Janssen Pharmaceutical K.K.

Statistical Analysis Plan

A Randomized, Double-blind, Multicenter, Placebo-controlled Study to Evaluate the Efficacy, Safety and Tolerability of Fixed Doses of Intranasal Esketamine in Japanese Subjects With Treatment Resistant Depression

Protocol 54135419TRD2005; Phase 2b

JNJ-54135419 (esketamine**)**

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

TABLE OF CONTENTS

AMENDMENT HISTORY

SAP Version	Issue Date
Original SAP	20 Oct 2017
Amendment 1	29 June 2018
Amendment 2	10 Sep 2019
Amendment 3	14 Jan 2020

Amendments below are listed beginning with the most recent amendment.

Amendment 3 (14 Jan 2020)

The overall reason for the amendment: to add additional PK/PD analysis

Applicable Section(s)	Description of Change (s)
Section 2.3	In visit window: Added week 6 (PT) and week 8 (PT) for PWC-20
Section 6.1	Added timepoints to boxplots
Section 6.2	PK/PD analysis: a) Added a safety parameter (CADSS total score); b) Added changes from predose for CADSS, SBP and DBP, changes from baseline for QTcF; c) By phases

Amendment 2 (10 Sep 2019)

The overall reason for the amendment: to update and clarify the details

Applicable Section(s)	Description of Change (s)
Section 2.3	In visit window: a) corrected the baseline for OL phase, 'Baseline (DB)' to 'Baseline (OL). b) updated HR to PULSE under vital signs part
Section 2.5	Added subgroup 'Concomitant use of benzodiazepine including sleep aids (Y/N)'
Sections 2.5, 3.1	Added '1' to the number of major depressive episodes (allowed enrollment of subjects with single episodes in protocol amend 4) Added "Had been considered to be eligible for electroconvulsive therapy (Y/N)" Clarified the definition for previous treatment as 'Number of Previous Treatments in Current Episode'.
Section 3.1	Added 'Functional Impairment based on Baseline SDS Total Score (not impaired [0-3], mild [4-11], moderate [12-19], marked [20-26] or extreme [27-30])'
Section 3.3	Clarified the rule of mode dose by adding 'The lowest mode dose is selected in case of ties'
Section 4.2.3.1	Specified the denominator degrees of freedom method
Section 4.3.3.2	Time to relapse analysis by combined esketamine groups and placebo is added
Section 5.1	AE of special interest has been updated to follow global phase 3 trials.

Amendment 1 (29 June 2018)

The overall reason for the amendment: to update analysis phases by separating posttreatment phase from double-blind follow-up phase

Applicable Section(s)	Description of Change (s)
Section 2.1	Updated analysis phases. 'A Double-blind Follow-up Phase' is splitted into 'A Double-blind Follow-up Phase (Non-Responders or subjects who withdraw from DB induction phase)' and 'A Posttreatment Phase (Responders only). Updated the definition of analysis phases and the start and end dates.
Sections 2.4.3, 2.4.4	Updated analysis sets based on analysis phases.
Section 2.5	Removed subgroup 'Concomitant use of Adjunctive antipsychotics (Y/N)'
Sections 2.5, 3.1	Excluded sleep aids from benzodiazepine.
Section 4.2.3.3	To follow TRD2003, the method to select the dose-response model is changed from 'Tmax' to 'AIC'. One candidate model changed from exponential(δ=-58.2) to exponential(δ=58.2).
Section 5.1	Added additional analysis for AE AE of special interest has been updated to follow global phase 3 trials
Section 5.3	Added additional analysis for vital signs.
Sections 5.5.4, 5.5.6, 5.5.7	Added additional analysis for MOAA/S, PWC-20 and POMS-2

ABBREVIATIONS

AD	antidepressant
AE	adverse event
ANCOVA	analysis of covariance
ASA	American Society of Anesthesiologists
BMI	body mass index
BP	Blood Pressure
BPRS+	Four-item positive symptom subscale of the Brief Psychiatric Rating Scale
CADSS	Clinician Administered Dissociative States Scale
CGADR	Clinical Global Assessment of Discharge Readiness
CGI-S	Clinical Global Impression – Severity
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
DB	Double-blind
D/C	discontinued
ECG	Electrocardiogram
eCRF	electronic case report form
F/U	Follow-Up
GAD-7	Generalized Anxiety Disorder 7-item scale
ICH	International Conference on Harmonization
LOCF	last observation carried forward
MADRS	Montgomery-Asberg Depression Rating Scale
MDD	major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effects model using repeated measures
MOAA/S	Modified Observer's Assessment of Alertness/Sedation
OL	open-label
PBO	placebo
PD	Pharmacodynamics
PK	pharmacokinetic(s)
PWC-20	Physician Withdrawal Checklist; 20 item
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SDS	Sheehan Disability Scale
SE	standard error
SNRI	Serotonin and Norepinephrine Reuptake Inhibitors
SSRI	Selective Serotonin Reuptake Inhibitors
TEAE	Treatment-emergent adverse event
TEMA	treatment-emergent markedly abnormal
TRD	Treatment Resistant Depression
ULN	upper limit of normal
XR	extended release

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for all planned analyses for the clinical study report (CSR) for study 54135419TRD2005.

This SAP does not include planned analyses on biomarkers or pharmacogenomics data which will be specified as appropriate in separate documents.

1.1. Trial Objectives

Primary Objective

The primary objective of the study is to evaluate the efficacy of fixed dosed intranasal esketamine compared to intranasal placebo, as an add-on to an oral antidepressant in Japanese subjects with treatment-resistant depression (TRD), in improving depressive symptoms.

Secondary Objective

- To assess the effect of intranasal esketamine compared with intranasal placebo as an add-on to an oral antidepressant in Japanese subjects with TRD, including the following parameters:
  - Dose response;
  - Depression response rates;
  - Depression remission rates;
  - Onset of clinical response;
  - Overall severity of depressive illness;
  - Anxiety symptoms;
  - Functioning and associated disability.
- To investigate the safety and tolerability of intranasal esketamine compared with intranasal placebo as an add-on to an oral antidepressant in Japanese subjects with TRD, including the following parameters:
  - TEAEs, including AEs of special interest;
  - Potential withdrawal or rebound symptoms or both following cessation of intranasal esketamine treatment;
  - Perceptual changes (dissociative symptoms);
  - Effects on alertness and sedation;
  - Effects on heart rate, blood pressure, respiratory rate, and blood oxygen saturation;
  - Potential effects on suicidal ideation/behavior;
  - Potential abuse-liability;
  - Potential psychosis-like effects.

- To evaluate the durability of intranasal esketamine as an add-on to an oral antidepressant in Japanese subjects with TRD, with attention to:
  - Time to relapse in the posttreatment phase for subjects in remission and for subjects who respond but are not in remission, at the end of the double-blind induction phase.
- To evaluate the PK of intranasally administered esketamine in Japanese subjects with TRD

Exploratory Objective

- To assess the comparability of the efficacy and safety of intranasal esketamine as an add-on to an oral antidepressant between the double-blind and open-label intranasal esketamine induction treatment courses;
- To evaluate the PK/PD relationship of intranasal esketamine and MADRS total score (and possibly selected AEs as additional PD parameters) in Japanese subjects with TRD;
- To examine the relationship between deoxyribonucleic acid (DNA) single nucleotide polymorphisms (SNPs) (including, but not limited to BDNF) with clinical outcome to intranasal esketamine in Japanese subjects with TRD;
- To assess the potential relationship of biomarkers with response, maintenance, relapse, and nonresponse to intranasal esketamine in Japanese subjects with TRD.

1.2. Trial Design

This is a randomized, double-blind, placebo-controlled, multicenter study designed to evaluate the efficacy, safety and tolerability of fixed dose of intranasal esketamine (28 mg, 56 mg, or 84 mg) as an add-on therapy to an oral antidepressant in Japanese subjects with TRD. A total of 183 subjects are planned to be enrolled in this study.

The study consists of the following phases: a screening phase (up to 4 weeks); a 6-week prospective oral antidepressant lead-in phase; a 4-week double-blind induction phase; a posttreatment phase (up to 24 weeks comprising of only oral antidepressant therapy), including an optional 4-week open-label induction phase; and a 4-week follow-up phase.

Thus, the duration of a subject's participation will be a maximum of 42 weeks, depending on whether they meet phase-specific criteria for response or relapse. The end-of-study (EOS) will occur when the last subject in the study completes his/her last study assessment (ie, last follow-up Visit).

Screening Phase

Japanese men and women aged 20 to 64 years old (both inclusive), who meet Diagnostic and Statistical Manual of Mental Disorders (fifth edition) (DSM-5) diagnostic criteria for recurrent major depressive disorder (MDD) without psychotic features, based upon clinical assessment, and confirmed by the MINI will be screened according to the inclusion/exclusion criteria.

To confirm eligibility for participation in the prospective lead-in phase, subjects will have a review of the inclusion/exclusion criteria in the screening phase. Subjects must not have responded to ≥1 but <5 different oral antidepressants taken at adequate dosage and for adequate

duration, as assessed on the Massachusetts General Hospital – Antidepressant Treatment Response Questionnaire (MGH-ATRQ) and documented by medical history/prescription records, for the current episode of depression. The subject's current major depressive episode, depression symptom severity (MADRS total score ≥28 required), and treatment response to antidepressant medication used in the current episode (retrospectively assessed) must be deemed valid for participation in the clinical study based on the SAFER interview, which is administered by a remote, independent rater. At the screening visit, subjects who continue to fulfill all inclusion criteria and none of the exclusion criteria will be enrolled.

SAFER interview will be conducted as early as feasible during the screening period, preferably in the first week after signing of informed consent form (ICF) before down-titration of antidepressants to avoid change of depressive symptoms because of tapering.

Subject's current antidepressant treatment(s), including adjunctive treatment for MDD, should be tapered and discontinued in this phase per the local prescribing information. Down-titration of antidepressants will be started after SAFER interview and will be completed in the screening phase basically. However, if clinically indicated, cross-tapering is allowed. Cross-tapering is defined as discontinuation of previous antidepressant treatment(s) by lowering the dose(s) per the local prescribing information and simultaneously increasing the dose of single new antidepressant treatment within the first 2 weeks of the prospective lead-in phase.

The subject's current antidepressant treatment(s) will not be discontinued for the sole purpose of participating in the study.

Prospective Lead-in Phase

After enrollment, eligible subjects will enter the 6-week OL prospective lead-in phase during which, subjects will receive a new antidepressant therapy (physician determined) daily for the duration of this phase.

The oral antidepressant will be 1 of the following: selective serotonin reuptake inhibitors or serotoninspecific reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), ormirtazapine (ie, escitalopram, paroxetine controlled-release [CR], sertraline, duloxetine, venlafaxine extended-release [XR], or mirtazapine), which the subject has not previously had a nonresponse to in the current depressive episode or has not been previously intolerant to (lifetime).

In the last 4 weeks during the prospective lead-in phase, 'oral antidepressant' must be single treatment of switched new oral antidepressant. New oral antidepressant treatment should be titrated to the approved maximum dose, to optimize the potential for response. The up-titration schedule should be per prescribing information. The dose, which is above the minimum therapeutic dose defined in MGH-ATRQ should be kept at last 4 weeks during the prospective lead-in phase, in case they start at lower doses.

The criteria of TRD is defined as nonresponse (≤25% improvement) to at least 1 antidepressant treatment determined retrospectively and 1 antidepressant prospectively in the current episode of

depression. After 6 weeks, subjects who are nonresponders to the new oral antidepressant treatment at the end of the prospective lead-in phase can be eligible to proceed to the double-blind induction phase. Nonresponse at the end of the prospective lead-in phase is defined as ≤25% improvement in the MADRS total score from Visits 2.1 to each of Visit 2.3 and 3.1 (prerandomization) respectively, and a MADRS total score of ≥28 on each of the Visits 2.1, 2.3, and 3.1 (prerandomization). Assessment of antidepressant treatment response at the end of the prospective lead-in phase will be performed by investigators. All other subjects who do not proceed to the double-blind induction phase will end study participation at this time. No follow-up or further study visits will be performed for these subjects. All subjects who are discontinued must be treated with an oral antidepressant after completion of the study, unless it is clinically inappropriate.

MADRS assessment throughout the study will be performed by an independent, remote, blinded rater. The remote MADRS interviews will be recorded to assess accuracy and thoroughness of the interviews and measure overall quality assurance.

Double-blind Induction Phase

The 4-week fixed dose double-blind induction phase will start on Day 1 and end at Day 28. A total of 183 subjects will be randomly assigned in a 2:1:1:1 ratio to receive double-blind intranasal treatment with either placebo, esketamine 28 mg, esketamine 56 mg, or esketamine 84 mg add-on to the continued stable oral antidepressant initiated in the prospective lead-in phase. The intranasal treatment sessions (esketamine or placebo) will occur twice weekly. Subjects will self-administer the intranasal study drug (esketamine 28 mg, 56 mg, 84 mg, or placebo) at treatment sessions occurring twice a week for 4 weeks at the clinical site under clinical supervision. The first treatment session will be on Day 1. Responders (subjects who have ≥50% reduction from baseline in MADRS total score) at the end of the double-blind induction phase will be eligible to proceed to the posttreatment phase; those who do not (ie, nonresponders) will proceed to the 4-week follow-up phase. Given the potential for treatment-emergent transient elevation in SBP and DBP, the guidance on Blood Pressure Monitoring should be followed on intranasal dosing days during the double-blind induction phase.

Posttreatment Phase

Responders who completed the double-blind induction phase will enter the 24-week posttreatment phase to evaluate durability of efficacy after cessation of add-on intranasal esketamine or placebo treatment while continuing the oral antidepressant treatment regimen, as assessed by the time to relapse and proportion of responders and remitters at each visit in this phase. All subjects who are discontinued must be treated with an oral antidepressant after completion of the study, unless it is clinically inappropriate.

Open-label Induction Phase

Subjects who relapsed in the posttreatment phase will receive a 4-week open-label induction treatment course of intranasal esketamine. The beginning of the OL induction phase should be at least 2 weeks (14 calendar days) after the last dose in the double-blind induction phase. Subjects who meet the relapse criteria before 2 weeks after the last dose in the double-blind induction

phase will not have an option for joining open label induction phase. They will withdraw from the posttreatment phase and move forward to the follow up phase.

Subjects who enter the OL induction phase will start treatment sessions with 56 mg of intranasal esketamine on the first day of OL induction phase (Day 1 OL). On the fourth day (Day 4 OL), the dose will be increased to 84 mg. On Day 8 OL and Day 11 OL, the dose may remain the same as 84 mg or could be reduced by 28 mg as determined by the investigator based on efficacy and tolerability. On Day 15 OL, a dose reduction is permitted if required for tolerability; no dose increase is permitted on Day 15 OL. After Day 15 OL, the dose should be stable (unchanged). If needed for tolerability, a dose reduction is permitted from Day 15 OL until Day 25 OL.

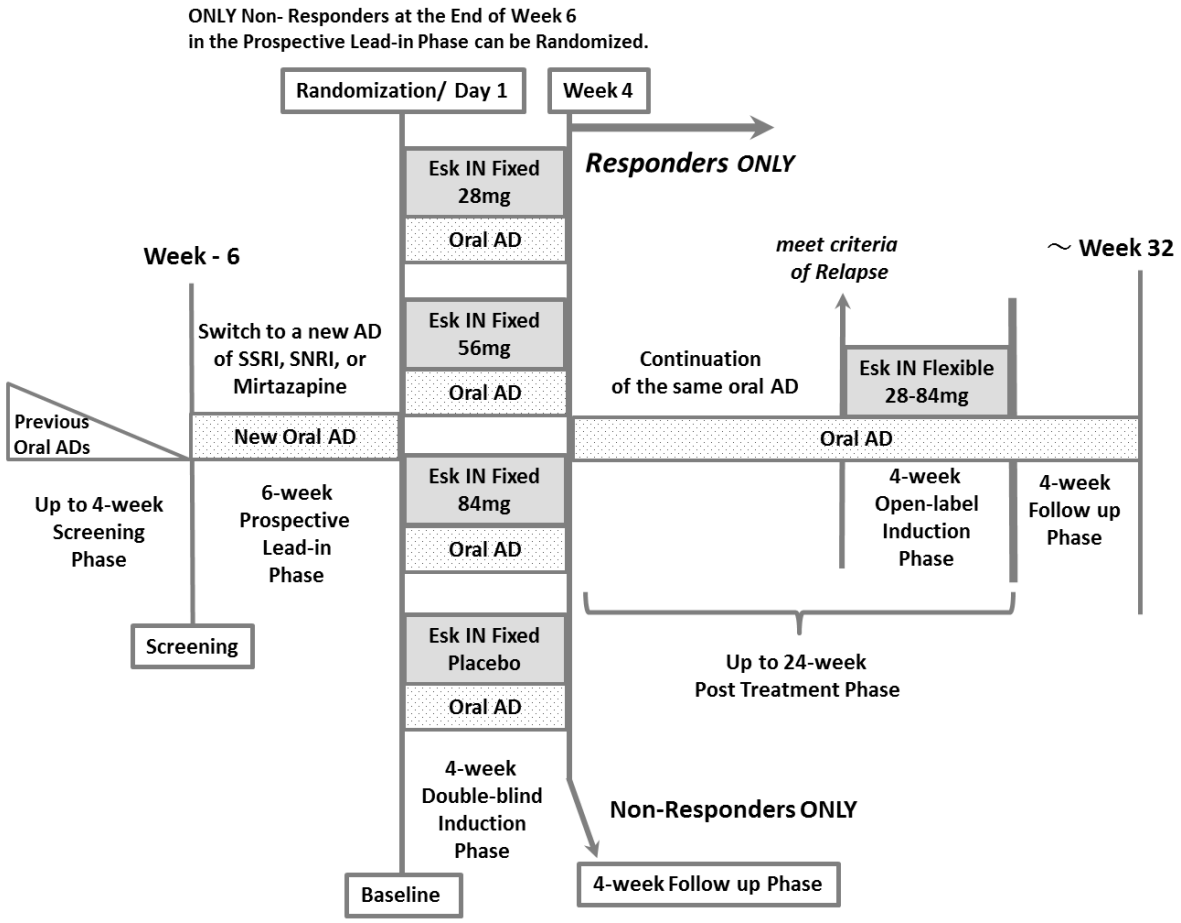
The oral antidepressant medication initiated from the prospective lead-in phase, which will continue in the posttreatment phase will also be maintained throughout this phase.

Follow-up Phase

Following subjects will have follow-up Visits; subjects who withdraw from double blind induction phase, nonresponders after double-blind induction phase, responders who withdraw within 4 weeks after the last dose of double blind intranasal drug and all subjects who receive open label intranasal drug. During this phase, further clinical/standard-of-care treatment will be provided by the study investigator however, in order to better assess potential withdrawal symptoms from intranasal study drug, the oral antidepressant medication must be continued for the follow-up phase unless determined as not clinically appropriate.

A schematic overview of the study design is provided in Figure 1.

Figure 1: Schematic Overview of the Study Design



Esk: esketamine; IN: intranasal; AD: Antidepressant Day 1: The first day in the double-blind induction phase.

* Only responders after completion of the double-blind induction phase are eligible to join the posttreatment phase. In the posttreatment phase, subjects who relapse within 20 weeks after the start of the posttreatment phase will receive an open-label treatment course of esketamine. Subjects who relapse more than 20 weeks after the start of the posttreatment phase will withdraw from the study and clinical/standard-of-care treatment will be arranged by the study investigator after relapse. The beginning of the open-label induction phase should be at least 2 weeks after the last dose in the double-blind induction phase.

** Following subjects will have follow-up Visits; subjects who withdraw from double blind induction phase, nonresponders after double-blind induction phase, responders who withdraw within 4 weeks after the last dose of double blind intranasal drug and all subjects who receive open label intranasal drug.

1.3. Statistical Hypotheses for Trial Objectives

The hypothesis for this study is that, at least one dose of intranasal esketamine (28, 56, and 84 mg) is superior to intranasal placebo in improving depressive symptoms in Japanese subjects with TRD, as assessed by the change from baseline in the MADRS total score at the end of the double-blind induction phase.

1.4. Sample Size Justification

The sample size for this study was calculated assuming a treatment difference for the double-blind induction phase of 4, 4.5, 5 points in MADRS total score between each dose (28 mg, 56 mg, 84 mg) of esketamine and the placebo respectively, a SD of 10 for each treatment group, a 1-

sided significance level of 0.05 and a drop-out rate of 12.5%. A total of 183 subjects will need to be randomized to treatment in a 2:1:1:1 ratio (72 subjects on placebo group and 37 subjects per intranasal esketamine dose group) to achieve 80% power to detect difference for at least one dose group of intranasal esketamine to placebo using a Dunnett adjustment. The treatment difference and SD used in this calculation were assumed based on results of Panel B of the ESKETINTRD2003 study with clinical consideration.

1.5. Randomization and Blinding

Randomization will be with an allocation ratio of 2:1:1:1 to intranasal placebo, intranasal esketamine 28 mg, intranasal esketamine 56 mg, or intranasal esketamine 84 mg. Randomization will be used in the double-blind induction phase to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints in this phase. Measures will be taken to ensure that the study subjects and study staff are not unblinded.

The placebo group is included in this design to maintain blinding in the double-blind phase of the study. A placebo group is necessary to allow an accurate assessment of the safety and efficacy of the study drug.

Randomization will be employed only in the double-blind induction phase of the study. Central randomization will be implemented in this study. Subjects will be randomly assigned to 1 of 4 treatment groups in a 2:1:1:1 ratio based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. Randomization will be balanced by using randomly permuted blocks across the 4 treatment groups. The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject.

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual subject.

Data that may potentially unblind the treatment assignment (eg, intranasal study drug plasma concentrations, treatment allocation) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding.

At the end of the double-blind induction phase the database will be locked for the analysis and reporting of this phase. The subject treatment assignment will be revealed only to sponsor's study staff. The investigators and the site personnel will be blinded to the treatment assignment until all subjects have completed study participation through the follow-up phase.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Analysis Phases

There are 5 analysis phases defined in this study:

- *A Double-blind Induction Phase*
- *A Double-blind Follow-up Phase* (Non-Responders or subjects who withdraw from DB induction phase)
- *A Posttreatment Phase* (Responders only)
- *An Open-Label Induction Phase* (Responders only)
- *An Open-Label Follow-up Phase* (Responders only)

Each analysis phase has its own analysis phase start and end dates.

2.1.1. Study Reference Start and End Dates

The reference start date for the study is defined as the date of the first dose of intranasal study medication (the date is missing for screened subjects who did not take any intranasal study medication). The reference end date for the study is the end of trial date including the last follow-up visit.

2.1.2. Analysis Phase Start and End Dates

Double-blind Induction Phase

The start date of the double-blind induction phase (referred to as 'DB start date') is the date of the first dose of intranasal study medication. The double-blind induction phase end date (referred to as 'DB end date') is the maximum of the date of the last visit in the double-blind induction phase and the date of completion/withdrawal from the double-blind induction phase.

The start date/time of the double-blind induction phase (referred to as, 'DB start date/time') is the DB start date and the time of the first dose of intranasal study medication.

Double-blind Follow-up Phase

The start date of the double-blind follow-up phase (referred to as 'DB FU start date') is the day after the DB end date. The double-blind follow-up phase end date (referred to as 'DB FU end date') is the maximum of the last DB follow-up visit date or the end of trial date.

Posttreatment Phase

The start date of the posttreatment phase (referred to as 'PT start date') is the day after the DB end date. The posttreatment phase end date (referred to as 'PT end date') is defined as: for subjects who entered OL phase, the day of OL start date (defined below); for subjects who did not enter OL, including responders who withdraw within 4 weeks after the last dose of DB intranasal drug, the maximum of the last posttreatment visit date or the end of trial date.

For subjects who entered OL phase, PT end date/time is one minute before OL start date/time (defined below).

Open-Label Induction Phase

The start date of the open-label induction phase (referred to as 'OL start date') is the date of the first dose of intranasal study medication in a second induction treatment course. The open-label induction phase end date (referred to as 'OL end date') is the maximum of the date of the last visit in the open-label induction phase and the date of completion/withdrawal from the open-label induction phase.

The start date/time of the open-label induction phase (referred to as, 'OL start date/time') is the OL start date and the time of the first dose of intranasal study medication in the second induction treatment course.

Open-Label Follow-up Phase

The start date of the open-label follow-up phase (referred to as 'OL FU start date') is the day after the OL end date. The open-label follow-up phase end date (referred to as 'OL FU end date') is the maximum of the last OL follow-up visit date or the end of trial date.

2.1.3. Study Day and Relative Day

Study day is calculated relative to the reference start date for the study. Relative day is calculated relative to the 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 - reference start date+1.

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

event date - reference start date

Relative day for an event on or after the analysis phase start date is calculated as:

event date - analysis phase start date + 1.

Relative day for an event prior to the analysis phase start date is calculated as:

event date - analysis phase start date.

There is no study Day 0 or relative Day 0.

2.2. Baseline and End Point

Baseline is defined for each parameter/assessment.

- Baseline (DB): The last assessment before receiving the first dose of intranasal study medication in the double-blind induction phase.

- Baseline (OL): The last assessment before receiving the first dose of intranasal study medication in the open-label induction phase.

Baseline (DB) will be used for DB induction phase, DB follow-up phase and posttreatment (PT) phase. Baseline (OL) will be used for OL induction phase and OL follow-up phase.

The 'End Point (DB)' value is defined as the last post baseline assessment value during the double-blind induction phase.

The 'End Point (OL)' value is defined as the last post baseline assessment value during the open-label induction phase.

2.3. 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 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[a]	Time Interval (label on output)	Time Interval[a] (Day)	Target Time Point[a] (Day)
MADRS	Screening /lead-in		Week -6 (SL)		
			Week -4 (SL)		
			Week -2 (SL)		
	DB	1	Baseline (DB)	≤1 (predose)	1
		2	Day 2 (DB)	2	2
		8	Day 8 (DB)	3-11	8
		15	Day 15 (DB)	12-18	15
		22	Day 22 (DB)	19-25	22
		28	Day 28 (DB)	26 to end of DB	28
		DB final visit	End Point (DB)	2 to end of DB	
	DB FU	DB F/U 7	Week 1 (DB F/U)	DB F/U start day-10	7
		DB F/U 14	Week 2 (DB F/U)	11-21	14
		DB F/U 28	Week 4 (DB F/U)	22 to end of DB F/U	28
		DB F/U final visit	End Point (DB F/U)	1 to end of DB F/U	
	PT[f] Weekly 1	32	Week 1 (PT)	PT start day to 35	32
	PT[f] Weekly x=2,3,….	25 + x*7	Week x (PT)	22 + x*7 to 28 + x*7	25 + x*7
	OL	OL 1	Baseline (OL)	≤1 (predose)	1

Table 1: Analysis Visits

Parameter	Analysis Phase	Scheduled Day[a]	Time Interval (label on output)	Time Interval[a] (Day)	Target Time Point[a] (Day)
		OL 8	Day 8 (OL)	2-11	8
		OL 15	Day 15 (OL)	12-18	15
		OL 22	Day 22 (OL)	19-25	22
		OL 28	Day 28 (OL)	26 to end of OL	28
		OL final visit	End Point (OL)	2 to end of OL	
	OL FU	OL F/U 7	Week 1 (OL F/U)	OL FU start day-10	7
		OL F/U 14	Week 2 (OL F/U)	11-21	14
		OL F/U 28	Week 4 (OL F/U)	22 to end of OL F/U	28
		OL F/U final visit	End Point (OL F/U)	1 to end of OL F/U	
POMS-2	DB	25	Day 25 (DB)	2 to end of DB	25
	DB FU	DB F/U 7	Week 1 (DB F/U)	DB F/U start day-10	7
		DB F/U 14	Week 2 (DB F/U)	11-21	14
		DB F/U 28	Week 4 (DB F/U)	22 to end of DB F/U	28
		DB F/U final visit	End Point (DB F/U)	1 to end of DB F/U	
	PT	32	Week 1 (PT)	PT start day to 35	32
		39	Week 2 (PT)	36-46	39
		53	Week 4 (PT)	47-60	53
		67	Week 6 (PT)	61-74	67
		81	Week 8 (PT)	75-95	81
		109	Week 12 (PT)	96-123	109
		137	Week 16 (PT)	124-151	137
		165	Week 20 (PT)	152-179	165
		193	Week 24 (PT)	180 to end of PT	193
	OL FU	OL F/U 7	Week 1 (OL F/U)	OL FU start day-10	7
		OL F/U 14	Week 2 (OL F/U)	11-21	14
		OL F/U 28	Week 4 (OL F/U)	22 to end of OL F/U	28
		OL F/U final visit	End Point (OL F/U)	1 to end of OL F/U	
SDS	DB	1	Baseline (DB)	≤1 (predose)	1
		28	Day 28 (DB)	2 to end of DB	28
	PT	39	Week 2 (PT)	PT start day to 46	39
		53	Week 4 (PT)	47-60	53
		67	Week 6 (PT)	61-74	67
		81	Week 8 (PT)	75-95	81
		109	Week 12 (PT)	96-123	109
		137	Week 16 (PT)	124-151	137
		165	Week 20 (PT)	152-179	165
		193	Week 24 (PT)	180 to end of PT	193
CGI-S	Screening /lead-in		Week -6 (SL)		
			Week -4 (SL)		
			Week -2 (SL)		
	DB	1	Baseline (DB)	≤1 (predose)	1
		8	Day 8 (DB)	2-11	8
		15	Day 15 (DB)	12-18	15
		22	Day 22 (DB)	19-25	22
		28	Day 28 (DB)	26 to end of DB	28
		DB final visit	End Point (DB)	2 to end of DB	
	DB FU	DB F/U 7	Week 1 (DB F/U)	DB F/U start day-10	7
		DB F/U 14	Week 2 (DB F/U)	11-21	14
		DB F/U 28	Week 4 (DB F/U)	22 to end of DB F/U	28
		DB F/U final visit	End Point (DB F/U)	1 to end of DB F/U	
	PT	32	Week 1 (PT)	PT start day to 35	32
		39	Week 2 (PT)	36-42	39
		46	Week 3 (PT)	43-49	46
		53	Week 4 (PT)	50-60	53
		67	Week 6 (PT)	61-74	67
		81	Week 8 (PT)	75-95	81
		109	Week 12 (PT)	96-123	109
		137	Week 16 (PT)	124-151	137
		165	Week 20 (PT)	152-179	165
		193	Week 24 (PT)	180 to end of PT	193
	OL	OL 1	Baseline (OL)	≤1 (predose)	1
		OL 8	Day 8 (OL)	2-11	8
		OL 15	Day 15 (OL)	12-18	15

Table 1: Analysis Visits

Parameter	Analysis Phase	Scheduled Day[a]	Time Interval (label on output)	Time Interval[a] (Day)	Target Time Point[a] (Day)
		OL 22	Day 22 (OL)	19-25	22
		OL 28	Day 28 (OL)	26 to end of OL	28
		OL final visit	End Point (OL)	2 to end of OL	
	OL FU	OL F/U 7	Week 1 (OL F/U)	OL FU start day-10	7
		OL F/U 14	Week 2 (OL F/U)	11-21	14
		OL F/U 28	Week 4 (OL F/U)	22 to end of OL F/U	28
		OL F/U final visit	End Point (OL F/U)	1 to end of OL F/U	
GAD-7	DB	1	Baseline (DB)	≤1 (predose)	1
		15	Day 15 (DB)	2-21	15
		28	Day 28 (DB)	22 to end of DB	28
		DB final visit	End Point (DB)	2 to end of DB	
Vital Signs (TEMP [predose at each visit], BP[b], PULSE, RESP [at each visit, predose, 40M, 1H, 1.5H])	Screening /lead-in		Week -10 (SL)		
			Week -6 (SL)		
			Week -4 (SL)		
	DB	1	Baseline (DB) Day 1: 40M (DB) Day 1: 1H (DB) Day 1: 1.5H (DB)	≤ 1 / predose	1
		4	Day 4: Predose (DB) Day 4: 40M (DB) Day 4: 1H (DB) Day 4: 1.5H (DB)	2-6	4
		8	Day 8: Predose (DB) Day 8: 40M (DB) Day 8: 1H (DB) Day 8: 1.5H (DB)	7-9	8
		11	Day 11: Predose (DB) Day 11: 40M (DB) Day 11: 1H (DB) Day 11: 1.5H (DB)	10-13	11
		15	Day 15: Predose (DB) Day 15: 40M (DB) Day 15: 1H (DB) Day 15: 1.5H (DB)	14-16	15
		18	Day 18: Predose (DB) Day 18: 40M (DB) Day 18: 1H (DB) Day 18: 1.5H (DB)	17-20	18
		22	Day 22: Predose (DB) Day 22: 40M (DB) Day 22: 1H (DB) Day 22: 1.5H (DB)	21-23	22
		25	Day 25: Predose (DB) Day 25: 40M (DB) Day 25: 1H (DB) Day 25: 1.5H (DB)	24 to end of DB	25
		DB final visit	End Point (DB)	Day 1: 40M to end of DB	
	OL	OL 1	Baseline (OL) Day 1: 40M (OL) Day 1: 1H (OL) Day 1: 1.5H (OL)	≤ 1 / predose	1
		OL 4	Day 4: Predose (OL) Day 4: 40M (OL) Day 4: 1H (OL) Day 4: 1.5H (OL)	2-6	4
		OL 8	Day 8: Predose (OL) Day 8: 40M (OL) Day 8: 1H (OL) Day 8: 1.5H (OL)	7-9	8
		OL 11	Day 11: Predose (OL) Day 11: 40M (OL) Day 11: 1H (OL) Day 11: 1.5H (OL)	10-13	11
		OL 15	Day 15: Predose (OL) Day 15: 40M (OL) Day 15: 1H (OL) Day 15: 1.5H (OL)	14-16	15

Table 1: Analysis Visits

Parameter	Analysis Phase	Scheduled Day[a]	Time Interval (label on output)	Time Interval[a] (Day)	Target Time Point[a] (Day)
		OL 18	Day 18: Predose (OL) Day 18: 40M (OL) Day 18: 1H (OL) Day 18: 1.5H (OL)	17-20	18
		OL 22	Day 22: Predose (OL) Day 22: 40M (OL) Day 22: 1H (OL) Day 22: 1.5H (OL)	21-23	22
		OL 25	Day 25: Predose (OL) Day 25: 40M (OL) Day 25: 1H (OL) Day 25: 1.5H (OL)	24 to end of DB	25
		OL final visit	End Point (OL)	Day 1: 40M to end of OL	
Weight and BMI	DB	Screening, 1	Baseline (DB)	≤ 1 / predose	1
		15	Day 15 (DB)	2-21	15
		28	Day 28 (DB)	22 to end of DB	28
		DB final visit	End Point (DB)	2 to end of DB	
	OL	OL 1	Baseline (OL)	≤ 1 / predose	1
		OL 15	Day 15 (OL)	2-21	15
		OL 28	Day 28 (OL)	22 to end of OL	28
		OL final visit	End Point (OL)	2 to end of OL	
ECG	DB	Screening, 1	Baseline (DB)	≤ 1 / predose	1
		1	Day 1: 1H (DB)	1	1
		8	Day 8: 1H (DB)	2-11	8
		15	Day 15: 1H (DB)	12-20	15
		25	Day 25: 1H (DB)	21 to end of DB	25
		DB final visit	End Point (DB)	2 to end of DB	
	OL	OL 1	Day 1: 1H (OL)	1	1
		OL 15	Day 15: 1H (OL)	2-20	15
		OL 25	Day 25: 1H (OL)	21 to end of OL	25
		OL final visit	End Point (OL)	2 to end of OL	
Lab (Hematology, Chemistry)	Screening /lead-in		Screening		
	DB	Screening, 1	Baseline (DB)	≤ 1 / predose	1
		28	Day 28 (DB)	2 to end of DB	28
	OL	OL 1	Baseline (OL)	≤ 1 / predose	1
		OL 28	Day 28 (OL)	2 to end of OL	28
C-SSRS	Screening /lead-in		Week -10 (SL)		
			Week -6 (SL)		
			Week -4 (SL)		
			Week -2 (SL)		
	DB	1	Baseline (DB)	≤1 (predose)	1
		4	Day 4 (DB)	2-6	4
		8	Day 8 (DB)	7-9	8
		11	Day 11 (DB)	10-13	11
		15	Day 15 (DB)	14-16	15
		18	Day 18 (DB)	17-20	18
		22	Day 22 (DB)	21-23	22
		25	Day 25 (DB)	24-26	25
		28	Day 28 (DB)	27 to end of DB	28
		DB final visit	End Point (DB)	2 to end of DB	
	DB FU	DB F/U 7	Week 1 (DB F/U)	DB F/U start day-10	7
		DB F/U 14	Week 2 (DB F/U)	11-21	14
		DB F/U 28	Week 4 (DB F/U)	22 to end of DB F/U	28
		DB F/U final visit	End Point (DB F/U)	1 to end of DB F/U	
	PT	32	Week 1 (PT)	PT start day to 35	32
		39	Week 2 (PT)	36-42	39
		46	Week 3 (PT)	43-49	46
		53	Week 4 (PT)	50-60	53
		67	Week 6 (PT)	61-74	67
		81	Week 8 (PT)	75-95	81
		109	Week 12 (PT)	96-123	109
		137	Week 16 (PT)	124-151	137
		165	Week 20 (PT)	152-179	165

Table 1: Analysis Visits

Parameter	Analysis Phase	Scheduled Day[a]	Time Interval (label on output)	Time Interval[a] (Day)	Target Time Point[a] (Day)
		193	Week 24 (PT)	180 to end of PT	193
	OL	OL 1	Baseline (OL)	≤1 (predose)	1
		OL 4	Day 4 (OL)	2-6	4
		OL 8	Day 8 (OL)	7-9	8
		OL 11	Day 11 (OL)	10-13	11
		OL 15	Day 15 (OL)	14-16	15
		OL 18	Day 18 (OL)	17-20	18
		OL 22	Day 22 (OL)	21-23	22
		OL 25	Day 25 (OL)	24-26	25
		OL 28	Day 28 (OL)	27 to end of OL	28
		OL final visit	End Point (OL)	2 to end of OL	
	OL FU	OL F/U 7	Week 1 (OL F/U)	OL FU start day-10	7
		OL F/U 14	Week 2 (OL F/U)	11-21	14
		OL F/U 28	Week 4 (OL F/U)	22 to end of OL F/U	28
		OL F/U final visit	End Point (OL F/U)	1 to end of OL F/U	
MOAA/S[c] Oxygen Saturation[d] (predose and every 15 minutes to 1.5H) BPRS+ and CADSS (predose, 40M, 1.5H) CGADR [e] (1H, 1.5H)	DB	1	Baseline (DB)	≤1	1
		4	Day 4 (DB)	2-6	4
		8	Day 8 (DB)	7-9	8
		11	Day 11 (DB)	10-13	11
		15	Day 15 (DB)	14-16	15
		18	Day 18 (DB)	17-20	18
		22	Day 22 (DB)	21-23	22
		25	Day 25 (DB)	24 to end of DB	25
		DB final visit	End Point (DB)	2 to end of DB	
	OL	OL 1	Baseline (OL)	≤1 (predose)	1
		OL 4	Day 4 (OL)	2-6	4
		OL 8	Day 8 (OL)	7-9	8
		OL 11	Day 11 (OL)	10-13	11
		OL 15	Day 15 (OL)	14-16	15
		OL 18	Day 18 (OL)	17-20	18
		OL 22	Day 22 (OL)	21-23	22
		OL 25	Day 25 (OL)	24 to end of OL	25
		OL final visit	End Point (OL)	2 to end of OL	
PWC-20	DB	25	Day 25 (DB)	2 to end of DB	25
	DB FU	DB F/U 7	Week 1 (DB F/U)	DB F/U start day-10	7
		DB F/U 14	Week 2 (DB F/U)	11-21	14
		DB F/U 28	Week 4 (DB F/U)	22 to end of DB F/U	28
		DB F/U final visit	End Point (DB F/U)	1 to end of DB F/U	
	PT	32	Week 1 (PT)	PT start day to 35	32
		39	Week 2 (PT)	36-42	39
		46	Week 3 (PT)	43-49	46
		53	Week 4 (PT)	50-60	53
		67	Week 6 (PT)	61-74	67
		81	Week 8 (PT)	75-95	81
	OL	OL 25	Day 25 (OL)	2 to end of OL	25
	OL FU	OL F/U 7	Week 1 (OL F/U)	OL FU start day-10	7
		OL F/U 14	Week 2 (OL F/U)	11-21	14
		OL F/U 28	Week 4 (OL F/U)	22 to end of OL F/U	28
		OL F/U final visit	End Point (OL F/U)	1 to end of OL F/U	
Pharmacokinetics	DB	4	Day 4 (DB)	2-6	4
		25	Day 25 (DB)	24 to end of DB	25
	OL	OL 25	Day 25 (OL)	24 to end of OL	25

[a] For DB and posttreatment phases, the time interval is relative to the first day of DB phase. For other phases, the time interval is relative to the first day of that phase.

[b] During the DB phase, at 1.5 hours post dose if the SBP is ≥160 and/or DBP≥100, assessments should continue every 30 minutes until the blood pressure is <160 and/or <100 or investigator's clinical judgment the subject it is clinical stable and can be discharged from the clinical site or subject is referred for appropriate medical care, if clinically indicated or the blood pressure remains ≥180 mm Hg SBP or ≥110 mm Hg DBP or both, 2 hours after dosing, the subject should be referred for immediate medical treatment.

[c] If the MOAA/S score is ≤ 3 at any time during the 1.5 hour 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=+1.5 hours post dose).

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

[e] If the response is not "Yes" at 1.5 hour postdose, the assessment will be repeated every 15 minutes until a "Yes" response is achieved or until the subject is referred for appropriate medical care if clinically indicated.

[f] In the posttreatment phase, MADRS assessments will be performed weekly through Week 24 or relapse, whichever occurs first.

2.4. Analysis Sets

Subjects will be classified into the following analysis sets: all randomized, full, safety, pharmacokinetic and PK/PD.

2.4.1. All Randomized Analysis Set

This analysis set will include all subjects who were randomized (ie, 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.

2.4.2. Full Analysis Set (FAS)

Efficacy analysis will be performed on the following FAS.

FAS (DB): All randomized subjects who received at least 1 dose of intranasal study medication during the DB induction phase.

FAS (OL): All subjects who received at least 1 dose of intranasal study medication during the OL induction phase.

FAS (responders): All randomized subjects who receive at least 1 dose of intranasal study medication during the double-blind induction phase and who are responders at the end of the double-blind induction phase and entered the posttreatment phase.

2.4.3. Safety Analysis Set

The following safety analysis sets are defined for each phase. Analyses of change from baseline will include only those subjects who have baseline and at least 1 postbaseline observation in that phase.

Safety (DB): All randomized subjects who receive at least 1 dose of intranasal study medication in the DB induction phase.

Safety (OL): All subjects who receive at least 1 dose of intranasal study medication in the OL induction phase.

Safety (responders): All randomized subjects who receive at least 1 dose of intranasal study medication during the double-blind induction phase and who are responders at the end of the double-blind induction phase and entered the posttreatment phase.

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

2.4.4. Follow-up Analysis Set

The following FU analysis sets are defined for each phase and will be used for both safety and efficacy analyses.

- FU (DB): All subjects who are not respond at the end of DB induction phase and enter the DB follow-up phase
- FU (OL): All Safety (OL) subjects who enter the OL follow-up phase

2.4.5. Pharmacokinetic Analysis Set

The PK Analysis Set includes all subjects, regardless of their compliance with the protocol, who received at least 1 dose of intranasal esketamine and at least 1 evaluable concentration data.

2.4.6. Pharmacokinetic/pharmacodynamic (PK/PD) Analysis Set

Blood pressure (DBP and SBP) and QTcF will be selected for safety parameter. The PK/PD analysis set includes all subjects who received at least 1 dose of intranasal esketamine, and have at least 1 time point with nominal time-matched plasma concentration and safety parameter.

2.5. Definition of Subgroups

Analyses will be provided for the primary endpoint, changes from baseline in MADRS total score, using the following subgroups.

- Sex
- Age Group (<45 years, ≥45 years)
- Number of Previous Treatments in Current Episode
- Functional Impairment based on Baseline SDS Total Score (not impaired [0-3], mild [4-11], moderate [12-19], marked [20-26] or extreme [27-30])
- Baseline MADRS total score (≤/> Median)
- Class of oral antidepressant (SNRI, SSRI or mirtazapine)
- BMI (≤/> Median)
- Number of major depressive episodes including current episode (1, 2-3, 3<)
- Duration of the current episode (≤ 26, >26-52, >52-104, >104 weeks)
- Concomitant use of benzodiazepine excluding sleep aids (Y/N)
- Concomitant use of benzodiazepine including sleep aids (Y/N)
- Had been considered to be eligible for electroconvulsive therapy (Y/N)

2.6. Imputation Rules for Missing Adverse Event (AE) Dates

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

Onset Date

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

1. 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
2. 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
3. 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 AE is missing both day and month, it will be set to the earliest of:

1. January 1 of the year of onset, as long as this date is after the DB start date.
2. One day after the DB start date, if this date is the same year that the AE occurred.
3. The day of AE resolution 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 day of DB start date or day of AE resolution date, whichever is earliest.

Similar rules will be applied for OL missing onset date.

Resolution Date

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

If the resolution date of an AE 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 AE that is not recorded as ongoing will be set to the date of study completion/discontinuation.

2.7. Imputation Rules for Missing AE Time of Onset/Resolution

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

1. 00:00 if the date of onset is after DB start date
2. The time of intranasal medication start in the double-blind induction 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.

2.8. Imputation Rules for Missing Concomitant Medication Dates

If a partial date is reported, it is assumed the medication (or therapy) was taken in all phases that overlap with the partial date. If both start and end dates are missing but this concomitant

medication was taken both prior to the study entry and still ongoing at study end, it is assumed medication was taken in all phases.

The rules for estimating an incomplete concomitant medication start date are as follows:

- If the month of the concomitant medication start date is equal to the month of the start of the induction phase, then the estimated start date is the DB start date;
- If the month of the concomitant medication start date is greater than the month of the start of the induction phase and earlier than the study end date, then the estimated start date of the concomitant medication is the first day of the month;
- If the month of the concomitant medication start date is greater than the month of the study end date, then no imputation will be done;
- If the month and year of the concomitant medication start date are known and the DB start date is after the month of the concomitant medication start date, then no imputation will be done;
- If either the month or year of the concomitant medication start date is missing, no imputation is to be performed.

3. SUBJECT INFORMATION

3.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics (Table 2) and psychiatric history at baseline (Table 3) will be summarized by treatment group and overall for the FAS (DB), FAS (responders) and FAS (OL) (described in Section 2.4). 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. Baseline (DB) will be used for these summaries.

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 (<45 years, ≥45 years)
- Sex (male, female)
- Baseline BMI (underweight: <18.5 kg/m^2, normal: 18.5 to <25 kg/m^2, overweight: 25 kg/m^2 to <30 kg/m^2, obese: 30 to <40 kg/m^2, morbidly obese:≥40 kg/m^2)
- Employment Status
- Hypertension status[a]
- Class of antidepressant (SSRI/SNRI/mirtazapine)
- Oral antidepressant
- Educational level

[a] Hypertension status =Yes if SBP>=140mmHg and/or DBP>=90mmHg at least one timepoint before DB Induction Phase. Hypertension status =No if SBP<140mmHg and DBP<90mmHg at all timepoints before DB Induction Phase.

Table 3: Psychiatric History at Baseline Variables

Continuous Variables:

- Baseline MADRS total score
- Baseline CGI-S score
- Age (years) when diagnosed with MDD

Categorical Variables:

- Baseline CGI-S score
- Baseline C-SSRS category (no event, suicidal ideation, suicidal behavior)
- Number of Previous Treatments in Current Episode
- Functional Impairment based on Baseline SDS Total Score (not impaired [0-3], mild [4-11], moderate [12-19], marked [20-26] or extreme [27-30])
- Family history of
  - Depression
  - Anxiety Disorder
  - Bipolar Disorder
  - Schizophrenia
  - Alcohol Abuse
  - Substance Abuse
- Number of episodes including current episode (1, 2-3, 3<)
- Duration of the current episode (≤ 26, >26-52, >52-104, >104 weeks)
- Use of Adjunctive antipsychotics at IC (Y/N)
- Use of benzodiazepine excluding sleep aids at IC (Y/N)
- Had been considered to be eligible for electroconvulsive therapy (Y/N)

A by-subject listing of the demographic and baseline characteristics will be provided.

Details of the medical history abnormalities will be presented in a by-subject listing.

3.2. Disposition Information

The number of screen failures will be summarized. A summary of each analysis set (defined in Section 2.4) will also be provided.

The following disposition summaries by treatment groups and overall will be provided for each phase separately.

- The number of subjects who entered a specific phase (DB induction, DB Follow-up, PT, OL induction and OL Follow-up phases)
- The number of subjects who completed a specific phase (DB induction, DB Follow-up, PT, OL induction and OL Follow-up phases)
- The number of subjects who discontinued a specific phase (DB induction, DB Follow-up, PT, OL induction and OL Follow-up phases) and their reasons for discontinuation

The number of subjects who terminated the trial and the reasons for ending study participation will also be summarized.

3.3. Extent of Exposure

Extent of exposure in terms of total duration of exposure and number of dosing sessions of intranasal study medication will be summarized by phase and treatment group for the FAS (DB), FAS (responders) and FAS (OL) (described in Section 2.4).

The total duration of exposure for the intranasal study drug and for each type of oral antidepressant (AD) during each phase is defined as the time between the first and the last dose of each type of study medication in that specific phase (last day of study medication-first day of study medication +1).

Descriptive statistics (N, mean, SD, median, minimum and maximum) of total duration of exposure of intranasal study drug will be presented for each induction phase. The total duration of intranasal study drug exposure for each induction phase will 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 of intranasal study medication for each induction phase will be presented, separately. The total duration of exposure of oral AD will be summarized similarly to the intranasal study drug, however the following categories will be used for the five analysis phases (described in Section 2.1): ≤7 days, 8-14 days, 15-21 days, 22-28 days, >28 days. Each type of oral AD will be summarized separately.

Modal dose for a subject is defined as the most frequently taken dose by a subject during that phase. Mean dose of a subject is calculated as the sum of doses during the phase divided by the total number of days exposed. The final dose is the last nonzero dose received during that phase. The calculation of mean, modal and final dose will exclude days off study drug.

Descriptive statistics (N, mean, SD, median, minimum and maximum) of modal dose, mean and final dose of intranasal study drug will be presented for OL induction phase. Doses of oral AD will be summarized using descriptive statistics of the mean dose (days on drug), mode dose (days on drug) and the final dose, by each type of oral AD for each analysis phase (DB induction, DB follow-up, PT, OL induction and OL follow-up). The lowest mode dose is selected in case of ties. In addition, percent compliance of the oral AD calculated as days actual dosed/days expected to be dosed*100, will be summarized.

A by-subject listing of study drug administration and oral AD will be provided.

3.4. Protocol Deviations

Deviations that occurred during the study will be tabulated for the All Randomized analysis set by treatment group. Major deviations will be tabulated as they are grouped prior to unblinding in the following categories: subject not withdrawn as per protocol, selection criteria not met, excluded concomitant treatment, treatment deviation, noncompliance, regulatory requirement. More categories may be included depending on the nature of the protocol deviation. A subject may be counted in more than one deviation category.

A by-subject listing showing the specific major protocol deviations will also be provided.

3.5. Prior and Concomitant Medications

Antidepressant medications taken prior to the baseline visit will be summarized by treatment group for the Safety (DB) analysis set.

The number and percent of subjects who receive concomitant therapies will be summarized by phase and treatment group using the generic term of the medication for the Safety (DB) and Safety (OL) analysis sets (described in Section 2.4).

A by-subject listing of all prior and concomitant medication will also be provided.

4. EFFICACY

Efficacy summaries for the DB induction phase and the OL induction phase will be based on FAS (DB) and FAS (OL), respectively. FAS (responders) will be applied for the summaries in posttreatment phase and for the analysis for time to relapse. Summaries for DB/OL follow up phase will be based on FU(DB)/ FU (OL).

4.1. Analysis Specifications

4.1.1. Level of Significance

The primary efficacy endpoint will be evaluated at a 1-sided significance level of 0.05 (2-sided significance level of 0.1) based on MMRM pairwise comparisons using a Dunnett adjustment. For all other analyses of the primary efficacy endpoint and for all other endpoints, no multiplicity adjustment will be done and nominal p-values will be presented.

4.1.2. Data Handling Rules

As a sensitivity analysis, the change in MADRS total score will be analyzed using an analysis of covariance (ANCOVA) model, using last observation carried forward (LOCF) data. The last post baseline observation during the double-blind induction phase will be carried forward as the “End Point” for that phase. Besides the observed cases and the end point assessment, the LOCF values will be created for intermediate postbaseline time points as well. These imputed time points will be labeled ‘DAY X LOCF’.

For the analyses of responders based on MADRS total score (Section 4.3.1), remitters based on MADRS total score (Section 4.3.2), subjects with missing values will be imputed as nonresponders/nonremitters.

4.1.3. Imputation Methods for Missing Items

Imputation of the MADRS total score is described in Section 4.2.1. For all other scales where multiple items are summed to create a total, if any item of the scale is missing at a visit, the total score for that scale at that visit will be left blank.

4.2. Primary Efficacy Endpoint

4.2.1. Definition

The primary efficacy endpoint is the change in MADRS total score as measured by the change from baseline (prior to randomization) to the end of the 4-week double-blind induction phase. The MADRS is a clinician-rated scale designed to measure depression severity and to detect changes due to antidepressant treatment.[6] The scale consists of 10 items, each of which is scored from 0 (item is not present or is normal) to 6 (severe or continuous presence of the symptoms), for a total possible score of 60. Higher scores represent a more severe condition. The MADRS evaluates apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, interest level, pessimistic thoughts, and suicidal thoughts. The test exhibits high inter-rater reliability.

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 sum of the nonmissing items multiplied by the ratio of the maximum number of items (ie, 10) to the number of nonmissing items.

4.2.2. Primary Estimand

The primary estimand, the main clinical quantity of interest to be estimated in the study, is defined by the following 4 components:

Population: Japanese subjects with treatment-resistant depression

Variable: change from baseline to Day 28 in the MADRS total score (see Section 4.2.1)

Intervention effect: the effect of the initially randomized treatment that would have been observed had all subjects remained on their treatment throughout the double-blind induction phase.

Summary measure: difference in variable means.

The primary analysis will be based on the FAS (DB), as described in Section 2.4.2, and the MADRS total scores collected during the double-blind induction phase.

4.2.3. Analysis Methods

Descriptive statistics of actual values and changes from baseline by treatment group will be presented for MADRS total score. The analysis of primary endpoint will only be applied for FAS (DB) during DB induction phase.

Means (+/-standard error [SE]), mean changes (+/-SE) from baseline, and least square mean changes (+/-SE) from baseline will be presented graphically in the double-blind induction phase.

4.2.3.1. MMRM

The primary efficacy variable, change from baseline in MADRS total score at Day 28 in the double-blind induction phase, will be analyzed using a Mixed-Effect Model for Repeated

Measures (MMRM) based on observed case data. The models will include baseline MADRS total score as a covariate, and treatment, day (see Table 1), and day-by-treatment interaction as fixed effects. The between-within approximation will be used to estimate the denominator degrees of freedom. The within-subject covariance 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 dose group with the placebo group will be performed with the appropriate contrast using a Dunnett adjustment.

The change from baseline in MADRS total score over time in the double-blind induction phase will be analyzed using the same MMRM as described above.

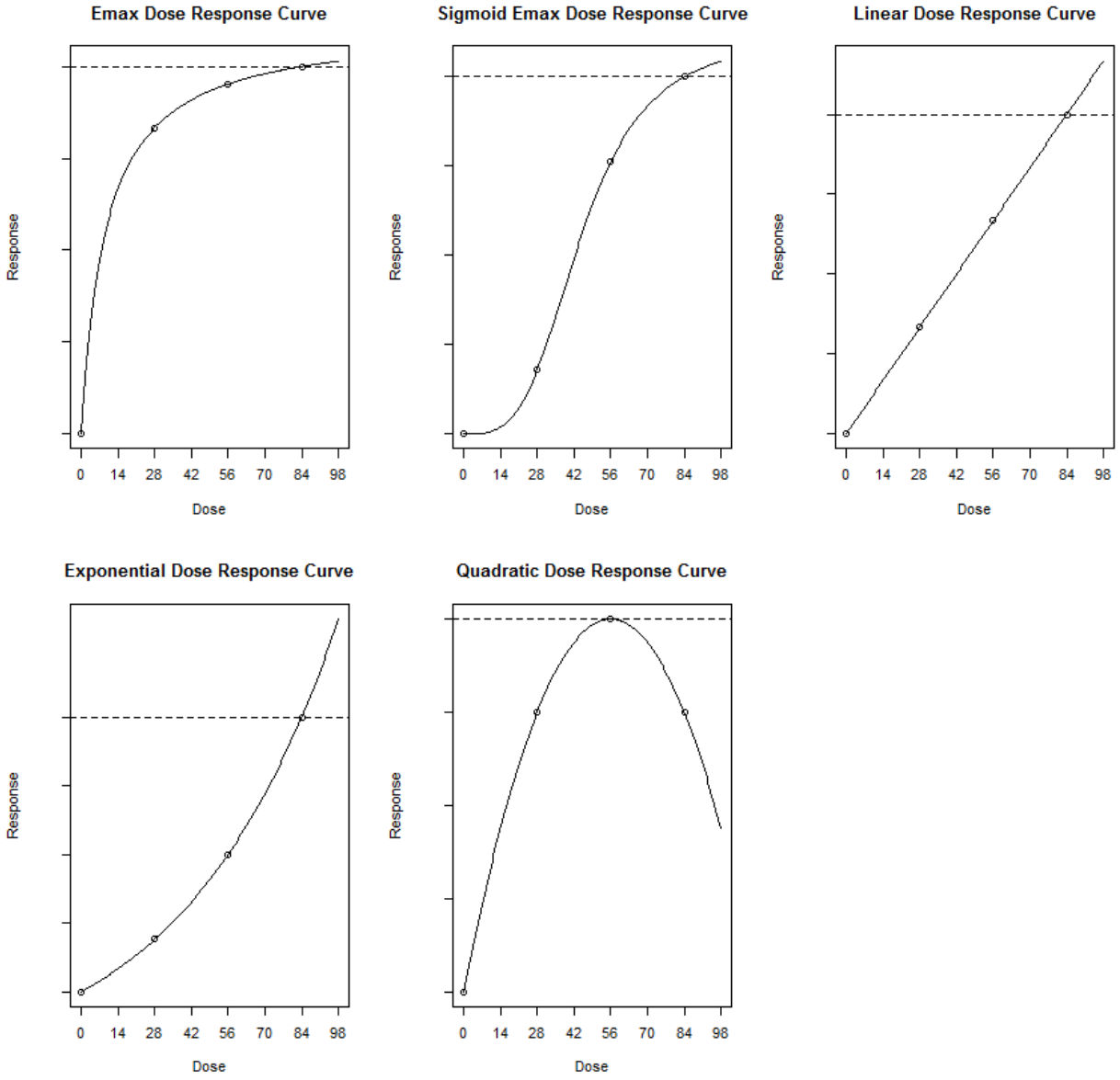
4.2.3.2. Model Diagnostics

The normality and equal variance assumptions underlying the primary MMRM models will be assessed graphically for the MADRS total score at end point. Residuals from the primary models 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.

4.2.3.3. MCP-Mod Analysis

Based on the MMRM, the least-squares (LS) mean estimates for each esketamine dose group and placebo group at Day 28 and the corresponding variances will be obtained. The generalized MCP-Mod approach will be applied towards the estimates obtained from the MMRM to analyze the dose-response relationship. This approach requires prespecification of a candidate model set. Using notation as in Bornkamp et al (2009)[1] the candidate set is constituted by the following 5 model profiles (with the corresponding parameters): E_{max} (ED_{50} =9.33), sigmoid E_{max} (ED_{50} =44.86, h=3.5), linear, exponential(δ=58.2) and quadratic(δ=-0.00893). The quadratic covers the scenario of a nonmonotonic relationship. The dose-response curves are shown below in Figure 2.

Figure 2: MCP-Mod Dose Response Curves



The significance of the dose-response signal associated with each candidate model will be determined using trend tests with model-specific optimal contrast coefficients. 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 at an overall level of 5% (1-sided) using MCP-Mod methodology. 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 statistic will be used to fit to the observed data and the one with the smallest Akaike Information Criterion (AIC) will be selected to represent the dose-response relationship. The corresponding confidence interval (CI) for the response at each dose will be computed based on a bootstrap approach.

4.2.3.4. Missing Data Sensitivity Analysis

The following table (Table 4) shows the assumptions of each considered analysis for the primary efficacy endpoint, all applied to FAS (DB) defined in Section 2.4.2.

Table 4: Analysis Types and Assumptions

Analysis Type	Analysis Method	Assumption
Primary Analysis	MMRM	Missing at Random – MAR
Sensitivity Analysis	ANCOVA model using change from baseline to Day 28 based on LOCF	Efficacy scores at time of discontinuation (DC) from the DB induction phase remain constant up to Day 28.
Sensitivity Analysis	MMRM model using change from baseline to Day 28 based on follow-up data	Efficacy scores during the DB follow-up phase can be used for the subjects who withdraw from the DB induction phase.
Sensitivity Analysis	Delta worsening adjustment applied to standard multiple imputation regression[7,8]	Efficacy scores worsen after study discontinuation

ANCOVA

The sensitivity analysis will be based on an analysis of covariance (ANCOVA) model using change from baseline to Day 28 based on LOCF data. The models will include factors for treatment and baseline MADRS total score as a continuous covariate. A 90% CI for the difference in LSMeans and P-value will be calculated based on the contrast test statistic for each esketamine dose level.

Additional to the ANCOVA model based on LOCF method, another sensitivity analysis using the same MMRM model will be done which includes the follow-up data from subjects who discontinued the double-blind induction phase. For subjects who discontinued from the double-blind induction phase, the measures on the follow-up visit will be treated as the data 'during DB induction phase' and the measure within the visit window for Day 28 and closed to the target date will be used.

The delta worsening adjustment analysis will be done only if the dropout rate is larger than 15%.

4.2.3.5. Subgroup Analysis

Forest plots will be provided displaying analysis results for each subgroup listed in Section 2.5. The point estimate of the treatment difference and its 90% confidence interval for each subgroup will be based on an MMRM analysis for the primary endpoint using the appropriate contrast. The model will include baseline MADRS total score as a covariate, and treatment, day, subgroup, day-by-treatment interaction and treatment-by-subgroup as fixed effects. The terms in the model will be adjusted for the subgroup of baseline MADRS total score (≤/>median). Baseline MADRS total score (as a continuous covariate) will not be included in the model when the dichotomized baseline MADRS total score is included in the model.

4.3. Secondary Endpoints

4.3.1. Responders

4.3.1.1. Definition

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 (eg, percent change ≤ -50% indicates improvement ≥50%). For the open-label induction phase, OL baseline will be used to calculate the percentage change as well.

A subject is defined a responder (yes=1 and no=0) at a given time point if the percent improvement in MADRS total score is ≥50%.

4.3.1.2. Analysis Methods

The proportion of subjects who achieve a response will be summarized at each time point for each induction phase (DB and OL). The proportion of responders during the double-blind induction phase in the esketamine dose group will be compared with the placebo group using Fisher's exact test with 90% CIs for the proportion provided by treatment group.

The cumulative response rate, defined as the percentage of subjects experiencing at least a given value of percent reduction from baseline to Day 28 in MADRS total score will be presented graphically.

The cumulative distribution function of the time to sustained response will be estimated by the Kaplan-Meier method for double-blind induction phase. Time to sustained response will be summarized (number of sustained responders, number of censored subjects, median, 25th and 75th percentile, if estimable) by treatment group. Sustained response is defined as the first occurrence of response that is maintained through the Day 28 assessment. Subjects are allowed one excursion (nonresponse) on a subsequent visit prior to Day 28, however the score must show at least 25% improvement. Subjects who discontinue early are not considered to have sustained response. Those subjects without sustained response will be censored at the last visit during double blind induction phase.

4.3.2. Remitters

4.3.2.1. Definition

Subjects who have a MADRS total score of ≤12 will be considered remitters.

4.3.2.2. Analysis Methods

The proportion of subjects who achieve remission will be summarized at each time point for each induction phase (DB and OL). The proportion of remitters during the double-blind induction phase in the esketamine dose group will be compared with the placebo group using Fisher's exact test with 90% CIs for the proportion provided by treatment group.

The cumulative distribution function of the time to sustained remission will be estimated by the Kaplan-Meier method for double-blind induction phase. Time to sustained remission will be summarized (number of sustained remitters, number of censored subjects, median, 25th and 75th percentile, if estimable) by treatment group. Sustained remission is defined as the first occurrence of remission that is maintained through the Day 28 assessment. Subjects are allowed one excursion (MADRS total score >12) on a subsequent visit prior to Day 28. Subjects who discontinue early are not considered to have sustained remission. Those subjects without sustained remission will be censored at the last visit during double-blind induction phase.

4.3.3. Time to Relapse

4.3.3.1. Definition

Time to relapse will be defined as the time between the end of the double-blind induction phase and the first documentation of a relapse event during the posttreatment phase. The relapse is defined as any of the following:

- MADRS total score ≥22 for 2 consecutive assessments. The date of the second MADRS assessment will be used for the date of relapse.
- Hospitalization for worsening depression or any other clinically relevant event determined per clinical judgment to be suggestive of a relapse of depressive illness such as suicide attempt, completed suicide, or hospitalization for suicide prevention. If hospitalized for any of these events, the start date of hospitalization will be used for the date of relapse. Otherwise the date of the event will be used if the subject is not hospitalized.
- In case both relapse criteria are met, the earlier date will be defined as the date of relapse for this subject.

Those subjects without relapse will be censored at the last visit (complete/withdraw) date in posttreatment phase.

4.3.3.2. Analysis Methods

The cumulative distribution function of the time to relapse will be estimated by the Kaplan-Meier method. Time to relapse will be summarized (number of relapses, number of censored subjects, median, 25th and 75th percentile, if estimable) by treatment group and the combined esketamine groups for the following groups separately.

1. In subjects who remit (MADRS total score ≤12) at the end of the double-blind induction phase
2. In subjects with response (≥50% reduction from baseline in MADRS total score) but who are not in remission at the end of the double-blind induction phase

4.3.4. Onset of Clinical Response

4.3.4.1. Definition

A subject is defined as having a clinical response if there is at least 50% improvement from baseline in the MADRS total score with onset by Day 2 that is maintained to Day 28. Subjects

are allowed one excursion (nonresponse) on Days 8, 15 or 22, however the score must show at least 25% improvement. Subjects who do not meet such criterion, or discontinue during the study before Day 28 for any reason will not be considered to have maintained clinical response and will be assigned the value of 0 (ie, no).

4.3.4.2. Analysis Methods

The proportion of subjects showing onset of clinical response by Day 2 that is maintained for the duration of the double-blind induction phase in the esketamine dose group will be compared with the placebo group using Fisher's exact test with 90% CIs for the proportion provided by treatment group. The proportion of responders with onset by Day 2 that is maintained to Day 8, Day 15, Day 22 and Day 28 will be test separately.

4.3.5. CGI-S

4.3.5.1. Definition

The Clinical Global Impression of Severity (CGI-S) provides an overall clinician-determined summary measure of the severity of the subject's illness that takes into account all available information, including knowledge of the subject's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the subject's ability to function. The CGI-S evaluates the severity of psychopathology on a scale of 0 to 7. Considering total clinical experience, a subject is assessed on severity of mental illness at the time of rating according to: 0=not assessed; 1=normal (not at all ill); 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=among the most extremely ill patients. The CGI-S permits a global evaluation of the subject's condition at a given time.

4.3.5.2. Analysis Methods

Descriptive statistics of actual values and changes from baseline by treatment group will be provided. Frequency distributions by treatment group will be provided at each time point for each analysis phase (DB induction, DB follow-up, PT, OL induction and OL follow-up).

The ranks of the change from baseline for CGI-S in the double-blind induction phase will be analyzed at each time point based on observed case using the same MMRM as described in Section 4.2.3.1 for primary efficacy endpoint, with the covariate "baseline MADRS total score" changed to "baseline CGI-S".

4.3.6. Sheehan Disability Scale (SDS)

4.3.6.1. Definition

The SDS is a subject-reported outcome measure and is a 5-item questionnaire which has been widely used and accepted for assessment of functional impairment and associated disability. The first three items assess disruption of (1) work/school, (2) social life, and (3) family life/home responsibilities using a 0-10 rating scale. The score for the first three items are summed to create a total score of 0-30 where a higher score indicates greater impairment. It also has one item on days lost from school or work and one item on days when underproductive. The recall period for

this study is 7 days. Scores ≤4 for each item and ≤12 for the total score are considered response. Scores ≤2 for each item and ≤6 for the total score are considered remission. If any of the first three items are missing, the total score will be set to missing as well as response and remission status.

4.3.6.2. Analysis Methods

Descriptive statistics of actual values and changes from baseline by treatment group will be provided at each time point for DB induction and PT phases. The total score as well as the individual item scores will be summarized separately. Graphical presentations will also be provided. In addition, the proportion of subjects who achieve response and remission will be summarized at each time point during the double-blind induction phase.

The change from baseline in SDS total score at Day 28 in the double-blind induction phase will be analyzed using the same MMRM as described in Section 4.2.3.1 for primary efficacy endpoint, with the covariate "baseline MADRS total score" changed to "baseline SDS total score".

4.3.7. GAD-7

4.3.7.1. Definition

The GAD-7 (Generalized Anxiety Disorder - 7 Items) is a brief and validated 7-item self-report assessment of overall anxiety.[10,11] Subjects respond to each item using a 4-point scale with response categories of 0=not at all, 1=several days, 2=more than half the days, and 3=nearly every day. Item responses are summed to yield a total score with a range of 0 to 21, where higher scores indicate more anxiety. The recall period is 2 weeks. The severity of the GAD-7 is categorized as follows: None (0-4), Mild (5-9), Moderate (10-14) and Severe (15-21).

4.3.7.2. Analysis Methods

Descriptive statistics of actual values and changes from baseline by treatment group will be provided at each time point during double-blind induction phase. A frequency distribution will also be provided for GAD-7 severity categories at each time point. Graphical presentations will also be provided.

The change from baseline in GAD-7 total score over time in the double-blind induction phase will be analyzed using the same MMRM as described in Section 4.2.3.1 for primary efficacy endpoint, with the covariate "baseline MADRS total score" changed to "baseline GAD-7 total score".

4.3.8. MADRS

4.3.8.1. Definition

The definition of MADRS is in section 4.2.1.

4.3.8.2. Analysis Methods

Descriptive statistics of actual values and changes from baseline will be summarized at each time point for each phase (DB induction, DB follow-up, PT, OL induction and OL follow-up). The total score as well as the individual item scores will be summarized separately. Graphical presentations will also be provided.

5. SAFETY

All safety summaries for induction phases will be based on the safety analysis sets described in Section 2.4.3. Safety summaries for the follow-up phases will be based on the follow-up analysis sets described in Section 2.4.4.

Unless specified otherwise, Baseline (DB) will be used for DB induction phase and DB follow-up phase. Baseline (OL) will be used for OL induction phase and OL follow-up phase.

5.1. Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) (version 20.0 or above) will be used to classify adverse events (AEs) by system organ class and preferred term. Treatment-emergent adverse events (TEAEs) that occurred in each analysis phase (DB induction, DB follow-up, PT, OL induction, OL follow-up) will be summarized by system organ class and preferred term.

The number (%) of subjects with TEAEs, serious TEAEs (SAEs), and TEAEs that led to study drug discontinuation, dose reduction will be summarized by system organ class and preferred term. TEAEs will be summarized by onset time (4 week intervals). Data listings will be generated for deaths, other SAEs, and discontinuations due to AEs.

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.

Treatment-emergent adverse events (TEAEs) are defined as follows for each analysis phase:

- TEAEs in DB induction phase:
  a. If AE onset time is not missing: DB start date/time ≤ AE onset date and time ≤ DB end date
  b. If AE onset time is missing: DB start date ≤ AE onset date ≤ DB end date
- TEAEs in OL induction phase:
  a. If AE onset time is not missing: OL start date/time ≤ AE onset date and time ≤ OL end date
  b. If AE onset time is missing: OL start date ≤ AE onset date ≤ OL end date
- AEs in DB follow-up phase: DB FU start date ≤ AE onset date ≤ DB FU end date
- AEs in OL follow-up phase: OL FU start date ≤ AE onset date ≤ OL FU end date

- For the AEs that have both day and month missing, treatment-emergent flag is assigned based on the rules presented in Section 2.6.

In addition, TEAEs will be summarized by severity and relationship to study medication using the preferred term. For the summaries of TEAEs by severity/relationship to study medication, the observation with the most severe occurrence/closest relationship to study medication will be chosen if there is more than one incident of an AE reported during the analysis phase by the subject.

Adverse Events of Special Interest

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

- Suggestive of abuse potential (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 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, 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 (Anticipatory anxiety, Anxiety, Anxiety disorder, Agitation, Fear, Feeling jittery, Irritability, Nervousness, Panic attack, Tension).

The number and percentage of subjects taking concomitant medication for dissociation events (preferred term of Dissociation) at any time during each induction phase will be provided.

5.2. Clinical Laboratory Tests

Descriptive statistics (N, mean, median, minimum, and maximum) for values and changes from baseline will be provided for clinical laboratory tests (hematology, chemistry and urinalysis) at each scheduled time point for each induction phase (DB and OL).

Clinical laboratory tests that meet the criteria for markedly abnormal will be listed by subject for each induction phase. The incidence of treatment-emergent markedly abnormal (TEMA) laboratory values that occurred at any time during each induction phase will be presented. Clinical laboratory test values will be considered TEMA using the criteria defined by Janssen Research & Development, LLC listed in Attachment 1. The identification of TEMA laboratory values is based on the postbaseline value being out of range while the baseline value is either missing or within the range given in Attachment 1. If postbaseline laboratory results are above the upper limit and the baseline value is below the lower limit, then the postbaseline abnormality will also be considered TEMA. The same applies to the postbaseline value being below the lower limit with the baseline value being above the upper limit.

The incidence of subjects with ALT values >3*upper normal limit (ULN) will be presented for each induction phase. Additionally, incidence of hepatic toxicity (Hy's Law)[12] defined as ALT values >3*ULN AND total bilirubin values >2*ULN will be presented for each induction phase. Similar to the markedly abnormal analysis, only subjects with baseline ALT 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.

5.3. Vital Signs, Weight, and BMI

Descriptive statistics (N, mean, median, minimum, and maximum) for values and changes from baseline at each time point during each induction phase (DB and OL) will be presented for temperature, systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, oxygen saturation, weight, 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. These summaries will also be provided by hypertension status (defined in Table 2, Yes/No). Descriptive statistics for maximum increases and maximum percent increase from predose will be provided for each dosing day. Frequency distributions of maximum percent change increase from predose and time of maximum percent change increase will also be presented. Note that if the maximum value within a phase occurs at multiple time points, the earliest time point is selected.

The proportion of subjects who have a treatment-emergent abnormality, as defined in Table 5 below, during each induction phase will be presented. Both the double-blind/open-label baseline and the predose assessment will be used to determine abnormal values. A listing of subjects meeting any of the criteria will also be provided for each induction phase.

Table 5: Treatment-Emergent Abnormality Categories for Vital Signs

	Postbaseline value outside of normal limit if:	
Vital Parameter	Abnormally low	Abnormally high
Pulse (bpm)	A decrease from baseline of ≥ 15 to a value ≤ 50	An increase from baseline of ≥ 15 to a value ≥ 100
Systolic BP (mm Hg)	A decrease from baseline of ≥ 20 to a value ≤ 90	An increase from baseline of ≥ 20 to a value ≥ 180
Diastolic BP (mm Hg)	A decrease from baseline of ≥ 15 to a value ≤ 50	An increase from baseline of ≥ 15 to a value ≥ 105

The proportion of subjects who experienced acute hypertension (systolic BP≥180 or diastolic BP≥110) at any time during the study will be summarized by analysis phase, treatment group and hypertension status.

Mean (+/-SE) values for systolic BP, diastolic BP and pulse rate will be presented graphically over each induction phase by treatment group and hypertension status. In addition, for subjects with hypertension who receive antihypertensive medication, the same graphs will be summarized by medication type (beta-blockers, all other agents).

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

5.4. Electrocardiogram

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 QTcB (Bazett) and QTcF (Fridericia).

Baseline ECG is defined as the average of all ECG results collected up to and including the day of the first dose of study medication. This baseline will be used as the baseline for change summaries and to determine abnormal values during each induction phase (DB and OL).

The maximum postbaseline value during each induction phase will be computed for each ECG parameter using data from both scheduled and unscheduled visits.

Summary tables for observed values and changes from baseline will be presented by treatment group at each time point during each induction phase.

The frequency of treatment-emergent abnormalities will be tabulated and presented for each induction phase. The identification of treatment-emergent abnormal ECG values is based on the postbaseline 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 postbaseline ECG results are above the upper limits (abnormally high) and the baseline value is below the lower limits (abnormally low), then the postbaseline abnormality will also be considered treatment-emergent. The same applies to the postbaseline value being below the lower limits (abnormally low) with the baseline value being above the upper limits (abnormally high). Abnormal ranges for the HR, PR, QRS and QT intervals are given in Table 6.

Table 6: Limits for HR, PR, QRS and QT Interval Abnormality

ECG parameter	Abnormally Low	Abnormally High
HR (bpm)	≤ 50	≥ 100
PR interval (msec)	--	≥ 210
QRS interval (msec)	≤ 50	≥ 120
QT interval (msec)	≤ 200	≥ 500

Based on the maximum QTc value for each subject during a given 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 values and changes from baseline are

given in Table 7 and are derived from the ICH E14 Guidance[3] (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 [a]	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
[a] Baseline is defined as the average predose.

The proportion of subjects with treatment emergent abnormalities will be presented for each induction phase. A listing of subjects with abnormalities will also be provided.

5.5. Other Safety Parameters

5.5.1. Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS (Columbia Suicide Severity Rating Scale) is a low-burden measure of the spectrum of suicidal ideation and behavior that was developed in the National Institute of Mental Health Treatment of Adolescent Suicide Attempters Study to assess severity and track suicidal events through any treatment.[9] It is a semi structured clinician-administered questionnaire designed to solicit the occurrence, severity, and frequency of suicide-related ideation and behaviors during the assessment period. Using the C-SSRS, potentially suicide-related events will be categorized using the following scores:

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 (non-fatal)
10. Completed Suicide

If no events qualify for a score of 1 to 10, a score of 0 will be assigned (0= "no event that can be assessed on the basis of C-SSRS"). Higher scores indicate greater severity.

The summaries of the C-SSRS outcomes will be applied for subjects who have at least 1 postbaseline C-SSRS measurement and a pretreatment C-SSRS assessment (assessment at Baseline visit).

A frequency distribution at each scheduled time point will be provided. Shifts from the baseline visit to the most severe/maximum score during each analysis phase (DB induction, DB follow-up, PT, OL induction and OL follow-up) will be summarized.

The maximum score assigned for each subject will also be summarized into one of three broad categories: No suicidal ideation or behavior (0), Suicidal ideation (1-5), Suicidal behavior (6-10). Shifts from the baseline visit to the maximum category during each analysis phase will be summarized.

5.5.2. Clinician Administered Dissociative States Scale (CADSS)

The CADSS (Clinician Administered Dissociative States Scale) is an instrument for the measurement of present-state dissociative symptoms, and is administered to assess treatment-emergent dissociative symptoms.[2] 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 = "Extremely"). The CADSS is divided into 3 components using the scoring method shown in Table 8.

Table 8: CADSS Scoring

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. If any response is missing the total score is set to missing. The CADSS is measured prior to each dose, at 40 minutes, and at 1.5 hours postdose during each induction phase (DB and OL).

Descriptive statistics (N, mean, median, minimum, and maximum) of the total scores and component scores, changes from the predose at each time point, and the proportion of subjects with an increase in CADSS total score from the predose value at any time during the study will be summarized. Mean (SE) CADSS values will be presented graphically for each dosing day.

5.5.3. Brief Psychiatric Rating Scale (BPRS)

The Brief Psychiatric Rating Scale (BPRS) is an 18-item rating scale which is used to assess potential treatment-emergent psychotic symptoms. The BPRS assesses a range of psychotic and affective symptoms rated from both observation of the subject and the subject's own report. Only the four-item positive symptom subscale (BPRS+) will be used in the study to assess treatment-emergent psychotic symptoms. 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 postdose during each induction phase (DB and OL).

Descriptive statistics (N, median, minimum, and maximum) of the total scores at each time point, the change from the predose at each time point, and the proportion of subjects with an increase in BPRS+ from the predose value at any time during the study will be summarized. The proportion of subjects with a total score of 3 or more at any time during the study will also be provided. Mean (SE) BPRS+ values will be presented graphically for each dosing day.

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

The Modified Observer's Assessment of Alertness/Sedation (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).

The MOAA/S is measured on each dosing day every 15 minutes from predose to 1.5 hours postdose or longer, if necessary, until the subject has a score of 5 during each induction phase (DB and OL).

- If the score is ≤3 at any time during the 1.5 hour 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=+1.5 hours postdose).
- If a subject does not have a score of 5 at t=+1.5 hours postdose, they should continue to be monitored. For subjects with a score of 4, the assessment should be repeated every 15 minutes. 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 (N, mean, median, minimum, and maximum) of the MOAA/S score, changes from predose, and the proportion of subjects experiencing sedation (score less than or equal to 3) will be summarized at each time point. The proportion of subjects with a total score of 3 or less will be summarized at any time during the study and by dose day. Mean (SE) MOAA/S values will be presented graphically for each dosing day.

5.5.5. Clinical Global Assessment of Discharge Readiness (CGADR)

The Clinical Global Assessment of Discharge Readiness (CGADR) will be used to measure a subject's current clinical status and is the clinician's assessment of the readiness to be discharged from the study site.

The clinician will answer "Yes" or "No" to the question "Is the subject considered ready to be discharged based on their overall clinical status (eg, sedation, blood pressure, and other adverse events)?"

On each intranasal dosing day, the CGADR will be performed at 1 hour and 1.5 hours postdose, repeated every 15 minutes if necessary until the response is 'Yes'. A subject should not be discharged prior to the 1.5-hour time point.

The proportion of subjects with a response of 'No' at each time point will be presented by treatment group during each induction phase (DB and OL).

5.5.6. 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 DB and Day 25 OL to establish a baseline prior to discontinuation of esketamine treatment.

The proportion of subjects with withdrawal symptoms at the end of induction phases (DB and OL) or during the DB follow-up phase, PT phase and the OL follow-up phase will be presented. In addition, symptoms at PT phase and follow-up phases will be compared to the last assessment in the relevant induction phase (DB and OL) and will be summarized using the following categories: new or worsened symptoms, symptoms present and unchanged, no symptoms, and improved.

5.5.7. Profile of Mood States 2nd edition (POMS-2)

The POMS-2 is a self-report measure that allows for the quick assessment of transient, fluctuating feelings, and enduring affect states.[4,5] Full-length versions (65 items) yield several scale scores: Anger-Hostility, Confusion-Bewilderment, Depression-Dejection, Fatigue-Inertia, Tension-Anxiety, Vigor-Activity and Friendliness. Each item is rated on a scale of 0 to 4 (0= "not at all", 1= "a little", 2= "moderately", 3= "quite a bit", 4= "extremely"). Total Mood Disturbance is a function of these 6 scale scores, shown in Table 9. The recall period for this study is 7 days.

Table 9: POMS-2 Scoring

Component	Questions
Anger-Hostility (AH)	Sum of 3, 14, 21, 28, 30, 35, 38, 43, 48, 49, 52
Confusion-Bewilderment (CB)	Sum of 6, 8, 15, 25, 34, 46, 50, 54, 58, 63
Depression-Dejection (DD)	Sum of 5, 11, 18, 20, 29, 32, 33, 40, 41, 44, 53, 56, 61
Fatigue-Inertia (FI)	Sum of 4, 26, 36, 42, 45, 59
Tension-Anxiety (TA)	Sum of 2, 9, 13, 17, 19, 23, 24, 31, 37, 65
Vigor-Activity (VA)	Sum of 7, 12, 16, 47, 55, 57, 60, 62, 64
Friendliness (F)*	Sum of 1, 10, 22, 27, 39, 51
Total Mood Disturbance (TMD)	AH + CB + DD + FI + TA – VA

*F does not contribute to TMD

Descriptive statistics (N, mean, median, minimum, and maximum) of the total scores and each component scores, as well as the changes from baseline will be summarized at each time point during PT phase and follow-up phases. Mean (SE) POMS-2 values, total scores and each component scores, will be presented graphically for PT phase and follow-up phases.

6. Pharmacokinetics/Pharmacodynamics Analysis

All plasma concentrations below quantification limit (BQL) or missing data will be labeled as such in the concentration data presentation. All subjects and samples excluded from the analysis will be clearly documented in the Clinical Study Report.

6.1. Pharmacokinetics (Plasma concentrations)

6.1.1. Statistical Analysis of Pharmacokinetics: (Descriptive Statistics)

Descriptive statistics (N, mean, standard deviation, %CV, median, minimum and maximum) will be calculated to summarize plasma esketamine and noresketamine concentrations at each sampling time point by esketamine treatment and study day (Day 4[DB], Day 25[DB] and Day 25[OL]). Subjects will be excluded from the PK analysis if their data did not allow for accurate assessment (eg, incomplete administration of the study drug; missing information of dosing and sampling times).

For descriptive statistics of the plasma esketamine and noresketamine, following data handing rules will be applied:

- Data from samples outside Visit window rule and Time window rule specified in Section 2.3 Table 1 and Table 10 will be excluded in the calculation.
- BQL will be substituted with “0 (zero)”.
- Number of plasma concentration data will be calculated based on the number of subjects with measurable value including BQL.
- When more than half (>50%) of plasma concentration are BQL at each scheduled time point, mean, median, and minimum will be shown as ‘BQL’’, and SD, and %CV will be shown as “NC” (not-calculated), respectively. If all plasma concentrations are BQL, maximum will also be shown as “BQL”.
- When number of plasma concentration data is equal to or less than 2, only N and mean will be calculated and SD, %CV, median, minimum and maximum will be shown as “NC” regardless of the proportion of BQL, respectively.
- If the dose level is modified from the initially planned dose on blood sampling day, plasma concentration data for that day will be excluded from the descriptive statistics.

Table 10: Pharmacokinetic sampling time per Protocol and for analysis

	Nominal time (Analysis time point) (h)	(min)	Time window (min)		
Postdose	0.67	40	32	-	48
	1	60	48 [a]	-	72
	2	120	96	-	144

[a]: If PK sample for 40 min post dose is collected at 48 min, 48 min is not included in the time window for PK sampling at 1 h post dose.

The plasma esketamine and noresketamine concentrations will be tabulated and summarized by esketamine treatment, respectively. Individual concentrations will be listed.

Population PK analysis of plasma concentration-time data of esketamine (and noresketamine or other metabolites, if needed) will be performed with non-linear mixed-effects modeling (NONMEM) approach. If deemed necessary, data will be combined with data from other studies. Details will be given in a population PK analysis plan will be presented in a separate report

6.1.2. Generating Pharmacokinetic Profiles

The following graphs will be produced:

- Boxplot of the esketamine exposure at 40 minutes, 1 and 2 hours postdose (DB induction phase, Study Day 4 and Study Day 25).
- Boxplot of the noresketamine exposure at 40 minutes, 1 and 2 hours postdose (DB induction phase, Study Day 4 and Study Day 25).

6.2. Pharmacokinetic/Pharmacodynamic Relationships

The PK/PD analysis will be based on the PK/PD analysis set (defined in Section 2.4.6) for nominal time-matched plasma concentrations and safety parameters.

Safety parameter: blood pressure (DBP and SBP), QTcF and CADSS total score

- DBP and SBP: 40 minutes and 1 hour postdose, Day 4(DB), 25(DB) and Day 25(OL)
- QTcF: 1 hour postdose, Day 25(DB) and Day 25(OL)
- CADSS total score: 40 minutes, Day 4(DB), 25(DB) and Day 25(OL)

The following plots will be generated to evaluate the relationship between safety parameter (absolute value and change [change from predose for SBP, DBP and CADSS total score, change from baseline for QTcF]) and plasma concentrations of esketamine by phases:

- DBP at each time-matched point of measurement from each dose will be plotted against the corresponding plasma concentration of esketamine.
- SBP at each time-matched point of measurement from each dose will be plotted against the corresponding plasma concentration of esketamine.
- QTcF at each time-matched point of measurement from each dose will be plotted against the corresponding plasma concentration of esketamine.

- CADSS total score at each time-matched point of measurement from each dose will be plotted against the corresponding plasma concentration of esketamine.
- Additional plots will be produced, if deemed necessary.

Pearson product moment correlations (R^2) will be calculated for nominal time-matched plasma concentrations and safety parameter.

The above analyses will be repeated for noresketamine.

Population PK/PD (MADRS total score and possibly selected AEs as additional PD parameters) analysis may be evaluated. If there is any visual trend in graphical analysis, suitable models will be applied to describe the PK/PD relationships. Details will be given in a PK/PD analysis plan will be presented in a separate report.

REFERENCES

1. Bornkamp, B., Pinheiro, J.C., and Bretz, F. (2009) MCPMod - An R Package for the Design and Analysis of Dose-Finding Studies. Journal of Statistical Software, 29(7), 1–23.
2. Bremner JD, Krystal JH, Putnam FW, Southwick SM, Marmar C, Charney DS, Mazure CM. Measurement of dissociative states with the Clinician-Administered Dissociative States Scale (CADSS). J Trauma Stress. 1998;11(1):125-136.
3. International Conference on Harmonization (ICH) Tripartite Guideline E14. London : s.n., 2005. pp. The clinical evaluation of QT/QTc interval prolongation and proarrhythmic for non-antiarrhythmic drugs.
4. Juvia PH, Douglas MM. Profile of Mood States. 2nd ed. Canada: Multi-Health Systems Inc., 2012.
5. Juvia PH, Douglas MM, Kazuhito Y (eds.). Profile of Mood States. 2nd ed. Japanese manual. Japan: Kanekoshobo, 2015.
6. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979;134:382-389.
7. National Research Council, Panel on Handling Missing Data in Clinical Trials [2010], The prevention and treatment of missing data in clinical trials. Available: http://www.nap.edu/catalog/12955.html
8. Permutt, T. Sensitivity analysis for missing data in regulatory submissions. Stat Med. 2015; Nov 15 (Epub ahead of print)
9. Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry. 2007;164:1035-1043.
10. Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med. 2006;166(10):1092-1097.
11. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. JAMA. 1999; 282:1737-1744.
12. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). [2009] Guidance for industry drug induced liver injury: premarketing clinical evaluation. Available: http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf

ATTACHMENTS

ATTACHMENT 1: CRITERIA OF MARKEDLY ABNORMAL LABORATORY VALUES

	Markedly Abnormal Limits	
Laboratory Parameter	Low	High
Albumin [g/L]	24	60
Alkaline phosphatase [U/L]	N/A	250
Alanine transaminase (SGPT) [U/L]	N/A	200
Alanine transaminase (SGPT) [U/L]	N/A	>3X ULN
Aspartate transaminase (SGOT) [U/L]	N/A	250
Bicarbonate [mmol/L]	15.1	34.9
Blood urea nitrogen [mmol/L]	N/A	17.9
Calcium [mmol/L]	1.5	3
Chloride [mmol/L]	94	112
Creatine kinase (U/L)	N/A	990
Creatinine [µmol/L]	N/A	265.2
Gamma glutamyl transferase [U/L]	N/A	300
Glucose [mmol/L]	2.2	16.7
Phosphate [mmol/L]	0.7	2.6
Potassium [mmol/L]	3.0	5.8
Sodium [mmol/L]	125	155
Bilirubin, total [µmol/L]	N/A	51.3
Protein, total [g/L]	50	N/A
Urine pH	N/A	8.0
Hematocrit [fraction] - female	0.28	0.5
- male	0.24	0.55
Hemoglobin [g/L]	80	190
Neutrophils, segmented [%]	30	90
Monocytes [%]	N/A	20
Eosinophils [%]	N/A	10
Basophils [%]	N/A	6
Lymphocytes [%]	10	60
Platelet count [$x10^9$/L]	100	600
Red blood cell count [$x10^{12}$/L] -- female	3.0	5.5
-- male	3.0	6.4
White blood cell count [$x10^9$/L]	2.5	15.0
Hy's Law criteria:		
Alanine transaminase (SGPT) [U/L]		> 3X ULN
AND		
Bilirubin, total [µmol/L]		>2X ULN

Note: The same limits apply to both males and females unless sex is indicated; N/A = Not applicable.