Janssen Research & Development *

Statistical Analysis Plan

A Double-blind, Randomized, Psychoactive Placebo-controlled, Study to Evaluate the Efficacy and Safety of 3 Fixed Doses (28 mg, 56 mg and 84 mg) of Intranasal Esketamine in Addition to Comprehensive Standard of Care for the Rapid Reduction of the Symptoms of Major Depressive Disorder, Including Suicidal Ideation, in Pediatric Subjects Assessed to be at Imminent Risk for Suicide

Protocol ESKETINSUI2002; Phase 2b

JNJ54135419 (esketamine)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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ABBREVIATIONS

AAP	American Academy of Pediatrics
AD	Antidepressant
ADHD	Attention-deficit hyperactivity disorder
AE	Adverse event
AIC	Akaike Information Criterion
BP	Blood pressure
BPRS+	Brief Psychiatric Rating Scale, positive symptom subscale
CADSS	Clinician-Administered Dissociative States Scale
CDI 2:SR	Children's Depression Inventory 2 Self-Report
CDI 2:SR[S]	Children's Depression Inventory 2: Self-Report (short version)
CDRS-R	Children's Depression Rating Scale-Revised
CGI-SS	Clinical Global Impression Severity of Suicidality
CGI-SR-I	Clinical Global Impression of Imminent Suicide Risk
CGI-SS-R	Clinical Global Impression of Severity of Suicidality, revised version
C-SSRS	Columbia-Suicide Severity Rating Scale
EU	European Union
DB	Double-blind
DBP	Diastolic blood pressure
DSM-5	Diagnostic and Statistical Manual of Mental Disorders (5th edition)
ECG	Electrocardiogram
ER	Emergency room
FDA	Food and Drug Administration
FU	Follow-up
GCP	Good Clinical Practice
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
LOCF	Last observation carried forward
MADRS	Montgomery-Asberg Depression Rating Scale
MDD	Major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MLE	Maximum likelihood estimates
MMRM	Mixed-effects model using repeated measures
MOAA/S	Modified Observer's Assessment of Alertness/Sedation
PWC-20	Physician Withdrawal Checklist
PK	Pharmacokinetic(s)
PCP	Phencyclidine
SAE	Serious AE
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SIBAT	Suicide Ideation and Behavior Assessment Tool
SoC	Standard of care
TEAE	Treatment-emergent adverse events
TEMA	Treatment emergent markedly abnormal
TLFB	Timeline Follow-Back
US	United States
YMRS	Young Mania Rating Scale

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for all planned analyses for study ESKETINSUI2002.

An analysis of efficacy and safety will be performed after the last subject completes the 25-day double-blind treatment Period (Day 25). This analysis will enable selection of a dose for the planned Phase 3 trial, facilitating Phase 3 trial design and preparation.Additional efficacy and safety analysis will also be performed after the last subject completes 8-week post-treatment follow-up phase (Day 81) and 6-month post-treatment follow-up phase (Day 200).

1.1. Trial Objectives

Primary Objective

The primary objective is to assess the efficacy of a single (first) dose of 3 fixed doses of intranasal esketamine (28 mg, 56 mg, and 84 mg) compared with psychoactive placebo (oral midazolam) in rapidly reducing the symptoms of MDD, including suicidal ideation, in subjects 12 to <18 years of age who are assessed to be at imminent risk for suicide. Efficacy will be assessed by the change from baseline in Children's Depression Rating Scale, Revised (CDRS-R) total score at 24 hours post first dose (Day 2).

Other Objectives

The other objectives are:

- To evaluate the dose response of intranasal esketamine compared with psychoactive placebo in reducing the symptoms of MDD, including suicidal ideation, as assessed by the change from baseline in CDRS-R total score at 24 hours post first dose (Day 2) and at Day 25.
- To evaluate the efficacy of single and repeated doses of intranasal esketamine compared with psychoactive placebo in reducing symptoms of suicidal ideation, as assessed by the Clinical Global Impression of Severity of Suicidality, revised version (CGI-SS-R) from the Suicide Ideation and Behavior Assessment Tool (SIBAT) at 4 hours and 24 hours post first dose and through the end of the double-blind treatment phase (Day 25).
- To evaluate the efficacy of single and repeated doses of intranasal esketamine compared with psychoactive placebo in reducing symptoms of MDD as assessed by the following:
  - CDRS-R total score at 4 hours post first dose, through the end of the double-blind Treatment phase (Day 25), and during the 6-month post-treatment follow-up phase.
  - MADRS total score at 4 hours and 24 hours post first dose, through the end of the double-blind Treatment phase (Day 25), and during the 6-month post-treatment follow-up phase.
  - Children's Depression Inventory 2: Self-Report (Short) version (CDI 2:SR[S])^{TM} score at 24 hours post first dose and through the end of the double-blind treatment phase (Day 25).
- To evaluate the efficacy of single and repeated doses of intranasal esketamine compared with psychoactive placebo in reducing symptoms of suicidal ideation, as assessed by the Clinical Global Impression – Imminent Suicide Risk (CGI-SR-I) from the SIBAT at 4 hours and 24 hours post first dose and through the end of the double-blind treatment phase (Day 25).

- To evaluate the efficacy of single and repeated doses of intranasal esketamine compared with psychoactive placebo in reducing suicidal thoughts, as assessed by the following:
  - Change from baseline in SIBAT Module 3 (My Current Thinking) and Module 5 (My Risk) Question 3 (patient-reported frequency of suicidal thinking) through the end of the double-blind Treatment phase (Day 25) and during the 6-month post-treatment follow-up phase.
- To characterize the pharmacokinetics of intranasal esketamine and its metabolite noresketamine.
- To evaluate the safety and tolerability of intranasal esketamine through the end of the double-blind treatment phase (Day 25) using the following assessments:
  - Effects on suicidal ideation and behavior using the SIBAT
  - Effects on dissociative symptoms using the Clinician-Administered Dissociative States Scale (CADSS)
  - Occurrence of psychosis-like side effects using a 4-item positive symptom subscale (consisting of: suspiciousness, hallucinations, unusual thought content, and conceptual disorganization) of the Brief Psychiatric Rating Scale, positive symptom subscale (BPRS+)
  - Occurrence of potential treatment-emergent symptoms of mania using the Young Mania Rating Scale (YMRS)
  - Effects on cognitive function as measured by the Cogstate® computerized cognitive battery
  - Effect on sedation using the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale
  - Local nasal tolerability, using targeted nasal examinations coupled with a nasal symptom questionnaire
- To evaluate the safety and tolerability of intranasal esketamine at specified times through the initial 25-day double-blind treatment period (Day 25), the 8-week post-treatment follow-up (Day 81) and 6-month post-treatment follow-up, with special attention given to the following assessments:
  - Effects on suicidal ideation and behavior using the SIBAT
  - Effects on cognitive function as measured by the Cogstate computerized cognitive battery
- To evaluate potential withdrawal symptoms during the post-treatment follow-up as measured by the Physician Withdrawal Checklist (PWC-20) on Days 25, 28, 32, 35 and 39.
- To evaluate the potential for ketamine or PCP abuse during the follow-up as measured by the Timeline Follow-Back (TLFB).
- To evaluate whether pretreatment concentrations of MDD-related biomarkers (eg, HPA axis function, immune system activation, growth factors, metabolic markers) correlate with clinical response or non-response, as measured by the MADRS following intranasal administration of esketamine.

- To explore the change in MDD-related biomarkers in relation to clinical response or non-response to intranasal esketamine.

1.2. Trial Design

This is a randomized, double-blind, double-dummy, psychoactive placebo-controlled, multicenter trial with 45 anticipated global sites. A target of 145 pediatric subjects, 12 to <18 years of age, will be enrolled in this study and randomized in a 1:1:1:2 ratio to one of 3 doses of intranasal esketamine (28, 56 or 84 mg) or a psychoactive placebo (oral midazolam 0.125 mg/kg), with approximately 29 subjects assigned to each dose of intranasal esketamine and approximately 58 subjects assigned to psychoactive placebo. All eligible subjects will have a diagnosis of MDD, and will have presented to an emergency room (ER) or other permitted setting and been assessed to be at imminent risk for suicide. Given the vulnerability of the population, this study will be conducted in the context of standard of care treatment. This includes initial hospitalization in an inpatient psychiatric unit or other permitted setting for a recommended duration of 5 days counted from randomization, with shorter or longer hospitalizations permitted if clinically warranted per local standard of care; initiation or optimization of allowed antidepressant medication therapy, participation in a specific psychological intervention (individual cognitive behavioral therapy [CBT]), interpersonal therapy, family therapy or psychodynamic psychotherapy), and close outpatient follow-up.

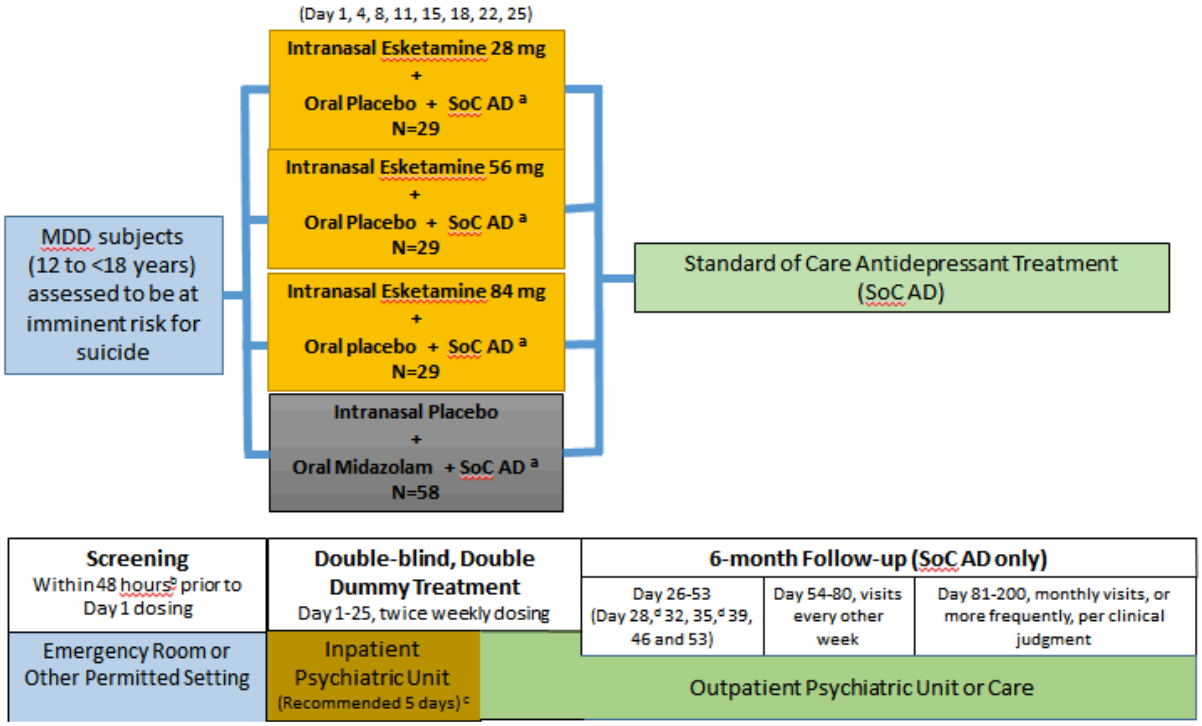
There is only 1 approved antidepressant for the treatment of MDD in children and adolescents in both the United States (US) and European Union (EU): fluoxetine; however, if treatment with fluoxetine is unsuccessful or is not tolerated because of side effects, guidelines recommend treatment with escitalopram and sertraline. Escitalopram (the S-enantiomer of citalopram) is also approved for use in adolescents in the US. Therefore, this multi-national study will permit the use of fluoxetine, escitalopram or sertraline as the standard of care antidepressants.

The study will be conducted in 4 phases: a screening evaluation performed within 48 hours prior to Day 1 intranasal dose (if possible, screening should occur within 24 hours prior to the Day 1 intranasal dose); a 25-day double-blind treatment phase (Days 1 - 25), during which study drug will be administered 2 times per week for 4 weeks on Days 1, 4, 8, 11, 15, 18, 22, and 25; an 8 week initial post-treatment phase (Days 25 - 81); and a subsequent phase to complete a full 6-month post-treatment follow-up (Days 81 - 200). During post-treatment follow-up phases, no study drug will be administered. The duration of the subject's participation will be approximately 29 weeks.

An Independent Data Monitoring Committee will be commissioned for this study.

A diagram of the study design is provided in Figure 1.

Figure 1: Schematic Overview of the Study



Abbreviations: AD = antidepressant; SoC = standard of care.

[a] It is recommended that standard of care antidepressant treatment will be initiated or optimized on Day 1, however, to reflect differing standard of care antidepressant treatment, antidepressant therapy may be started within 7 days after the first dose of study medication.

[b] If possible, screening should be performed within 24 hours prior to Day 1 intranasal dose.

[c] Hospital discharge before 5 days (from randomization) must be discussed with and approved by the sponsor's medical monitor. The investigator must discuss the need for continued hospitalization beyond 10 days and thereafter on a weekly basis with the sponsor's medical monitor.

[d] Remote contact.

An additional age cohort is added in Protocol Amendment 4/USA-2. It is planned in the United States (US) to explore the efficacy and safety of 56 mg dose of intranasal esketamine in addition to comprehensive standard care for the rapid reduction of the symptoms of major depressive disorder, including suicidal ideation, in pediatric subjects aged 9 - < 12 years assessed to be at imminent risk for suicide. Subjects aged 9 - <12 years old will be enrolled in this study and randomized in a 1:1 ratio to a blinded treatment of 56-mg dose of intranasal esketamine or a psychoactive placebo (oral midazolam 0.125 mg/kg). Further details please refer the Protocol Amendment 4/USA-2.

No sample size calculation is conducted for this cohort. The number of subjects enrolled in 9 - <12 years old cohort will not impact the sample size from the main protocol (12 -< 18 year old subjects). There will be no hypothesis testing for the 9 - <12 year old cohort.

Data collected from this cohort will be presented sperately and for descriptive purposes only.

1.3. Statistical Hypotheses for Trial Objectives

The primary hypothesis of this study is that, in addition to standard of care, intranasal esketamine is superior to psychoactive placebo in rapidly reducing the symptoms of MDD, including suicidal ideation, as assessed by the change from baseline in CDRS-R at 24 hours post first dose in subjects 12 to <18 years of age who are assessed to be at imminent risk for suicide.

1.4. Sample Size Justification

The sample size for this study was calculated assuming an effect size of 0.65 between any dose of esketamine and psychoactive placebo for the change from baseline at 24 hours postdose for the CDRS-R total score and a 2-sided significance level of 0.05. A total of 145 subjects will be randomized in this study. Using a 1:1:1:2 randomization ratio (esketamine 28 mg: esketamine 56 mg: esketamine 84 mg: psychoactive placebo), approximately 58 subjects will need to be randomized to psychoactive placebo and 29 subjects will need to be randomized to each esketamine treatment group to achieve 94% power for the comparison of the pooled doses of esketamine 56 mg and esketamine 84 mg versus psychoactive placebo and 92% power for at least one of esketamine dose (56-mg and 84-mg) versus psychoactive placebo. The effect size of 0.65 is based on results from study ESKETINSUI2001 (mean difference between treatment groups of -7.2 and a pooled SD of 11.02) for MADRS total score.[2]

1.5. Randomization and Blinding

Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Randomization will be stratified by study center.

Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints. Administration of esketamine, however, is associated with a number of transient adverse events, including sedation, dissociative symptoms, and elevation of blood pressure. To minimize the risk of unblinding the treatment assignment, a psychoactive placebo, midazolam, will be used. Midazolam has been used as a psychoactive placebo in previous studies of ketamine[5] because of its similar onset of action and side effect profile.

The effect of a placebo response is of particular concern in clinical trials of MDD[6]. Because a lower likelihood of randomization to placebo has been shown to be associated with placebo response[6], a treatment allocation of 1:1:1:2 for 28 mg: 56 mg: 84 mg: psychoactive placebo is being used to minimize expectancy bias and to mitigate placebo response.

A double-dummy design will be used in order to preserve the blind since the active study drug (intranasal esketamine) and the psychoactive placebo (oral midazolam) are administered via different routes. Therefore, 2 matching placebo formulations, intranasal and oral, will be included in the treatment regimen. In order to maintain the blind, subjects randomized to intranasal esketamine will also receive an oral placebo, and subjects randomized to oral midazolam will also be administered an intranasal placebo.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Pooling Algorithm for Analysis Centers

Pooling may be conducted only for randomized subjects only if a sufficient number of subjects are not randomized to a site. If necessary, small study centers with fewer than 4 subjects in Full Efficacy Analysis Set will be combined for the purpose of analysis within each region (North America, Europe, and South America). These small centers will be ordered according to the total number of subjects and then sequentially using the center number. The pooling will be carried out sequentially beginning with the smallest center. The size of any pooled analysis center should be as large as possible and not be larger than the size of the largest center in the region. If the number of small centers is large, and one pooled analysis center cannot include all small centers, then the second (or more) pooled analysis center(s) will be formed after the first one is filled with as many small centers as possible. Pooled sites as described are called analysis centers and will be used in the analyses as center effect.

2.2. Analysis Phases

There are 2 analysis phases defined in this study: double-blind and follow-up (post treatment). The follow-up phase is a full 6-month post-treatment phase, including the 8-week initial post-treatment follow-up phase till Day 81 and extended post-treatment follow-up phase (Day 81 – Day 200). Each analysis phase has its own analysis reference start and end dates.

2.2.1. Analysis Phase Start and End Dates

Double-Blind Phase

The double-blind (referred to as, 'DB') start date is the date of the first dose of double-blind medication. The DB end date is the date of the last visit (excluding remote contact visits) in the double-blind phase, or the date of the early withdrawal for patients who discontinued from the double-blind phase. For randomized subjects who did not receive any medication in the double-blind phase, both the DB start date and end date are missing.

Follow-up Phase

Start and end dates for the follow-up (referred to as, 'F/U') phase are only defined for subjects who completed the DB phase and continued into the F/U phase (including a visit in the F/U phase or adverse event data collected in the F/U phase). The analysis reference start date of the follow-up analysis phase is the day after the reference end date for the double-blind analysis phase. The analysis reference end date is the date of the early withdraw for subjects who discontinue during the follow-up phase. For the subjects who discontinued between Day 25 and Day 28 remote contact without an early withdrawal visit in the follow-up phase, end date is the date of the Day 28 remote contact. Otherwise, it is the maximum of the last follow-up visit date and the end of trial date.

2.2.2. Study Reference Start and End Dates

The overall reference start date for the study is defined as the date of the first dose of DB medication (the date is missing for screened subjects who did not receive a dose of DB medication). The overall reference end date for the study is the maximum of the date of last visit and trial completion/discontinuation.

2.2.3. Study Day and Relative Day

Study day is calculated relative to the overall reference start date for the study. Relative day is calculated relative to the analysis reference start date of the analysis phase in which the data are captured. A minus (-) sign indicates days prior to the start of study or prior to the start of the analysis phase.

Study day for an event on or after the start of the study is calculated as:

event date - study start date + 1.

Study day for an event prior to the start of the study is calculated as:

event date - study start date

Relative day for an event on or after a reference start date is calculated as:

event date - reference start date + 1.

Relative day for an event prior to a reference start date is calculated as:

event date - reference start date.

2.3. Baseline and End Point

The double-blind baseline value will be the last observation before receiving the first dose of the study drug in the double-blind phase and is denoted as ‘Baseline (DB)’. Baseline is defined for each parameter/assessment.

For each variable measured over time, the ‘End Point (DB)’ is defined as the last post-baseline value assessed during the double-blind phase, and the ‘End Point (F/U)’ is defined as the final value assessed during the follow-up phase.

2.4. Visit Windows

As subjects do not always adhere to the protocol visit schedule (including permitted visit windows), the following rules are applied to assign actual visits to protocol visits. Listed below are the visit windows for analysis and the target days for each visit. The reference day is Study Day 1 (which is the first day that any study drug was taken in the double-blind phase).

If a subject has 2 or more scheduled or unscheduled visits in one visit window, the visit closest to the target day will be used as the protocol visit for that visit window. If 2 actual visits are equidistant from the target day within a visit window, the later visit is used. If a visit window has

no scheduled visits but does have unscheduled visits, then the unscheduled visit closest to the scheduled visit will be used.

All assignments will be made in chronological order. Once a visit is assigned to a visit window, it will no longer be used for a later time point except for the end point. Listed below are the visit windows and the target days (if applicable) for each visit defined in the protocol for all phases (Table 1).

Table 1: Analysis Visits

Parameter	Analysis Phase	Scheduled Day	Time Interval (label on output)	Time Interval[a] (Day)	Target Time Point[a] (Day)
CDRS-R[b], MADRS[b]	DB	1	Baseline (DB)	≤ 1 / predose	1
			Day 1 (DB): 4H		
		2	Day 2 (DB)	2	2
		4	Day 4 (DB)	3 - 6	4
		8	Day 8 (DB)	7 - 9	8
		11	Day 11 (DB)	10 - 12	11
		15	Day 15 (DB)	13 - 16	15
		18	Day 18 (DB)	17 - 19	18
		22	Day 22 (DB)	20 - 23	22
		25	Day 25 (DB): Predose	24 - end of DB	25
			Day 25 (DB): 4H		
		DB final visit	End Point (DB)	Day 1 (DB): 4H - end of DB	
	F/U	28	Day 28 (F/U)	Day 1 (F/U) - 4	3
		32	Day 32 (F/U)	5 - 8	7
		35	Day 35 (F/U)	9 - 11	10
		39	Day 39 (F/U)	12 - 17	14
		46	Day 46 (F/U)	18 - 24	21
		53	Day 53 (F/U)	25 - 34	28
		67	Day 67 (F/U)	35 - 48	42
		81	Day 81 (F/U)	49 - 69	56
		109	Day 109 (F/U)	70 - 97	84
		137	Day 137 (F/U)	98 - 125	112
		165	Day 165 (F/U)	126 - 157	140
		200	Day 200 (F/U)	158 - end of F/U	175
		F/U final visit	End Point (F/U)	Day 1 (F/U) - end of F/U	
SIBAT (Module 1), Height	DB	1	Baseline (DB)	≤ 1 / predose	1
SIBAT (Module 2)	DB	1	Baseline (DB)	≤ 1 / predose	1
		8	Day 8 (DB)	2 - 11	8
		15	Day 15 (DB)	12 - 19	15

Table 1: Analysis Visits

Parameter	Analysis Phase	Scheduled Day	Time Interval (label on output)	Time Interval[a] (Day)	Target Time Point[a] (Day)
		25	Day 25 (DB)	20 - end of DB	25
		DB final visit	End Point (DB)	2 - end of DB	
	F/U	39	Day 39 (F/U)	Day 1 (F/U) - 27	14
		67	Day 67 (F/U)	28 - 48	42
		81	Day 81 (F/U)	49 - 69	56
		109	Day 109 (F/U)	70 - 97	84
		137	Day 137 (F/U)	98 - 125	112
		165	Day 165 (F/U)	126 - 157	140
		200	Day 200 (F/U)	158 - end of F/U	175
		F/U final visit	End Point (F/U)	Day 1 (F/U) - end of F/U	
SIBAT (Modules 3 and 5)	DB	1	Baseline (DB)	≤ 1 / predose	1
			Day 1 (DB): 4H		
		2	Day 2 (DB)	2	2
		4	Day 4 (DB)	3 - 6	4
		8	Day 8 (DB)	7 - 9	8
		11	Day 11 (DB)	10 - 12	11
		15	Day 15 (DB)	13 - 16	15
		18	Day 18 (DB)	17 - 19	18
		22	Day 22 (DB)	20 - 23	22
		25	Day 25 (DB)	24 - end of DB	25
		DB final visit	End Point (DB)	Day 1 (DB): 4H - end of DB	
	F/U	32	Day 32 (F/U)	Day 1 (F/U) - 10	7
		39	Day 39 (F/U)	11 - 17	14
		46	Day 46 (F/U)	18 - 24	21
		53	Day 53 (F/U)	25 - 34	28
		67	Day 67 (F/U)	35 - 48	42
		81	Day 81 (F/U)	49 - 69	56
		109	Day 109 (F/U)	70 - 97	84
		137	Day 137 (F/U)	98 - 125	112
		165	Day 165 (F/U)	126 - 157	140
		200	Day 200 (F/U)	158 - end of F/U	175
		F/U final visit	End Point (F/U)	Day 1 (F/U) - end of F/U	
SIBAT (Module 4)	DB	8	Day 8 (DB)	1 - 9	8
		11	Day 11 (DB)	10 - 12	11
		15	Day 15 (DB)	13 - 16	15
		18	Day 18 (DB)	17 - 19	18

Table 1: Analysis Visits

Parameter	Analysis Phase	Scheduled Day	Time Interval (label on output)	Time Interval[a] (Day)	Target Time Point[a] (Day)
		22	Day 22 (DB)	20 - 23	22
		25	Day 25 (DB)	24 - end of DB	25
		DB final visit	End Point (DB)	10 - end of DB	
	F/U	32	Day 32 (F/U)	Day 1 (F/U) - 10	7
		39	Day 39 (F/U)	11 - 17	14
		46	Day 46 (F/U)	18 - 24	21
		53	Day 53 (F/U)	25 - 34	28
		67	Day 67 (F/U)	35 - 48	42
		81	Day 81 (F/U)	49 - 69	56
		109	Day 109 (F/U)	70 - 97	84
		137	Day 137 (F/U)	98 - 125	112
		165	Day 165 (F/U)	126 - 157	140
		200	Day 200 (F/U)	158 - end of F/U	175
		F/U final visit	End Point (F/U)	Day 1 (F/U) - end of F/U	
SIBAT (Modules 6 and 7)	DB	1	Baseline (DB)	≤ 1 / predose	1
			Day 1 (DB): 4H		
		2	Day 2 (DB)	2	2
		4	Day 4 (DB)	3 - 6	4
		8	Day 8 (DB)	7 - 9	8
		11	Day 11 (DB)	10 - 12	11
		15	Day 15 (DB)	13 - 16	15
		18	Day 18 (DB)	17 - 19	18
		22	Day 22 (DB)	20 - 23	22
		25	Day 25 (DB)	24 - end of DB	25
		DB final visit	End Point (DB)	Day 1 (DB): 4H - end of DB	
	F/U	39	Day 39 (F/U)	Day 1 (F/U) - 27	14
		67	Day 67 (F/U)	28 - 48	42
		81	Day 81 (F/U)	49 - 69	56
		109	Day 109 (F/U)	70 - 97	84
		137	Day 137 (F/U)	98 - 125	112
		165	Day 165 (F/U)	126 - 157	140
		200	Day 200 (F/U)	158 - end of F/U	175
		F/U final visit	End Point (F/U)	Day 1 (F/U) - end of F/U	
SIBAT (Module 8)	DB	1	Baseline (DB)	≤ 1 / predose	1
		2	Day 2 (DB)	2	2
		8	Day 8 (DB)	3 - 11	8

Table 1: Analysis Visits

Parameter	Analysis Phase	Scheduled Day	Time Interval (label on output)	Time Interval[a] (Day)	Target Time Point[a] (Day)
		15	Day 15 (DB)	12 - 19	15
		25	Day 25 (DB)	20 - end of DB	25
		DB final visit	End Point (DB)	Day 2 (DB)- end of DB	
	F/U	39	Day 39 (F/U)	Day 1 (F/U) - 27	14
		67	Day 67 (F/U)	28 - 48	42
		81	Day 81 (F/U)	49 - 69	56
		109	Day 109 (F/U)	70 - 97	84
		137	Day 137 (F/U)	98 - 125	112
		165	Day 165 (F/U)	126 - 157	140
		200	Day 200 (F/U)	158 - end of F/U	175
		F/U final visit	End Point (F/U)	Day 1 (F/U) - end of F/U	
CDI 2:SR	DB	1	Baseline (DB)	≤ 1 / predose	1
		2	Day 2 (DB)	2	2
		25	Day 25 (DB)	3 - end of DB	25
		DB final visit	End Point (DB)	Day 2 (DB) - end of DB	
Hematology, Chemistry, Urinalysis	DB	Screening	Baseline (DB)	≤ 1	≤ 1
		25	Day 25 (DB)	2 - end of DB	25
		DB final visit	End Point (DB)	2 - end of DB	
	F/U	81	Day 81 (F/U)	Day 1 (F/U) - end of F/U	56
		F/U final visit	End Point (F/U)	Day 1 (F/U) - end of F/U	
Nasal examination	DB	Screening	Baseline (DB)	≤ 1	≤ 1
		25	Day 25 (DB)	2 - end of DB	25
		DB final visit	End Point (DB)	2 - end of DB	
Nasal symptom questionnaire	DB	1	Baseline (DB)	≤ 1 / predose	1
			Day 1 (DB): 1H		
		4	Day 4 (DB): Predose	2 - 7	4
			Day 4 (DB): 1H		
		11	Day 11 (DB): Predose	8 - 14	11
			Day 11 (DB): 1H		
		18	Day 18 (DB): Predose	15 - 21	18
			Day 18 (DB): 1H		
		25	Day 25 (DB): Predose	22 - end of DB	25
			Day 25 (DB): 1H		

Table 1: Analysis Visits

Parameter	Analysis Phase	Scheduled Day	Time Interval (label on output)	Time Interval[a] (Day)	Target Time Point[a] (Day)
Vital Signs (TEMP [predose], BP, HR, RESP [predose, 40M, 1H and 1.5H]))	DB	Screening	Screening	< 1	< 1
		1	Day 1 (DB): Predose	1 / predose	1
			Day 1 (DB): 40M		
			Day 1 (DB): 1H		
			Day 1 (DB): 1.5H		
		4	Day 4 (DB): Predose	2 - 5	4
			Day 4 (DB): 40M		
			Day 4 (DB): 1H		
			Day 4 (DB): 1.5H		
		8	Day 8 (DB): Predose	6 - 9	8
			Day 8 (DB): 40M		
			Day 8 (DB): 1H		
			Day 8 (DB): 1.5H		
		11	Day 11 (DB): Predose	10 - 12	11
			Day 11 (DB): 40M		
			Day 11 (DB): 1H		
			Day 11 (DB): 1.5H		
		15	Day 15 (DB): Predose	13 - 16	15
			Day 15 (DB): 40M		
			Day 15 (DB): 1H		
			Day 15 (DB): 1.5H		
		18	Day 18 (DB): Predose	17 - 19	18
			Day 18 (DB): 40M		
			Day 18 (DB): 1H		
			Day 18 (DB): 1.5H		
		22	Day 22 (DB): Predose	20 - 23	22
			Day 22 (DB): 40M		
			Day 22 (DB): 1H		
			Day 22 (DB): 1.5H		
		25	Day 25 (DB): Predose	24 - end of DB	25
			Day 25 (DB): 40M		
			Day 25 (DB): 1H		
			Day 25 (DB): 1.5H		
		DB final visit	End Point (DB)	Day 1 (DB): 40M - end of DB	
	F/U	200	Day 200 (F/U)	Day 1 (F/U) - end of F/U	175

Table 1: Analysis Visits

Parameter	Analysis Phase	Scheduled Day	Time Interval (label on output)	Time Interval[a] (Day)	Target Time Point[a] (Day)
ECG	DB	Screening	Baseline (DB)	< 1	< 1
		1	Day 1 (DB): 1H	1	1
		8	Day 8 (DB): 1H	2 - 16	8
		25	Day 25 (DB): 1H	17 - end of DB	25
		Maximum (DB)	Maximum (DB)	Day 1 (DB): 1H - end of DB	
		DB final visit	End Point (DB)	Day 1 (DB): 1H - end of DB	
	F/U	200	Day 200 (F/U)	Day 1 (F/U) - end of F/U	175
Pulse oximetry[c], MOAA/S[d]	DB	1	Baseline (DB)/Day 1 (DB): Predose	≤ 1 / predose	1
			Day 1 (DB): 15M		
			Day 1 (DB): 30M		
			Day 1 (DB): 45M		
			Day 1 (DB): 1H		
			Day 1 (DB): 1.25H		
			Day 1 (DB): 1.5H		
		4	Day 4 (DB): Predose	2 - 5	4
			Day 4 (DB): 15M		
			Day 4 (DB): 30M		
			Day 4 (DB): 45M		
			Day 4 (DB): 1H		
			Day 4 (DB): 1.25H		
			Day 4 (DB): 1.5H		
		8	Day 8 (DB): Predose	6 - 9	8
			Day 8 (DB): 15M		
			Day 8 (DB): 30M		
			Day 8 (DB): 45M		
			Day 8 (DB): 1H		
			Day 8 (DB): 1.25H		
			Day 8 (DB): 1.5H		
		11	Day 11 (DB): Predose	10 - 12	11
			Day 11 (DB): 15M		
			Day 11 (DB): 30M		
			Day 11 (DB): 45M		
			Day 11 (DB): 1H		
			Day 11 (DB): 1.25H		
			Day 11 (DB): 1.5H		

Table 1: Analysis Visits

Parameter	Analysis Phase	Scheduled Day	Time Interval (label on output)	Time Interval[a] (Day)	Target Time Point[a] (Day)
		15	Day 15 (DB): Predose	13 - 16	15
			Day 15 (DB): 15M		
			Day 15 (DB): 30M		
			Day 15 (DB): 45M		
			Day 15 (DB): 1H		
			Day 15 (DB): 1.25H		
			Day 15 (DB): 1.5H		
		18	Day 18 (DB): Predose	17 - 19	18
			Day 18 (DB): 15M		
			Day 18 (DB): 30M		
			Day 18 (DB): 45M		
			Day 18 (DB): 1H		
			Day 18 (DB): 1.25H		
			Day 18 (DB): 1.5H		
		22	Day 22 (DB): Predose	20 - 23	22
			Day 22 (DB): 15M		
			Day 22 (DB): 30M		
			Day 22 (DB): 45M		
			Day 22 (DB): 1H		
			Day 22 (DB): 1.25H		
			Day 22 (DB): 1.5H		
		25	Day 25 (DB): Predose	24 - end of DB	25
			Day 25 (DB): 15M		
			Day 25 (DB): 30M		
			Day 25 (DB): 45M		
			Day 25 (DB): 1H		
			Day 25 (DB): 1.25H		
			Day 25 (DB): 1.5H		
		DB final visit	End Point (DB)	Day 1 (DB): 0H - end of DB	
Weight	DB	Screening	Baseline (DB)	≤ 1	≤ 1
		25	Day 25 (DB)	2 – end of DB	25
		DB final visit	End Point (DB)	2 – end of DB	
	F/U	200	Day 200 (F/U)	Day 1 (F/U) - end of F/U	175
CADSS[e], BPRS+	DB	1	Day 1 (DB): Predose	≤ 1 / predose	1
			Day 1 (DB): 40M		

Table 1: Analysis Visits

Parameter	Analysis Phase	Scheduled Day	Time Interval (label on output)	Time Interval[a] (Day)	Target Time Point[a] (Day)
			Day 1 (DB): 1.5H		
		4	Day 4 (DB): Predose	2 - 5	4
			Day 4 (DB): 40M		
			Day 4 (DB): 1.5H		
		8	Day 8 (DB): Predose	6 - 9	8
			Day 8 (DB): 40M		
			Day 8 (DB): 1.5H		
		11	Day 11 (DB): Predose	10 - 12	11
			Day 11 (DB): 40M		
			Day 11 (DB): 1.5H		
		15	Day 15 (DB): Predose	13 - 16	15
			Day 15 (DB): 40M		
			Day 15 (DB): 1.5H		
		18	Day 18 (DB): Predose	17 - 19	18
			Day 18 (DB): 40M		
			Day 18 (DB): 1.5H		
		22	Day 22 (DB): Predose	20 - 23	22
			Day 22 (DB): 40M		
			Day 22 (DB): 1.5H		
		25	Day 25 (DB): Predose	24 - end of DB	25
			Day 25 (DB): 40M		
			Day 25 (DB): 1.5H		
YMRS	DB	1	Baseline (DB)	≤ 1	1
		8	Day 8 (DB)	2 - 16	8
		25	Day 25 (DB)	17 - end of DB	25
		DB final visit	End Point (DB)	2 - end of DB	
PWC-20	DB	25	Day 25 (DB)	1 - end of DB	25
	F/U	28	Day 28 (F/U)	Day 1 (F/U) - 4	3
		32	Day 32 (F/U)	5 - 8	7
		35	Day 35 (F/U)	9 - 11	10
		39	Day 39 (F/U)	12 - end of F/U	14
		F/U final visit	End Point (F/U)	Day 1 (F/U) - end of F/U	
TLFB	F/U	53	Day 53 (F/U)	Day 1 (F/U) - 41	28

Table 1: Analysis Visits

Parameter	Analysis Phase	Scheduled Day	Time Interval (label on output)	Time Interval[a] (Day)	Target Time Point[a] (Day)
		81	Day 81 (F/U)	42 - 115	56
		200	Day 200 (F/U)	116 - end of F/U	175
		F/U final visit	End Point (F/U)	Day 1 (F/U) - end of F/U	
C-SSRS (9 -< 12 year old)	DB	1	Baseline (DB)	≤ 1 / predose	1
			Day 1 (DB): 4 H		
		4	Day 4 (DB)	2 - 5	4
		8	Day 8 (DB)	6 - 9	8
		11	Day 11 (DB)	10 - 12	11
		15	Day 15 (DB)	13 - 16	15
		18	Day 18 (DB)	17 - 19	18
		22	Day 22 (DB)	20 - 23	22
		25	Day 25 (DB)	24 - end of DB	25
		DB final visit	End Point (DB)	Day 1 (DB): 4 H - end of DB	
	F/U	32	Day 32 (F/U)	Day 1 (F/U) - 10	7
		39	Day 39 (F/U)	11 - 17	14
		46	Day 46 (F/U)	18 - 24	21
		53	Day 53 (F/U)	25 - 34	28
		67	Day 67 (F/U)	35 - 48	42
		81	Day 81 (F/U)	49 - 69	56
		109	Day 109 (F/U)	70 - 97	84
		137	Day 137 (F/U)	98 - 125	112
		165	Day 165 (F/U)	126 - 157	140
		200	Day 200 (F/U)	158 - end of F/U	175
		F/U final visit	End Point (F/U)	Day 1 (F/U) - end of F/U	

[a] Time interval and Target time point is relative to the first day of each phase.

[b] For DB phase, 4-hour postdose time point on Day 1 and Day 25, the sleep item score is not assessed for CDRS-R and MADRS. Sleep item recorded predose on the same day will be carried forward to calculate the total score.

[c] If oxygen saturation level is < 93% at any time during the 1.5 hour postdose interval, pulse oximetry will be recorded every 5 minutes until levels return to ≥ 93% or until the subject is referred for appropriate medical care, if clinically indicated.

[d] If the MOAA/S score is ≤ 3 at any time during the 90 minute postdose interval, the MOAA/S will be performed every 5 minutes until a score of 4 is reached (at which point a frequency of every 15 minutes can be resumed until t = 90 minutes postdose). If a subject does not have a score of at least 5 at t = 90 minutes postdose, the subject should continue to be monitored. For subjects with a score of 4, the assessment should be repeated every 15 minutesand for subjects with a score of ≤ 3, the assessment should be repeated every 5 minutes until the score returns to 5 or the subject is referred for appropriate medical care, if clinically indicated.

[e] If any CADSS items are scored zero at 40 minutes, these items will not be repeated at 1.5 hours postdose.

Table 1: Analysis Visits

Parameter	Analysis Phase	Scheduled Day	Time Interval (label on output)	Time Interval[a] (Day)	Target Time Point[a] (Day)

Note: if patients early withdrew in DB phase, analysis visits for the remote contacts conducted after discountinuation in DB phase will be assigned using the window defined, however these will be denoted as RC. Assessments conducted in follow-up phase will be assigned using the visit from the protocol. If patients early withdrew in the F/U phase, analysis visits for the remote contacts which are conducted after discountinuation in F/U will be assigned using window defined as above but noted with RC. RC for remote contact will only be noted for the visits which are conducted after the early withdrawal.

2.5. Analysis Sets

Subjects will be classified into the following analysis sets: all randomized, full efficacy, safety and follow-up. These analysis sets will only include12 -< 18 year old subjects.

Subjects from site PL10006 will be excluded from the safety analysis set, full efficacy analysis set and follow-up analysis set due to non-compliance with GCP principles. However, data for this site will be presented in listings and sensitivity analyses for the primary endpoint will be provided.

2.5.1. All Randomized Analysis Set

This analysis will include all subjects who were randomized (i.e., subjects who reported a randomization date, or were assigned a randomization number) regardless of whether or not treatment was received. This analysis set will be used for summarizing the overall study completion/withdrawal information.

2.5.2. Full Efficacy Analysis Set

The efficacy analyses of data in the double-blind phase will be based on the full efficacy analysis set. The full efficacy analysis set is defined as all randomized subjects who received at least 1 dose of double-blind study medication during the double-blind phase and have both a baseline and a post dose evaluation for the CDRS-R total score.

2.5.3. Safety Analysis Set

Safety analyses for the double-blind phase will be performed on the safety analysis set. It will include all randomized subjects who receive at least 1 dose of study medication in the double-blind phase.

Screen failures and randomized subjects who received no double-blind study medication will be excluded from the safety analysis set. Subjects who received an incorrect treatment will be analyzed under the planned treatment.

2.5.4. Follow-up Analysis Set

The follow-up analysis set is defined as all subjects who completed the double-blind phase and either entered the follow-up phase or have provided adverse event data after the double-blind phase. This analysis set will be used for both efficacy and safety analyses.

2.6. Analysis for 9 - < 12 Year Old Cohort

All effcacy and safety data from the 9 - < 12 year old cohort will be summarized separately. All randomized subjects between 9-<12 years old who receive at least 1 dose of study medication in the double-blind phase will be included in these summaries. Descriptive summaries and listings will be provided for efficacy and safety variables. Continuous variables will be summarized using descriptive statistics (N, mean, standard deviation [SD], median, minimum and maximum) and categorical variables will be summarized using frequency distributions with the number and percentage of subjects in each category.

2.7. Definition of Subgroups

Descriptive statistics will be provided for the change from baseline of primary endpoint of CDRS-R total score, by the following subgroups.

- Sex
- Race (White, Black, Other)
- Country
- Region (North America, Europe, South America)
- Baseline CDRS-R total score (≤ / > median)
- Baseline SIBAT: Prior Suicide Attempt (Yes, No) (Module 1: “I have made one or more suicide attempts to end my life”)
- Baseline Suicide attempt within the last month (Yes, No)

2.8. Incomplete/Missing Dates for Adverse Events

Treatment-emergent adverse events (AEs) for the double-blind phase are those events with an onset date/time on or after the start of double-blind study medication, and occurred on or before the end of the double-blind phase. Adverse events (AEs) for the follow-up phase are those events with an onset date on or after the start of the follow-up phase, and occurred on or before the end of the follow-up phase. A conservative approach will be used to handle the missing dates for adverse events.

Onset Date

If the onset date of an adverse event is missing day only, it will be set to:

i) First day of the month that the AE occurred, if month/year of the onset of AE is different than the month/year of DB start date

ii) The day of DB start date, if the month/year of the onset of AE is the same as month/year of the DB start date and month/year of the AE resolution date is different

iii) The day of DB start date or day of AE resolution date, whichever is earliest, if month/year of the onset of AE and month/year of the DB start date and month/year of the AE resolution date are the same.

If the onset date of an adverse event is missing both day and month, it will be set to the earliest of:

i) January 1 of the year of onset, as long as this date is after the DB start date.

ii) DB start date, if this date is the same year that the AE occurred.

A completely missing onset date of an adverse event will be set to the DB start date.

Resolution Date

The missing day of resolution of an adverse event will be set to the last day of the month of resolution.

If the resolution date of an adverse event is missing both day and month, it will be set to the earlier of the date of withdrawal, study completion, or December 31 of the year.

A completely missing resolution date of an adverse event that is not recorded as ongoing will be set to the date of withdrawal or study completion.

Imputation Rules for Missing AE Time of Onset/Resolution

If the time of onset is missing, it will be imputed as follows:

i) 00:00 if the date of onset is after DB start date

ii) 00:00 if the date is the same as DB start date, but the intranasal study medication in the double-blind induction phase was started after the oral antidepressant medication in this phase

iii) The time of intranasal medication start in the double-blind induction phase if the intranasal medication was started on or before the oral antidepressant medication in this phase

If the time of resolution is missing, it will be set to 23:59.

If a missing time is associated with a partial or missing date, the date will be imputed first prior to imputing the time.

3. DATA MONITORING COMMITTEE REVIEW

In addition to investigator judgment concerning standard of care and subject safety, an external Independent Data Monitoring Committee (IDMC), comprised of individuals with appropriate pediatric expertise including pediatric psychiatric expertise, will be established to monitor data on an ongoing basis, to ensure the continuing safety of the subjects enrolled in this study. The committee will meet periodically to review safety data. After the review, the IDMC will make recommendations regarding the continuation of the study. The details will be provided in a separate IDMC charter.

The IDMC will consist of at least one medical expert in the relevant therapeutic area and at least one statistician. The IDMC responsibilities, authorities, and procedures will be documented in its charter.

4. SUBJECT INFORMATION

4.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics (Table 2) and psychiatric history at baseline (Table 3) will be summarized by treatment group for the safety and full efficacy analysis sets. Continuous variables will be summarized using descriptive statistics (N, mean, standard deviation [SD], median, minimum and maximum). Categorical variables will be summarized using a frequency distribution with the number and percentage of subjects in each category.

Table 2: Demographic Variables and Baseline Characteristics

Continuous Variables:
- Age (years)
- Baseline weight (kg)
- Baseline height (cm)
- Baseline BMI (kg/m^2) calculated as Weight (kg)/[Height (m)]^2

Categorical Variables:
- Age group[a]: 12-14, 15-17
- Sex (male, female)
- Race (White, Black or African American, Asian, American Indian or Alaskan native, Native Hawaiian or other Pacific islander, other)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)
- Baseline BMI (underweight <18.5 kg/m^2, normal 18.5 - <25 kg/m^2, overweight 25 - <30 kg/m^2, obese ≥30 kg/m^2)
- Country[a]

[a] Not requied for 9 - < 12 year old cohort

[b] If multiple race categories are indicated, then Race is recorded as “Multiple”.

Table 3: Psychiatric History at Baseline Variables

Continuous Variables:
- Baseline CDRS-R total score
- Baseline MADRS total score
- Baseline CDI 2:SR[S] total score

Categorical Variables:
- Baseline CGI-SS-R
- Baseline CGI-SR-I
- Baseline SIBAT Module 1 (“I have made one or more suicide attempts to end my life”): Prior Suicide Attempt (Yes, No)

- Baseline SIBAT Module 5 (My Risk) Question 3 "Which of the following ratings best describes your thinking about suicide right now" (patient-reported frequency of suicidal thinking)
- Baseline Suicide attempt within the last month (Y/N)
- Module 7: Assessment of Frequency of Suicidal Thinking (FoST)
- Baseline MINI: make a suicide attempt in your lifetime

Psychiatric history at baseline below (Table 3a) will be summarized for 9-<12 year old cohort.

Table 3a: Psychiatric History at Baseline Variables for 9- < 12 Year Old

Continuous Variables:
- Baseline CDRS-R total score
- Baseline MADRS total score
- Baseline CDI 2:SR[S] total score

Categorical Variables:
- Baseline CGI-SS-R
- Baseline CGI-SR-I
- Module 7: Assessment of Frequency of Suicidal Thinking (FoST)
- Baseline MINI: make a suicide attempt in your lifetime
- C-SSRS Actual attempt
- Baseline Suicide attempt within the last month (Y/N)

4.2. Disposition Information

The distribution of the number of subjects who are randomized, receive double-blind treatment, and complete the double-blind phase will be presented by treatment group. In addition, the distribution of treatment termination reasons will be presented. These summaries will be provided for the all randomized and safety analysis sets. A subject will be considered to have completed the double-blind phase if he or she has completed assessments through Day 25.

The distribution of the number of subjects who complete the study, including the follow-up phase will be presented by treatment group. The reasons for discontinuation will be summarized.

4.3. Extent of Exposure

The total duration in the double-blind phase is defined as time between the first and the last day of study medication in the double-blind phase.

Descriptive statistics (N, mean, SD, median, minimum and maximum) of total duration will be presented by treatment group for the full efficacy and safety analysis sets. The total duration of study drug exposure in the double-blind phase will also be presented using the following categories: ≤7 days, 8-14 days, 15-21 days, 22-25 days, >25 days.

A frequency distribution of the total number of dosing sessions with study medication received during the double-blind phase will be presented by treatment group. Descriptive statistics (mean, SD, median, minimum and maximum) of the total number of dosing sessions with study drug will

also be displayed. In addition, descriptive statistics (mean, SD, median, minimum and maximum) will be provided for the midazolam dose.

4.4. Protocol Deviations

Deviations that occurred during the study will be tabulated by treatment group. Major deviations will be tabulated as they are grouped by the Data Management Group prior to unblinding in the following categories: entered but did not satisfy criteria; received a disallowed concomitant treatment; received wrong treatment or incorrect dose; other; etc. More categories may be included depending on the nature of the protocol deviation.

4.5. Prior and Concomitant Medications

The number and percent of subjects receiving prior antidepressant medications will be summarized by treatment group for the safety analysis set.

The number and percent of subjects who receive concomitant therapies will be summarized by treatment group using the generic term of the medication for the safety analysis set and for the follow-up analysis set. The standard of care antidepressant treatment during the double-blind phase and the follow-up phase will also be summarized.

5. EFFICACY

An analysis of efficacy will be performed after the last subject completes the 25-day double blind treatment phase (Day 25), 8-week post-treatment follow-up phase (Day 81) and 6-month post-treatment follow-up phase (Day 200). The efficacy variables for this study are listed in Table 4.

Table 4: Efficacy Variables

Efficacy Variable		Endpoint
CDRS-R	• Change in CDRS-R from Baseline to 24 hours post first dose (Day 2)	Primary
	• Dose response at 24 hours post first dose (Day 2) and on Day 25	Other
	• Change in CDRS-R from Baseline to 4 hours post first dose (Day 1)	Other
	• Change in CDRS-R from Baseline through the end of DB treatment phase (Day 25)	Other
	• Change in CDRS-R from Baseline during the 6-month post-treatment FU phase	Other
	• Remission of CDRS-R (CDRS-R total score ≤28) at 4 hours and 24 hours post first dose, and through the end of the DB treatment phase (Day 25) and 6-month post-treatment FU phase	Other
	• Response rates (at least 50% improvement from baseline) at 4 hours and 24 hours post first dose, and through the end of the DB treatment (Day 25) and 6-month post-treatment FU phase	Other
MADRS	• Change in MADRS from Baseline to 4 hours (Day 1) and 24 hours (Day 2) post first dose	Other
	• Change in MADRS from Baseline through the end of the DB treatment phase (Day 25)	Other

	• Change in MADRS from Baseline during the 6-month post-treatment FU phase	Other
	• Remission of MADRS (MADRS total score ≤12) at 4 hours and 24 hours post first dose, and through the end of the DB treatment phase (Day 25) and 6-month post-treatment FU phase	Other
	• Response rates (at least 50% improvement from baseline) at 4 hours and 24 hours post first dose, and through the end of the DB treatment (Day 25) and 6-month post-treatment FU phase	Other
SIBAT – CGI-SS-R	• Change in CGI-SS-R from Baseline to 4 hours (Day 1) and 24 hours (Day 2) post first dose, and through the end of the DB treatment phase (Day 25) and 6-month post-treatment FU phase	Other
	• Resolution of suicidality over time	Other
SIBAT – CGI-SR-I	• Change in CGI-SR-I from Baseline to 4 hours (Day 1) and 24 hours (Day 2) post first dose, and through the end of the DB treatment phase (Day 25) and 6-month post-treatment FU phase	Other
CDI 2:SR[R]	• Change in CDI 2:SR[R] from Baseline to 24 hours post first dose (Day 2)	Other
	• Change in CDI 2:SR[R] from Baseline through the end of the DB treatment phase (Day 25) and 6-month post-treatment FU phase	Other
SIBAT – Module 3 (My Current Thinking)	• Change in SIBAT from Baseline through the end of the double-blind treatment phase (Day 25)	Other
	• Change in SIBAT from Baseline during the 6-month post-treatment FU phase	Other
SIBAT – Module 5 (My Risk) Question 3	• Change in SIBAT from Baseline through the end of the double-blind treatment phase (Day 25)	Other
	• Change in SIBAT from Baseline during the 6-month post-treatment FU phase	Other
SIBAT – Module 7 (Global Clinical Impression) FoST	• Change in SIBAT – Module 7 (Global Clinical Impression) FoST from Baseline through the end of the DB treatment phase (Day 25) and 6-month post-treatment FU phase	Other
SIBAT – Module 7 (Global Clinical Impression) CGI-SR-LT	• Change in CGI-SR-LT from Baseline through the end of the DB treatment (Day 25) and 6-month post-treatment FU phase	Other
SIBAT – Module 8 (Clinical Judgment of Optimal Suicide Management)	• Change in SIBAT – Module 8 (Clinical Judgment of Optimal Suicide Management) from Baseline through the end of the DB treatment (Day 25) and 6-month post-treatment FU phase	Other

5.1. Analysis Specifications

5.1.1. Level of Significance

A pooled sequential multiple testing procedure will be implemented to control for type I error. The esketamine 56-mg and 84-mg treatment groups will be pooled and compared with

psychoactive placebo at a 2-sided significance level of 0.05. If this comparison achieves statistical significance in favor of esketamine, the 56-mg dose and the 84-mg dose will each be simultaneously tested versus psychoactive placebo at the 2-sided significance level of 0.05 based on the closed testing procedure. Esketamine 28 mg will be tested at the 2-sided significance level of 0.05 only if both the individual doses of 56 mg and 84 mg are shown to be significant.

There will be no multiplicity adjustment for secondary endpoints.

5.1.2. Data Handling Rules

For endpoints using analysis of covariance (ANCOVA), the last observation carried forward (LOCF) method will be applied to the CDRS-R, MADRS, CGI-SS-R, CGI-SR-I and CDI 2:SR[R] for the double-blind phase and follow-up phase. If a subject does not enter the follow-up phase, double-blind observations will not be carried forward into the follow-up phase.

The last post baseline observation during the double-blind phase will be carried forward as the "End Point" for the double-blind phase. The last post baseline observation in the follow-up phase will be carried forward as the "End Point" for the follow-up phase. Besides the observed cases and the end point assessment, the LOCF values will be created for intermediate post-baseline time points as well. These imputed time points will be labeled 'DAY X(DB) LOCF'or 'DAY X (F/U) LOCF'.

5.1.3. Imputation Methods for Missing Items

Imputation of missing individual item scores will apply to MADRS and is described in Section 5.3.4.1. For all other scales where multiple items are summed to create a total, if any item of the scale is missing on one visit, the total score for that scale at that visit will be left blank.

5.1.4. Change from Baseline

For all efficacy variables changes from baseline will be determined over time for both the double-blind and the follow-up phases, using double-blind baseline.

5.2. Primary Efficacy Endpoint

5.2.1. Definition

The primary efficacy endpoint is the change in CDRS-R total score from Baseline (Day 1, predose) to 24 hours post first dose in the double-blind phase. The typical recall period for the CDRS-R is 7 days. The CDRS-R will also be administered using a since-last-assessment recall, a 4-hour recall on Day 1 and Day 25 postdose, and a 24-hour recall on Day 2. The CDRS-R is a validated 17-item, clinician-rated instrument developed to assess depressive symptomatology in children that measures the severity of a patient's depressive symptoms. The 17-item includes 14 best description items that will be determined by CDRS-R raters based on their scores from interviewing of the subject and caregiver, and 3 nonverbal behavior ratings. For the CDRS-R performed at 4 hours postdose on Days 1 and 25, the CDRS-R scores for the sleep disturbance, impaired schoolwork and difficulty having fun recorded predose on the same day will be carried forward to calculate the total score. For the CDRS-R performed at 24 hours postdose, the CDRS-R scores for impaired

schoolwork recorded at predose Day 1 will be carried forward. The 17 item scores range from 1 to 5 or 1 to 7, with a possible total score ranging from 17 to 113. A higher score represents a more severe condition.

5.2.2. Estimand

The primary estimand, the main clinical quantity of interest to be estimated in the study, is defined by the following 5 components:

- Study Intervention:

  Experimental: esketamine 28 mg, esketamine 56 mg, esketamine 84 mg

  Control: Placebo
- Population: subjects with MDD who are at imminent risk of suicide;
- Variable: change from baseline to 24 hours post first dose (Day 2) in the CDRS-R total score;
- Intercurrent event: no intercurrent events to be taken into account;
- Population-level summary: difference in mean change from baseline to 24 hours post first dose (Day 2) in the CDRS-R total score between treatment conditions.

The primary analysis will be based on the full efficacy analysis set and the CDRS-R total scores collected at Day 2 (24 hours post first dose).

5.2.3. Analysis Methods

ANCOVA

The primary efficacy endpoint, change from Baseline (Day 1, predose) to 24 hours post first dose (Day 2) in CDRS-R total score, will be analyzed using analysis of covariance (ANCOVA) with factors for treatment and analysis center and baseline CDRS-R total score as a continuous covariate. First, the pooled esketamine doses of 84 mg and 56 mg will be compared to placebo at the 2-sided 0.05 significance level using the appropriate contrast statement in SAS GLM (i.e. 0.5, 0.5, 0, -1 for esketamine doses of 84 mg, 56 mg 28 mg and placebo) If this comparison achieves statistical significance in favor of esketamine, the 56-mg dose and the 84-mg dose will each be simultaneously tested versus psychoactive placebo at the two-sided significance level of 0.05 using the ANCOVA model specified above with the appropriate contrast statetments in SAS GLM (i.e. 1, 0, 0, -1 for 84 mg vs. placebo and 0, 1, 0, -1 for 56 mg vs. placebo) Esketamine 28 mg will be tested at the two-sided 0.05 significance level using the ANCOVA model specified above with the appropriate contrast statement in SAS GLM (0, 0, 1, -1 for 28 mg vs. placebo) only if both the individual doses of 56 mg and 84 mg are shown to be significant. The treatment effects will be estimated using least square means. Point estimates and 95% confidence intervals for the treatment differences, along with the associated p-value will be provided. Since subjects are hospitalized at the time of the primary endpoint, it is anticipated that missing data will be infrequent. However, if a subject has a CDRS-R total score at a time earlier than 24 hours post first dose but does not have the 24-hour value, the earlier value will be used for the primary efficacy analysis (i.e. LOCF). In

addition, descriptive statistics (N, mean, SD, median, minimum and maximum) of the primary efficacy variable will be provided by analysis center.

Descriptive statistics (N, mean, SD, median, minimum and maximum) for the CDRS-R total score and the change from baseline will be provided for both the observed case and LOCF data during the double-blind and follow-up phases. The ANCOVA model, as described above, will also be used to analyze all other post baseline time points for both observed case and LOCF data. An additional analysis of "End Point (DB)" including remote contact data for subjects who discontinue during the double-blind phase using this ANCOVA model will be performed.

Least square mean changes (±SE) from baseline over time will be presented graphically for the double-blind and follow-up phases based on LOCF data.

Model Assumptions

The normality and equal variance assumptions underlying the ANCOVA model will be assessed graphically for the CDRS-R total score at 24 hours post first dose. Residuals from the primary model will be plotted against the predicted values and a QQ plot of the residuals versus the expected quantiles of the standard normal distribution will be presented. If either the equal variance or the normality assumption appears to be grossly violated, other methods including an ANCOVA on ranks model or an appropriate transformation of the primary endpoint might be considered.

MMRM

To assess the sensitivity of the results of the ANCOVA analysis at End Point (DB) and End Point (F/U), a mixed-effects model using repeated measures (MMRM) based on observed case data will be performed comparing treatments for the change from Baseline (Day 1, predose) to Day 25 (DB) and Day 81 (F/U) in CDRS-R total score. The model will include baseline CDRS-R total score as a continuous covariate, and treatment, analysis center, day, and day-by-treatment interaction as fixed effects, and a random subject effect. The within-subject variance between visits will be estimated via an unstructured variance-covariance matrix. In case of convergence problems, alternative variance-covariance structures will be tried in the following order, with the first structure that converges being used in the analysis: heterogeneous Toeplitz, standard Toeplitz, and AR(1) with separate subject random effect. Comparison of each esketamine group versus placebo will be performed using the appropriate contrast. Point estimates and 95% confidence intervals for the treatment differences will be provided. Least square mean changes (±SE) from baseline over time will be presented graphically for the double-blind and follow-up phase.

Sensitivity Analysis for Missing Data

If the overall missingness of the primary endpoint at 24 hours is above 15% then sensitivity analyses will be performed to assess the impact of a range of non-ignorable missingness patterns on the robustness of the ANCOVA results for the primary efficacy measure. One set of sensitivity analyses will utilize a model-based multiple imputation approach with different imputation parameter values. A range of plausible assumptions for the missing data distribution will be used to produce imputed datasets to evaluate the impact on the primary analysis. Another potential set

of sensitivity analyses will use a bootstrap-based framework, by constructing a set of missing data generating models, evaluating the primary analysis method under each of the data generating models and thereby establishing the relationship between selection bias and the missing data impact.

Additional Sensitivity Analysis

The primary efficacy endpoint will be analyzed using ANCOVA as described above with the inclusion of subjects from site LP10006 as a sensitivity analysis.

Subgroup Analyses

Forest plots will be provided displaying analysis results for each subgroup listed in Section 2.7. The point estimate of the treatment difference and its 95% confidence interval for each subgroup will be based on an ANCOVA analysis for the primary endpoint using the appropriate contrast. The model will include factors for treatment, analysis center, subgroup and treatment-by-subgroup, and baseline CDRS-R total score as a continuous covariate. Analysis center will not be included when modeling the subgroups of country and region. Additionally, the terms in the models will be adjusted for the subgroup of baseline CDRS-R total score (≤/>median). Baseline CDRS-R total score (as a continuous covariate) will not be included in the model when the dichotomized baseline CDRS-R total score is included in the model.

5.3. Other Efficacy Endpoints

5.3.1. Dose Response

5.3.1.1. Definition

The detailed definition of CDRS-R has been described in Section 5.2.1. The other efficacy endpoint based on CDRS-R is to evaluate dose response at 24 hours post first dose (Day 2) and on Day 25.

5.3.1.2. Analysis Methods

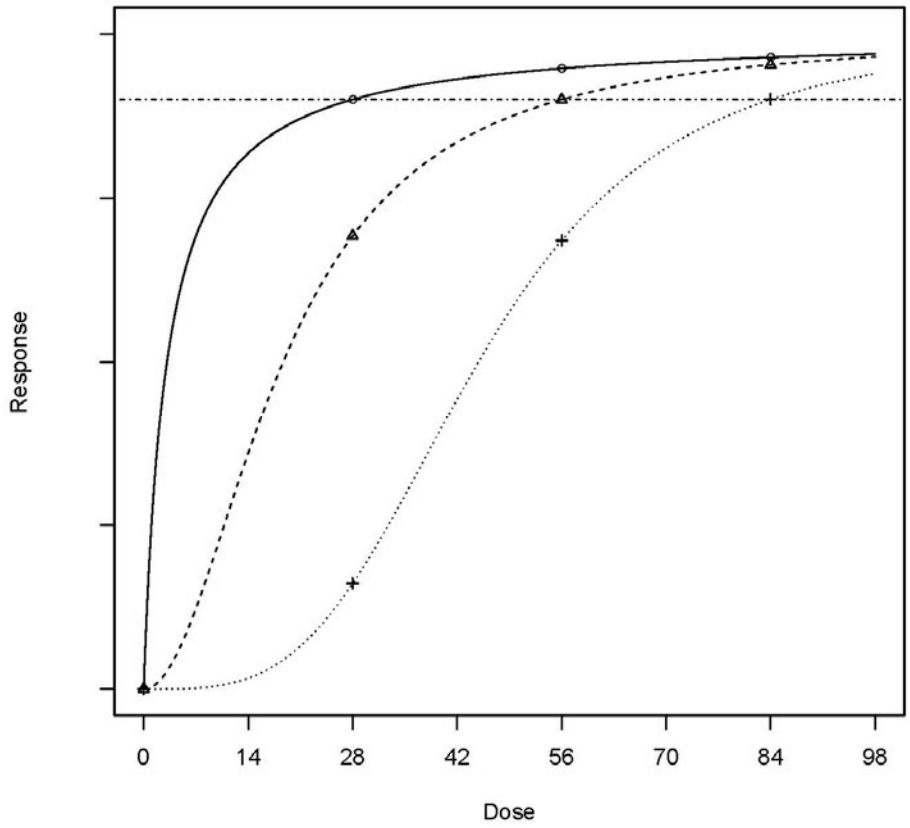
A dose response analysis for the change from baseline in CDRS-R total score at 24 hours post first dose and on Day 25 will be conducted with various dose response models.

Sigmoid E_{max} Model

In order to provide adequate sensitivity to detect a positive dose response over a range of dose-response patterns, sigmoid E_{max} model is being considered. Under the model, the placebo effect is parameterized to be zero, and therefore the value at a given dosage represents the effect of that dosage compared with placebo.

Under the most favorable scenario with the given dose range, the drug is effective at low dosages where ED_{90} is 28 mg and the sigmoid shape parameter is 1. A more realistic scenario may be the one where ED_{90} is 56 mg with 2 for the shape parameter. For the least favorable scenario with the selected dose range, ED_{90} is 84 mg, with 3.5 for the shape parameter. The dose-response curves are shown in Figure 2.

Figure 2: Dose Response Curves



A trend test statistic will be derived from an ANCOVA model on the change in CDRS-R total score, including terms for a linear trend scale, which is derived from a given dose-response curve, a factor for analysis center, and baseline CDRS-R total score as a continuous covariate. For a given dose-response curve, an optimal linear trend scale will be derived. This gives rise to 3 trend test statistics. A p-value will be derived from the maximum of the 3 trend test statistics and the multivariate normal distribution of the 3 trend statistics under the null hypothesis of no dose response. The combination test statistic is the weighted sum of the normal inverses of the triple trend test p-values.

Best Fit E_{max} model

Additional dose response analysis will be the estimation of the best fit sigmoidal E_{max} model based on the observed study efficacy data using the full efficacy analysis set, and a bootstrapping technique for the calculation of 95% confidence intervals around the estimated treatment effect for a pre-specified set of doses, including the study doses.

The sigmoidal E_{max} model is selected because of its flexibility to capture a wide range of dose-response relationships and the clear interpretation of its parameters. In this model,

$$\mu(dose) = \mu + \tau \frac{dose^{\rho}}{\left(\frac{1}{0.90}-1\right)\times ED_{90}^{\rho} + dose^{\rho}},$$

where μ measures the placebo (dose=0) response and τ measures the maximum effect of the drug.

The maximum likelihood estimates (MLE) of μ, τ, ED_{90}, and ρ are determined using a discretized approach. It can be shown that given a set of values for the ED_{90} and ρ parameters it is possible to identify the conditional MLE's of μ and τ. This is accomplished by computing a trend score for each subject based on the dose received,

$$X(dose; ED_{90}; \rho) = \frac{dose^{\rho}}{\left(\frac{1}{0.90}-1\right)\times ED_{90}^{\rho}+dose^{\rho}}.$$

The trend scores $\underline{X}$ are then used in the ANCOVA model,

$$\underline{Y} = \mu + \tau\underline{X} + \underline{C}\underline{\zeta}^{T} + \underline{e},$$

to identify the conditional MLE's of μ and τ. In the ANCOVA model Y is the vector of observed change in CDRS-R total score, C is the design matrix representing the covariates, and e is the vector of error terms, which are independent and identically distributed following a normal distribution with mean zero and common standard deviation.

A wide range of ED_{90} and ρ values are considered, and for each pair in the grid search the ANCOVA model will be fit with the corresponding trend scores. The candidate $ED_{0.90}$ values are a sequence from 14 mg [half the lowest dose in this study] to 168 mg [twice the highest dose in this study] with an increment of 7 mg [0.25 x lowest dose]. The candidate ρ values are a sequence from 0.50 to 15 with an increment of 0.25. The MLE's are obtained from the ANCOVA model selecting the one associated with the minimum Akaike's Information Criteria among all candidate models. An estimate of the treatment effect at a particular dose, including those not directly evaluated in the study, is obtained by multiplying $\hat{\tau}_{MLE}$ by the trend score $X\left(dose; ED_{90,MLE}; \rho_{MLE}\right)$.

A single dose response curve will be estimated by the weighted average of the predicted treatment effects at each dose from the best fit sigmoid E_{max} models.

Bootstrapping will be used to construct the confidence intervals for the treatment effect estimates of the selected doses[3]. The original data will be stratified by treatment group, and for each group a random sample equal in size to the original one will be drawn. For each subject, all of their data will be used. The results will comprise the MLE's of μ, τ, ED_{90}, and ρ for the sigmoidal E_{max} model that best fits the observed data, as well as the treatment effect estimates for the doses in the study. The 95% confidence intervals for the treatment effect associated with these doses will be computed and plotted against the dose level.

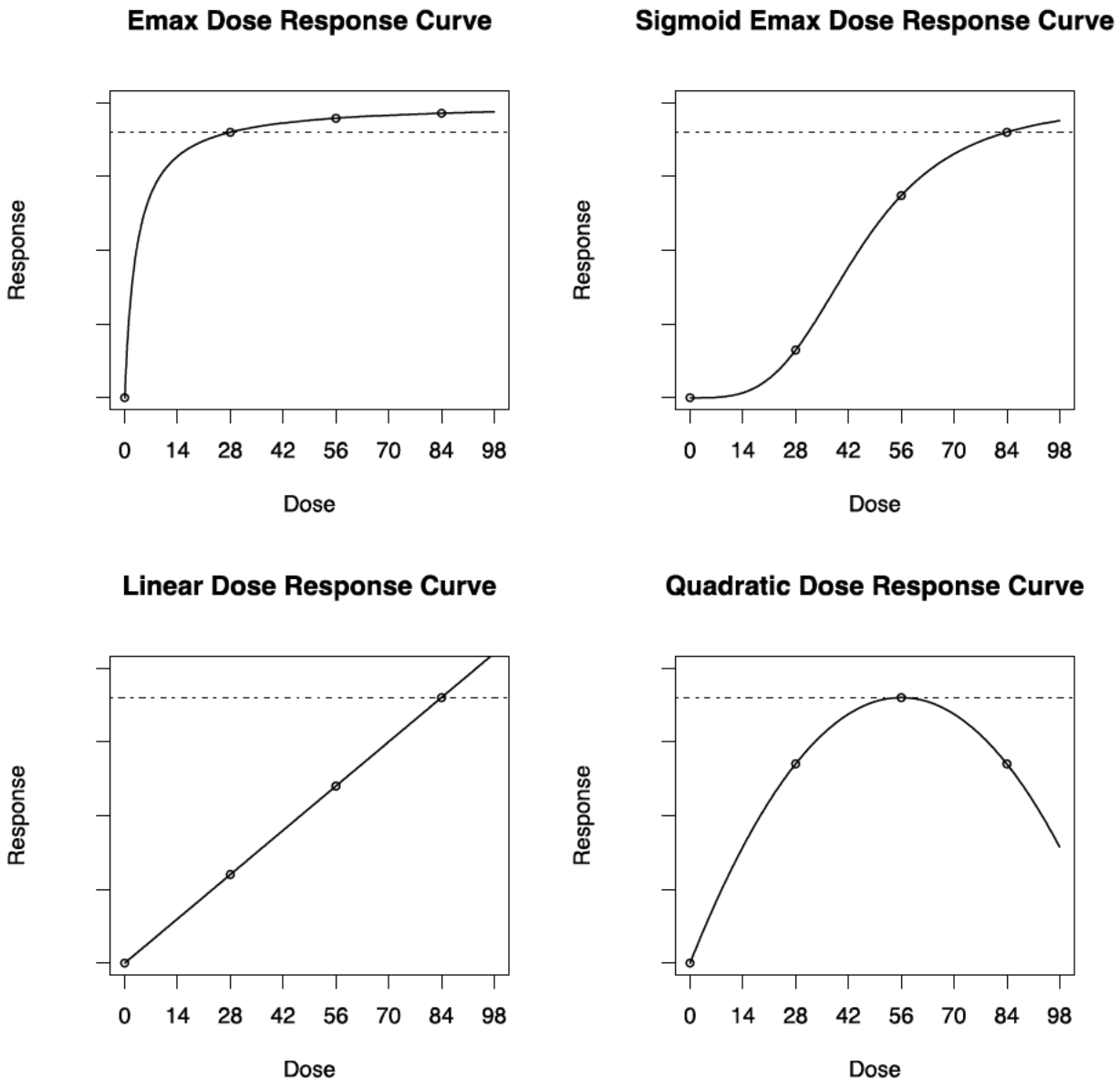
MCP-Mod Method

Additional candidate models for the dose response relationship will be investigated using the MCP-Mod procedure[1]. The set of candidate models includes sigmoid E_{max} models corresponding

to the most favorable and least favorable scenarios for the triple trend test, linear and quadratic. The quadratic covers the scenario of a non-monotonic relationship (see Figure 3).

The significance of dose response signal associated with each candidate model will be determined using trend tests with model-specific optimal contrast coefficients, based on the same ANCOVA model described for the triple-trend test. The maximum of the candidate model trend test statistics will be used to evaluate the presence of a dose-response signal, properly accounting for multiplicity. If the maximum test statistic is not significant, no dose-response relationship will be further explored. Otherwise, the model families corresponding to individual candidate models with significant trend test statistics will be fit to the observed data (including the same covariates as in the ANCOVA model as linear terms) and the one with the smallest Akaike Information Criterion (AIC) will be selected to represent the dose response relationship. Using that model a confidence interval for the response at each dose will be computed based on a bootstrap approach.

Figure 3: Candidate Models for Dose Response Relationship



A single dose response curve will be estimated by the weighted average of the predicted treatment effects at each dose from the best models, with confidence intervals derived via bootstrapping.

Spline Model

A nonparametric spline model will also be fit for the primary efficacy endpoint (change from baseline in CDRS-R total score at 24 hours post first dose and on Day 25). The spline model has the form

$$Y_i = f(d_i) + e_i$$

where i is the subject number, Y_i is the value for the primary efficacy endpoint, d_i is the dose level used in the study period, f is an unknown nonparametric function assumed to be smooth and e_i are independent, zero-mean random errors. The function f is estimated by minimizing the penalized least squares function using the penalty term for the thin-plate smoothing spline method.

The spline model will be used to estimate the response at different dose levels and bootstrap confidence intervals will be computed.

5.3.2. Remission of MDD

5.3.2.1. Definition

A subject is defined to be in remission of MDD at a given time point if the CDRS-R total score is ≤28. Subjects who do not meet such criterion or discontinue prior to the time point for any reason will not be considered to be in remission.

5.3.2.2. Analysis Methods

Frequency distributions of subjects meeting criteria for remission will be provided at each time point during the double-blind and follow-up phases. The estimates of the treatment difference in proportions and the 95% CIs will be reported at each time point.

5.3.3. Responder

5.3.3.1. Definition

The percentage change from baseline at Day X is calculated as 100*(CDRS-R total score at Day X – Baseline CDRS-R total score)/(Baseline CDRS-R total score – 17). Negative percent changes in CDRS-R total score indicate improvement (e.g., percent change ≤-50% indicates improvement ≥50%).

A subject is defined a responder at a given time point if the percent improvement in CDRS-R total score is ≥50%. Subjects who do not meet such criterion or discontinue prior to the time point for any reason will not be considered a responder.

5.3.3.2. Analysis Methods

Frequency distributions of subjects who achieve a response will be provided at each time point during the double-blind and follow-up phases. The estimates of the treatment difference in proportions and the 95% CIs will be reported at each time point.

5.3.4. MADRS

5.3.4.1. Definition

The baseline assessment and assessments during the follow-up phase use a 7 day recall period while the Day 1, 4-hour postdose assessment, together with other assessments in the double-blind

phase, use a since-last-assessment recall period. The MADRS consists of 10 items that cover all of the core depressive symptoms (apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, interest level, pessimistic thoughts, and suicidal thoughts). For the MADRS performed at 4 hours postdose on Day 1 and 25, the MADRS scores for the sleep item recorded predose on the same day will be carried forward. Each item is scored from 0 (item is not present or is normal) to 6 (severe or continuous presence of the symptom). A total score (0 to 60) is calculated by adding the scores of all 10 items. For each item as well as the total score, a higher score represents a more severe condition. If 2 or more items are missing, no imputation will be performed and the total score will be left missing. Otherwise, the total score will be calculated as the sum of the items present multiplied by the ratio of the maximum possible number of items (i.e., 10) to the number of items present.

5.3.4.2. Analysis Methods

The change from Baseline (Day 1, predose) to 24-hour postdose (Day 2) in MADRS total score will be analyzed using ANCOVA model, with factors for treatment and analysis center, and baseline MADRS total score as a continuous covariate. The treatment effects will be estimated using least square means. Point estimates and 95% confidence intervals for the treatment differences will be provided.

Descriptive statistics (mean, SD, median, minimum and maximum) for the MADRS total score and the change from baseline will be provided for both the observed case and LOCF data during the double-blind and follow-up phases. The ANCOVA model, as described above, will also be used to analyze all other post baseline time points for both observed case and LOCF data. An additional analysis will be performed of “End Point (DB)” including remote contact data for subjects who discontinue during the double-blind phase using the ANCOVA model will be performed.

Additionally, an MMRM analysis based on observed case data will be performed comparing treatments for the change from Baseline (Day 1, predose) to Day 25 (DB) and Day 81 (F/U) in MADRS total score. The model will include baseline MADRS total score as a continuous covariate, and treatment, analysis center, day, and day-by-treatment interaction as fixed effects, and a random subject effect. The within-subject variance between visits will be estimated via an unstructured variance-covariance matrix. In case of convergence problems, alternative variance-covariance structures will be tried in the following order, with the first structure that converges being used in the analysis: heterogeneous Toeplitz, standard Toeplitz, and AR(1) with separate subject random effect. Comparison of each esketamine group versus placebo will be performed using the appropriate contrast. Point estimates and 95% confidence intervals for the treatment differences will be provided.

Least square mean changes (±SE) from baseline will be presented graphically for the double-blind and follow-up phases for the ANCOVA LOCF and MMRM analyses.

Correlation between CDRS-R total scores and MADRS total scores during double-blinded phasewill be explored. Pearson correlations and 95% CI will be reported over time.

5.3.4.3. Remission of MDD

A subject is defined to be in remission of MDD at a given time point if the MADRS total score is ≤12. Subjects who do not meet such criterion or discontinue prior to the time point for any reason will not be considered to be in remission.

Frequency distributions of subjects meeting criteria for remission will be provided at each time point during the double-blind and follow-up phases. The estimates of the treatment difference in proportions and the 95% CIs will be reported at each time point.

5.3.4.4. Responder

The percentage change from baseline at Day X is calculated as 100*(MADRS total score at Day X – Baseline MADRS total score)/(Baseline MADRS total score). Negative percent changes in MADRS total score indicate improvement (e.g., percent change ≤-50% indicates improvement ≥50%).

A subject is defined a responder at a given time point if the percent improvement in MADRS total score is ≥50%. Subjects who do not meet such criterion or discontinue prior to the time point for any reason will not be considered a responder.

Frequency distributions of subjects who achieve a response will be provided at each time point during the double-blind and follow-up phases. The estimates of the treatment difference in proportions and the 95% CIs will be reported at each time point.

5.3.4.5. Dose Response

A dose response analysis for the change from baseline in MADRS total score at 24 hours post first dose and on Day 25 will be conducted with various dose response models as decribed in Section 5.3.1.

5.3.5. CGI-SS-R

5.3.5.1. Definition

One module of the SIBAT includes a revised version of the Clinical Global Impression – Severity of Suicidality. The CGI-SS-R summarizes the clinician's overall impression of severity of suicidality. The CGI-SS-R rating will be based on the totality of information available to the clinician, including information from the SIBAT. This rating operates like numerous other CGI-severity scales that have been used in other psychiatric studies. These instruments have shown clinical validity and sensitivity to change. The CGI-SS-R rating is scored on a 7-point scale from 0 (normal, not at all suicidal) to 6 (among the most extremely suicidal patients).

5.3.5.2. Analysis Methods

The change from Baseline (Day 1, predose) to 24-hour postdose (Day 2) in CGI-SS-R will be analyzed using an ANCOVA model on the ranks of change with factors for treatment and analysis center, and baseline CGI-SS-R (unranked) as a covariate. The treatment difference will be estimated using the Hodges-Lehmann estimate, which is the median of all possible paired

differences for the change from baseline for CGI-SS-R at 24 hours. Ranks of changes from baseline over time for CGI-SS-R will be analyzed based on observed case and LOCF data using an ANCOVA model with treatment and analysis center as factors, and baseline value (unranked) as a covariate. The Hodges-Lehmann estimates and the corresponding 95% CIs for the treatment differences will be provided.

CGI-SS-R will be also analyzed using un-ranked data. Changes from baseline over time for CGI-SS-R will be analyzed based on observed case and LOCF data using an ANCOVA model with treatment and analysis center as factors, and baseline value as a covariate. Point estimates and 95% confidence intervals for the treatment differences will be provided. At each time point during the double-blind and follow-up phases, a frequency distribution of the CGI-SS-R score and change from baseline will be provided for both the observed case and LOCF data. In addition, descriptive statistics (N, median, minimum, and maximum) for these scores and the changes from Baseline will be provided for both the observed case and LOCF data.

Both observed case data and LOCF frequency distributions will be presented graphically using stacked bar charts for baseline, 4-hour post first dose (Day 1), 24-hour post first dose (Day 2), and Day 25.

5.3.6. Resolution of Suicidality

5.3.6.1. Definition

A subject is defined to have achieved resolution of suicidality at a given time point if the CGI-SS-R score is 0 (normal, not at all suicidal) or 1 (questionably suicidal). Subjects who do not meet such criterion or discontinue prior to the time point for any reason will not be considered to have resolution of suicidality.

5.3.6.2. Analysis Methods

Frequency distributions of subjects meeting criteria for resolution of suicidality will be provided at each time point during the double-blind and follow-up phases. The estimates of the treatment differences in proportions and 95% CIs will be reported.

5.3.7. CGI-SR-I

5.3.7.1. Definition

One module of the SIBAT includes the Clinical Global Impression of Imminent Suicide Risk. The CGI-SR-I is a scale summarizing the clinician’s best assessment of the likelihood that the subject will attempt suicide in the next 7 days.The CGI-SR-I rating is scored on a 7-point scale from 0 (no imminent suicide risk) to 6 (extreme imminent suicide risk).

5.3.7.2. Analysis Methods

CGI-SR-I will be analyzed similarly to CGI-SS-R.

5.3.8. SIBAT – Module 3 (My Current Thinking), Module 5 (My Risk) Question 3, Module 7 (Global Clinical Impression) FoST, CGI-SR-LT, and Module 8 (Clinical Judgment of Optimal Suicide Management)

5.3.8.1. Definition

Module 3 (My Current Thinking), Question 3 (patient-reported frequency of suicidal thinking) in Module 5 (My Risk), Module 7 (Global Clinical Impression) Assessment of Frequency of Suicidal Thinking (FoST), CGI-SR-LT and Module 8 (Clinical Judgment of Optimal Suicide Management) from the SIBAT will be used to assess patient and clinician reported suicidality. Module 3 consists of 48 patient-reported items about their current thinking and takes approximately 7 minutes to complete. Each item has 6 response options ranging from "Strongly disagree" to "Strongly agree". A total score is calculated by adding the scores of all 48 items with higher values indicating higher symptomatology (Attachment 3). Question 3 from Module 5 asks patients to describe their thinking about suicide right now. There are 5 response options ranging from "I have no suicidal thoughts" to "I have suicidal thoughts all of the time." Module 7 FoST is a clinician-reported global impression with response options of "Never", "Rarely", "Sometimes", "Often", "Most of the time", and "All of the time". The CGI-SR-LT is a scale summarizing the clinician's best assessment of subjects' long-term risk for suicide. The CGI-SR-LT rating is scored on a 7-point scale from 0 (no suicide risk in the long term) to 6 (extreme risk for suicide in the long term). Module 8 asks clinicians about their assessment of the best clinical management for the subject. The score range is from 1 (No special management needed) to 10 (Psychiatric hospitalization required with constant visual observation and use of physical or chemical restraints.

5.3.8.2. Analysis Methods

Frequency distributions for Module 5 (My Risk) Question 3, Module 7 (Global Clinical Impression) FoST, CGI-SR-LT and Module 8 (Clinical Judgment of Optimal Suicide Management) will be summarized over time during the double-blind and follow-up phases. In addition, descriptive statistics for these scores and Module 3 (My Current Thinking) total score and the changes from baseline will be provided.

5.3.9. CDI 2:SR[S]

5.3.9.1. Definition

The CDI 2:SR[S] assessment is a multi-rater assessment of depressive symptoms in youth aged 7 to 17 years and an efficient screening measure that contains 12 items and takes 5 to 10 minutes to administer. The CDI 2:SR[S] has excellent psychometric properties and yields a total score that is generally very comparable to the one produced by the full-length version, Children's Depression Inventory 2 (CDI 2), a validated screening instrument for depression in children. Scoring the CDI-2 involves summing the items to obtain raw scores which are then converted to T scores and percentiles based on specific age and gender groups. The groups are separated by gender for two age groups: 7–12 and 13–17. A higher score indicates a greater problem. Interpretation of the T-scores will also fall into five categories: Very Elevated (T -score 70+), Elevated (T -score 65-69), High Average (T -score 60-64), and Average or Lower (T -score <=59) (see Attachment 1).

5.3.9.2. Analysis Methods

The change from Baseline (Day 1, predose) to 24-hour postdose (Day 2) in CDI 2:SR[S] total score will be analyzed using an ANCOVA model, with factors for treatment and analysis center, and baseline CDI 2:SR[S] score as a continuous covariate. The treatment effects will be estimated using least square means.

Descriptive statistics (mean, SD, median, minimum and maximum) for the CDI 2:SR[S] score and the change from baseline will be provided for both the observed case and LOCF data during the double-blind phase. The ANCOVA model, as described above, will also be used to analyze Day 25 for both observed case and LOCF data. Frequency distributions for categorized T-scores will be summarized.

Least square mean changes (±SE) from baseline will be presented graphically for the double-blind phase.

6. SAFETY

Safety analyses will be performed after the last subject completes the 25-day double blind treatment phase (Day 25), 8-week post-treatment follow-up phase (Day 81) and 6-month post-treatment follow-up phase (Day 200).

6.1. Adverse Events

Adverse events (AEs) are coded using the MedDRA dictionary (version 18.1 or above). Treatment-emergent adverse events (TEAEs) that occurred in the double-blind phase will be summarized by system organ class, preferred term, and treatment group. Adverse events that occurred in the follow-up phase will be summarized separately. For each AE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group.

Adverse events occurring in different phases of the study are defined as below:

- Treatment-emergent adverse events during the double-blind phase are defined as AEs with an onset during the double-blind phase. In other words, treatment-emergent AE during the double-blind phase should satisfy the condition: double-blind start date/time ≤ AE onset date/time ≤ double-blind end date. If onset time is missing and AE onset date is the same as the double-blind start date, the AE is defined to be treatment emergent in the double-blind phase.
- Adverse events during the follow up phase are defined as AEs with an onset during the follow-up phase. AEs during the follow up phase should satisfy the condition: follow-up phase start date ≤ AE onset date ≤ follow up phase end date.

A TEAE is an event that is new in onset or increased in severity following treatment initiation. An event that starts prior to, and ends after the initiation of study medication will be considered treatment-emergent only if the severity increases after the start of medication. Adverse events will not be considered treatment-emergent if they occur or increase in severity during the follow-up phase. Adverse events occurring during the follow up phase will be summarized separately. In addition, AEs will be summarized by severity and relationship to study drug using the preferred

term. For the summaries of AEs by severity/relationship to study drug, the observation with the most severe occurrence/closest relationship to study drug will be chosen if there is more than one incident of an adverse event reported during the analysis phase by the subject. The proportion of TEAEs occurring on dosing days and the proportion of TEAEs that occur on dosing days with same day resolution will be summarized. Duration and resolution time of severe TEAEs will also be summarized.

Serious AEs (SAEs) and AEs that lead to study discontinuation will be summarized separately by treatment group, system organ class, and preferred term. Data listings will also be generated for deaths, other SAEs, and discontinuations due to AEs.

Adverse Events of Special Interest

Clinically relevant TEAEs of special interest will be examined separately grouped in the following categories:

- drug abuse, dependence and withdrawal (Aggression, Confusional state, Decreased activity, Dependence, Disorientation, Dissociation, Dissociative disorder, Dizziness, Drug abuse, Drug abuser, Drug dependence, Drug use disorder, Drug detoxification, Drug diversion, Drug rehabilitation, Drug tolerance, Drug tolerance increased, Drug withdrawal convulsions, Drug withdrawal headache, Drug withdrawal syndrome, Euphoric mood, Feeling abnormal, Feeling drunk, Feeling of relaxation, Hallucination, Hallucination, auditory, Hallucination, gustatory, Hallucination, olfactory, Hallucination, synaesthetic, Hallucination, tactile, Hallucination, visual, Hallucinations, mixed, Inappropriate affect, Mental impairment, Product tampering, Psychomotor hyperactivity, Psychotic disorder, Rebound effect, Somatic hallucination, Somnolence, Substance abuse, Substance abuser, Substance dependence, Substance use, Substance use disorder, Substance-induced mood disorder, Substance-induced psychotic disorder, Thinking abnormal, Withdrawal arrhythmia, Withdrawal syndrome);
- increased blood pressure (Blood pressure increased, Blood pressure diastolic increased, Blood pressure systolic increased, Hypertensive crisis, Hypertensive emergency, Hypertension)
- increased heart rate (Heart rate increased, Tachycardia, Extrasystoles)
- transient dizziness/vertigo (Dizziness, Dizziness exertional, Dizziness postural, Dizziness procedural, Procedural dizziness, Vertigo, Vertigo labyrinthine, Vertigo positional, Vertigo CNS origin);
- impaired cognition (Cognitive disorder);
- cystitis (Allergic cystitis, Chemical cystitis, Cystitis, Cystitis erosive, Cystitis haemorrhagic, Cystitis interstitial, Cystitis noninfective, Cystitis ulcerative, Cystitis-like symptom, Pollakiuria, Dysuria, Micturition urgency, Nocturia);
- anxiety (Agitation, Anticipatory anxiety, Anxiety, Anxiety disorder, Fear, Feeling jittery, Irritability, Nervousness, Panic attack, Tension);
- Suicidality (Completed suicide, Depression suicidal, Intentional overdose, Intentional self-injury, Multiple drug overdose intentional, Poisoning deliberate, Self-injurious behavior, Self-injurious ideation, Suicidal behavior, Suicidal ideation, Suicide attempt, Suicide threat)

In addition, a summary of treatment-emergent AEs of cardiac safety (preferred terms: cardiac flutter, electrocardiogram QT prolonged, palpitations, seizure, sudden cardiac death, sudden death, syncope, torsade de pointes, ventricular arrhythmia, ventricular fibrillation, ventricular flutter, ventricular tachycardia) will be provided.

6.2. Clinical Laboratory Tests

Descriptive statistics (N, mean, median and range) for observed values and changes from baseline will be provided for clinical laboratory tests (hematology, chemistry and urinalysis) at each scheduled time point in the double-blind and follow-up phases. The baseline laboratory result is defined as the last result collected prior to Day 1 predose.

Clinical laboratory tests that meet the criteria for markedly abnormal will be listed by subject for the double-blind phase and follow-up phase. The incidence of treatment emergent markedly abnormal laboratory values that occurred at any time during the double-blind phase will be presented. Clinical laboratory test values will be considered "treatment emergent markedly abnormal" (TEMA) using the criteria defined by the Sponsor (Janssen Research & Development, LLC) listed in Attachment 2. The identification of TEMA laboratory values is based on the post-baseline value being out of range while the baseline value is either missing or within the range given in Attachment 2. If post-baseline laboratory results are above the upper limit and the baseline value is below the lower limit, then the post-baseline abnormality will also be considered TEMA. The same applies to the post-baseline value being below the lower limit with the baseline value being above the upper limit.

The incidence of subjects with ALT or AST values > 3*upper normal limit (ULN) will be presented for each study phase. Additionally, incidence of hepatic toxicity (Hy's Law[7]) defined as ALT or AST values >3*ULN AND total bilirubin values >2*ULN will be presented for the double-blind and follow up phases. Similar to the markedly abnormal analysis, only subjects with baseline ALT or AST values ≤3*ULN (AND baseline total bilirubin values ≤2*ULN for hepatic toxicity) (or if baseline value is missing) will be eligible for these analyses.

6.3. Vital Signs, Weight, and BMI

Descriptive statistics for values and changes from baseline at each scheduled time-point during the double-blind and follow-up phases will be presented for blood pressure (systolic and diastolic), pulse (heart) rate, respiratory rate, oxygen saturation, weight, temperature, and BMI. In addition, descriptive statistics of pulse rate and blood pressure (systolic and diastolic) values, changes and percent changes from predose will be provided for each dosing day. Frequency distributions of maximum percent change from predose and time of maximum percent change will also be presented for blood pressure. Note that if the maximum value within a phase occurs at multiple time points, the earliest time point is selected. Furthermore, descriptive statistics for highest value and greatest change from predose over all visits will be presented for blood pressure (systolic and diastolic).

The frequency of subjects with treatment-emergent abnormal vital signs in the double-blind and follow-up phases will be summarized. The identification of treatment-emergent abnormal vital

signs is based on the post-baseline value (a value occurring after the first study drug administration) being out of range while the baseline (DB) value is either missing or within the limits given in Table 5. If post-baseline values are above the upper limits and the baseline (DB) value is below the lower limits, then the post-baseline abnormality will also be considered treatment-emergent. The same applies to the post-baseline value being below the lower limits with the baseline value being above the upper limits. A listing of subjects meeting any of the criteria will also be provided for the double-blind phase.

Table 5: Criteria for Treatment-emergent Abnormal Vital Signs

Vital Parameter	Lower Range	Upper Range
Systolic BP (mmHg)	<86	>130
Diastolic BP (mmHg)	<50	>89
Pulse (bpm)	<50	>119

Note: The lower and upper range for pulse (bpm) in the 9 -< 12 age cohort are < 60(bpm) and > 140(bpm), respectively

In addition, descriptive statistics (N, mean, SD, median, minimum and maximum) will be provided for the maximum increase from predose at each dosing day.

Mean (+/-SE) values for systolic BP, diastolic BP and heart rate will be summarized and presented graphically over the double-blind phase by treatment group. A seperate lisitng will also be provided for the subjects of all ages whose postdose SBP or DBP measures meet withdrawal criteria (see Section 10.2. in the protocol).

A listing of subjects with oxygen saturation less than 93% will be provided.

6.4. Nasal Examination and Nasal Symptom Questionnaire

Targeted nasal examinations (including the upper respiratory tract/throat) will be conducted by a qualified healthcare practitioner. The objective of the examination at Screening is to rule out any subjects with anatomical or medical conditions that may impede drug delivery or absorption.

Subsequent examinations will consist of a visual inspection of the nostrils, nasal mucosa, and throat for nasal erythema, rhinorrhea, rhinitis, capillary/blood vessel disruption and epistaxis and graded as follows: absent, mild, moderate, or severe. Any treatment emergent change or worsening from baseline examination will be recorded as an adverse event.

A shift table for changes in rating for each examination will be presented for the double-blind phase. Changes in findings from the baseline nasal examination (including the upper respiratory tract/throat) will be listed by treatment group.

Data from the nasal symptom questionare with results of mild, modrate and severe will be provided in listing.

6.5. Electrocardiogram

The ECG variables that will be analyzed include heart rate, RR, PR interval, QRS interval, QT interval and QTc intervals. The corrected QT (QTc) intervals will include the QTcB (Bazett) and QTcF (Fridericia).

The maximum post-baseline value during the double-blind phase will be computed for each ECG parameter using data from both scheduled and unscheduled visits.

The effects on cardiovascular variables will be evaluated by means of descriptive statistics and frequency tabulations. Summary tables for values and changes from baseline will be presented at each time point during the double-blind phase.

The frequency of treatment-emergent abnormalities will be tabulated and presented for the double-blind phase. The identification of treatment-emergent abnormal ECG values is based on the post-baseline value (a value occurring after the first study drug administration) being out of range while the baseline value is either missing or within the limits given in Table 6. If post-baseline ECG results are above the upper limits (abnormally high) and the baseline value is below the lower limits (abnormally low), then the post-baseline abnormality will also be considered treatment-emergent. The same applies to the post-baseline value being below the lower limits (abnormally low) with the baseline value being above the upper limits (abnormally high). Abnormal ranges for the RR, PR, QRS and QTc intervals are given in Table 6.

Table 6: Limits for RR, PR, QRS and QTc Interval Abnormality

ECG parameter	Abnormally Low	Abnormally High
RR (msec)	< 600	> 1200
PR interval (msec)	--	> 200
QRS interval (msec)	--	> 99
QTc interval (msec)	--	> 449

Note: in the 9-<12 age cohort, the upper range is >180 msec for PR interval, and >89 msec for QRS interval.

Based on the maximum QTc value for each subject during the double-blind phase (separate for each QTc correction) the incidence of abnormal QTc values and changes from baseline will be summarized by treatment group. Criteria for abnormal corrected QT intervals and changes from baseline are given in Table 7 and are derived from the ICH E14 Guidance[4] (the same criteria apply to all QT corrections).

Table 7: Criteria for Abnormal QTc Values and Changes From Baseline

Parameter	Classification	Criteria
Clinically Significant QTc Value	No	≤500
	Yes	>500
QTc change from baseline	No concern	≤30
	Concern	>30 – 60
	Clear concern	>60
QTc value	Normal	≤450

	>450 - 480	>450 - ≤480
	>480 - 500	>480 - ≤500
	>500	>500

These criteria are based on ICH E14 Guideline

The proportion of subjects with treatment emergent abnormalities will be presented for the double-blind phase. A listing of subjects with abnormalities will also be provided.

6.6. Other Safety Parameters

6.6.1. Modified Observer's Assessment of Alertness/Sedation (MOAA/S)

The MOAA/S will be used to measure treatment-emergent sedation with correlation to levels of sedation defined by the American Society of Anesthesiologists (ASA) continuum. The MOAA/S scores range from 0 [No response to painful stimulus; corresponds to ASA continuum for general anesthesia] to 5 [Readily responds to name spoken in normal tone (awake); corresponds to ASA continuum for minimal sedation].

On each intranasal dosing day, the MOAA/S will be performed every 15 minutes from predose to 1.5 hours postdose.

If the score is ≤ 3 at any time during the 90 minute postdose interval, the MOAA/S will be performed every 5 minutes until a score of 4 is reached (at which point a frequency of every 15 minutes can be resumed until t = 90 minutes postdose).

If a subject does not have a score of at least 5 at t = 90 minutes postdose, the subject should continue to be monitored. For subjects with a score of 4, the assessment should be repeated every 15 minutes. And for subjects with a score of ≤ 3, the assessment should be repeated every 5 minutes until the score returns to 5 or the subject is referred for appropriate medical care, if clinically indicated.

Descriptive statistics of the MOAA/S score and changes from pre-dose will be summarized at each scheduled time point. In addition, the proportion of subjects experiencing sedation (score less than or equal to 3) will be presented by treatment group during the double-blind phase. A separate listing of subjects with a MOAA/S score of 0 or 1 at any time point during the double-blind phase will be presented.

Mean MOAA/S scores will be presented graphically for each dosing day.

6.6.2. Clinician Administered Dissociative States Scale (CADSS)

The Clinician Administered Dissociative States Scale (CADSS) is an instrument for the measurement of present-state dissociative symptoms and will be administered to assess treatment-emergent dissociative symptoms. On each dosing day, the CADSS will be performed predose, and at 40 minutes and 1.5 hours postdose. The CADSS comprises 23 subjective items and participant's responses are coded on a 5-point scale (0 = "Not at all", 1 = "Mild", 2 = "Moderate", 3 = 'Severe"

and 4 = "Extreme"). If any CADSS items are scored zero at 40 minutes, these items will not need to be repeated at 1.5 hours postdose. The CADSS is divided into 3 components using scoring method shown in Table 8.

Table 8: CADSS Scoring Method

Component	Questions	Range
Depersonalization	Sum of 3, 4, 5, 6, 7, 20, 23	0-28
Derealization	Sum of 1, 2, 8, 9, 10, 11, 12, 13, 16, 17, 18, 19, 21	0-52
Amnesia	Sum of 14, 15, 22	0-12
Total Score	Sum of 1 through 23	0-92

For the total score and each component, a higher score represents a more severe condition.

Descriptive statistics (N, mean, SD, median, minimum, and maximum) of the total scores and component scores at each time point and visit, along with change from the pre-dose time point within each visit, will be presented. Descriptive statistics of highest value and greatest change for the CADSS total score after dosing across all visits will be presented.

In addition, the proportion of subjects with an increase in CADSS total score from the pre-dose value at any visit during the double-blind phase will be presented by treatment group. A frequency distribution of subjects with an increase in CADSS total score >4 at any visit during the double-blinded phase will be presented by treatment group.

Mean changes in CADSS total score from pre-dose value will be presented graphically for each dosing day. Boxplots of CADSS total score over time will be provided. The highest value and greatest change for CADSS total score after dosing across visits will be presented graphically by treatment group.

6.6.3. Columbia Classification Algorithm for Suicide Assessment (C-CASA)

Responses from the SIBAT will be mapped to corresponding categories of the C-CASA (Columbia Classification Algorithm for Suicide Assessment) 2012 Plus[8,9,10]. Attachment 4 contains the mapping algorithm. Using the C-CASA 2012 Plus, potentially suicide-related events will be classified using the following 16 categories:

Suicidal Ideation (SI-1 to SI-X)

SI-1: Passive Suicidal ideation

SI-2: Active Suicidal Ideation: Non-specific (no method, intent or plan)

SI-3: Active Suicidal Ideation: method, but no intent or plan

SI-4: Active Suicidal Ideation: method and intent, but no plan

SI-5: Active Suicidal Ideation: method, intent and plan

SI-X: Active Suicidal Ideation: other

Suicidal Behavior (SB-1 to SB-5)

SB-1: Completed Suicide

SB-2: Suicide Attempt

SB-3: Interrupted Suicide Attempt

SB-4: Aborted Suicide Attempt

SB-5: Preparatory acts towards imminent suicidal behavior

Self-Injurious Behavior (SIB-1 to SIB-2)

SIB-1: Self-Injurious Behavior Without Suicidal Intent

SIB-2: Self-Injurious Behavior, Intent unknown

No Suicidal Ideation or Behavior / Not Enough Information / Other (13-17)

13: Not enough information (fatal)

14: Not enough information (non fatal)

15: Other (accidental, psychiatric medical), no deliberate self-harm

16: No suicidal ideation or behavior

17: Not mapped to categories above

A frequency distribution of the 18 categories at each scheduled time point by treatment will be provided. In addition, the proportion of subjects classified in a more severe C-CASA category compared the baseline category at any visit during the double-blind and follow-up phases will be presented by treatment group.

The most severe category for each subject will also be summarized into one of four broad categories: No suicidal ideation or behavior/Other/Not enough information, Self-Injurious behavior, Suicidal ideation, and Suicidal behavior. A frequency distribution of the most severe category during the double-blind and follow-up phases will be summarized by treatment group. Shifts from the baseline visit to the most severe category during the double-blind and follow-up phases will be summarized by treatment.

6.6.4. Brief Psychiatric Rating Scale, Positive Symptom Subscale (BPRS+)

The Brief Psychiatric Rating Scale (BPRS) is aninstrument that uses a 4-item positive symptom subscale to assess psychosis-like side effects. The BPRS+ consists of: suspiciousness, hallucinations, unusual thought content and conceptual disorganization. Each symptom is rated on a scale of 0 to 6 as follows: 0: not present, not evident or absent; 1: very mild; 2: mild; 3: moderate; 4: moderate severe; 5: severe; or 6: extreme. A total score will be derived by summing

the individual items, with a range of 0 to 24 with a higher score representing a more severe condition.
The BPRS+ is measured prior to each dose, at 40 minutes, and at 1.5 hours post dose during each of the dosing phase.

Descriptive statistics (N, median, minimum, and maximum) of the total scores at each time point, change from the pre-dose time point within each visit, and the proportion of subjects with an increase in total BPRS+ from the pre-dose value at any time during the study will be provided for double-blinded treatment phase. The proportion of subjects with a total score of 3 or more at any time during the study will also be provided. Mean changes in BPRS+ from pre-dose value will be presented graphically for each intranasal dosing day.

6.6.5. Young Mania Rating Scale (YMRS)

The treatment-emergent occurrence and severity of manic episodes will be assessed by Young Mania Rating Scale (YMRS). The YMRS has 11 items and is based on the patient's subjective report of his or her clinical condition. Additional information is based upon clinical observations made during the course of the clinical interview. There are four items that are graded on a 0 to 8 scale (irritability, speech, thought content, and disruptive/aggressive behavior), while the remaining seven items are graded on a 0 to 4 scale. These four items are given twice the weight of the others to compensate for poor cooperation from severely ill patients.

Descriptive statistics (N, mean, SD, median, minimum, and maximum) of YMRS total score (0 – 60) will be summarized at designated scheduled visit by treatment group. In addition, the proportion of subjects with a YMRS total score >12 at any post-dose time point during the double-blind phase will be presented.

6.6.6. Physician Withdrawal Checklist (PWC-20)

The PWC-20 is a 20-item simple and accurate method to assess potential withdrawal symptoms following cessation of intranasal esketamine treatment. The PWC-20 will be performed for all subjects on Day 25 to establish a baseline prior to discontinuation of esketamine treatment. If subjects withdraw early from the study during the DB phase, the PWC-20 will be conducted at the Early Withdrawal Visit. For those subjects who enter the post-treatment follow-up phase, the PWC-20 will be conducted on Day 28 (F/U), Day 32 (F/U), Day 35 (F/U) and Day 39 (F/U).

The proportion of subjects with withdrawal symptoms at the end of double-blind phase or during the follow-up phase will be presented by treatment. In addition, symptoms at follow-up will be compared to the end of double-blind phase and will be summarized using the following categories: new or worsened symptoms, symptoms present and unchanged, no symptoms, and improved.

6.6.7. Columbia Suicide Severity Rating Scale (C-SSRS) (9 -< 12 Year Old Chort)

The C-SSRS is a low-burden measure of the spectrum of suicidal ideation and behavior that was developed to assess severity and track suicidal events through any intervention (Posner 2007). It is a clinical interview providing a summary of both suicidal 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 has been used frequently in clinical studies, and is a validated, standard measure for suicidal ideation assessment. Using the C-SSRS, the outcomes will be categorized using the scoring for the 11 categories:

Suicidal Ideation (1-5)
1 Wish to be dead
2 Non-specific active suicidal thoughts
3 Active suicidal ideation with any methods (not plan) without intent to act
4 Active suicidal ideation with some intent to act, without specific plan
5 Active suicidal ideation with specific plan and intent

Suicidal Behavior (6-10)
6 Preparatory acts or behavior
7 Aborted attempt
8 Interrupted attempt
9 Actual attempt
10 Suicide

Non-suicidal self-injurious behavior (11)
11 Non-suicidal self-injurious behavior

If no events qualify for a score of 1 to 10, a score of 0 will be assigned (0="no suicidal ideation or behavior that can be assessed on the basis of C-SSRS"). A participant with a score of 11 will be considered as not having suicidal ideation or behavior.

A frequency distribution of the scores for the 11 categories will be provided at each time point for each phase.

6.6.8. Cogstate® Computerized Cognitive Battery

Please see the Attachment 5.

6.6.9. Timeline Follow-Back (TLFB)

The Timeline Follow-Back (TLFB) will be used to assess the potential for ketamine and phencyclidine (PCP) abuse during the follow-up phase. Quantitative estimates and drug use-consumption variables can be used to measure change in drug use levels in outcome monitoring. The TLFB asks clients to retrospectively estimate their drug use during the double-blink phase and capture the frequency of drug use (i.e., used or did not use).

The proportion of subjects with at least 1 yes during follow-up phase will be provided for ketamine and PCP.

7. PHARMACOKINETICS/PHARMACODYNAMICS

Details of the pharmacokinetic and pharmacodynamic analysis is provided in a separate document.

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ATTACHMENTS

Attachment 1: Scoring Guide for CDI 2:SR[S]

By Maria Kovacs, Ph.D.

CDI 2 SELF-REPORT SHORT

Name/ID: _____ Date of Birth: _____/_____/_____ (Year / Month / Day)

Age:____ Grade: _____ Sex: Male Female Today's Date: _____/_____/_____ (Year / Month / Day)

Kids sometimes have different feelings and ideas.

This form lists the feelings and ideas in groups. From each group of three sentences, pick **one** sentence that describes you best for the **past 24 hours**. After you pick a sentence from the first group, go on to the next group.

There is no right or wrong answer. Just pick the sentence that best describes the way you have been recently. Put a mark like this ☒ next to your answer. Put the mark in the box next to the sentence that you pick.

Here is an example of how this form works. Try it. Put a mark next to the sentence that describes you best.

Example:

- ❑ I read books all the time.
- ❑ I read books once in a while.
- ❑ I never read books.

Remember, for each group, pick out the sentence that describes you best in the PAST 24 HOURS.

Item 1 ❑ I am sad once in a while. ❑ I am sad many times. ❑ I am sad all the time.	**Item 7** ❑ I feel cranky all the time. ❑ I feel cranky many times. ❑ I am almost never cranky.
Item 2 ❑ Nothing will ever work out for me. ❑ I am not sure if things will work out for me. ❑ Things will work out for me O.K.	**Item 8** ❑ I cannot make up my mind about things. ❑ It is hard to make up my mind about things. ❑ I make up my mind about things easily.
Item 3 ❑ I do most things O.K. ❑ I do many things wrong. ❑ I do everything wrong.	**Item 9** ❑ I have to push myself all the time to do my schoolwork. ❑ I have to push myself many times to do my schoolwork. ❑ Doing schoolwork is not a big problem.
Item 4 ❑ I have fun in many things. ❑ I have fun in some things. ❑ Nothing is fun at all.	**Item 10** ❑ I am tired once in a while. ❑ I am tired some of the time. ❑ I am tired most of the time.
Item 5 ❑ I am important to my family. ❑ I am not sure if I am important to my family. ❑ My family is better off without me.	**Item 11** ❑ Most of the time I do not feel like eating. ❑ Some of the time I do not feel like eating. ❑ I eat pretty well.
Item 6 ❑ I hate myself. ❑ I do not like myself. ❑ I like myself.	**Item 12** ❑ I do not feel alone. ❑ I feel alone many times. ❑ I feel alone all the time.

By Maria Kovacs, Ph.D.

CDI 2 SELF-REPORT SHORT

Name/ID:_____ Date of Birth: ____/____/____ (Year / Month / Day)

Age:_____ Grade:_____ Sex: Male Female Today's Date: ____/____/____ (Year / Month / Day)

Kids sometimes have different feelings and ideas.

This form lists the feelings and ideas in groups. From each group of three sentences, pick **one** sentence that describes you best for the **past two weeks**. After you pick a sentence from the first group, go on to the next group.

There is no right or wrong answer. Just pick the sentence that best describes the way you have been recently. Put a mark like this ☒ next to your answer. Put the mark in the box next to the sentence that you pick.

Here is an example of how this form works. Try it. Put a mark next to the sentence that describes you best.

Example:

- ❑ I read books all the time.
- ❑ I read books once in a while.
- ❑ I never read books.

Remember, for each group, pick out the sentence that describes you best in the PAST TWO WEEKS.

Item 1 ❑ I am sad once in a while. ❑ I am sad many times. ❑ I am sad all the time.	**Item 7** ❑ I feel cranky all the time. ❑ I feel cranky many times. ❑ I am almost never cranky.
Item 2 ❑ Nothing will ever work out for me. ❑ I am not sure if things will work out for me. ❑ Things will work out for me O.K.	**Item 8** ❑ I cannot make up my mind about things. ❑ It is hard to make up my mind about things. ❑ I make up my mind about things easily.
Item 3 ❑ I do most things O.K. ❑ I do many things wrong. ❑ I do everything wrong.	**Item 9** ❑ I have to push myself all the time to do my schoolwork. ❑ I have to push myself many times to do my schoolwork. ❑ Doing schoolwork is not a big problem.
Item 4 ❑ I have fun in many things. ❑ I have fun in some things. ❑ Nothing is fun at all.	**Item 10** ❑ I am tired once in a while. ❑ I am tired many days. ❑ I am tired all the time.
Item 5 ❑ I am important to my family. ❑ I am not sure if I am important to my family. ❑ My family is better off without me.	**Item 11** ❑ Most days I do not feel like eating. ❑ Many days I do not feel like eating. ❑ I eat pretty well.
Item 6 ❑ I hate myself. ❑ I do not like myself. ❑ I like myself.	**Item 12** ❑ I do not feel alone. ❑ I feel alone many times. ❑ I feel alone all the time.

By Maria Kovacs, Ph.D.

CDI 2
SELF-REPORT SHORT
Scoring page

Name/ID: _____ Date of Birth: ____/____/____ (Year / Month / Day)

Age: Grade: Sex: Male Female (Circle one) Today's Date: ____/____/____ (Year / Month / Day)

Instructions:

1. Make sure only one box is marked for each item.
2. Add the numbers next to all checked boxes.
3. Write the sum in the **Total Raw Score** box.
4. Transfer the value to the Profile Form on the next page.

Item 1
- ❑ 0
- ❑ 1
- ❑ 2

Item 2
- ❑ 2
- ❑ 1
- ❑ 0

Item 3
- ❑ 0
- ❑ 1
- ❑ 2

Item 4
- ❑ 0
- ❑ 1
- ❑ 2

Item 5
- ❑ 0
- ❑ 1
- ❑ 2

Item 6
- ❑ 2
- ❑ 1
- ❑ 0

Item 7
- ❑ 2
- ❑ 1
- ❑ 0

Item 8
- ❑ 2
- ❑ 1
- ❑ 0

Item 9
- ❑ 2
- ❑ 1
- ❑ 0

Item 10
- ❑ 0
- ❑ 1
- ❑ 2

Item 11
- ❑ 2
- ❑ 1
- ❑ 0

Item 12
- ❑ 0
- ❑ 1
- ❑ 2

TOTAL RAW SCORE

By Maria Kovacs, Ph.D.

CDI 2
SELF-REPORT SHORT
Profile

Name/ID: _____ Date of Birth: ____/____/____ (Year / Month / Day)

Age:____ Grade: _____ Sex: Male Female (Circle one) Today's Date: ____/____/____ (Year / Month / Day)

Instructions:

1. Circle the Total Raw Score from the Scoring Page under the appropriate sex and age column.
2. Follow the row across to find the corresponding *T*-score and classification.
3. Transfer the *T*-score to the box on the bottom of the page.

T	Females		Total Classification	Males		*T*
	7–12	13–17		7–12	13–17	
90+	13+	19+	Very Elevated	15+	15+	90+
89						89
88		18		14	14	88
87	12					87
86						86
85		17			13	85
84				13		84
83	11					83
82		16				82
81				12	12	81
80		15				80
79	10					79
78				11	11	78
77		14				77
76						76
75	9					75
74		13		10	10	74
73						73
72		12				72
71	8			9	9	71
70						70
69		11	Elevated			69
68						68
67	7			8	8	67
66		10				66
65						65
64		9	High Average	7	7	64
63	6					63
62						62
61		8		6		61
60	5				6	60
59			Average or Lower			59
58		7				58
57				5	5	57
56	4	6				56
55						55
54				4		54
53		5			4	53
52	3					52
51						51
50		4		3	3	50
49						49
48	2	3				48
47				2		47
46					2	46
45		2				45
44	1			1		44
43		1			1	43
42						42
41						41
≤40	0	0		0	0	≤40

T =

Attachment 2: Criteria of Markedly Abnormal Laboratory Values

	Markedly Abnormal Limits	
Laboratory Parameter	Low	High
Alanine Aminotransferase (ALT) [U/L]	NA	> 3 x ULN
Albumin [g/L]	< 25	60g/L
Alkaline Phosphatase (ALP) [U/L]	NA	> 400
Aspartate Aminotransferase (AST) [U/L]	NA	> 3 x ULN
Bicarbonate [mmol/L]	< 17	> 35
Bilirubin (Total) [µmol/L]	NA	> 2 x ULN
Blood Urea Nitrogen [mmol/L]	NA	12.495
Calcium [mmol/L]	1.743	2.739
Chloride [mmol/L]	< 90	> 120
Creatine Kinase [U/L]	NA	> 3 x ULN
Creatinine [µmol/L]	NA	176.8
Gamma Glutamyl Transferase [U/L]	NA	> 3 x ULN
Glucose (Fasting) [mmol/L]	2.775	13.875
Lactate Dehydrogenase [U/L]	NA	> 3 x ULN
Phosphate [mmol/L]	0.646	1.615
Potassium [mmol/L]	< 3	> 5.5
Protein (Total) [g/L]	50 g/L	> 2 x ULN
Sodium [mmol/L]	< 130	> 155
Urate [umol/L]	89.2	594.8
Hemoglobin [g/L]	< 100	> 190
Erythrocytes (RBC) [$x10^{12}$/L]	< 3	6.6
Leukocytes (WBC) [$x10^{9}$/L]	< 2.5	> 15
Platelets [$x10^{9}$/L]	< 100	> 600

Attachment 3: SIBAT Module 3 Scoring

SIBAT Module 3: Each of the 48 items of SIBAT Module 3 has 6 response options: "Strongly Disagree", "Disagree", "Slightly Disagree", "Slightly Agree", "Agree", "Strongly Agree", with the corresponding scores listed below. The total score is calculated by adding the scores of the 48 items.

1	*I am glad to be alive.*	*5*	*4*	*3*	*2*	*1*	*0*
2	*I feel worthless.*	*0*	*1*	*2*	*3*	*4*	*5*
3	*It is difficult to control my urges to end my life.*	*0*	*1*	*2*	*3*	*4*	*5*
4	*I feel powerless to improve my situation.*	*0*	*1*	*2*	*3*	*4*	*5*
5	*My spiritual/religious beliefs prevent me from ending my life.*	*5*	*4*	*3*	*2*	*1*	*0*
6	*I wish to die in my sleep in the near future.*	*0*	*1*	*2*	*3*	*4*	*5*
7	*My concern for others prevents me from ending my life.*	*5*	*4*	*3*	*2*	*1*	*0*
8	*If I developed a life-threatening illness, I would make every effort to overcome it.*	*5*	*4*	*3*	*2*	*1*	*0*
9	*Nothing in life gives me pleasure.*	*0*	*1*	*2*	*3*	*4*	*5*
10	*I have been shamed and should die.*	*0*	*1*	*2*	*3*	*4*	*5*
11	*I feel so depressed that I would be better off dead.*	*0*	*1*	*2*	*3*	*4*	*5*
12	*I think I will end my life within the next year.*	*0*	*1*	*2*	*3*	*4*	*5*
13	*I feel lonely.*	*0*	*1*	*2*	*3*	*4*	*5*
14	*My emotional distress is so severe that I want to end my life.*	*0*	*1*	*2*	*3*	*4*	*5*
15	*I feel so stressed that it would be better if I were dead.*	*0*	*1*	*2*	*3*	*4*	*5*
16	*People or forces in the world want me to be dead.*	*0*	*1*	*2*	*3*	*4*	*5*
17	*I feel guilty about things I have done.*	*0*	*1*	*2*	*3*	*4*	*5*
18	*Others would be better off if I were dead.*	*0*	*1*	*2*	*3*	*4*	*5*
19	*There is no future for me.*	*0*	*1*	*2*	*3*	*4*	*5*
20	*I worry that there will be no one to help care for me.*	*0*	*1*	*2*	*3*	*4*	*5*
21	*I fantasize about ending my life.*	*0*	*1*	*2*	*3*	*4*	*5*
22	*I have life goals that are important to me.*	*5*	*4*	*3*	*2*	*1*	*0*
23	*I wish I were dead.*	*0*	*1*	*2*	*3*	*4*	*5*
24	*I feel trapped in my current unhappy situation.*	*0*	*1*	*2*	*3*	*4*	*5*
25	*I am a good person.*	*5*	*4*	*3*	*2*	*1*	*0*
26	*My life is hopeless and ending my life is the only way out.*	*0*	*1*	*2*	*3*	*4*	*5*
27	*There is a greater purpose for my life.*	*5*	*4*	*3*	*2*	*1*	*0*
28	*My thoughts are mixed up and I am confused.*	*0*	*1*	*2*	*3*	*4*	*5*
29	*I want to make my life a better one.*	*5*	*4*	*3*	*2*	*1*	*0*
30	*I feel neglected.*	*0*	*1*	*2*	*3*	*4*	*5*
31	*Death is the only solution to my problems.*	*0*	*1*	*2*	*3*	*4*	*5*
32	*Some people in my life give me happiness.*	*5*	*4*	*3*	*2*	*1*	*0*
33	*I am fully prepared to end my life.*	*0*	*1*	*2*	*3*	*4*	*5*

34	*Helping others gives my life purpose.*	*5*	*4*	*3*	*2*	*1*	*0*
35	*Nobody will care if I am dead.*	*0*	*1*	*2*	*3*	*4*	*5*
36	*I want to stay alive.*	*5*	*4*	*3*	*2*	*1*	*0*
37	*My physical pain is so severe that I want to end my life.*	*0*	*1*	*2*	*3*	*4*	*5*
38	*My emotional (mental) pain is so severe that I want to end my life.*	*0*	*1*	*2*	*3*	*4*	*5*
39	*I want to spend more time alone.*	*0*	*1*	*2*	*3*	*4*	*5*
40	*I feel anxious much of the time.*	*0*	*1*	*2*	*3*	*4*	*5*
41	*I feel agitated much of the time.*	*0*	*1*	*2*	*3*	*4*	*5*
42	*I feel frightened much of the time.*	*0*	*1*	*2*	*3*	*4*	*5*
43	*I am talented and skilled.*	*5*	*4*	*3*	*2*	*1*	*0*
44	*I feel in control of my life.*	*5*	*4*	*3*	*2*	*1*	*0*
45	*I am a burden to others.*	*0*	*1*	*2*	*3*	*4*	*5*
46	*I am scared of dying.*	*5*	*4*	*3*	*2*	*1*	*0*
47	*I have troubling thoughts that I cannot control.*	*0*	*1*	*2*	*3*	*4*	*5*
48	*I am having a crisis in my life.*	*0*	*1*	*2*	*3*	*4*	*5*

Attachment 4: SIBAT Mapping to the C-CASA 2012 Plus

	C-CSSRS / Expanded C-CASA Code Number	2012 C-CASA Plus Category
1	SI-1	Passive Suicidal ideation
2	SI-2	Active Suicidal Ideation: Non-specific (no method, intent or plan)
3	SI-3	Active Suicidal Ideation: method, but no intent or plan
4	SI-4	Active Suicidal Ideation: method and intent, but no plan
5	SI-5	Active Suicidal Ideation: method, intent and plan
X	SI-X	Active Suicidal Ideation: other
6	SB-1	Completed Suicide
7	SB-2	Suicide Attempt
8	SB-3	Interrupted Suicide Attempt
9	SB-4	Aborted Suicide Attempt
10	SB-5	Preparatory acts towards imminent suicidal behavior
11	SIB-1	Self-Injurious Behavior Without Suicidal Intent
12	SIB-2	Self-Injurious Behavior, Intent unknown
13	Other	Not enough information (fatal)
14	Other	Not enough information (non-fatal)
15	Other	Other (accidental, psychiatric medical), no deliberate self-harm
16	Other	No suicidal ideation or behavior
17	Other	Not mapped

Baseline

	C-CSSRS / Expanded C-CASA Code Number	2012 Expanded C-CASA Category	How SIBAT maps to 2012 C-CASA Plus Categories Lifetime (BASELINE)
1	SI-1	Passive Suicidal ideation	Inclusion: About Me: #17 = Yes Or My Current Thinking: #6, or 10, or 11, or 15, or 18, or 23, or 31 = Slightly Agree/Agree/Strongly Agree Or My Risk: #1 = 1/2/3/4 Or Exclusion: About Me: #18 = Yes Or My Risk/Protective Factors: #7, 15, or 19 = rarely, sometimes, often, most of the time, all the time Or My Current Thinking #3, 12, 14, 21, 26, 33, 37 or 38 = Slightly Agree/Agree/Strongly Agree Or My Risk: #2 or 3 = 1 /2 /3 /4 Or My Risk: #4 = 2 /3 /4 Or My Risk: #5 = 3 / 4

	C-CSSRS / Expanded C-CASA Code Number	2012 Expanded C-CASA Category	How SIBAT maps to 2012 C-CASA Plus Categories Lifetime (BASELINE)
2	SI-2	Active Suicidal Ideation: Non-specific (no method, intent or plan)	Inclusion: About Me: #18b = Yes Or My Risk/Protective Factors: #7, 15, or 19 = rarely, sometimes, often, most of the time, all the time Or My Current Thinking: #3, 12, 14, 21, 26, 33, 37, or 38 (Slightly Agree/Agree/Strongly Agree) Or My Risk: #2 or 3 = 1 /2 /3 /4 Or My Risk: #5 = 3 / 4 Exclusion: About Me: #18c or 18d or 18g or 18h or 18j or 18k = Yes Or My Risk: #4 = 2 /3 /4
3	SI-3	Active Suicidal Ideation: method, but no intent or plan	Inclusion: About Me: #18 and 18d = Yes Exclusion: About Me: #18c, or 18g or 18h or 18j or 18k = Yes Or My Risk: #4 = 2 /3 /4
4	SI-4	Active Suicidal Ideation: method and intent, but no plan	Inclusion: About Me: #18 and 18c = Yes or My Risk: #4 = 2 /3 /4 AND About Me 18d = Yes Exclusion: About Me: #18g or 18h or 18j or 18k = Yes
5	SI-5	Active Suicidal Ideation: method, intent and plan	Inclusion: About Me: #18 and 18c = Yes or My Risk: #4 = 2 /3 /4 AND About Me 18d=Yes AND About Me (18g or 18h or 18j or 18k) = Yes Exclusion: None
X	SI-X	Active Suicidal Ideation: Other	Inclusion: About Me: #18b = Yes Or My Risk/Protective Factors: #7, Or 15, Or 19 = rarely, sometimes, often, most of the time, all the time Or My Current Thinking: #3, OR 12, OR 14, OR 21, OR 26, OR 33, OR 37, OR 38 (Slightly Agree/Agree/Strongly Agree) Or My Risk: #2 = 1/2/3/4 Or My Risk: #3 = 1 /2 /3 /4 Or My Risk: #4 = 2 /3 /4 Or My Risk: #5 = 3 / 4 Or About Me: #18c or 18d or 18g or 18h or 18j or 18k = Yes Exclusion: Map to any of the following categories: SI-2, OR SI-3, OR SI-4, OR SI-5
6	SB-1	Completed Suicide	Inclusion: Not Applicable
7	SB-2	Suicide Attempt	Inclusion: About Me: #18L = Yes Exclusion: None
8	SB-3	Interrupted Suicide Attempt	Inclusion: About Me: #18v= Yes Exclusion: None
9	SB-4	Aborted Suicide Attempt	Inclusion: About Me: #18s = Yes Exclusion: None

	C-CSSRS / Expanded C-CASA Code Number	2012 Expanded C-CASA Category	How SIBAT maps to 2012 C-CASA Plus Categories Lifetime (BASELINE)
10	SB-5	Preparatory acts towards imminent suicidal behavior	Inclusion: About Me: #18i or 18j= Yes Exclusion: None
11	SIB-1	Self-Injurious Behavior Without Suicidal Intent	Inclusion: About Me: #19 = Slightly Agree/Agree/Strongly Agree Exclusion: None
12	SIB-2	Self-Injurious Behavior, Intent unknown	Inclusion: About Me: #19 'not sure' Exclusion: None
13	Other	Not enough information (fatal)	Inclusion: Not Applicable Exclusion: None
14	Other	Not enough information (non-fatal)	Inclusion: Not Applicable Exclusion: None
15	Other	Other (accidental, psychiatric medical), no del berate self-harm	Inclusion: About Me: (#14 or 15 = Yes) AND (#18L = No AND #19 = Never) Exclusion: None
16	Other	No suicidal ideation or behavior	Inclusion: My Current Thinking: # 12 and 23 = Disagree/Strong Disagree Exclusions: About Me: #17 or #18 = Yes Or My Risk/Protective Factors: #7, 15, and 19 = rarely, sometimes, often, most of the time, all the time Or My Current Thinking #3 or 6 or 10 or 11 or 12 or 14 or 15 or 18 or 21 or 23, or 26, or 31, or 33 or 37 or 38 = Slightly Agree/Agree/Strongly Agree Or My Risk: #1 or 2 or 3 = 1 /2 /3 /4 Or My Risk: #4 = 2 /3 /4 Or My Risk: #5 = 3 / 4
17	Other	Not Mappable	Y: If mapping to C-CASA Code Number 1 and 2 and 3 and 4 and 5 and 6 and 7 and 8 and 9 and 10 and 11 and 12 and 13 and 14 and 15 and 16 and X = No or missing, then YES N: If not YES, then NO

Initial Most Severe category:
SI: 5 > 4 > X > 3 > 2 > 1
SB: 6 > 7 > 8 > 9 > 10
SIB: 12 > 11

Overall severity determination: 6 > 7 > 8 > 9 > 10 > 5 > 4 > X > 3 > 2 > 1 > 12 > 11 > 13 > 14 > 16 > 15 > 17

If both inclusion and exclusion criteria are met, the exclusion criterion takes precedence over the inclusion criterion and the mapping condition is NOT met.

Post-Baseline

	C-CSSRS / Expanded C-CASA Code Number	2012 Expanded C-CASA Category	How SIBAT maps to 2012 C-CASA Plus Categories Post Baseline
1	SI-1	Passive Suicidal ideation	Inclusion: My Current Thinking: #6, or 10, or 11, or 15, or 18, or 23, or 31 = Slightly Agree/Agree/Strongly Agree Or My Risk: #1 = 1/2/3/4 Exclusion: My Risk/Protective Factors: #7, 15, or19 = rarely, sometimes, often, most of the time, all the time Or My Current Thinking #3, 12, 14, 21, 26, 33, 37 or 38 = Slightly Agree/Agree/Strongly Agree Or My Actions: #10 = Yes Or My Risk: #2 or 3 = 1 /2 /3 /4 Or My Risk: #4 = 2 /3 /4 Or My Risk: #5 = 3 / 4
2	SI-2	Active Suicidal Ideation: Non-specific (no method, intent or plan)	Inclusion: My Risk/Protective Factors: #7, 15, or 19 = rarely, sometimes, often, most of the time, all the time Or My Current Thinking: #3, 12, 14, 21, 26, 33, 37, or 38 = Slightly Agree/Agree/Strongly Agree Or My Actions: #10 a = Yes Or My Risk: #2 or 3 = 1 /2 /3 /4 Or My Risk: #5 = 3 / 4 Exclusion: My Actions: #10b or 10c or 10d or 10g = Yes, or #10e is any answer other than 'NO' Or My Risk: #4 = 2 /3 /4
3	SI-3	Active Suicidal Ideation: method, but no intent or plan	Inclusion: My Actions: #10c = Yes Exclusion: My Actions: #10b or 10d or 10g = Yes, or #10e is any answer other than 'NO' Or My Risk: #4 = 2 /3 /4
4	SI-4	Active Suicidal Ideation: method and intent, but no plan	Inclusion: My Actions: (# 10b or 10g = Yes) or My Risk: #4 = 2 /3 /4 AND My Actions 10c = Yes Exclusion: My Actions: #10d = Yes, or #10e is any answer other than 'NO'
5	SI-5	Active Suicidal Ideation: method, intent and plan	Inclusion: My Actions: (# 10b or 10g = Yes) or My Risk: #4 = 2 /3 /4 AND My Actions 10c = Yes AND My Actions (#10d = Yes or #10e is any answer other than 'NO') Exclusion: None

	C-CSSRS / Expanded C-CASA Code Number	2012 Expanded C-CASA Category	How SIBAT maps to 2012 C-CASA Plus Categories Post Baseline
X	SI-X	Active Suicidal Ideation: other	Inclusion: My Risk/Protective Factors: #7, or 15, or 19 = rarely, sometimes, often, most of the time, all the time Or My Current Thinking: #3, OR 12, OR 14, OR 21, OR 26, OR 33, OR 37, or 38 (Slightly Agree/Agree/Strongly Agree) Or My Actions: #10 a = Yes Or My Risk: #2 or 3 = 1 /2 /3 /4 Or My Risk: #4 = 2 /3 /4 Or My Risk: #5 = 3 / 4 Or My Actions: #10b or 10c or 10d or 10g = Yes, or #10e is any answer other than 'NO' Exclusion: Map to any of the following categories: SI-2, OR SI-3, OR SI-4, OR SI-5
6	SB-1	Completed Suicide	Inclusion: Introduction: Response 1a1 Exclusion: None
7	SB-2	Suicide Attempt	Inclusion: Introduction: Response 1a4 Or My Actions: #3 or 5 = Yes Exclusion: None
8	SB-3	Interrupted Suicide Attempt	Inclusion: My Actions: #8 = Yes Exclusion: None
9	SB-4	Aborted Suicide Attempt	Inclusion: My Actions: #7= Yes Exclusion: None
10	SB-5	Preparatory acts towards imminent suicidal behavior	Inclusion: My Actions: # 10f or 10g = Yes Exclusion: None
11	SIB-1	Self-Injurious Behavior Without Suicidal Intent	Inclusion: My Actions: # 2 = Yes AND #3 = No Or My Actions: # 4 = Yes AND #3 = No Or My Actions: #9= Yes Exclusion: None
12	SIB-2	Self-Injurious Behavior, Intent unknown	Inclusion: My Actions: (Either #2 or 4 = Yes) AND #3 = Uncertain) Or My Actions: #9 = Uncertain Exclusion: None
13	Other	Not enough information (fatal)	Inclusion: Introduction: Response 1a2 or 1a3 Exclusion: None
14	Other	Not enough information (non-fatal)	Inclusion: Introduction: Response 1a6 Exclusion: None
15	Other	Other (accidental, psychiatric medical), no del berate self-harm	Inclusion: My Actions: #1 = No Or My Actions: #1 = Yes AND (My Actions #2 and 3 = No) Or Introduction: Response 1a5 Exclusion: None

	C-CSSRS / Expanded C-CASA Code Number	2012 Expanded C-CASA Category	How SIBAT maps to 2012 C-CASA Plus Categories Post Baseline
16	Other	No suicidal ideation or behavior	Inclusion: My Current Thinking: #12 and 23 = Disagree/Strong Disagree Exclusion: My Risk/Protective Factors: #7, 15, or 19 = rarely, sometimes, often, most of the time, all the time Or My Current Thinking #3 or 6 or 10 or 11 or 12 or 14 or 15 or 18 or 21 or 23, or 26, or 31, or 33 or 37 or 38 = Slightly Agree/Agree/Strongly Agree Or My Actions: #3 or 5 or 7 or 8 or 10 = Yes Or My Risk: #1 or 2 or 3 = 1 /2 /3 /4 Or My Risk: #4 = 2 /3 /4 Or My Risk: #5 = 3 / 4
17	Other	Not mapped	Y: If mapping to C-CASA Code Number 1 and 2 and 3 and 4 and 5 and 6 and 7 and 8 and 9 and 10 and 11 and 12 and 13 and 14 and 15 and 16 and X = No or missing, then YES N: If not YES, then NO

Initial Most Severe category:
SI: 5 > 4 > X > 3 > 2 > 1
SB: 6 > 7 > 8 > 9 > 10
SIB: 12 > 11

Overall severity determination: 6 > 7 > 8 > 9 > 10 > 5 > 4 > X > 3 > 2 > 1 > 12 > 11 > 13 > 14 > 16 > 15 > 17

If both inclusion and exclusion criteria are met, the exclusion criterion takes precedence over the inclusion criterion and the mapping condition is NOT met.

Attachment 5: SAP for Cognition Tests