facing materials will be submitted for IRB approval.

8.1.11 Inclusion of Children

Adolescents between the ages of 18 and 21 will be elegible for enrollment. We are not including children younger than age 18. We have decided to exclude children under the age of 18 because there are specific safety considerations, as well as treatment considerations in pediatric bipolar depression that exceed the scope of this study. However, if treatments from this proposal are found efficacious and well tolerated, a next step may be the consideration of use in children of younger ages.

8.2 Procedures

8.2.1 Laboratory/Diagnostic Procedures

Clinical laboratory safety testing will be conducted locally by the study site using CLIA-approved laboratories that have been audited by study personnel for compliance. Once the subject has signed the informed consent document, the urine pregnancy test will be performed at the Screen Visit, and Visits 5 and 9. ECGs will be measured at the Screen Visit, the Baseline Visit (at the 24-hour time point), and at Visits 5 and 9. Chemistry and complete blood count (CBC) will also be obtained at the Screen Visit, and at Visits 5 and 9. Weight, BMI, oral temperature, seated pulse and seated blood pressure (vital signs) will be recorded at each visit. At

Screen, and Visit 5 and 10, subjects will have a physical examination. The laboratory tests required are listed in Table 4, below.

Table 4 Laboratory Assessments

Laboratory Test	Frequency
CBC	Screen, Visits 5 and 9
Chemistry (Total bilirubin, AST, ALT, GGT, ALK Phosphatase, Creatine, BUN/Urea, Glucose, Uric Acid)	Screen, Visits 5 and 9
HbA1c (only for diabetics)	Screen
Pregnancy Test	Screen, Visits 5 and 9
Urine Toxicity Screen	Screen, Visits 5 and 9

8.2.2 Drug Levels

Blood samples for monitoring therapeutic drug levels will be collected on all subjects to verify exposure and consistency with the randomization schedule. The timing of the blood draws are defined in Table 3 and include both pre-dosage (time 0) and post initial dosing of investigational product within the first 2 hours. Analyses of the samples will be conducted by the central laboratory.

8.2.3 Randomization phase

Following the documented observance of a therapeutic response to IV ketamine as defined by a 25% or greater reduction in the baseline MADRS and a C-SSRS $\leq$ 3 at 24 hours post infusion, subjects will be randomized 2:1:1 to either a fixed dose combination of experimental drug NRX-101 (DCS + lurasidone) or to an identical capsule containing placebo + lurasidone or to an identical capsule containing placebo. Institution balancing will be used to ensure that treatment and control groups are balanced with stratification according to C-SSRS 24 hours post-infusion (1, 2). Subjects who respond to ketamine will be followed for 6 weeks or until they require additional treatment.

8.2.4 Blinding Procedures

Investigational product will be provided in a blinded fashion to sites for dispensation to subjects.

8.2.5 Outcome and Safety Measures

8.2.5.1 Outcome Measures

8.2.5.1.1 Primary Efficacy Endpoint

The primary outcome measure will be time to relapse, defined as (1) a return to a score of $\geq$4 on the C-SSRS, (2) a score of $\geq$20 on the MADRS subset of the BISS following a response to

ketamine at 24 hours, or (3) the treating physician's determination that a change in treatment plan, such as re-hospitalization, ECT, or addition of new antidepressant drugs is required.

All site-defined relapses will be adjudicated by a Relapse Adjudication Committee (RAC) which will review documentation provided by the site for each incidence and determine whether the relapse meets the protocol definition of relapse. The RAC will meet monthly. The RAC is authorized to determine that relapse occurred even if the site does not make this determination.

8.2.5.1.2. Secondary Efficacy Endpoints

Additionally, symptom improvement will be evaluated by assessing changes in the secondary outcome measures: C-SSRS, Concise Health Risk Tracking –Clinician, -Self-Rated **(**CHRT-C and –SR), and BISS. These measures will be assessed at the times specified on the Schedule of Study Activities, Table 3.

The C-SSRS (and the retrospective Columbia-Classification Algorithm of Suicide Assessment (C-CASA component), Suicide Ideation and Behavior Questionnaire (SIBQ), BPRS, CHRT-C and –SR, will be evaluated within and between study treatment groups. Mean changes from baseline for the differences from baseline and after randomization baseline will be evaluated using a paired t-test within each study group and an unpaired t-test for K/N vs. K/L and K/P.

8.2.5.1.3. Diagnostic Metric

The following diagnostic metric will be evaluated at baseline:

- MINI 7.0.2

8.2.5.1.4. Additional Endpoints

The following additional endpoints will be recorded and analyzed for both study stages:

- Study dose per treatment group
- All-cause discontinuation (and reason for discontinuation)
- Suicide rates
- Incidence of hospitalization and ER visits for disease-related outcomes
- Proportion of subjects who are treated with new SSRIs or have increased SSRI dosages
- Proportion of subjects who discontinue SSRIs or have reduced SSRI dosages.

8.2.5.2 Safety Endpoints

8.2.5.2.1. Overall Adverse Events

Separate safety analyses will be performed for the two stages for the Safety population. Safety endpoints will include adverse events (AE), vital signs, and relevant clinical chemistries and hematology parameters.

The principle of treatment emergence will be employed for the analysis of AE data. Treatment emergence is defined to be any event that occurred during the observation period and was not present at baseline, or one which represents an exacerbation of a condition present at baseline.

Events emerging during ketamine treatment will be counted during the randomized phase of the study if not resolved by the start of randomized treatment initiation. Unresolved AE outcomes at the end of randomized treatment will be followed for an additional seven days or until resolution, whichever occurs earlier.

Adverse events will be classified by MedDRA. For each study treatment, safety data will be collected and analyzed per stage or until treatment-emergent AEs are resolved. The type, incidence, timing (onset, duration), relationship, and severity of AEs will be reported for treatment-emergent and suspected adverse reactions. Reasons for withdrawal due to AEs will also be reported. Narratives will be written for every AE classified as serious or associated with death. Safety results will be displayed separately for each stage and combined.

Safety and tolerability will be assessed using two-sided Fisher Exact tests to compare K/N vs. K/L and K/P. Mean changes from baseline will be displayed for each serum chemistry and hematology parameter as well as the shift; unpaired t-tests will be used to compare K/N vs. K/L and K/P; in addition, paired t-tests will be performed for the changes from baseline for each study treatment group.

8.2.5.2.2. Safety Measures

The Patient Rated Inventory of Side Effects (PRISE), CADSS, and Barnes Akathesia Scale (BARS) (including the global severity rating) will be evaluated within and between study treatment groups. Mean changes from baseline for the differences from baseline and after randomization baseline will be evaluated using a paired t-test within each study group and an unpaired t-test for K/N vs. K/L and K/P.

8.2.5.2.3. Other Safety Measures

It is expected that some subjects in both groups (more among those randomized to placebo+lurasidone and placebo) will have recurrence of their depression and, possibly suicidality. Therefore, the investigators plan to effect careful surveillance of all study subjects as follows:

Subjects who receive ketamine will be maintained under continuous professional observation until stabilization is documented or ketamine is deemed not to have achieved stabilization and the treating physician has elected another therapeutic option (which in most cases will be hospitalization with ECT). In general, study subjects will be maintained under direct observation in a mental health center or inpatient setting during the 24 hour stabilization period. At the election of the treating physician in consultation with the patient and family, patients may return home during the 24 hour stabilization period, provided the treating physician has made

arrangements with the patient and family to maintain close professional contact during this period and a responsible adult will be escorting the patient at all times. Participants who cannot ensure a reliable adult transport will not be allowed to enroll in the study. Subjects will be instructed not to drive or operate heavy machinery for at least 24 hours post-administration.

Daily contact with a physician, psychologist, or psychiatric nurse who will assess symptoms and any subject or family/significant other concerns. The contact will be either through a telephone or actual visit. All on-site study visits will include a meeting with a study psychiatrist.

The study will employ the use of HIPAA-compliant, electronic video monitoring of medication compliance, with the capability to send an immediate alert for outreach with any missed doses of medication. A non-adherence period of 12 hours (i.e. 2 missed doses will trigger outreach by study personnel).

In case of loss of phone contact or repeated non-adherence to medication, study staff will contact an identified family member/significant other. If study staff determines that hospitalization is urgent, either the family member will take the subject to the emergency room or the staff will contact 911 for an ambulance.

The investigators recognize that although DCS has been used as an anti-infective in millions of individuals without report of significant safety concerns, DCS has thus far been used in 21 subjects at the 1000mg dose in formal studies of psychiatric illness. Therefore, the study medical monitors will surveil for safety issues via frequent safety listings reviews.

The timing and incidence of adverse findings will be compiled following planned surveillance of all study subjects by study medical monitors. The number of such episodes will be evaluated using a Poisson regression model to compare study treatment groups controlling for C-SSRS 24 hours post infusion (1, 2), age (<25, 25-39, ≥40), and gender.

Vital signs will be obtained at every office visit. ECGs will be measured at the Screen Visits, and at Visits 1, 5, and 10. Digital ECGs will be obtained after the subject has been resting in a semi-recumbent position for at least 10 minutes. All digital ECGs will be documented by recording date, time, heart rate, QRS duration, PR interval, RR interval, QT, and QTcF intervals. Mean differences will be calculated using the Fridericia formula (Puddu et al., 1988). Vital signs and ECGs will also be evaluated within and between study treatment groups. If indicated, additional ECG assessments can be made at the discretion of the investigator. The investigator will judge the overall interpretation as normal or abnormal. If abnormal, it will be decided as to whether or not the abnormality is clinically significant or not clinically significant and the reason for the abnormality will be recorded on the eCRF. Abnormal values shall not be recorded as AEs unless deemed clinically significant.

At the Screen visit, and at Visits 1, 5, and 9, subjects will have their blood drawn for chemistry and CBC blood tests. At Screen, and at Visits 5 and 10, subjects will have a physical examination. If these tests or exams are abnormal per established site-specific normal ranges, it will be decided by the site investigator whether or not the abnormality is clinically significant or

not clinically significant and recorded on the eCRF. Abnormal and clinically significant lab values will be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the study drug. Abnormal lab values (clinically significant and clinically non-significant), will be reviewed monthly by the medical monitor for trends. Should any abnormal lab values exceed rates described in the IB, the FDA and SPONSOR will be notified within regulatory timelines. McNemar paired comparison tests will be performed within study treatment groups for the abnormal percents while two-sided Fisher Exact tests will be performed between treatment groups.

8.2.6 Study Instruments

Study instruments will be administered in accordance to the schedule in Table 3.

8.2.6.1 Efficacy Measures

Bipolar Inventory of Symptom Scale (BISS) (Bowden et al., 2007): The BISS is a 44-item clinician-rated scale (22 items for the depression subscale and 22 items for the mania scale), in which each items is rated on a 0-4 severity scale which is which operationally defines each item, confining the assessment to only one behavioral construct. Items are grouped into 10 established symptom clusters, based on prior studies of phenomenology and reports of symptom clusters and principal components in ratings of BD. The timeframe for the BISS is the past 7 days. The BISS scale has been found to have high internal consistency (Chronbach's alpha=0.93 for the Total Scale, 0.92 for the depression subscale, and 0.90 for the mania subscale) and inter-rater reliability (ICC=0.96 for total scale, 0.98 for depression subscale, and 0.95 for mania subscale) (Gonzalez, et al, 2008). Regarding discriminant validity, the BISS total score was able to significantly distinguish between patients in a depressed, manic or mixed episode from subsyndromal patients, recovered patients, and healthy controls (Gonzalez et al, 2008). Convergent validity was demonstrated by strong Pearson correlations (i.e., r=.64 to .94) between the BISS total score and the BISS depression subscale and the MADRS, and between the BISS total score and the mania subscale and the YMRS across all patient and control groups described above; divergent validity was demonstrated by smaller and (i.e., r=-.14-0.30) correlations between the BISS depression subscale and the YMRS scale, and between the BISS mania scale and the MADRS (r=-.06-.31).

The Columbia Suicide Severity Rating Scale (C-SSRS) (Posner et al., 2007): 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. It is a clinical interview providing a summary of both ideation and behavior that can be administered during any evaluation or risk assessment to identify the level and type of suicidality present. The C-SSRS can also be used during treatment to monitor for clinical worsening. The C-SSRS will be performed to assess suicidal ideation and behavior. C-CASA is the retrospective counterpart of the more detailed

classification instrument C-SSRS. The C-SSRS tool was first developed for a prospective national study of treatment for adolescent suicide attempts. C-SSRS was developed by reliance on evidence stemming from two decades of research. It contains a 1-to-5 rating scale for suicidal ideation of increasing severity (from a "wish list to die" to an "active thought of killing oneself with plan and intent"), in contrast to C-CASA, which only has one ideation item. (IOM, 2010) The time frame 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.

Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1962): The BPRS is an 18-item clinician rated scale that is used to assess a range of psychotic and affective symptoms, rated from both observation of the subject and the subject's own report. It has been widely used to measure change in pharmacologic and nonpharmacologic treatment trials and provides a rapid and efficient evaluation of treatment response in clinic drug studies and in clinical settings. Only the 4-item positive symptom subscale BPRS+ (i.e., suspiciousness, hallucinations, unusual thought content, and conceptual disorganization) will be used in this study. It is highly sensitive to change, and excellent inter-rater reliability can be achieved (i.e., ICC>.80) with training and a standard interview procedure. Concurrent validity has been established by r=.92 between the positive symptom subscale and the corresponding subscale of the Positive and Negative Syndrome Scale, and sensitivity to change has been demonstrated by significant associations in change between the BPRS total score and the CGI and the HDRS.

Concise Health Risk Tracking – Self Report (CHRT-SR) and Clinician Rating (CHRT-C) scales (Trivedi et al, 2011): This is both a subject self-report assessment of suicidality and related thoughts and behaviors, with a corresponding clinician rated scale. The scales are designed to quickly and easily track suicidality in a manner consistent with the Columbia Classification Algorithm of Suicide Assessment (C-CASA) (Posner et al, 2007). 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 5-point Likert scale with responses ranging from 1 (strongly disagree) to 5 (strongly agree). The time frame is the past seven (7) days. The CHRT-SR has good internal consistency (Cronbach's alpha 0.88-0.90), convergent validity with MADRS suicide item (r=.60) and QIDS suicide item (r=0.59), and divergent validity with the YMRS (r=.02). Predictive validity was established by prospective prediction of suicidality-related serious adverse events among 482 patients with bipolar disorder in a multicenter trial (Reilly-Harrington et al, 2016).

Suicidal Ideation and Behavior Questionnaire (SIBQ): The purpose of this instrument is to ensure clinicians properly assess and document suicidal ideation and behavior as well as any study decisions (study exclusion of subject, filing of a serious adverse event) pertaining to suicidality. It will be completed by site investigators during all visits.

8.2.6.2 Safety Measures

In addition to the measures described under efficacy, including CSSR-S, BISS (MADRS) CHRT-SR and CHRT-C and SIBQ, the following safety measures will be employed:

Patient Rated Inventory of Side Effects (PRISE): The self-reported PRISE questionnaire will be used for the specific symptoms considered by the patients as more or less tolerable drug side effects. The nine domains (gastrointestinal, heart, skin, nervous system, genital/urinary, sleep, sexual functioning, and other symptoms) will be individually and cumulatively evaluated using a paired t-test with each study group and an unpaired t-test for K/N vs. K/L and K/P to assess the mean side effect or adverse event. Reasons for premature discontinuation and dose reduction, including intolerable side effects, will be recorded. Drug interactions between DCS and lurasidone will be examined.

Clinician-Administered Dissociative States Scale (CADSS): The CADSS is a 23-item scale (Bremner et al 1998). It is a reliable, valid instrument. The severity of each dissociative symptom ranges from 0 (not present) to 4 (extreme). The CADSS total score will be calculated as the sum of the individual item scores. For the CADSS, change from the first time point to each subsequent time point will be calculated as the 40-minute, 80-minute, and 120-minute assessment minus the 0 (-5 minutes) score. The scale is administered at 0 (-5 minutes), 40, 80, and 120 minutes from the start of the infusion. The timeframe is "at this moment". The CADSS has been validated in healthy subjects and patients with psychiatric illness.

Barnes Akathesia Scale (BARS): The Barnes Akathesia Scale (Barnes TR, 1989) is a clinician-rated scale to assess drug-induced akathisia and classify it 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. It is the scale used most commonly in trials comparing incidence and severity of akathisia between antipsychotic medications and placebo. The time frame is "at this time". With trained raters, the BARS has demonstrated strong inter-rater reliability (Kappa= 0.74-0.95) (Barnes , 2003). The BARS has been used to support the concurrent validity of actigraphic monitoring in akathisia (Barnes, 2003).

8.2.6.3 Other Diagnostic Instruments

MINI 7.0.2: The M.I.N.I. International Neuropsychiatric Interview (M.I.N.I.) 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.

8.2.7 Reliability Training

All clinicians chosen to be involved in the assessment of study subjects are experienced using standardized clinician-rated measures. They will have all received extensive training in the use of these instruments in coordination with MGH CTNI. Raters will be certified in the use of the C-SSRS and the BISS prior to participation in the study.

8.2.8 Subject Adherence to Protocol

Every effort will be made to encourage subjects to comply with the procedures and the assessments involved in study. Subjects will be compensated for their time at each visit, at a rate determined appropriate by the sponsor and the IRB (estimated compensation: $20/hour). We believe that this level of subject compensation, while non-coercive, facilitates adherence to assessments and procedures that require frequent, inconvenient visits.

Table 5 Protocol Violation Definitions

	Major Protocol Violation	Minor Protocol Violation
The list of examples is intended as a guide and is not all-inclusive.		
Definition	A violation that **may:** • Impact subject safety, • Affect the integrity of study data, and/ or • Affect the subject's willingness to participate in the study, and/or • Introduce bias.	A violation that **does not:** • Impact subject safety, • Compromise the integrity of study data, and/ or • Affect the subject's willingness to participate in the study, and/or • Introduce bias.
Examples (not all-inclusive)	• Failure to obtain informed consent • Informed consent obtained by an unauthorized individual • Enrollment of a subject who did not meet eligibility criteria for whom a protocol exception was not obtained • Performing a study procedure that is not approved by the IRB and/or is not in the protocol • Failure to perform a required lab test that, in the opinion of the Site Investigator, may affect subject safety or data integrity • Failure to perform or follow a study procedure that, in the opinion of the Site Investigator, may affect subject safety or data integrity • Failure to follow safety (AE) management plan • Failure to report a SAE to the IRB and/or Coordination Center	• Implementation of unapproved recruitment procedures • Only a photocopy of the signed/ dated consent form is available (the original is missing) • Pages are missing from the signed/ dated informed consent form • Use of invalid consent form (i.e., without IRB approval or outdated/expired form) • Failure to perform or follow an approved study procedure that, in the opinion of the Site Investigator, **does not** affect subject safety or data integrity • Study procedure conducted out of sequence • Failure to perform a required lab test • Missing lab results • Study Visit out of approved window • Over-enrollment • Enrollment of subjects after IRB approval of the study has expired • Failure to submit a continuing review application to the IRB before study expiration
Reporting Requirements	• Record the date discovered, date occurred, description of event in the Protocol Deviation Log. • Notify the Coordinating Center within 24 business hours.	• Record the date discovered, date occurred, description of event in the Protocol Deviation Log. • Notify the Coordinating Center

A Relapse Adjudication Committee (RAC) will be assembled and managed by MGH CTNI. All site-reported relapse events will be reviewed by the RAC, and a determination made as to whether the event met study criteria for relapse. The results of each adjudication will be entered into the study database. The RAC will meet monthly to adjudicate the events.

9. TREATMENT OF SUBJECTS

9.1 Investigational Drug Dose and Administration

In our planned study, physicians will have the ability to increase the lurasidone at any point after the initial titration period for control of agitation, or decrease both the DCS and lurasidone dose according to the titration table below, in response to somnolence or extrapyramidal side effects. This titration will be effected while maintaining a blinded study design. The titration strategy is outlined in Table 6.

Table 6 Dose Titration

	AM dose		PM dose		Total Daily dose	
Day	**DCS**	**Lurasidone**	**DCS**	**Lurasidone**	**DCS**	**Lurasidone**
1	350	16.5	0	16.5	350	33
2	475	16.5	0	16.5	475	33
3	350	16.5	350	33	700	49.5
4	350	16.5	475	33	825	49.5
5	475	33	475	33	950	66
Uptitration for Agitation						
step 1	475	33	475	66	950	99
step 2	475	66	475	66	950	132
Stepdown for Somnolence						
step 1	350	16.5	475	33	825	49.5
step 2	350	16.5	350	16.5	700	33
Preferred dose	**475**	**33**	**475**	**33**	**950**	**66**

9.2 Treatment Compliance

Subjects who miss one visit will be allowed to make up that visit at the end of the dosing week. Subjects who miss more than one visit will be discontinued from the study.

Subjects will be allowed to titrate up or down, as outlined above, in the event of intolerable side effects. No other dose modifications will be allowed.

A statement has been added to the Product Monograph specifying the contraindication of lurasidone with strong CYP3A4 inhibitors (e.g., ketoconazole) and strong CYP3A4 inducers (e.g., rifampin). Lurasidone dose should not exceed 40 mg/day if co-administered with moderate CYP3A4 inhibitors. DCS has never been reported to have any interaction with lurasidone.

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

1. Approved antidepressants (e.g., SSRIs, SNRIs, TeCAs, fluoxetine), but no 5-HT-2a antagonists (lurasidone, olanzapine, quetiapine).
2. Mood stabilizers (e.g., lithium, carbamazepine, valproic acid)

Subjects will be permitted into the study if they are treated with no more than 1 from each category of the indicated classes. Approved antidepressants and mood stabilizers will be maintained at pre-existing 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. Subjects taking either olanzapine or quetiapine will have these medications discontinued in order to avoid overlap with lurasidone. Subjects taking more than 66 mg of lurasidone per day at baseline will be maintained on this higher dose as a protocol exception.

Subject compliance with dosing will be monitored using HIPAA-compliant, visual imaging technology allowing for confirmation of oral dosing of investigational product and date/time of the dosing.

9.3 Randomization/Method of Assigning Subjects to Treatment

Following the documented observance of a therapeutic response to intravenous ketamine as defined by a 25% or greater reduction in the MADRS score and a score of ≤3 on the C-SSRS, at 24 hours post infusion, patients will be randomized 2:1:1 to either a fixed dose combination of DCS + lurasidone (NRX-101), to an identical capsule containing placebo+lurasidone, or to an identical capsule containing placebo. Site blocking will be used to ensure that treatment and control groups are balanced per site.

9.4 Blinding

The investigator, subject, and study staff will be blinded. Packaging and labeling of the study drugs will be performed in a way to ensure blinding throughout the study.

No member of the study team at study sites nor the CRO (the group responsible for study data management and site monitoring) will have access to the randomization scheme during the conduct of the study with the exception of the group responsible for maintaining the IWRS. That group will be able to identify patient-specific treatment according to the uniquely assigned kit number.

The unblinding of specific kits will be performed by the sponsor's Chief Medical Officer.

No treatment groups or kits will be otherwise unblinded after database lock.

Breaking the blind in a clinical trial on an emergency basis by the site should only occur when knowledge of the treatment to which a subject was allocated would have implications for the medical management of the subject in case of a Serious Adverse Event (SAE). However, subjects that relapse or experience a SAE will require real-time interaction with the medical monitor to confirm the event and to decide if the event must be reported to regulatory agencies or IRBs.

The Data Safety and Monitoring Board (DSMB) (refer to Section 14.2) can request a code break, either for an individual subject or on a group basis as described in the DSMB charter. The DSMB may request to break the blind if:

- There is an imbalance in safety parameters between groups

and/or

- In case of single or multiple significant AEs/SAEs that might be drug-related.

In such a case, the chair of the DSMB would request unblinding, either of an individual subject or on a group basis, and the CRO would then request unblinding from the third party keeper of the randomization codes.

9.5 Dose Adjustment and Stopping Rules

Subjects will be allowed to titrate up or down, as outlined above, in the event of intolerable side effects. No other dose modifications will be allowed.

Every effort will be made to keep the subject in the study for the full study period consisting of 7 days of acute treatment plus 6 weekly follow-up assessments (Days 10, 14, 21, 28, 35, and 42). Acceptable reasons for early discontinuation include the following: 1) non-response to ketamine treatment, 2) request of subject, 3) decision of physician, 4) SAE, 5) and protocol violation.

A subject who decides to discontinue the investigational product will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an investigator. Adverse events will be followed up (see Section 12.6) until resolution.

If a subject discontinues from the study before randomization to Stage 2, then no further follow-up will be expected. However, if the subject discontinues after randomization, to Stage 2 but before receiving any study treatment, the subject will be asked to return for a final study visit, during which the procedures outlined in the Early Termination Visit procedures will be completed, including AEs and concomitant medication assessments.

If a subject discontinues from the study before completion of Stage 2 and has received at least 1 dose of study drug, the subject will be asked to return for a final study visit, at which the procedures outlined in the Early Termination Visit will be completed. Every effort will be made to follow up with subjects who discontinue from the study prior to Visit 10 (Day 42). If subjects refuse to return to the clinic for the study-related assessments, a modified follow-up through, for example, regular telephone contact or a contact at study closure will be arranged, if agreed to by the subject and in compliance with local data privacy laws/practices. If the subject refuses follow-up, the reason for the refusal and last contact date will be documented in the eCRF and source documents.

Subjects who discontinue from the study will not be replaced.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1 Study Drugs

Ketalar (ketamine hydrochloride injection) will be purchased from PAR Sterile Products, 870 Parkdale Rd, Rochester, MI 48307. It will be provided as IV infusion administration.

The Investigational Product (IP) is a capsule intended for oral administration. Each capsule contains DCS and lurasidone hydrochloride. Inactive ingredients include mannitol, croscarmellose sodium, silica dioxide, and magnesium stearate.

10.2. Packaging and Labeling

Medication will be supplied in 23 cc wide mouth HDPE bottles with screw top closure. Each bottle will contain 2 capsules, the required dose for either morning or evening administration, and desiccant to aid stability. The bottles will be packaged into a cardboard kit containing 2 bottles for each day. Six different kit types will be available. Kit 1 will contain a 5-day titration pack with 10 bottles, each containing 2 capsules, for the first 5 days of the study. Kits 2 to 5 will contain 3-day step-up or step-down packs with 6 bottles, each containing 2 capsules. Kit 6 will contain a 7-day preferred dose pack with 14 bottles, each containing 2 capsules. A description of the 6 kit types is provided in Table 7.

Table 7 NRX-101 Kits

Kit Type	Day	Morning Dose		Evening Dose		Total Dose	
		DCS	Lurasidone	DCS	Lurasidone	DCS	Lurasidone
1 (7 Days)	1	350	16.5	0	16.5	350	33
	2	475	16.5	0	16.5	475	33
	3	350	16.5	350	33	700	49.5
	4	350	16.5	475	33	825	49.5
	5	475	33	475	33	950	66
	6	475	33	475	33	950	66
	7	475	33	475	33	950	66
	Uptitration for Agitation						
2 (3 Days)	step 1	475	33	475	66	950	99
3 (3 Days)	step 2	475	66	475	66	950	132
	Stepdown for Somnolence						
4 (3 Days)	step 1	350	16.5	475	33	825	49.5
5 (3 Days)	step 2	350	16.5	350	16.5	700	33
6 (7 Days)	Preferred Dose	**475**	**33**	**475**	**33**	**950**	**66**

The composition and physical description of each capsule is below (Table 8 throughTable 11 Investigational Product (NRX-101)Identification

Table 8 Active Capsule Composition and Physical Description

Strength	237.5/8.25	237.5/16.5	237.5/33	175/8.25	175/16.6	0/8.25
Size	0el	0el	0el	0	0	0
Color	Light Blue	Swedish Orange	White	Light Blue	Swedish Orange	Light Blue
d-Cycloserine	242.1 mg / 39.69%	242.1 mg / 39.69%	242.1 mg / 39.69%	178.4 mg / 33.66%	178.4 mg / 33.66%	0 mg / 0%
Lurasidone	8.27 mg / 1.56%	16.55 mg / 3.12%	33.10 mg / 6.25%	8.27 mg / 1.56%	16.55 mg / 3.12%	8.27 mg / 2.07%
Mannitol 50C	311.03 mg / 50.99%	302.75 mg / 49.63%	286.20 mg / 46.92%	300.93 mg / 56.78%	292.65 mg / 55.22%	359.17 mg / 89.79%
Croscarmellose Sodium	39.50 mg / 6.48%	39.50 mg / 6.48%	39.50 mg / 6.48%	34.45 mg / 6.50%	34.45 mg / 6.50%	26.00 mg / 6.50%
Hyroxypropylmethyl cellulose E5 (6% solution)	0 mg / 0%	0 mg / 0%	0 mg / 0%	0 mg / 0%	0 mg / 0%	4.56 mg / 1.14%
Silica Dioxide	6.1 mg / 1.0%	6.1 mg / 1.0%	6.1 mg / 1.0%	5.30 mg / 1.0%	5.30 mg / 1.0%	0 mg / 0%
Magnesium Stearate	3.00 mg / 0.49%	3.00 mg / 0.49%	3.0 mg / 0.49%	2.65 mg / 0.50%	2.65 mg / 0.50%	2.00 mg / 0.50%
Total	610.0 mg / 100%	610.0 mg / 100%	610.0 mg / 100%	530.0 mg / 100%	530.0 mg / 100%	400.0 mg / 100%

Table 9 Lurasidone Capsule Composition and Physical Description

Strength	0/8.25	0/16.5	0/33	0/8.25	0/16.6
Size	0el	0el	0el	0	0
Color	Light Blue	Swedish Orange	White	Light Blue	Swedish Orange
Lurasidone	8.27 mg / 1.80%	16.55 mg / 3.60%	33.10 mg / 7.20%	8.27 mg / 2.07%	16.55 mg / 4.14%
Mannitol 50C	414.29 mg / 90/06%	406.01 mg / 88.26%	389.46 mg / 84.67%	359.17 mg / 89.79%	350.89 mg / 87.72%
Croscarmellose Sodium	29.90 mg / 6.50%	29.90 mg / 6.50%	29.90 mg / 6.50%	26.00 mg / 6.50%	26.00 mg / 6.50%
Hyroxypropylmethyl cellulose E5 (6% solution)	5.24 mg / 1.14%	5.24 mg / 1.14%	5.24 mg / 1.14%	4.56 mg / 1.14%	4.56 mg / 1.14%
Magnesium Stearate	2.30 mg / 0.50 %	2.30 mg / 0.50 %	2.30 mg / 0.50 %	2.00 mg / 0.50%	2.00 mg / 0.50%
Total	460 mg / 100%	460 mg / 100%	460 mg / 100%	400.0 mg / 100%	400.0 mg / 100%

Table 10 Placebo Capsule Composition and Physical Description

Strength	0/0	0/0	0/0	0/0	0/0
Size	0el	0el	0el	0	0
Color	Light Blue	Swedish Orange	White	Light Blue	Swedish Orange
Mannitol 50C					
Croscarmellose Sodium					
Hyroxypropylmethyl cellulose E5 (6% solution)					
Magnesium Stearate					
Total					

The NRX-101 capsule is supplied in 5 strengths as described below. Matching placebos containing either 8.25, 16.5, or 33 mg of lurasidone and no d-cycloserine (DCS) will also be supplied as well as a full placebo containing no DCS or lurasidone.

Table 11 Investigational Product (NRX-101)Identification

D-cycloserine (mg)	Lurasidone (mg)	Capsule Color	Capsule Size
237.5	33	White	0EL
237.5	16.5	Swedish Orange	0EL
237.5	8.25	Light Blue	0EL
175	16.6	Swedish Orange	0
175	8.25	Light Blue	0

Each IP formulation label will include the following information:

- Name of sponsor and address
- Protocol number
- Quantity of capsules
- Storage conditions
- Investigational drug statement (for clinical trial use only)
- Drug packager lot number
- Kit/Medication number
- Contents
- Administration statement
- Spaces for Study Coordinator to insert:
    - Subject number
    - Date Dispensed

When the study drug bottle is dispensed to a subject, the second panel of the label or a copy should be detached and affixed to the drug accountability page in the subject's study source document.

Sites will enter the subject screening ID number into the Randomization Page of the IVRS system, and the subject will be assigned to one of the three treatment groups. The bottle number Medication ID generated by the IVRS for each subject will be noted in the Randomization Page. Drug for each treatment day will be dispensed in 2 bottles each containing 2 capsules. Subjects will be instructed to take two capsules, each morning and evening.

10.1.1 Storage

Capsules will be packaged in white HDPE bottles containing desiccant with a PP closure and a foil induction seal. Bottles will be stored at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°to 86°F).

10.1.2 Accountability

The clinical site is required to maintain current drug dispensation and accountability logs throughout the study. All unused supplies will be checked against the drug movement records during the study and/or at the end of the study.

10.1.3 Handling and Disposal

There are no special handling constraints for the IP. Unused IP will be returned to the CRO for disposal.

11. ASSESSMENT OF EFFICACY

The primary outcome measure will be time to relapse, defined as a return to a score of ≥4 on the C-SSRS, and/or a score of 20 on the MADRS subset of the BISS. The RAC will adjudicate each site reported instance of relapse for compliance the protocol definition of time to relapse.

Relapse is a time-to-event outcome reflective of this multi-component disorder. Time to relapse is more sensitive measure than an assessment at a fixed time. Time to relapse will be displayed using a Kaplan-Meier lifetable with the treatment groups compared using a two-sided Wilcoxon-Gehan test and a proportional hazard model to include the above cited covariates.

Titration of DCS or lurasidone within the dosing range will not be considered to be a relapse.

All of the instruments used to measure ASIB or depression constitute serial continuous and ordinal outcomes which will be analyzed using MMRM, which accounts for missing data and early discontinuations. These instruments include the following:

- C-SSRS (and the retrospective C-CASA component)
- CHRT (CHRT-SR and CHRT-C)
- BISS
- SIBQ
- BPRS

The models will include treatment group, study visit, the interaction between study visit and treatment group, the baseline of the variable being analyzed, C-SSRS 24 hours post infusion (1, 2), age (<25 yrs, 25-39 yrs, >40 yrs), and gender as fixed effects. The reason for missing data will be evaluated as a condition of MMRM analysis.

Means, mean changes, standard deviations, and ranges will be presented separately for Stage 1 and then for each Stage 2 treatment group over time. These endpoints will be evaluated within the three study treatment groups for the change from Stage 1 and Stage 2 baselines 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.

12. ASSESSMENT OF SAFETY

12.1 Suicidal Ideation and Clinical Management

The documentation and proper management of suicidal ideation by sites will be documented with the use of the Suicidal Ideation and Behavior Questionnaire (SIBQ), completed by site clinicians during all visits, and by remote, independent third party raters during the screening period.

Any subject who, based on the investigator's judgment, poses an imminent risk of suicide should be discontinued from the study (see Section 9.2). All efforts will be taken to minimize the risk of suicide and the investigator will carefully monitor the subject. If during the course of the study, subjects show evidence of suicidal behavior, the subjects will be evaluated immediately or referred to their attending psychiatrist, a local emergency room, or another appropriate clinical setting for further evaluation to see if they are safe to continue in the study. The site will have the ability to direct any subject who requires emergency hospitalization to an emergency room or inpatient psychiatric unit that is within a 50-mile radius of the site. In addition, the subject will be able to contact someone at the site 24 hours a day should they have serious worsening of their condition.

Suicide and attempted suicide, irrespective of the method, but occurring in connection with the use of IP, will be reported as AEs (all suicides are SAEs; attempted suicides can be either serious or non-serious AEs). 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 Sections 12.3 and 12.6.1.1. If a suicide attempt does not meet the criteria for an SAE, it will be considered a reportable AE and a Suicidal Ideation and Behavior Reportable Event Form will be completed by the investigator.

All events of suicidal ideation and behavior will be carefully monitored. These include events of suicide attempts, emergence or significant worsening of suicidal ideation, completed suicides, and suicidal behavior. As described in Section 8.3.5.1.1, the C-SSRS and MADRS items of the BISS, as well as the clinician's judgment, will be used in the assessment of suicidal risk by the investigator. The investigator's clinical judgment and conclusion regarding suicidal risk will be documented in the SIBQ for that visit. Clinically significant (in the opinion of the site investigator) emergence or worsening of suicidal ideation and/or behavior will be considered reportable events and documented as AEs, and a Suicidal Ideation and Behavior Reportable Event Form will be completed and submitted to medical monitor within 24 business hours of the site's knowledge of the ideation or behavior. The subject should be withdrawn from the study and the event will be adjudicated by the RAC as a potential endpoint event.

If suicidal behavior meets the criteria for a SAE, according to the guidelines in Section 12.3, investigators are required to report the event according to the guidelines for SAEs in Sections 12.3 and 12.6.1.1 and submit the completed SAE form to the medical monitor within 24

business hours. The subject should be withdrawn from the study and the event will be adjudicated by the RAC as a potential endpoint event.

The SAE Form will include the exact nature of the event and the circumstances of the subject at the time of the event, in addition to the usual information required to document AEs or SAEs. Data on all of the above will be collected on separate eCRF pages.

The latest version of the AE dictionary, MedDRA, will be used by the CRO for the classification and analysis of AEs entered in the study database. For regulatory reporting, SAEs will be processed in the Electronic Data Capture (EDC) System and coded using MedDRA.

If a subject (or subject'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. Pregnancy in 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. 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 subject will be discontinued from study medication.

12.2 Definition of Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with 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. (Definition per ICH).

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 intensity or changes in intensity
- Whether the AE is serious or not
- Expectedness
- Investigator causality rating against study drug (yes or no)
- Action taken with regard to the Investigational Product (IP)

- AE caused subject's withdrawal from the study (yes or no)
- Outcome

Any AEs that are unresolved at the subject's last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. MGH CTNI or its representative retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

12.3 Definition of Serious Adverse Events

The following criteria define a Serious Adverse Event:

- 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 subject or may require intervention to prevent one of the other outcomes listed in the definition above. These will usually be considered serious.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study drug and the event (e.g., death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (e.g., all-cause mortality).

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

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death

- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to study drug
- Causality assessment in relation to other medication
- Description of AE

Intensities will be reported for each AE in the following categories: a) Mild (awareness of sign or symptom, but easily tolerated); b) Moderate (discomfort sufficient to cause interference with normal activities); c) Severe (incapacitating, with inability to perform normal activities).

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by these criteria. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but would be an SAE.

Worsening symptoms of the primary study condition (i.e., bipolar depression) will not be recorded as an AE. However, if inpatient hospitalization results from worsening psychiatric symptoms or suicidal ideation, the hospitalization will be recorded as an SAE in the eCRF.

Study drug abuse is an SAE, even when there are no symptoms or additional AEs, and will be reported according to the guidelines in Section 12.5. Misuse of IP is an AE, but is not considered an SAE unless accompanied by serious sequelae.

Should an overdose of study drug occur, it must be reported in accordance with the procedures described in Section 12.5. An overdose associated with symptoms must be reported as an AE, while an overdose without associated symptoms, must be reported only on the separate Clinical Study Overdose Report Form.

12.4 Relationship to Study Drugs

Adverse events and SAEs will be collected from the time of signature of informed consent throughout the treatment period. Unsolicited SAEs will be collected 30 days post last study treatment.

The investigator will assess the causal relationship (i.e., the relationship to study treatment) between the IP and AEs, and answer “yes” or “no” to the question “Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?” Causal relationship in cases where the depression or suicidal ideation has deteriorated due to lack of effect will be classified as no reasonable possibility. For SAEs, causal relationship will also be assessed. Note that for SAEs that could be associated with any study procedure, the causal relationship is implied as “yes.”

An AE is considered unexpected if it is not listed in the IB, or the nature or severity is not consistent with the applicable reference in the IB.

12.5 Recording of Adverse Events

AEs spontaneously reported by the subject in response to the open question from the study personnel: "Have you had any health problems since the previous visit?" or revealed by observation will be collected at each visit; classified as mild, moderate, or severe; and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a 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.

Subjects shall be encouraged to contact the investigator or a member of the clinical site staff at any time between visits concerning AEs or worsening of symptoms.

Abnormal and clinically significant lab values will be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the study drug. The principal investigator and the study biostatistician will establish the rules for what will constitute abnormal and clinically significant lab values based on established site-specific lab normal ranges. Adverse events, including abnormal lab values (clinically significant and clinically non-significant), will be reviewe monthly for trends by the principal investigator and the medical monitor. Should any abnormal lab values exceed rates described in the IB, the FDA will be notified within regulatory timelines. If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible, the reporting investigator will use the clinical, rather than the laboratory term (e.g., anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters will be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the study drug is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of worsening bipolar depression will be considered as disease progression and not an AE. Events (except for suicidal ideation or behavior) which are unequivocally due to disease progression will not be reported as an AE during the study.

12.6 Reporting of Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated Informed Consent Form (ICF) is obtained until completion of the subject's last study-related procedure (which may include contact for follow-up of safety). Serious adverse events, including those spontaneously reported to the site-investigator from the time a signed and dated ICF is obtained until within 30 days after the last dose of study drug, must be reported using the Serious Adverse Event Form. CRO will evaluate any safety information that is spontaneously reported by a site investigator beyond the time frame specified in the protocol.

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

All AEs, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the eCRF. 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"). Investigators must record in the CRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to CRO instructions.

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. CRO, on behalf of the sponsor, will also report to site investigators all SAEs that are unlisted (unexpected) and associated with the use of the study drug. CRO will report these events to the designated IRB, on behalf of the sponsor.

12.6.1 Reporting of Serious Adverse Events

The EDC platform will provide a mechanism for sites to report SAEs, and for the site investigators and medical monitor to sign off on the SAE reports. Reportable SAEs will be sent to the FDA by the sponsor. CRO will notify sites of reportable SAEs, as outlined in Section 12.6.1.1.

When a SAE is discovered, it will be reported immediately (within 24 business hours) to the Medical Monitor, as described below. Serious adverse events will be reported within 24 business hours of the site's knowledge of the event to the IRB (see below). 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 site Principal Investigator will determine whether the event is study-related. All SAEs and reportable events will be reported within 48 business hours of [CRO] receipt of an SAE or other reportable event form to the sponsor, Medical Monitor, and the study site investigators.

12.6.1.1 Procedures for Assessing, Recording, and Reporting Adverse Events and Serious Adverse Events

Throughout the duration of the study, the Investigator will closely monitor each subject for evidence of drug intolerance and for the development of clinical or laboratory evidence of adverse events. All adverse events (expected or unexpected) which occur during the course of the study, whether observed by the Investigator or by the subject, and whether or not thought to be drug-related, will be reported and followed until resolution or until they become stable.

The description of the adverse event will include description of event, start date, stop date, intensity, if it was serious, relationship to test drug, change in test drug dosage, if the subject died, and if treatment was required.

Events will be coded to one of the following intensity categories below:

Severity	Definition
Mild	Awareness of signs or symptoms, but no disruption of usual activity
Moderate	Event sufficient to affect usual activity (disturbing)
Severe	Event causes inability to work or perform usual activities (unacceptable)

Events will be coded into one of the following causality categories as defined below:

Category	Definition
Unrelated	Clearly and incontrovertibly due only to extraneous causes, and does not meet criteria listed under possible or probable.
Unlikely	Does not follow a reasonable temporal sequence from administration. May have been produced by the subject's clinical state or by environmental factors or other therapies administered.
Possible	Follows a reasonable temporal sequence from administration, but may have been also produced by the subject's clinical state, environmental factors or other therapies administered.
Probable	Clear-cut temporal association with administration with improvement on cessation of investigational medicinal product or reduction in dose. Reappears upon rechallenge. Follows a known pattern of response to the investigational medicinal product.

Adverse events with the causality assessed as unrelated or unlikely are categorized as not related to study medication.

Adverse events with the causality assessed as possible or probable are categorized as related to study medication and are called adverse drug reactions.

All SAEs must be reported immediately (no more than 24 hours after becoming aware of the event). The investigator must complete the SAE Report Form and notify according to the Serious Adverse Event Report Form Instructions.

13. STATISTICS

The study analyses will be conducted in a GCP environment (ICH E6). All analyses will be pre-specified in a Statistical Analysis (SAP) prior to beginning subject enrollment.

13.1 Study Design

This is a two-stage design with two pre-defined interim looks during the second stage. The first stage is a direct assignment to Ketamine while the second stage is a randomized phase for those subjects following a documented Ketamine response.

13.2 Randomization

Following the documented observance of a therapeutic response to intravenous ketamine as defined by a 25% or greater reduction in the MADRS score and a score of < 3 on the C-SSRS, at 24 hours post infusion, patients will be randomized 2:1:1 to either a fixed dose combination of DCS + lurasidone (NRX-101), to an identical capsule containing placebo+lurasidone, or to an identical capsule containing placebo. Site blocking will be used to ensure that treatment and control groups are balanced per site.

13.3 Study Populations

The study will have prospectively defined study populations including separate evaluability rules for the Ketamine treatment (Stage 1) and randomized treatment (Stage 2).

For Stage 1, the Intent-to-Treat population will include all subjects who received the Ketamine infusion and they have the 24 hours post-infusion efficacy assessments. The Per-Protocol population will include the subset of ITT subjects who were eligible, who had the 24 hour post-infusion efficacy assessments within 18 to 30 hours post the start of the initial infusion, and who had no major protocol violations. The Safety Population will include all subjects treated with Ketamine and with any post-baseline safety data.

For Stage 2, the Intent-to-Treat population will include all subjects who received the randomized study treatment and have any post-baseline efficacy assessments. The Per-Protocol population will include the subset of ITT subjects who were eligible, who have any post-baseline efficacy assessments within 1 day of scheduled visits through Day 7 and within 3 days of scheduled visits through Day 42, and who had no major protocol violations. The Safety Population will include all subjects as treated with study treatment and with any post-baseline safety data.

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

Every effort will be made to encourage patients to comply with the procedures and the assessments involved in study. Non-compliance will be tracked. Protocol violations will be reviewed in real time; prospective rules will be set for exclusions from the PP population.

13.4 Hypothesis Tests

13.4.1 Primary Hypotheses

The primary study hypothesis (alternative hypothesis) is that Ketamine and experimental drug NRX-101 (K/N) delays the time to documented relapse as compared to both lurasidone (L) and placebo (P) as measured by the hazard ratio (h) versus the null hypothesis of no delay in time to relapse for either comparator treatment (Ketamine/lurasidone [K/L] and Ketamine/placebo [K/P]) as follows:

- H0: $h_{NRX-101} < h_L$ and h_P
- Ha: $h_{NRX-101} > h_L$ and h_P

13.4.2 Secondary Hypotheses

The secondary study hypotheses relating to secondary ASIB and BPD endpoints (alternative hypotheses favoring K/N vs. K/L and K/P) are the following:

1. K/N will favorably separate from both K/L and K/P by 72 hours, with sustained difference between groups thereafter.
2. All cause discontinuation (including discontinuation for continued suicidal ideation) will be lower for K/N than both K/L and K/P.
3. K/N will favorably separate from K/L and K/P starting at day 7, with sustained difference thereafter.
4. Improvements within the K/N group observed at Week 2 will remain stable to end of study.
5. C-SSRS scores will remain <4 for 4 weeks following treatment discontinuation (i.e. any "crisis" will resolve within the 6 week time period with more favorable outcomes in the K/N group as compared to K/L and K/P.

13.5 Efficacy Endpoints

13.5.1 Primary Efficacy Endpoint

The primary outcome measure will be time to relapse, defined as the need to implement a new treatment plan (not a dose increase, decrease, or suspension) or as a return to a score of ≥4 on the C-SSRS, and/or a score of 20 on the MADRS subset of the BISS

13.5.2 Secondary Efficacy Endpoints

Additionally, symptom improvement will be evaluated by assessing changes in the secondary outcome measures: C-SSRS, CHRT, BISS (MADRS), and BPRS. These measures will be assessed at the times specified on the Study Activity Schedule, Table 3.

The C-SSRS (and the retrospective C-CASA component), CHRT (CHRT-SR and CHRT-C), BISS and BPRS (including the global severity rating) will be evaluated within and between study

treatment groups. The time frame 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. Mean differences will be evaluated using a paired t-test with each study group and an unpaired t-test for K/N vs. K/L and K/P.

13.5.3 Diagnostic Metrics

The following metrics will be evaluated at baseline:

- MINI 7.0.2

13.6 Additional Endpoints

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

- Study dose per treatment group
- All-cause discontinuation (and reason for discontinuation)
- Suicide rates
- Incidence of hospitalization and ER visits for disease-related outcomes
- Proportion of subjects who are treated with new SSRIs or have increased SSRI dosages
- Proportion of subjects who discontinue SSRIs or have reduced SSRI dosages.

13.7 Safety Endpoints

13.7.1 Overall Adverse Events

Separate safety analyses will be performed for the two stages for the Safety population. Safety endpoints will include adverse events (AE), vital signs (VS), and relevant clinical chemistries and hematology parameters.

The principle of treatment emergence will be employed for the analysis of AE data. Treatment emergence is defined to be any event that occurred during the observation period and was not present at baseline, or one which represents an exacerbation of a condition present at baseline.

Events emerging during Stage 1 will be counted during Stage 2 if not resolved by the start of randomized treatment initiation. Unresolved adverse event outcomes at the end of Stage 2 will be followed for an additional seven days or until resolution, whichever occurs earlier.

Adverse events will be classified by MedDRA. For each study treatment, safety data will be collected and analyzed per stage 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 SARs. Reasons for withdrawal due to AEs will also be reported. Narratives will be written for every AE classified as serious or associated with death. Safety results will be displayed separately for each stage and combined.

Safety and tolerability will be assessed using two-sided Fisher Exact tests to compare K/N vs. K/L and K/P. Mean changes from baseline will be displayed for each serum chemistry and hematology parameter as well as the shift; unpaired t-tests will be used to compare K/N vs. K/L and K/P; in addition, paired t-tests will be performed for the change from baseline for each study treatment group.

13.7.2 Other Safety Measures

The study is being conducted in a population who would likely have been admitted to a psychiatric hospital, if they did not have a positive response to ketamine. Moreover, it is expected that some subjects in the K/L and K/P treatment groups will have recurrence of their depression and, possibly suicidality. The timing and incidence of adverse findings will be compiled following planned surveillance of all study subjects by a designated safety monitor. The number of such episodes will be evaluated using a Poisson regression model to compare study treatment groups controlling for C-SSRS 24 hours post infusion (1, 2), age (<25, 25-39, ≥40), and gender.

Vital signs and ECGs will also be evaluated within and between study treatment groups. Mean differences in heart rate, QRS duration, PR interval, RR interval, QT, and QTcF. QTcF intervals will be calculated using the Fridericia formula (Puddu et al, 1988). The overall interpretation will be reported as normal or abnormal; if abnormal, then the percents clinically significant will be reported. Abnormal values shall not be recorded as AEs unless deemed clinically significant. McNemar paired comparison tests will be performed within study treatment groups for the abnormal percents while Fisher Exact tests will be performed between treatment groups.

While symptom improvement will be evaluated by assessing changes in the secondary outcome measures: C-SSRS, CHRT, BISS (MADRS), SIBQ and BPRS, safety measures in the PRISE, CADSS and BARS (including the global severity rating) will be evaluated within and between study treatment groups. The time frame 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. Mean differences will be evaluated using a paired t-test with each study group and an unpaired t-test for K/N vs. K/L and K/P.

13.8 Sample Size Calculations

13.8.1 Allocation

To encourage study participation, a 2:1:1 randomization will be used where at most half as many subjects will be assigned to the lurasidone and placebo arms as compared to the K/N study arm. The goal will be to have 62 subjects randomized to K/N and 31 subjects randomized to each of K/L and K/P for a total of 124 randomized subjects. The randomization takes place among Ketamine responders once confirmed by Medical Monitor.

13.8.2 Stage 1

The study goal is to achieve a total of 124 Ketamine responders for the Stage 2 evaluation. A total of 192 subjects are projected to be enrolled but this number may be reached sooner if the cumulative effect of the Ketamine response rate exceeding 70%, if the Stage 1 loss rate being less than 8% (15 subjects), or if the Stage 2 loss rate being less than 8% (9 subjects). Thus, there would be 177 subjects who complete Stage 1 before considering Ketamine response. The literature and prior experience suggests that 70% of those treated with ketamine will have an adequate reduction in depression and suicidality which equates to 124 Ketamine responders (177 x 0.7) who would be available for randomization. More subjects will need to be enrolled if the Ketamine response rate was lower than 70% or the randomization refusal rate was higher than 8%, considered to be part of Stage 2 losses.

13.8.3 Stage 2

Stage 2 will investigate the study hypotheses. The primary efficacy hypothesis is that K/N will delay the time to relapse relative to K/L and K/P. The goal will be to have 62 subjects randomized to K/N and 31 subjects randomized to K/L and K/P. These numbers are based on the Ketamine Responders. See **Error! Reference source not found.** for the total number of K/N and K/L subjects required to test the primary efficacy hypothesis. The sample size requirements are shown just for K/N and K/L. .

The study is powered based on the number of subjects randomized to K/N vs. K/L. In order to achieve 90% study power with two-sided 0.05 Type I error, a total of 56 K/N subjects, 28 K/L subjects, and 28 K/P subjects must be evaluated for time to relapse over the full 6 weeks. This is based on the assumption of a 30% relapse rate in the K/N treatment group and a 70% relapse rate in the K/L and K/P treatment groups. A larger gap in the relapse rate is expected based on the literature, so this is believed to be a conservative assumption. These calculations assume a loss of 8% during Stage 2.

Table 12 Time to Relapse: K/N and K/L Groups Followed for 6 Weeks

	90% Power	Reaching Significance
Test significance level, α	0.05	0.05
1 or 2 sided test?	2	2
K/L relapse-free % p_1 at Week 6	30%	30%
K/N relapse-free % p_2 at Week 6	52%	70%
Hazard ratio, $h=\ln(p_1) / \ln(p_2)$	1.841	3.376
Power (%)	90	N/A
Total N	112	112
Total N of relapses required, R	48	62
Total N accounting for 8% Stage 2 losses	124	124
Total N accounting for 30% K non-responders	177	177
Total N accounting for 8% Stage 1 losses	192	192

The secondary efficacy hypotheses will also be evaluated using a hierarchical testing strategy where testing to support labeling claims continues as long as two-sided p=0.05 is reached. The first such hypothesis to be tested for the depression endpoints if whether K/N separates from K/L and K/P by 72 hours, with sustained difference between groups thereafter (see **Error! Reference source not found.**). There will be 90% power and two-sided 5% Type I error to detect a 0.754 effect size for the comparison of the K/N against the K/L and K/P treatment groups.

Table 13 Two Group T-test: Equal Effect Sizes

	90% Power	Reaching Significance
Test significance level, α	0.05	p=0.05
1 or 2 sided test?	2	2
Effect size, $\delta = \lvert\mu_1 - \mu_2\rvert / \sigma$	0.754	0.456
Power (%)	90	N/A
Total N	112	112

Next, all-cause discontinuation (including discontinuation for continued suicidal ideation) will be tested. The hypothesis is that the percent discontinued prior to Week 6 will be lower in K/N than K/L and K/P using a lifetable approach (see **Error! Reference source not found.**).

Table 14 Two Group Log Rank Test: Time to All-cause Discontinuation

	90% Power	Reaching Significance
Test significance level, α	0.05	0.05
1 or 2 sided test?	2	2
K/L success rate p_1 at Week 6	0.225	0.225
K/N success rate p_2 at Week 6	0.6	0.43
Hazard ratio, $h=\ln(p_1) / \ln(p_2)$	3.89	1.77
Power (%)	90	N/A
Total N	112	112
Total # discontinued required, D	60	72

The next hypothesis to be tested is whether K/N will separate from K/L and K/P starting at Day 7, with sustained difference thereafter (see **Error! Reference source not found.**).

The next hypothesis to be tested is whether improvements within the K/N group observed at Week 2 will remain stable to end of study (see **Error! Reference source not found.**).

Table 15 One Group t-test: No Mean Change

	1	2	3	4
Test significance level, a	0.050	0.050	0.050	0.050
1 or 2 sided test?	2	2	2	2
Effect size, d = $\|m_A - m_0\| / s$	0.441	0.636	0.267	0.384
Power (%)	90	90	50	50
N	56	28	56	28

The last secondary hypothesis to be tested is whether C-SSRS scores will remain < baseline for 4 weeks following treatment discontinuation (i.e., "crisis" will resolve within the 6 week time period with most favorable outcomes in the K/N group as compared to K/L (see **Error! Reference source not found.**).

Table 16 Fisher Exact Test: Normalized C-SSRS Score Percent Scenarios

	1	2	3	4
Test significance level, a	0.050	0.050	0.050	0.050
1 or 2 sided test?	2	2	2	2
Control Success %, p_1	30%	40%	50%	60%
K/N Success %, p_2	66.7%	76%	84%	91%
Odds ratio, $y=p_2(1-p_1)/[p_1(1-p_2)]$	4.674	4.750	5.250	6.741
Power (%)	90	90	90	90
n_1	28	28	28	28
n_2	56	56	56	56
Ratio: n_2 / n_1	2	2	2	2
Pairwise $N = n_1 + n_2$	84	84	84	84

13.9 Overall Type 1 Error Control

The overall Type I error is two-sided 5%. No interim analyses are planned.

A hierarchical testing plan is in place to control Type I error to extend labeling claims in the following pre-defined testing order where statistical significance (two-sided $p<0.05$) is required at each step:

1. Primary: K/N will delay time to relapse relative to K/L and K/P
2. Secondary: K/N will separate from K/L and K/P by 72 hours, with sustained difference between groups thereafter

3. Secondary: All-cause discontinuation (including discontinuation for continued suicidal ideation) will be lower in K/N than K/L and K/P.
4. Secondary: K/N will separate from K/L and K/P starting at Day 7, with sustained difference thereafter
5. Secondary: Improvements within the K/N group observed at Week 2 will remain stable to end of study.

13.10 Analysis Approach

13.10.1 Software

All calculations will be performed using SAS statistical software, version 9.1 or later, and StatXact, version 10 or later.

13.10.2 Display Formats

All efficacy and safety data will be displayed in tables and listings. Separate analyses will be performed for Stage 1, Stage 2, and for combined stages (primary efficacy endpoint). Post-Text TLFs will be provided in collated electronic MS Word .rtf files (i.e. table columns and rows appear in MS Word Table format).

13.10.3 Conventions

Means, mean changes, standard deviations, and ranges will be presented separately for Stage 1 and then for each Stage 2 treatment group over time. These endpoints will be evaluated within the three study treatment groups for the change from Stage 1 and Stage 2 baselines 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. Unless otherwise specified minimum and maximum values will be reported to the same number of decimal places as the recorded measurements, mean and median are reported to one more decimal place and standard deviation one additional decimal place more than the mean.

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

Adverse events, medical histories and concomitant medications will be reported on a subject and an event basis. The percentages will be calculated using the number of subjects in the population Analysis Set as the denominator.

All hypotheses will be tested at 5% (final analysis) level of significance using a two-sided test unless otherwise specified.
P-values will be rounded to four decimal places. If a p-value is less than 0.0001 it will be reported as "<0.0001." If a p-value is greater than 0.9999 it will be reported as ">0.9999".

13.10.4 General Methodology

Time to event analyses will be performed using a Kaplan-Meier lifetable, two-sided Wilcoxon-Gehan test, and proportional hazard models (PHREG) including the following covariates: study treatment, C-SSRS 24 hours post infusion (1,2, or 3), age (<25, 25-39, >40), and gender. The proportional hazard model results for the Intention-to-treat (ITT) population will be considered to be the primary analysis for the primary efficacy endpoint while the MMRM results for the ITT population will be considered to be the primary analysis for the secondary efficacy endpoints.

All of the instruments used to measure ASIB or depression constitute serial continuous and ordinal outcomes which will be analyzed using Mixed-Effect Model Repeated Measure (MMRM) 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 of the variable being analyzed, C-SSRS 24 hours post infusion (1, 2, or 3), age (<25, 25-39, >40), and gender as fixed effects. The reason for missing data will be evaluated as a condition of MMRM analysis.

An autoregressive (AR1) variance covariance structure will be assumed for this analysis. To account for mis-specification of the covariance structure, the Liang and Zeger's "sandwich" estimator (via the EMPIRICAL option in SAS PROC MIXED) will be used. Restricted maximum likelihood (REML) will be used to estimate all parameters and will be the basis for all hypothesis testing (SAS default). For the primary model including the interaction term, the hypothesis test to perform on the fixed effects will be Type III (SAS® option htype = 3). SAS® PROC MIXED will be used.

13.10.5 Primary Efficacy Endpoint

The primary endpoint in the study will be the time to relapse measured from the day that Ketamine infusion was started.

Relapse is a time to event outcome reflective of this multi-component disorder. Time to relapse is more sensitive measure than an assessment at a fixed time. Time to relapse will be displayed using a Kaplan-Meier lifetable with the treatment groups compared using a two-sided Wilcoxon-Gehan test and a proportional hazard model to include the above cited covariates.

Relapse will be judged in real-time by the study physician using baseline measures of depression and suicidality as a guide.

13.10.6 Secondary Efficacy Endpoints

All of the instruments used to measure ASIB or depression constitute serial continuous and ordinal outcomes which will be analyzed using MMRM, which accounts for missing data and early discontinuations. These instruments are listed in Section 11.

The models will include treatment group, study visit, the interaction between study visit and treatment group, the baseline of the variable being analyzed, C-SSRS 24 hours post infusion (1, 2), age (<25 yrs, 25-39 yrs, >40 yrs), and gender as fixed effects. The reason for missing data will be evaluated as a condition of MMRM analysis.

13.10.7 Other Endpoints

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

- Dose per treatment group
- All-cause discontinuation (and reason for discontinuation)
- Suicide rates
- Incidence of hospitalization and ER visits for disease-related outcomes
- Proportion of subjects who are treated with new SSRIs or have increased SSRI dosages
- Proportion of subjects who discontinue SSRIs or have reduced SSRI dosages.

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

Time to all-cause discontinuation will be displayed using a Kaplan-Meier lifetable and compared between treatments using a Wilcoxon-Gehan test.

Suicide rates will be evaluated using a Fisher Exact test to compare K/R vs. K/L and K/P.

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

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

13.10.8 Safety Endpoints

Separate safety analyses will be performed for Stage 1, Stage 2, and combined across stages.

Adverse events will be classified by MedDRA. For each study treatment, safety data will be collected and analyzed while on Stage 1 or Stage 2 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.

Planned surveillance findings according to the designated safety monitor will also be analyzed. Adverse event timing will be displayed graphically. Overall incidence will be compared using a two-sided Fisher Exact test. The cumulative number of such episodes will be evaluated using a Poisson regression model to compare study treatment groups controlling for C-SSRS 24 hours post infusion (1, 2), age (<25, 25-39, >40), and gender.

Vital signs and ECGs (means and mean changes from Stage 1 and Stage 2 baselines) will also be evaluated within treatment groups using paired t-tests and between study treatment groups using unpaired t-tests. Percents 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 percents 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.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1 Study Monitoring

Potential study sites will be evaluated by the sponsor in conjunction with the CRO to determine suitability for the proposed study. Information reviewed will include, but is not limited to, facility details and site capabilities, past performance in similar studies, investigator, and staff experience, ongoing studies at the site, projected enrollment in this study, and FDA or other agency audit findings. Study sites may be asked to complete a study-specific Site Selection Questionnaire and other documents for consideration for participation and CRO clinical study monitors may make a Site Qualification Visit prior to completing the evaluation process.

Upon completion of this evaluation, the sponsor will invite the chosen sites for participation.

Prior to subject enrollment, a study initiation visit will be completed at each investigational site to ensure the following: IRB approval has been obtained and documented prior to subject screening, the investigators and study personnel are appropriately trained and clearly understand the study, the investigators and study personnel accept the obligations incurred in undertaking this clinical investigation.

Raters proposed by each site will be evaluated on the basis of experience and education for each instrument used in the study. Raters with the appropriate levels of experience and education will be trained by an independent third party in the use of each instrument, and approved to administer that instrument in the study. Sites will not be approved to begin enrollment activities until they have at least one rater approved for each clinician-administered instrument.

Qualified clinical monitors or qualified contract monitors will conduct investigational site monitoring visits to ensure that all investigators conduct the study in compliance with the protocol and applicable regulations. The site will receive notification prior to each monitoring visit during the course of the study. It is expected that the investigator and/or sub-investigator and other appropriately trained study staff are available on the day of the visit in case any questions might arise.

Periodic monitoring visits will be made in accordance with the approved monitoring plan at all active study sites throughout the clinical study to assure that the investigator obligations are fulfilled and all applicable regulations and guidelines are being followed. These visits will assure that the facilities are still acceptable, the protocol and investigational plan are being followed, the IRB has been notified of approved protocol changes as required, complete records are being maintained, appropriate and timely reports have been made to the sponsor, CRO, and the IRB, and the site Principal Investigator is executing all agreed activities.

The sponsor retains the right to remove either the site-investigator or the investigational site from the study for issues of non-compliance with the protocol or regulatory requirements.

On one or more occasions, the study site may be inspected or audited by the sponsor representative or a third party. The investigator will be informed in advance of this visit.

Upon completion of the clinical study (when all subjects at the site have completed follow up visits, all data has been entered in EDC and cleaned, all queries resolved, and final electronic signatures have been obtained), a study closeout visit will be performed. Any unused study materials and equipment will be collected and returned to sponsor. The monitor will ensure that the investigator's regulatory files are up to date and complete and that any outstanding issues from previous visits have been resolved. Other issues which will be reviewed at this visit include: discussing retention of study files, possibility of site audits, publication policy, and ensuring that the investigator will notify the IRB regarding study closeout.

14.2 Audits and Inspections

Subcontracts with study sites will specify that sponsor or its representatives will have direct access to source data and documents for study monitoring. Additionally, the IRB and FDA may review source data following appropriate guidelines for this process.

The Data and Safety Monitoring Board (DSMB) functions include, among others, ongoing assessment of masked data to determine whether any of the treatment arms show increased risk for AEs. The main purpose of the DSMB is to assess safety of the intervention by determining whether an increased number of AEs are occurring among study participants in any one of the treatment groups. Data will be reviewed every 4 months after the DSMB approval of the DSMB Charter. Frequent interim review of the data for SAEs does not require statistical adjustment for repeated testing or analyses.

The Medical Monitor for this trial will be designated by sponsor/CRO. The Medical Monitor will review and approve the eligibility of all screened subjects, review all AEs, assess the benefits and risks of protocols on an ongoing basis, and work in collaboration with the IRB and RAC to identify safety signals and trends.

In addition, the Medical Monitor will be available for site questions. The Medical Monitor will be available to sites for questions regarding inclusion/exclusion criteria, protocol conduct, and safety. Trained and qualified physicians will be available to provide coverage during times when the medical monitor is unavailable. Sites will be provided with the Medical Monitor's cell phone number for emergency situations. Otherwise, sites are instructed to contact the Medical Monitor through email. All conversations with sites will be documented by the Medical Monitor and reviewed periodically by the sponsor.

Each month the Medical Monitor will receive a listing of protocol violations for review and identification of possible trends.

Serious adverse events will be reported to the CRO by the site within 24 business hours of the site's knowledge of the event. For reportable unexpected and/or related SAEs, the Medical Monitor will contact NeuroRx within 48 business hours of the notice by the site. In addition, the

Medical Monitor may request individual subject records, including laboratory data, clinical records, and other study related data, to evaluate these events against the known safety profile of the study treatment and the disease. Any records sent to the Medical Monitor by the site will be redacted for any identifying information before transmission. The Medical Monitor may recommend actions including partial or complete unblinding, and/or modifying or terminating the study.

Urgent Clinical Situations: During the course of the study, a subject will be reassessed for continued participation based on clinical judgment of the investigators. All subjects will be offered access to 24/7 coverage for medical emergencies through the clinical staff at each site. Treatment options and their risks and benefits, including continued study participation and other treatment options, will be sensitively explained. All study investigators have extensive clinical experience in the treatment of BPD and suicidal ideation, and can make the decision (while blinded) as to removal of subjects from the trial, particularly in the event of clinical deterioration or emergence/worsening of suicidal ideation. When a subject is removed from the trial based on clinical judgment, investigators will implement an appropriate treatment plan and arrange for follow-up for the subject.

14.3 Institutional Review Board (IRB)

The study protocol and any amendments will be reviewed by an Institutional Review Board (IRB). The IRB will review the informed consent form, their updates (if any), and any written materials given to the subjects. A list of all IRBs and contact information will be included in the study report.

IRB approval will be obtained and documented prior to subject enrollment and screening. Before study initiation, the investigator must have written and dated approval from the IRB for the protocol, consent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects.

The investigator will provide the IRB with reports, updates, and other information (e.g., Safety Updates, Amendments, and Administrative Letters) according to regulatory requirements and Institution procedures.

A detailed list of required regulatory documents, also to be submitted to the CRO and/or sponsor, will be sent upon final approval of the protocol.

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Source Data and Records

Source data are all the information in original records and certified copies of original records of clinical findings, observations, laboratory reports, data sheets provided by the sponsor or other activities in the study, which are necessary for the reconstruction and evaluation of the study. The investigator will permit study-related monitoring, audit(s), IRB review(s) and regulatory inspection(s), with direct access to all the required source records.

All study records will be retained for a period of time as defined by the regulatory authority for the country in which the investigation is conducted. Generally, this means at least 2 years following the date on which the drug is approved by the regulatory authority for marketing for the purposes that were the subject of the investigation. In other situations (e.g., where the investigation is not in support of or as part of an application for a research or marketing permit), a period of 2 years following the date on which the entire clinical program is completed, terminated or discontinued or the investigational application under which the investigation is being conducted is terminated or withdrawn by the regulatory authorities.

In the event the Investigator retires, relocates or for any other reason withdraws from the responsibility for maintaining records for the period of time required, custody of the records may be transferred to any other person who will accept responsibility for the records. Notice of such a transfer must be given in writing to the Sponsor. The Investigator must contact the Sponsor prior to disposal of any records related to this study.

15.2 Reporting of Results

The Case Report Form (CRF) is an integral part of the study and subsequent reports. The CRF must be used to capture all study data recorded in the patient's medical record. The CRF must be kept current to reflect patient status during the course of the study. Only a patient screening and randomization number will be used to identify the patient.

The monitor is responsible for performing on-site monitoring at regular intervals throughout the study to verify adherence to the protocol; verify adherence to local regulations on the conduct of clinical research; and ensure completeness, accuracy, and consistency of the data entered in the CRF.

The CRO will monitor completed Case Report Forms (CRFs). A case report form will be provided for each screened patient.

All protocol-required information collected during the study must be entered by the Investigator, or designated representative, in the Target e*CRF™, an Internet-based electronic data collection system. All details of the CRF completion and correction will be explained to the investigator. The management module of Target e*CRF™ includes edit check and query systems that seamlessly integrate with the data entry system. All modifications to the data in the eCRF are tracked by an electronic audit trail (date and identity of the person making the change are instantaneously recorded). Target e*CRF™ is 21CFR Part 11 compliant.

If the Investigator authorizes other persons to make entries in the CRF, the names, positions, and signatures of these persons must be supplied to the sponsor.

The Investigator, or designated representative, should complete the eCRF as soon as possible after information is collected, preferably on the same day that a study patient is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. By design, an explanation must be provided for all missing data, altered data, and/or out of range data.

The completed case report form must be reviewed and signed by the Investigator named in the study protocol or by a designated sub investigator.

Final monitored and audited eCRFs will be provided by the Sponsor to the sites at the end of the study in the format of a PDF file.

15.3 Confidentiality of Subject Data

The risk of loss of privacy is judged to be minimal. Confidentiality will be maintained by numerically coding all data, by disguising identifying information, and by keeping all data in locked file drawers or on password-protected databases on password-protected and encrypted computers in locked offices. Subject information will be accessible only to research staff. Information about study participants will not leave our institution in any form that would identify individual subjects. Sites will enter subject data directly into the EDC system, which will be managed by the [CRO/data management] team. Subjects will be assigned study ID numbers.

Potential risks to data confidentiality will be mitigated by requirements for the de-identification of all study data and by security protocols for all data capture systems. All users of the EDC system will be tracked and provided access in a secure fashion following established Standard Operating Procedures (SOPs) for this process.

As with all research data, information gathered by the study will be used only for aggregate analysis; it will not be released with any information that identifies research participants. Pharmacogenetic information, in particular, will be coded and unlinked to individual respondent identifiers. The data managers, biostatistician, and study sponsor do not have access to the identities of subjects. That information is retained only at the clinical sites. Uses and risks related to data collection will be outlined in the informed consent and reviewed with the subjects.

16. ETHICAL CONSIDERATIONS

16.1 Ethics Review

Anticipated benefits of the research to participants and others: This study will potentially help individuals with BPD and acute suicidal intention. If we discover that this intervention is effective, these results will lead to a full clinical development program of this treatment for BPD and acute suicidal intention.

Risks to subjects relative to the anticipated benefits to research participants and others: The treatment has been selected with consideration of safety in mind. Additionally, adequate protections are in place to carefully monitor the medical wellbeing of participants. In contrast, the morbidity and mortality associated with BPD and suicidal ideation are known to be very high.

Risks to subjects in relation to the importance of the knowledge that reasonably may be expected to result: The benefit to society from the development of efficacious interventions with rapid onset for BPD and acute suicidal ideation would be a substantial public health benefit.

Vulnerable populations will not be included, except for adolescents ages 18 to 21. Pregnant women will not be included in the study. Prisoners will not be included. Subjects under the age of 18 years will not be included.

16.2 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki, in compliance with the approved protocol, GCP and applicable regulatory requirements.

Participants must be capable of understanding the nature of this study, its potential risks, discomforts and benefits. Study physicians will obtain consent after they have fully explained the study purpose and its procedures, and potential participants have demonstrated an understanding of the protocol, willingness to participate, and competency to consent.

All subjects will receive monitoring for clinical deterioration, support, attention, and reassurance in the context of a therapeutic alliance. By definition, the target population is one in which subjects have not responded to available antidepressant therapies. Both active treatment and placebo/control groups in each trial will receive comprehensive evaluation and careful monitoring. Close monitoring by a trained psychiatrist is beneficial for individuals with mood disorders. If subjects are in need of more intensive psychiatric treatment at any time during the course of the trial, study personnel will assist in needed evaluation and referral to appropriate treatment settings. Subjects will be carefully monitored regarding depressive and other psychiatric symptoms. Non-responders to study treatment will be offered referrals for treatment at the end of the trial.

The investigators recognize that although DCS has been used in millions of individuals without report of significant safety concerns, DCS has thus far been used in 21 subjects at the 1000mg dose in formal studies of psychiatric illness. Therefore, the investigators will appoint a designated safety monitor to surveil for any safety signals that may arise in the course of the study.

Lurasidone is an FDA-approved medication which is indicated in the treatment of bipolar depression and is a member of a class of medications (5-HT2A antagonists) that is routinely used in treating bipolar depression. Neither lurasidone, nor any other member of this class has successfully demonstrated efficacy against suicidality – in fact the medication bears a warning about potential suicide risk. However, its efficacy against bipolar depression is established.

16.3 Subject Information and Consent

Participants must be capable of understanding the nature of this study, its potential risks, discomforts and benefits. Study physicians will obtain consent after they have fully explained the study purpose and its procedures and the potential participant has demonstrated an understanding of the protocol, willingness to participate and competency to consent.

The investigator must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the site-specific consent form is the responsibility of the site Principal investigator and must include all elements required by CFR 21 Part 50.25 and the IRB.

All subjects will receive the consent form for the study. These documents will be read by the subjects and also reviewed by the subject with a clinician on the research staff prior to participating in the study. Any questions, concerns, or ambiguities will be clarified by the site's site investigator or another study clinician prior to the subject signing consent. Subjects will sign informed consent and only then will begin participation in the study.

17. DATA HANDLING AND RECORDKEEPING

17.1 Data Capture

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the investigational product or entered as a control in the investigation.

17.2 Retention of Records

The investigator must retain investigational product disposition records, case report forms, and source documents for the maximum period required by applicable regulations and guidelines, or Institution procedures, and at least for 10 years.

If the investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another investigator, IRB, sponsor). Notice of such transfer will be given in writing to sponsor.

17.3 Use of Information and Publication Policy

All publications will be reviewed by the sponsor for accuracy before submission to peer reviewed journals or scientific meetings. Abstracts should be submitted for review at least 10 days before submission, and publications should be submitted for review at least 30 days before submission. The study will be posted to Clinicaltrials.gov and results reported in accordance with Clinicaltrials.gov guidelines.

18. PROTOCOL SIGNATURE PAGE

I have read this protocol and agree to adhere to the requirements. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding the conduct of the study according to 21 CFR parts 50, 54, 56 and 812, 45 CFR 46, to GCP as described in ICH guideline E6 and to hospital Institutional Review Boards.

_____ _____

Clinical Site Investigator Signature Date

_____

Clinical Site Investigator Printed Name

_____ _____

Investigator-Sponsor Signature Date

_____

Investigator-Sponsor Printed Name

19. REFERENCES

Ballard ED, Ionescu DF, Vande Voort JL, Niciu MJ, Richards EM, Luckenbaugh DA, et al. Improvement in suicidal ideation after ketamine infusion: relationship to reductions in depression and anxiety. J Psychiat Res. 2014;58:161-6.

Barnes TR. A rating scale for drug-induced akathisia. Br J Psychiatry. 1989 May;154:672-6

Barnes TRE (2003). The Barnes Akathisia Rating Scale - Revisited. J Psychopharmacology. 174(4), 365-370.

Beck AT Kovacs M Weissman A. Assessment of suicidal intention: The scale of suicide ideation. J Consult Clin Psychology. 1979; 47: 343-352.

Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, et al. Antidepressant effects of ketamine in depressed patients. Biol Psychiat. 2000;47(4):351-4.

Bowden, C. L., Singh, V., Thompson, P., Gonzalez, J. M., Katz, M. M., Dahl, M., Prihoda, T. J. and Chang, X. (2007), Development of the Bipolar Inventory of Symptoms Scale. Acta Psychiatrica Scandinavica, 116: 189–194. doi: 10.1111/j.1600-0447.2006.00955.x

Bucco, T. (1970). Neurotoxic effects of cycloserine therapy in pulmonary tuberculosis of adolescents and young adults. *Scandinavian Journal Respiratory Diseases (Supplement), 71*, 259-265.

Coryell W, Kriener A, Butcher B, Nurnberger J, McMahon F, Berrettini W, Fiedorowicz J. Risk factors for suicide in bipolar I disorder in two prospectively studied cohorts. J Affective Disorders. 2016; 190:1-5.

Crane GE. Cycloserine as an anti-depressant agent. Am J Psychiat. 1959;115:1025–9.

Crane GE. The psychotropic effects of cycloserine: a new use for an antibiotic. Compr Psychiat. 1961;2:51–9.

Desseilles M, Witte J, Chang TE, et.al. Massachusetts General Hospital SAFER Criteria for Clinical Trials and Research. Harvard Review of Psychiatry 2013:21(5);1-6

DiazGranados N, Ibrahim LA, Brutsche NE, Ameli R, Henter ID, Luckenbaugh DA, et al. Rapid resolution of suicidal ideation after a single infusion of an N-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. J Clin Psychiat. 2010;71(12):1605-11.

Guy, W. Clinical Global Impression (CGI) ECDEU Assessment manual for Psychopharmacology. Rockville, MD: U.S. Dept Health Education and Welfare 1976.

Harada T, Inada K, Yamada K, Sakamoto K, Ishigooka J. A prospective naturalistic study of antidepressant-induced jitteriness/anxiety syndrome. Neuropsychiatric disease and treatment. 2014;10:2115-21.

Heresco-Levy U, Javitt DC, Gelfin Y, Gorelik E, Bar M, Blanaru M, et al. Controlled trial of D-cycloserine adjuvant therapy for treatment-resistant major depressive disorder. J Affect Disorders. 2006;93(1-3):239-43.

Heresco-Levy U, Gelfin G, Bloch B, Levin R, Edelman S, Javitt DC, et al. A randomized add-on trial of high-dose d-cycloserine for treatment-resistant depression. Int J Neuropsychop. 2013;16(3):501-6.

Hood WF, Compton RP, Monahan JB. D-cycloserine: a ligand for the N-methyl-D-aspartate coupled glycine receptor has partial agonist characteristics. Neurosci Lett. 1989;98(1):91-5.

Javitt DC, Composition and method for treatment of psychosis and depression in humans. US patent application 2014/0018348, filed Jan 2014. www.uspto.gov.

Kantrowitz JT, Halberstam B, Gangwisch J. Single-Dose ketamine followed by daily D-Cycloserine in treatment-resistant bipolar depression. J Clin Psychiat. 2015;76(6):737-8.

Kessler RC, Chiu WT, Demler O, Walters EE. Prevalence, severity, and comorbidity of twelve-month DSM-IV disorders in the National Comorbidity Survey Replication (NCS-R). Archives of Genera. Psychiatry, 2005 Jun;62(6):617-27.

Loebel A, Cucchiaro J, Silva R, Kroger H, Hsu J, Sarma K, et al. Lurasidone monotherapy in the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. Am J Psychiat. 2014a;171(2):160-8.

Loebel A, Cucchiaro J, Silva R, Kroger H, Sarma K, Xu J, et al. Lurasidone as adjunctive therapy with lithium or valproate for the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. Am J Psychiat. 2014b;171(2):169-77.

Lopes T, Neubauer P, Boje KM. Chronic administration of NMDA glycine partial agonists induces tolerance in the Porsolt swim test. Pharmacol Biochem Be. 1997;58(4):1059-64.

Mahli, GS, Thoughts on suicidal thinking in bipolar disorder. Bipolar Disord. 2015 Feb; 17(1):19-21. doi: 10.1111/bdi.12276. Epub 2014 Nov 3.

Montgomery SA and Asberg M. A new depression rating scale designed to be sensitive to change. Br J Psychiatry 1979. 134:382–389.

Nierenberg, A. A., Gray, S. M., & Grandin, L. D. (2001). Mood disorders and suicide. *J Clin Psychiatry, 62 Suppl 25*, 27-30.

Nolen-Hoeksema, S., & Morrow, J. (1991). A prospective study of depression and posttraumatic stress symptoms after a natural disaster: The 1989 Loma Prieta earthquake. Journal of Personality and Social Psychology, 61, 115–121. doi:10.1037/0022-3514.61.1.115

Overall JE, Gorham DR, (1962). The brief psychiatric rating scale. Psychological Reports 1962 vol. 10, pp799-812

Pompili M, Gonda X Serafini G. Epidemiology of Suicide in Bipolar Depression. Bipolar Disorders. 2013;15(5):457-490.

Popovic D, Vieta E, Azorin JM, Angst J, Bowden CL, Mosolov S, et al. Suicide attempts in major depressive episode: evidence from the BRIDGE-II-Mix study. Bipolar Disorders. 2015.

Posner K, Oquendo MA, Gould M, Stanley B, and Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry 2007. 164:1035-1043.

Puddu PE., Jouve R., Marlotti S., et al. Evaluation of 10 QT prediction formulas in 881 middle-aged men from the Seven Countries study: emphasis on the cubic root Fridericia's equation. J Electrocardiol 1988. 2:219–229.

Reilly-Harrington NA et al (2016). J Affective Disord, 192: 212-218. [need to add title]

Sachdev PS, Brune M. Animal models of acute drug-induced akathisia - a review. Neurosci Behav R. 2000;24(3):269-77.

Skolnick P, Layer RT, Popik P, Nowak G, Paul IA, Trullas R. Adaptation of N-methyl-D-aspartate (NMDA) receptors following antidepressant treatment: implications for the pharmacotherapy of depression. Pharmacopsychiatry. 1996;29(1):23-6.

Stone M, Laughren T, Jones ML, Levenson M, Holland PC, Hughes A, et al. Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration. BMJ. 2009;339: b2880.

Trivedi MH, Wisniewski SR, Morris DW, Fava M, Gollan JK, Warden D, Nierenberg AA, Gaynes BN, Husain MM, Luther JF, Zisook S, Rush AJ Concise Health Risk Tracking scale: a brief self-report and clinician rating of suicidal risk J Clin Psychiatry 2011 Jun 72 6 757-64

Trullas R, Skolnick P. Functional antagonists at the NMDA receptor complex exhibit antidepressant actions. Eur J Pharmacol. 1990;185(1):1-10.

Wisniewski SR, Rush AJ, Balasubramani GK, Trivedi MH, Nierenberg AA, for the STARD Investigators. Self-rated global measure of the frequency, intensity, and burden of side effects. J Psychiatr Pract 2006;12:71–79

20. 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 3 days for each episode, and may not be taken the day of the infusion starting at midnight. 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 PPD 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. 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, and pregabalin are allowed. Other anticonvulsants are not allowed, including lamotrigine and carbamazepine. 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 is excluded.
Antidiarrheal preparations	Y	N	Only loperamide HCl (Imodium), bismuth subsalicylate (Pepto-Bismol), and kaolin preparations are allowed.
Antifungals, systemic	N	Y	—
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.)

Drug Name or Class	Episodic Use (PRN)	Chronic Use	Restrictions/Comments
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.
Antifungal	Y	Y	Itraconazole is excluded
Antimigraine	N	N	Triptans are not allowed
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 antihistamines).
Antineoplastics/ Immunosuppressant agents	N	Y[c]	Interferons, methotrexate, and other immunosuppressant agents are not allowed. Call PPD Medical Monitor for approval for certain cases in cancer remission maintaining therapy.

Drug Name or Class	Episodic Use (PRN)	Chronic Use	Restrictions/Comments
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.
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, indinavir, nelfinavir, ritonavir, saquinavir 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. Benzodiazepines should not be taken within 2 hours of infusion.
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 subjects who have symptoms of obstructed voiding should not be included in the study. Surgically or medically treated subjects must be asymptomatic and receiving a stable dosage of allowed medications (α-1 blockers, finasteride, or dutasteride) for 1 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 phenylephrineCombination 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.
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.

Drug Name or Class	Episodic Use (PRN)	Chronic Use	Restrictions/Comments
Hormones: reproductive	N	Y	Systemic hormonal contraceptives (oral contraceptives of estrogen and progestin combinations, depot injections such as Depo-Provera, the contraceptive implant Implanon, or transdermally delivered contraceptives such as Ortho Evra) are allowed
Hormones: thyroid	N	Y	Thyroid hormone replacement is allowed (dosage of thyroid medication should be stable for 3 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 not 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.

Drug Name or Class	Episodic Use (PRN)	Chronic Use	Restrictions/Comments
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
Proton pump inhibitors or H2 receptor blockers	Y	Y	Cimetidine
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. Patients should not take benzodiazepines, within 2 hours of infusion
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 notallowed
Vaccines	Y	NA	—

a If being taken prior to enrolling in the study.

b If being taken for at least 3 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: Assessment Tools

- MINI 7.0.2
- C-SSRS (and the retrospective C-CASA component)
- CHRT (CHRT-SR and CHRT-C)
- BISS
- PRISE
- SIBQ
- CADSS
- BPRS
- BARS (including the global severity rating)