Janssen Research & Development *

Statistical Analysis Plan

An Open-label Long-term Extension Safety Study of Intranasal Esketamine in Treatment-resistant Depression

Safety and Sustenance of Esketamine Treatment Response With Repeated Doses at Intervals Determined by Symptom Severity (SUSTAIN-3)

Protocol 54135419TRD3008; Phase 3

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).

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AMENDMENT HISTORY

SAP Version	Issue Date
SAP 1.0	08 March 2019
Amendment 1	30 June 2020
Amendment 2	14 February 2023

Amendment 1 (SAP 2.0)
The overall reason for the amendment: few updated are made to be consistent with the MDSI program and Amendment 3 of the protocol.

Applicable Section(s)	Description of Change (s)
6.1 Adverse Events	The preferred terms for transient dizziness/vertigo and impaired cognition have been updated. Base on the protocol amendment 3, additional adverse events of special interest have been added, including symptoms of dissociation persisting beyond the typical ≤2 hour post esketamine administration, delirium, psychosis and mania.
2.3 Visit Window	Window for PWC has been added to allow the summarization of PWC data for French subjects.

Amendment 2 (SAP 3.0)

Applicable Section(s)	Description of Change (s)
5.2.3 PHQ-9	A subject is defined as a remitter at a given time point if the PHQ-9 total score is <5 at that time point. The original cut off of <=5 is updated to <5 based on clinical comment.
5.2.6 TSQM-9	Transformed scores are used in analysis. The scoring algorithm is added.
6.6.2 MOAA/S	Sedation with score less than or equal to 3 is updated to less than or equal to 4 based on the comments from CSR interim analysis 3.

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ABBREVIATIONS

AE	Adverse Event
ASA	American Society of Anesthesiologists
BMI	Body Mass Index
BP	Blood Pressure
CGADR	Clinical Global Assessment of Discharge Readiness
CGI-S	Clinical Global Impression – Severity
CIOMS	Council for International Organizations of Medical Sciences
C-SSRS	Columbia-Suicide Severity Rating Scale
DBP	Diastolic Blood Pressure
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram
EQ-5D-5L	EuroQol Group; 5 Dimension; 5 level
EQ VAS	EuroQol Group: Visual Analogue Scale
EW	Early Withdrawal
FDA	Food and Drug Administration
HRUQ	Healthcare Resource Use Questionnaire
HVLT-R	Hopkins Verbal Learning Test-Revised
IDMC	Independent Data Monitoring Committee
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
MOAA/S	Modified Observer's Assessment of Alertness/Sedation
PHQ-9	Patient Health Questionnaire – 9 item
PWC-20	Physician's Withdrawal Checklist
QLDS	Quality of Life in Depression Scale
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDS	Sheehan Disability Scale
SE	Standard Error
SBP	Systolic Blood Pressure
TEAEs	Treatment-emergent Adverse Events
TEMA	Treatment-emergent Markedly Abnormal
TRD	Treatment Resistant Depression
TSQM-9	Treatment Satisfaction Questionnaire for Medication
ULN	Upper Limit of Normal

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for all planned analyses for study JNJ-54135419-54135419TRD3008.

1.1. Trial Objectives

Primary Objectives

The primary objective of this study is to assess the safety and tolerability of intranasal esketamine in subjects with Treatment Resistant Depression (TRD), with special attention to the following:

- Potential long term effects on cognitive function
- Treatment-emergent adverse events (TEAEs), including TEAEs of special interest
- Post dose effects on heart rate, blood pressure, respiratory rate and blood oxygen saturation
- Potential effects on suicidal ideation/behavior

Secondary Objective

The secondary objective is to assess long-term efficacy, including effects on:

- Depressive symptoms (clinician and self-reported),
- Overall severity of depressive illness,
- Functioning and associated disability,
- Health-related quality of life and health status,

Exploratory Objectives

The exploratory objectives are to assess:

- Medical resource utilization
- Response and remission rates to a second induction phase in eligible subjects who had relapsed in study ESKETINTRD3003
- Subject treatment satisfaction
- Subject tradeoff preferences for key benefit and harm outcomes associated with TRD treatment, using a stated-choice preference survey

1.2. Trial Design

This is a multicenter, open-label long term extension study to evaluate the safety, tolerability, and efficacy of intranasal esketamine in subjects with TRD. The study population will include adult and elderly men and women who previously participated in studies ESKETINTRD3001, ESKETINTRD3002, ESKETINTRD3003, ESKETINTRD3004, ESKETINTRD3005, or ESKETINTRD3006 (US sites only) and will have met the inclusion/exclusion criteria for entry into those prior studies.

For subjects who participated in studies ESKETINTRD3003, ESKETINTRD3004, ESKETINTRD3005 or ESKETINTRD3006 (US sites only) and have responded to intranasal esketamine treatment, it is considered an ethical obligation to provide continued intranasal esketamine treatment if the benefit/risk profile was favorable for the subject at the time of completion of the previous study. Subjects in the placebo-controlled, double blind ESKETINTRD3005 and who are non-responders at the end of the induction phase were eligible to enter the open label induction phase of ESKETINTRD3004, therefore if enrollment in the ESKETINTRD3004 had completed these subjects were given the opportunity to enter this study, if clinically appropriate. For subjects who completed the induction phase and 6-month follow up phase of the ESKETINTRD3001 or ESKETINTRD3002 study, this study provided an opportunity for subjects to have an induction phase with open-label intranasal esketamine.

An Independent Data Monitoring Committee (IDMC) is commissioned for this study to review safety data periodically.

This study (54135419TRD3008) has 2 open label phases:

- A 4-week induction phase (if applicable)
- A variable duration optimization/maintenance phase

The duration that a subject may participate in the study is variable and is based on the subject's point of entry into the study and the timing of when the predefined criteria (below) for ending study participation occurs.

Study participation will be stopped:

- At the time intranasal esketamine is commercially available or a pre-approval access program is available to the subject in the subject's respective country; or
- The subject no longer benefits from further treatment (based on the investigator's clinical judgment), or withdraws consent; or
- The company terminates clinical development of intranasal esketamine for TRD.

Subjects will have a final study visit within 1 week of the last dose of intranasal esketamine.

A description of the study phases is provided below.

Induction Phase

The following subjects are eligible to enter the study at the induction phase:

- Subjects who relapsed during the ESKETINTRD3003 maintenance phase, or
- Subjects who were in the induction phase of ESKETINTRD3005 study at the time enrollment into the ESKETINTRD3004 study was closed and, after completion of the induction phase, were determined to be a non-responder, or
- Subjects who completed the induction phase and the 2 week follow up phase visit in ESKETINTRD3001 or ESKETINTRD3002 studies

Subjects will self-administer open-label intranasal esketamine as a flexible dose regimen twice a week for 4 weeks. Subjects who are < 65 years old will start intranasal esketamine with an initial dose of 56 mg on Day 1, with the dose adjusted based on efficacy and tolerability in the subsequent visits of the induction phase (flexible dose: 56 or 84 mg). Subjects who are ≥ 65 years old will start intranasal esketamine with an initial dose of 28 mg on Day 1, with the dose adjusted based on efficacy and tolerability in the subsequent visits of the induction phase (flexible dose: 28, 56 or 84 mg).

At the end of the induction phase, subjects may be eligible to proceed to the optimization/maintenance phase, according to the investigator's clinical assessment of the benefit versus risk for the subject.

If a subject withdraws from the study before the end of the induction phase for reasons other than withdrawal of consent, or is not eligible to proceed to the optimization/maintenance phase, an Early Withdrawal (EW) visit will be conducted within 1 week of the last intranasal dose.

Subjects who are currently in the induction phase at the time the 54135419TRD3008 study is completed will conduct an "End of Study" visit as their final study visit within 1 week of the last intranasal dose.

Optimization/Maintenance Phase

The following subjects are eligible to enter the study at the optimization/maintenance phase:

- Subjects who completed the induction phase of ESKETINTRD3001 or ESKETINTRD3002 and were responders, and study ESKETINTRD3003 is terminated.
- Subjects who were in the induction phase of ESKETINTRD3003 and ESKETINTRD3004 studies at the time these studies were terminated and, after completion of the induction phase, were determined to be a responder.
- Subjects who completed the optimization/maintenance phase of ESKETINTRD3004
- Subjects who were in the optimization, maintenance or optimization/maintenance phase of ESKETINTRD3003 and ESKETINTRD3004 studies, respectively, at the time these studies were terminated
- Subjects who were in the induction phase of ESKETINTRD3005 study at the time enrollment into the ESKETINTRD3004 study was closed and, after completion of the induction phase, were determined to be responders.
- Subjects (US only) who completed the induction phase of ESKETINTRD3006 and were responders.

Subjects will self-administer the intranasal study drug at treatment sessions at the study site.

For the first 4 weeks of this phase (Week 1 to Week 4), subject will self-administer the intranasal esketamine drug either weekly or have the option to have their current intranasal dosing frequency adjusted at the time of entry into 54135419TRD3008, with the dose adjusted based on efficacy and tolerability.

After Week 4 (i.e. starting from Week 5), based on the investigator's clinical judgment, the dose of esketamine for all subjects can be adjusted based upon efficacy and tolerability. Starting at Week 4, the frequency for subsequent intranasal treatment sessions will be adjusted (if applicable) based on the Clinical Global Impression – Severity (CGI-S) score at current visit (weekly, every other week or every 4 weeks). For CGI-S ≤ 3, the intranasal treatment session frequency will be changed from weekly to every other week, or from every other week to every 4 weeks; for CGI-S > 3, the intranasal treatment session frequency will be changed from every 4 weeks to weekly or every other week, or from every other week to weekly. The adjustment of the intranasal treatment session frequency is only permitted at the fixed 2-week interval (based on CGI-S performed at that visit), and every 4 weeks for subjects at the 4-week interval.

If a subject withdraws from the study before the end of the optimization/maintenance phase for reasons other than withdrawal of consent, an EW visit will be conducted within 1 week of the last intranasal dose.

Subjects who are currently in the optimization/maintenance phase at the time the 54135419TRD3008 study is completed will conduct an "End of Study" visit as their final study visit within 1 week of the last intranasal dose.

Induction Phase and Optimization/Maintenance Phase - Study Entry

The following subjects are eligible to enter the study at either the Induction Phase or the Optimization/Maintenance Phase:

- Subjects in ESKETINTRD3003, who at Week 16 of Optimization were not eligible to proceed to the maintenance phase and the sponsor has approved subject's entry into 54135419TRD3008; or

- Subjects in ESKETINTRD3003 and ESKETINTRD3004, who were in the induction phase and (for ESKETINTRD3003, after completion of the induction phase) were determined to not meet response criteria, and sponsor has approved subject's entry into 54135419TRD3008; or

- Subjects in ESKETINTRD3006 (US sites only) who completed the induction phase but did not meet the response criteria, and sponsor has approved subject's entry into 54135419TRD3008.

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

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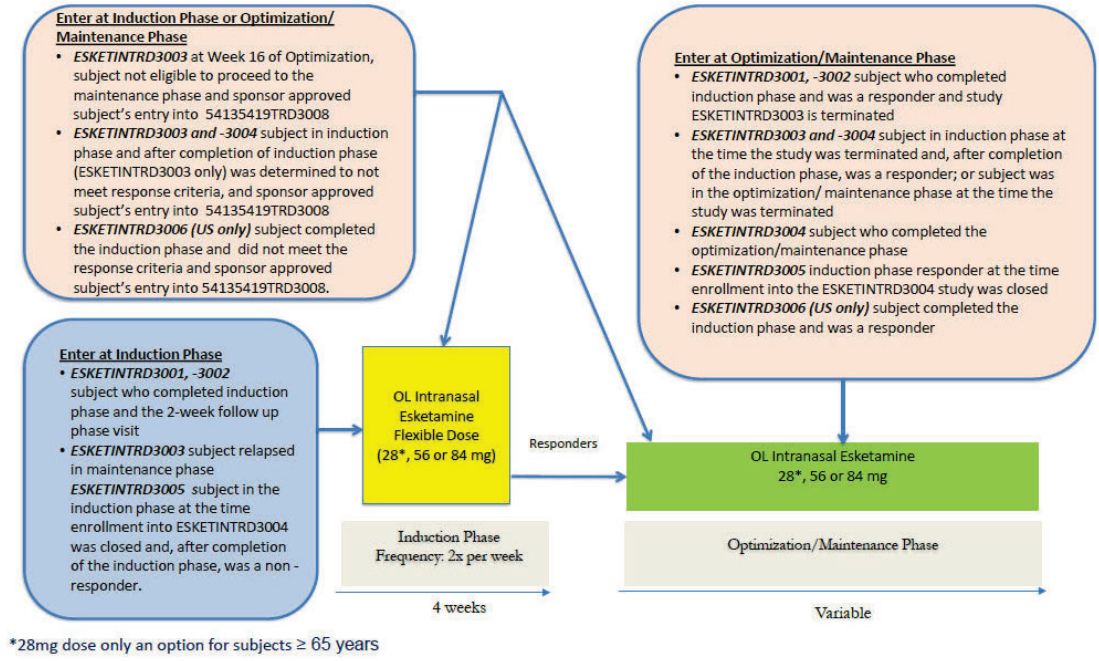
Figure 1: Study Design for 54135419TRD3008



1.3. Statistical Hypotheses for Trial Objectives

There is no formal hypothesis for this safety study.

1.4. Sample Size Justification

No formal sample size calculation was performed for the study. All the subjects entering this study (54135419TRD3008) are from 1 of the following esketamine Phase 3 studies ESKETINTRD3001, ESKETINTRD3002, ESKETINTRD3003, ESKETINTRD3004, ESKETINTRD3005, and ESKETINTRD3006 (US sites only) and will have met the inclusion/exclusion criteria for entry into those studies. It is unknown how many subjects from the previous Phase 3 studies would participate in this study (54135419TRD3008).

1.5. Randomization and Blinding

This is an open label study. Randomization and blinding procedures will not be applicable for this study. All subjects will be allocated to open-label esketamine treatment.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Analysis Phases

This study has 2 analysis phases:

- A 4-week induction phase;
- A variable duration optimization/maintenance phase.

For France, there is an additional 4-week follow-up phase.

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

2.1.1. Study Reference Start and End Dates

For subjects who enter the study at the induction phase, the reference start date for the study is defined as the first dose of intranasal study drug in the induction phase. For subjects who directly enter the optimization/maintenance phase of this study, the reference start date is defined as the first dose of intranasal study drug in the optimization/maintenance phase. The reference end date for subjects who have completed/discontinued from the study is the maximum of the date of last visit and trial completion/discontinuation.

2.1.2. Analysis Phase Start and End Dates

Induction Phase

The start date of the induction phase (referred to as, 'IND start date') is the date of the first dose of intranasal study medication in the induction phase. For subjects who continue to the optimization/maintenance phase, the induction phase end date (referred to as, 'IND end date') is the date of first dose of intranasal study medication taken in the optimization/maintenance phase or the date of the last visit in the induction phase if date of the first dose is missing. For subjects who discontinue in the induction phase, IND end date is the maximum of the date of the last visit in the induction phase or the date of early termination from the induction phase.

The start date/time of the induction phase (referred to as, 'IND start date/time') is the IND start date and the time of the first dose of intranasal study medication in this phase. If no intranasal study medication is administered, the time will be left blank.

The start and end dates for the induction phase are only defined for subjects who enter the study at the induction phase.

Optimization/Maintenance Phase

The start date of the optimization/maintenance phase (referred to as, 'OP/MA start date') is the OP/MA start date of the first dose of intranasal study medication in this phase. For subjects who complete/discontinue from the optimization/maintenance phase, the phase end date (referred to as, 'OP/MA end date') is the maximum of the date of the last visit in the optimization/maintenance phase or the date of completion/withdrawal from the optimization/maintenance phase.

The start date/time of the optimization/maintenance phase (referred to as, 'OP/MA start date/time') is the OP/MA start date and the time of the first dose of intranasal study medication in this phase.

Follow-Up Phase

The start date of the follow-up (post-treatment) phase (referred to as, 'F/U start date') is the day after the end date of the last treatment phase in which the subject participated. For subjects who complete/discontinue from the follow-up phase, the follow-up phase end date (referred to as, 'F/U end date') is the maximum of the last follow-up visit date or 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 analysis phase 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.

- Study Baseline: For subjects who enter the study at the induction phase, the last observation prior to or on the start date of induction phase is denoted as 'Baseline'; for subjects who directly enter the study at the optimization/maintenance phase, the last observation prior to or on the start date of optimization/maintenance phase is denoted as 'Baseline'.
- Baseline (OP/MA): The last observation prior to or on the start date of the optimization/maintenance phase is denoted as 'Baseline (OP/MA)'.

Note:

  - The 'Study Baseline' value is used to describe the change from baseline in the safety analysis unless otherwise specified.
  - For subjects who enter the study at the induction phase, the 'Baseline (IND)' value is used for the efficacy analysis for the induction phase.; for subjects who enter the optimization/maintenance phase, the 'Baseline (OP/MA)' is used for the efficacy analysis for the optimization/maintenance phase.

For each variable measured over time, the 'End Point (IND)' value is defined as the last postbaseline assessment value during the induction phase for subjects who enter the study at the induction phase.

The 'End Point (OP/MA)' value is defined as the last postbaseline assessment value during the optimization/maintenance phase.

2.3. Visit Windows

As subjects do not always adhere to the protocol visit schedule, the following rules are applied to assign actual visits to protocol visits. Listed below are the visit windows and the target days for each visit. The reference day is Study Day 1 (which is the first day that any study drug was taken in the induction phase for subjects who enter the study at the induction phase, and the first day any study drug was taken in the optimization/maintenance phase for responders from induction phase and subjects directly entering the optimization/maintenance phase of this study).

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)
Montgomery-Asberg Depression Rating Scale (MADRS)	IND	1	Baseline	≤ 1	1
		8	Day 8 (IND)	2 - 11	8
		15	Day 15 (IND)	12 - 18	15
		22	Day 22 (IND)	19 - 24	22
		28	Day 28 (IND)	25 to end of IND	28
		IND final visit	End Point (IND)	2 to end of IND	
	OP/MA i=1,2,3,...	1	Baseline (OP/MA)	≤ 1	1
		15	Week 3 (OP/MA)	2 - 32	15
		50	Week 8 (OP/MA)	33 - 64	50
		50 + i*28	Week (8 + i*4) (OP/MA)	37 + i*28 to 64 + i*28	50 + i*28
		OP/MA final visit	End Point (OP/MA)	2 to end of OP/MA	
CGI-S	IND	1	Baseline	≤ 1	1
		4	Day 4 (IND)	2 - 6	4
		8	Day 8 (IND)	7 - 9	8
		11	Day 11 (IND)	10 - 13	11
		15	Day 15 (IND)	14 - 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)
		22	Day 22 (IND)	19 - 24	22
		28	Day 28 (IND)	25 to end of IND	28
		IND final visit	End Point (IND)	2 to end of IND	
	OP/MA i=1,2,3,...	1	Baseline (OP/MA)	≤ 1	1
		8	Week 2 (OP/MA)	2 - 11	8
		15	Week 3 (OP/MA)	12 - 18	15
		22	Week 4 (OP/MA)	19 - 29	22
		22 + i*14	Week (4 + i*2) (OP/MA)	16 + i*14 to 29 + i*14	22 + i*14
		OP/MA final visit	End Point (OP/MA)	2 to end of OP/MA	
Patient Health Questionnaire – 9 item (PHQ-9), EuroQol Group; 5 dimension; 5 level (EQ-5D-5L), Quality of Life in Depression Scale (QLDS)	IND	1	Baseline	≤ 1	1
		15	Day 15 (IND)	2 - 21	15
		28	Day 28 (IND)	22 to end of IND	28
		IND final visit	End Point (IND)	2 to end of IND	
	OP/MA i=1,2,3,...	1	Baseline (OP/MA)	≤ 1	1
		15	Week 3 (OP/MA)	2 - 32	15
		50	Week 8 (OP/MA)	33 - 64	50
		50 + i*28	Week (8 + i*4) (OP/MA)	37 + i*28 to 64 + i*28	50 + i*28
		OP/MA final visit	End Point (OP/MA)	2 to end of OP/MA	
Sheehan Disability Scale (SDS)	IND	1	Baseline	≤ 1	1
		28	Day 28 (IND)	2 to end of IND	28
		IND final visit	End Point (IND)	2 to end of IND	
	OP/MA i=1,2,3,...	1	Baseline (OP/MA)	≤ 1	1
		15	Week 3 (OP/MA)	2 - 32	15
		50	Week 8 (OP/MA)	33 - 64	50
		50 + i*28	Week (8 + i*4) (OP/MA)	37 + i*28 to 64 + i*28	50 + i*28
		OP/MA final visit	End Point (OP/MA)	2 to end of OP/MA	
Treatment Satisfaction Questionnaire for Medication (TSQM-9)	IND	1	Baseline	≤ 1	1
		28	Day 28 (IND)	2 to end of IND	28
		IND final visit	End Point (IND)	2 to end of IND	
	OP/MA i=1,2,3,...	1	Baseline (OP/MA)	≤ 1	1
		50	Week 8 (OP/MA)	2 - 64	50
		50 + i*28	Week (8 + i*4) (OP/MA)	37 + i*28 to 64 + i*28	50 + i*28
		OP/MA final visit	End Point (OP/MA)	2 to end of OP/MA	
	IND	28	Day 28 (IND)	1 to end of IND	28

Table 1: Analysis Visits

Parameter	Analysis Phase	Scheduled Day[a]	Time Interval (label on output)	Time Interval[a] (Day)	Target Time Point[a] (Day)
Patient Stated-choice Preference	OP/MA	22	Week 4 (OP/MA)	1 to end of OP/MA	22
Nasal exam	IND	1	Baseline	≤ 1	1
		28	Day 28 (IND)	2 to end of IND	28
		IND final visit	End Point (IND)	2 to end of IND	
Vital Signs: Temperature (TEMP) (IND [predose], OP/MA [predose]), Blood Pressure (BP)[b], Hear Rate (HR), Respiratory (RESP) (IND [predose, 40M, 1H, 1H30M], OP/MA [predose, 40M, 1H])	IND	1	Baseline	≤ 1 / predose	1
			Day 1 (IND): 40M		
			Day 1 (IND): 1H		
			Day 1 (IND): 1H30M		
		4	Day 4 (IND): Predose	2 - 6	4
			Day 4 (IND): 40M		
			Day 4 (IND): 1H		
			Day 4 (IND): 1H30M		
		8	Day 8 (IND): Predose	7 - 9	8
			Day 8 (IND): 40M		
			Day 8 (IND): 1H		
			Day 8 (IND): 1H30M		
		11	Day 11 (IND): Predose	10 - 13	11
			Day 11 (IND): 40M		
			Day 11 (IND): 1H		
			Day 11 (IND): 1H30M		
		15	Day 15 (IND): Predose	14 - 16	15
			Day 15 (IND): 40M		
			Day 15 (IND): 1H		
			Day 15 (IND): 1H30M		
		18	Day 18 (IND): Predose	17 - 20	18
			Day 18 (IND): 40M		
			Day 18 (IND): 1H		
			Day 18 (IND): 1H30M		
		22	Day 22 (IND): Predose	21 - 23	22
			Day 22 (IND): 40M		
			Day 22 (IND): 1H		
			Day 22 (IND): 1H30M		
		25	Day 25 (IND): Predose	24 to end of IND	25
			Day 25 (IND): 40M		
			Day 25 (IND): 1H		
			Day 25 (IND): 1H30M		
		IND final visit	End Point (IND)	Day 1 (IND): 40M to end of IND	

Table 1: Analysis Visits

Parameter	Analysis Phase	Scheduled Day[a]	Time Interval (label on output)	Time Interval[a] (Day)	Target Time Point[a] (Day)
	OP/MA i=1,2,3,...	1	Baseline (OP/MA)	≤ 1	1
			Week 1 (OP/MA): 40M		
			Week 1 (OP/MA): 1H		
		8	Week 2 (OP/MA): Predose	2 - 11	8
			Week 2 (OP/MA): 40M		
			Week 2 (OP/MA): 1H		
		15	Week 3 (OP/MA): Predose	12 - 18	15
			Week 3 (OP/MA): 40M		
			Week 3 (OP/MA): 1H		
		22	Week 4 (OP/MA): Predose	19 - 25	22
			Week 4 (OP/MA): 40M		
			Week 4 (OP/MA): 1H		
		22 + i*7	Week (4 + i*1) (OP/MA): Predose	19 + i*7 to 25 + i*7	22 + i*7
			Week (4 + i*1) (OP/MA): 40M		
			Week (4 + i*1) (OP/MA): 1H		
		OP/MA final visit	End Point (OP/MA)	Week 1: 40M to end of OP/MA	
Weight and body mass index (BMI), Hematology and Chemistry, Urinalysis	IND	1	Baseline	≤ 1	1
		28	Day 28 (IND)	2 to end of IND	28
		IND final visit	End Point (IND)	2 to end of IND	
	OP/MA i=1,2,3,...	1	Baseline (OP/MA)	≤ 1	1
		106	Week 16 (OP/MA)	2 - 148	106
		106 + i*84	Week (16 + i*12) (OP/MA)	65 + i*84 to 148 + i*84	106 + i*84
		OP/MA final visit	End Point (OP/MA)	2 to end of OP/MA	
Electrocardiogram (ECG)	IND	1	Baseline	≤ 1 / predose	1
			Day 1 (IND): 1H		
		15	Day 15 (IND): 1H	2 - 20	15
		25	Day 25 (IND): 1H	21 to end of IND	25
		IND final visit	End Point (IND)	Day 1 (IND): 1H to end of IND	
	OP/MA i=1,2,3,...	1	Baseline (OP/MA)	≤ 1	1
			Week 1 (OP/MA): 1H		
		50	Week 8 (OP/MA): 1H	2 - 64	50
		50 + i*28	Week (8 + i*4) (OP/MA): 1H	37 + i*28 to 64 + i*28	50 + i*28

Table 1: Analysis Visits

Parameter	Analysis Phase	Scheduled Day[a]	Time Interval (label on output)	Time Interval[a] (Day)	Target Time Point[a] (Day)
		OP/MA final visit	End Point (OP/MA)	Week 1: 1H to end of OP/MA	
Columbia-Suicide Severity Rating Scale(C-SSRS)	IND	1	Baseline	≤ 1	1
		4	Day 4 (IND)	2 - 6	4
		8	Day 8 (IND)	7 - 9	8
		11	Day 11 (IND)	10 - 13	11
		15	Day 15 (IND)	14 - 16	15
		18	Day 18 (IND)	17 - 20	18
		22	Day 22 (IND)	21 - 23	22
		25	Day 25 (IND)	24 - 26	25
		28	Day 28 (IND)	27 to end of IND	28
		IND final visit	End Point (IND)	2 to end of IND	
	OP/MA i=1,2,3,...	1	Baseline (OP/MA)	≤ 1	1
		8	Week 2 (OP/MA)	2 - 11	8
		15	Week 3 (OP/MA)	12 - 18	15
		22	Week 4 (OP/MA)	19 - 29	22
		22 + i*14	Week (4 + i*2) (OP/MA)	16 + i*14 to 29 + i*14	22 + i*14
		OP/MA final visit	End Point (OP/MA)	2 to end of OP/MA	
MOAA/S[c] (IND and OP/MA [predose and every 15 minutes to 1H]), CGADR[d] (IND and OP/MA [30M; if not "Yes", repeat every 15 minutes until "Yes"]	IND	1	Day 1 (IND)	≤ 1	1
		4	Day 4 (IND)	2 - 6	4
		8	Day 8 (IND)	7 - 9	8
		11	Day 11 (IND)	10 - 13	11
		15	Day 15 (IND)	14 - 16	15
		18	Day 18 (IND)	17 - 20	18
		22	Day 22 (IND)	21 - 23	22
		25	Day 25 (IND)	24 to end of IND	25
		IND final visit	End Point (IND)	2 to end of IND	
	OP/MA i=1,2,3,...	1	Week 1 (OP/MA)	≤ 1	1
		8	Week 2 (OP/MA)	2 - 11	8
		15	Week 3 (OP/MA)	12 - 18	15
		22	Week 4 (OP/MA)	19 - 25	22
		22 + i*7	Week (4 + i*1) (OP/MA)	19 + i*7 to 25 + i*7	22 + i*7
		OP/MA final visit	End Point (OP/MA)	2 to end of OP/MA	
Pulse Oximetry[e] (IND [predose and every 15 minutes to 1H],	IND	1	Baseline	≤ 1	1
		4	Day 4 (IND)	2 - 6	4
		8	Day 8 (IND)	7 - 9	8

Table 1: Analysis Visits

Parameter	Analysis Phase	Scheduled Day[a]	Time Interval (label on output)	Time Interval[a] (Day)	Target Time Point[a] (Day)
OP/MA [predose, 30M, 1H])		11	Day 11 (IND)	10 - 13	11
		15	Day 15 (IND)	14 - 16	15
		18	Day 18 (IND)	17 - 20	18
		22	Day 22 (IND)	21 - 23	22
		25	Day 25 (IND)	24 to end of IND	25
		IND final visit	End Point (IND)	2 to end of IND	
	OP/MA i=1,2,3,...	1	Week 1 (OP/MA)	≤ 1	1
		8	Week 2 (OP/MA)	2 - 11	8
		15	Week 3 (OP/MA)	12 - 18	15
		22	Week 4 (OP/MA)	19 - 25	22
		22 + i*7	Week (4 + i*1) (OP/MA)	19 + i*7 to 25 + i*7	22 + i*7
		OP/MA final visit	End Point (OP/MA)	2 to end of OP/MA	
Healthcare Resource Use Questionnaire (HRUQ)	OP/MA i=1,2,3,...	1	Week 1 (OP/MA)	≤ 1	1
		22	Week 4 (OP/MA)	2 - 36	22
		22 + i*28	Week (4 + i*4) (OP/MA)	9 + i*28 to 36 + i*28	22 + i*28
		OP/MA final visit	End Point (OP/MA)	2 to end of OP/MA	
PWC	OP/MA	End Point (OP/MA)	End Point (OP/MA)	1 to end of OP/MA	
	FU	7	Week 1 (F/U)	1 to 10	7
		14	Week 2 (F/U)	11 to 17	14
		21	Week 3 (F/U)	18 to 24	21
		28	Week 4 (F/U)	25 to end of F/U	28
		F/U final visit	End Point (F/U)	1 to end of F/U	

[a] For IND phase, time interval is relative to the first day of the induction phase.

For OP/MA phase, time interval is relative to the first day of the optimization/maintenance phase.

[b] During the IND and OP/MA phase, at 1.5 hours postdose if the systolic blood pressure (SBP) is ≥ 160 and/or the diastolic blood pressure (DBP) is ≥ 100, blood pressure monitoring should continue every 30 minutes until the blood pressure if SBP < 160 and DBP < 100, or investigator's clinical judgment the subject it is clinically stable and can be discharged from the study site or the subject is referred for appropriate medical care if clinically indicated. if the blood pressure remains ≥180 mmHg SBP and/or ≥110 mmHg DBP, 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 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 hours post dose)

[d] If the response is "No", 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. On all intranasal treatment session days, subjects must remain at the clinical site until study procedures have been completed and the subject is ready for discharge.

[e] If pulse oximetry is < 93% at any time during the 1 hour postdose interval, pulse oximetry will be recorded every 5 minutes until levels return to ≥ 93% or until the subject is referred for appropriate medical care, if clinically indicated

2.4. Analysis Sets

Subjects will be classified into the following analysis sets: all enrolled and full analysis sets. Analyses of change from baseline will include only those subjects who have both baseline and at least 1 post-baseline observation in that phase.

2.4.1. All Enrolled Analysis Set

This analysis set will include all subjects who are eligible to enter this study and received at least 1 dose of intranasal study medication.

2.4.2. Full Analysis Set

The following analysis sets will be used to summarize efficacy and safety data and are defined for each phase. Analyses of change from baseline will include only those subjects who have both baseline and at least 1 post-baseline observation in that phase.

Full (IND) analysis set: All subjects who receive at least 1 dose of intranasal study medication in the induction phase.

Full (OP/MA) analysis set: All subjects who receive at least 1 dose of intranasal study medication in the optimization/maintenance phase.

2.4.3. Follow-up Analysis Set

The Follow-up analysis set includes all subjects who enter the follow-up phase. This analysis set will be used to summarize all safety evaluations during the follow-up phase.

2.5. Definition of Subgroups

Descriptive statistics will be provided for the response and remission rates to a second induction phase in the subgroup of subjects who had relapsed in study ESKETINTRD3003.

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

Treatment-emergent adverse events (TEAEs)

- For subjects who enter the study at the induction phase, treatment-emergent AEs are those events with an onset date/time on or after the start of IND phase study medication, and occurred on or before the end of the optimization/maintenance phase. A conservative approach will be used to handle the missing dates for AEs

- For subjects who directly enter the optimization/maintenance phase of this study, treatment-emergent AEs are those events with an onset date/time on or after the start of OP/MA phase study medication, and occurred on or before the end of the optimization/maintenance phase. A conservative approach will be used to handle the missing dates for AEs

Onset Date

AEs for each phase are those events with an onset date/time on or after the start of that particular phase and occurred on or before the end of that phase. The rules for estimating incomplete AE onset dates will be as follows:

Subject Entry into 54135419TRD3008 at the IND Phase:

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

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

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

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

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

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

ii) One day after the IND start date, if this date is the same year that the AE occurred.

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

Subject Entry into 54135419TRD3008 at the OP/MA Phase:

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

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

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

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

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

i) January 1 of the year of onset, as long as this date is after the OP/MA start date

ii) One day after the OP/MA start date, if this date is the same year that the AE occurred.

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

Resolution Date

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

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

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

Subject Entered into 54135419TRD3008 at the IND Phase:

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

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

ii) The time of intranasal medication start in the IND phase if the date of onset is the same as IND start date

Subject Entered into 54135419TRD3008 at the OP/MA Phase:

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

i) 00:00 if the date of onset is after OP/MA start date

ii) The time of intranasal medication start in the OP/MA phase if the date of onset is the same as OP/MA start date

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

2.7. 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:

Subject Entered into 54135419TRD3008 at the IND Phase:

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 IND 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 IND 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.

Subject Entered into 54135419TRD3008 at the OP/MA Phase:

If the month of the concomitant medication start date is equal to the month of the start of the optimization phase, then the estimated start date is the OP/MA start date;

If the month of the concomitant medication start date is greater than the month of the start of the OP/MA 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 OP/MA 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. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

An IDMC will be established to monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study. The committee will meet every 6 months to review safety data. After the reviews, the IDMC will make recommendations regarding the continuation of the study.

The IDMC will review CIOMS (Council for International Organizations of Medical Sciences) reports and summaries of AEs including AEs by preferred term, serious adverse events (SAE), and discontinuations due to AEs. Details about the review to be performed and the roles and responsibilities of the IDMC are presented in a separate IDMC charter.

Interim analyses will be performed on as needed basis (e.g. request from health authorities). Details of statistical output required for the interim analyses will be defined in the Data Presentation Specifications.

Sensitivity/exploratory analyses may be conducted for efficacy and safety variables of interest to evaluate the impact missed doses and/or remote visits which occurred due to COVID-19.

4. SUBJECT INFORMATION

4.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics (Table 2) and psychiatric history at baseline (Table 3) will be summarized for the All Enrolled analysis set (described in Section 2.4.1). 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 values (described in Section 2.2) 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 in years (18 - 44, 45 - 64, 65 – 74, ≥ 75)
- Sex (male, female)
- Race[a] (White, Black or African American, Asian, American Indian or Alaskan native, Native Hawaiian or other Pacific islander, other)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)
- Baseline BMI (underweight: < 18.5 kg/m^2, normal: 18.5 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
- Country
- Region

[a] If multiple race categories are indicated, then Race is recorded as "Multiple".

Table 3: Psychiatric History at Baseline Variables

Continuous Variables:

- Baseline MADRS total score
- Baseline PHQ-9 total score
- Baseline CGI-S score
- Age (years) when diagnosed with major depressive disorder (MDD)
- Duration of current episode

Categorical Variables:

- Baseline CGI-S score
- Baseline C-SSRS category (no event, suicidal ideation, suicidal behavior)
- Family history of
  - Depression
  - Anxiety Disorder
  - Bipolar Disorder
  - Schizophrenia
  - Alcohol Abuse
  - Substance Abuse

Note: The psychiatric history is derived from the first study subjects participated in. For example, if a subject first participated in ESKETINTRD3001, then went on to ESKETINTRD3003 and continued to participate in 54195413TRD3008, the psychiatric history is obtained from the ESKETINTRD3001 database and will be copied to the 54195413TRD3008 database.

4.2. Disposition Information

The number of subjects who enrolled from studies ESKETINTRD3001, ESKETINTRD3002, ESKETINTRD3003, ESKETINTRD3004, ESKETINTRD3005, or ESKETINTRD3006 (US sites only) will be provided.

The following disposition summaries will be provided for IND and OP/MA phases separately. These summaries will be provided for each of the Full analysis sets described in Section 2.4.2.

- The number of subjects who entered a specific treatment phase
- The number of subjects who discontinued a specific treatment phase prematurely and their reasons for discontinuation
- The number of subjects who are ongoing in each phase at the time the sponsor terminated the study.

The number of subjects who terminated the trial and the reasons for ending study participation throughout the study will also be summarized. This will be summarized for All Enrolled analysis set described in Section 2.4.1.

4.3. 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 for the Full analysis sets and across both phases for the All Enrolled analysis set described in Section 2.4.2.

- The total duration of exposure for the intranasal study drug for each phase is defined as the time between the first and the last dose of study medication in that specific phase (last day of study medication - first day of study medication + 1). If a subject only receives a partial dose it is considered as a day of dosing.

  Descriptive statistics (N, mean, SD, median, minimum and maximum) and frequency distribution of total duration of exposure of intranasal study drug will be presented. A frequency distribution of the total number of dosing sessions of intranasal study medication will be presented.

  Starting at Week 4, during the optimization/maintenance phase, the number and percentage of subjects at each dosing frequency (weekly, every other week and every 4 weeks) and the number of subjects who changed their frequency will be summarized every 4 weeks.
- Modal dose for a subject is defined as the most frequently taken dose by a subject. Mean dose of a subject is calculated as the sum of doses during the phase divided by the total number of days exposed in the phase. The final dose is the last non-zero dose received during the 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 by phase. A frequency distribution of dose level (28, 56 and 84 mg) will be presented at each dosing session. In addition, at end of each phase the number and percentage of subjects at each dose (28, 56 and 84 mg) of intranasal study medication will be provided.

4.4. Protocol Deviations

Deviations that occurred during the study will be tabulated for the All Enrolled analysis set. Major deviations will be tabulated for the following categories: subject not withdrawn as per protocol, selection criteria not met, excluded concomitant treatment, treatment deviation, non-compliance, regulatory requirement. More categories may be included depending on the nature of the protocol deviation.

4.5. Concomitant Medications

The number and percent of subjects who receive concomitant therapies will be summarized by phase using the generic term of the medication for the Full (IND, OP/MA) analysis sets described in Section 2.4.2.

5. EFFICACY

5.1. Analysis Specifications

5.1.1. Data Handling Rules

For the efficacy scales MADRS, CGI-S, PHQ-9, and SDS both observed case and last observation carried forward (LOCF) values will be determined for the induction, optimization/maintenance phases. For analysis performed by phase, LOCF will be performed within the respective phase. For analysis performed for entire treatment phase, induction data will be carried forward to optimization/maintenance. 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 as ‘Day X LOCF’ or ‘Week X LOCF’

5.1.2. Imputation Methods for Missing Items

Imputation of the MADRS total score is described in Section 5.2.1.1. 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 considered missing.

5.2. Efficacy Endpoints

Efficacy analyses during the induction phase and the optimization/maintenance phase will be provided for the Full analysis sets defined in Section 2.4.2.

5.2.1. Montgomery-Asberg Depression Rating Scale (MADRS)

5.2.1.1. Definition

The MADRS is a clinician-rated scale designed to measure depression severity and to detect changes due to antidepressant treatment[5]. 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 non-missing items multiplied by the ratio of the maximum number of items (i.e., 10) to the number of non-missing items.

A subject is defined a responder at a given time point if the percent improvement in MADRS total score is $\geq$ 50%.

A subject is defined as a remitter at a given time point if the MADRS total score of $\leq$ 12 at that time point.

5.2.1.2. Analysis Methods

Descriptive statistics of the total score and change from baseline (of the respective phase) will be provided for each visit during both IND and OP/MA phases. Graphical presentations will be provided. In addition, the proportion of subjects who responded and remitted based on the MADRS total score will be provided over time for each phase. Summaries of both observed and LOCF data will be presented.

For subjects who had relapsed in ESKETINTRD3003 and participated in a second induction treatment phase, the proportion of responders and remitters using the MADRS total score at the end of the second induction phase will be provided.

5.2.2. Clinical Global Impression – Severity (CGI-S)

5.2.2.1. Definition

The 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[3]. 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.

5.2.2.2. Analysis Methods

Descriptive statistics of the medians and median change from baseline (of the respective phase) will be provided for each visit during both IND and OP/MA phases. In addition, a frequency distribution will be provided for each visit for both phases. Summaries of both observed and LOCF data will be presented.

5.2.3. Patient Health Questionnaire – 9 item (PHQ-9)

5.2.3.1. Definition

The PHQ-9 is a 9-item, self-report scale assessing depressive symptoms[8]. Each item is rated on a 4-point scale (0 = Not at all, 1 = Several Days, 2 = More than half the days, and 3 = Nearly every day), with a total score range of 0-27. A higher score indicates greater severity of depression. The recall period is 2 weeks. The scale scores each of the nine symptom domains of the Diagnostic and Statistical Manual of Mental Disorders (DSM) Major Depressive Disorder criteria and it has been used both as a screening tool and a measure of response to treatment for depression. The severity of the PHQ-9 is categorized as follows: None-minimal (0 - 4), Mild (5 - 9), Moderate (10 - 14), Moderately Severe (15 - 19) and Severe (20 - 27). A subject is defined as a responder at a given time point if the percent improvement from baseline in PHQ-9 total score is ≥ 50%. A subject is defined as a remitter at a given time point if the PHQ-9 total score is <5 at that time point.

5.2.3.2. Analysis Methods

Descriptive statistics of the total score and change from baseline (of the respective phase) will be provided for each visit during both IND and OP/MA phases. The frequency of severity categories will be summarized over time during each phase. Graphical presentations will be provided. In addition, the proportion of subjects who achieve response and remission based on the PHQ-9 total score will be summarized for each visit during both phases. Summaries of both observed and LOCF data will be presented.

For subjects who had relapsed in ESKETINTRD3003 and participated in a second induction treatment phase, the proportion of subjects who achieve response and remission at the end of the second induction phase will be provided.

5.2.4. Sheehan Disability Scale (SDS)

5.2.4.1. 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.

5.2.4.2. Analysis Methods

Descriptive statistics of the total score and change from baseline (of the respective phase) will be provided for each visit during both IND and OP/MA phases. Graphical presentations will be provided. Summaries of both observed and LOCF data will be presented. The total score as well as the individual item scores will be summarized. In addition, the proportion of subjects who achieve response and remission will be summarized at each time point.

5.2.5. EuroQol Group; 5 Dimension; 5 level (EQ-5D-5L)

5.2.5.1. Definition

The EQ-5D-5L[1,2] is a standardized 2-part instrument for use as a measure of health outcome, primarily designed for self-completion by respondents. It essentially consists of the EQ-5D-5L descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each of the 5 dimensions is divided into 5 levels of perceived problems (Level 1 indicating no problem, Level 2 indicating slight problems, Level 3 indicating moderate problems, Level 4 indicating severe problems, and Level 5 indicating extreme problems).

The subject selects an answer for each of the 5 dimensions considering the response that best matches his or her health "today." The descriptive system can be represented as a health state. The EQ VAS self-rating records the respondent's own assessment of his or her overall health status at the time of completion, on a scale of 0 (the worst health you can imagine) to 100 (the best health you can imagine).

The time taken to complete the questionnaire varies with age, health status, and setting but is likely to be around 1 minute.

Individual scores from the 5 dimensions will be used to obtain a weighted health status index as shown below:

i) Scores from each dimension will be combined to obtain a 5L profile score or health state: e.g., a score of 1 for each dimension will give a 5L profile score of 11111. Dimension scores will be combined in the following order: Mobility, Self-Care, Usual Activities, Pain/Discomfort, Anxiety/Depression

ii) The value set of the Health Status Index for various values of 5L profile scores is published for Canada in the following website: https://www.ncbi.nlm.nih.gov/pubmed/26492214

iii) The Canadian value set will be used to get the HSI values for all the countries participating in the study

In addition, a sum score will be derived as follows: The scores of the five dimensions (values 1-5) will be added (sums between 5 and 25). From this score, subtract 5 (range 0-20) and multiply by 5 (range 0-100).

5.2.5.2. Analysis Methods

Descriptive statistics of actual values and changes from baseline for the weighted EQ-5D health status index, the EQ VAS, and the sum score will be summarized for each visit for both IND and OP/MA phases. In addition, a frequency distribution will be provided for each individual dimension at each visit for both phases. Summaries of observed data will be presented.

5.2.6. Treatment Satisfaction Questionnaire for Medication (TSQM-9)

5.2.6.1. Definition

The TSQM-9 is a 9-item generic patient reported outcome instrument to assess patients' satisfaction with medication. It is derived from the longer TSQM Version 1.4 and covers domains of effectiveness (item 1-Satisfied, Ability to Treat; item 2-Satisfied, Relieves Symptoms; item 3-Satisfied, Time It Takes to Work), convenience (item 4-Easy/Difficult to Use the Med; item 5-Easy/Difficult to Plan the Use; item 6 -Convenient, Take Med as Instructed) and global satisfaction (item 7-Confident Taking This Med Is Good; item 8-Certain, Good Things Outweigh Bad; item 9-How Satisfied, Overall). The instrument is scored by domain with a transformed scores ranging from 0-100 where a lower score indicates lower satisfaction. The recall period is "the last 2-3 weeks".

Scoring algorithm

Effectiveness:
([(Item 1 + Item 2 + Item 3) − 3] divided by 18) × 100
If one item is missing: [Sum of two completed items − 2] divided by (12) × 100

Convenience:
([Sum of Item 4 to Item 6) − 3] divided by 18) × 100
If one item is missing: [Sum of two completed items − 2] divided by (12) × 100

Overall satisfaction:
([Sum(Item 7 to Item 9) – 3] divided by 14) * 100
If either Item 7 or 8 is missing
([(Sum(the two completed items)) – 2] divided by 10) * 100
If Item 9 is missing
([(Sum(Item 7 and Item 8)) – 2] divided by 8) * 100

5.2.6.2. Analysis Methods

Descriptive statistics of the transformed score and change from baseline (of the respective phase) will be provided for each domain by visit during both IND and OP/MA phases. Summaries of observed data will be presented.

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5.2.7. Quality of Life in Depression Scale (QLDS)

5.2.7.1. Definition

The QLDS is a disease specific PRO designed to assess health related quality of life in patients with Major Depressive Disorder. The instrument has a recall period of “at the moment", contains 34-items with “yes” / “no” response options and takes approximately 5-10 minutes to complete. The score range is from 0 (good quality of life) to 34 (very poor quality of life).

5.2.7.2. Analysis Methods

Descriptive statistics of the total score and change from baseline (of the respective phase) will be provided for each visit during both IND and OP/MA phases. Summaries of observed data will be presented.

6. SAFETY

Safety data for the induction and optimization/maintenance phases will be presented separately for each phase. Summaries for each phase will be based on the Full analysis sets described in Section 2.4.2. In addition, adverse event and cognition data will be summarized for the entire treatment period combining the induction and optimization/maintenance phases. Summaries for the entire treatment period will be based on the All Enrolled analysis set described in Section 2.4.1.

6.1. Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) (version 18.1 or above) will be used to classify AEs by system organ class and preferred term. TEAEs that occurred in each study phase 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 will be summarized by system organ class and preferred term. Data listings will be generated for deaths, other SAEs, and discontinuations due to AEs.

In addition, data listing and summary will be provided for subjects with AEs ongoing at the time of entry into this study.

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 study phase:

- TEAEs in the induction phase:
  a. If AE onset time is not missing:
     i) If subjects continue to OP/MA phase: IND phase start date/time ≤ AE onset date and time < IND phase end date
     ii) If subjects discontinue in the IND phase: IND phase start date/time ≤ AE onset date and time ≤ IND phase end date

b. If AE onset time is missing:

i) If subjects continue to OP/MA phase: IND phase start date/time ≤ AE onset date < IND phase end date

ii) If subjects discontinue in the IND phase: IND phase start date/time ≤ AE onset date ≤ IND phase end date

- TEAEs in the optimization/maintenance phase:

a. If AE onset time is not missing: OP/MA phase start date/time ≤ AE onset date and time ≤ OP/MA phase end date

b. If AE onset time is missing: OP/MA phase start date ≤ AE onset date ≤ OP/MA phase 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. AE duration for transient dizziness/vertigo and anxiety will also be summarized.

Adverse Events of Special Interest

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

- drug abuse, dependence and withdrawal (Aggression, Confusional state, Decreased activity, Dependence, Disorientation, Dissociation, Dissociative disorder, Dizziness, Drug use disorder, Drug abuse, Drug abuser, Drug dependence, 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);
- events potentially related to suicidality (Completed suicide, Depression suicidal, Intentional overdose, Intentional self-injury, Multiple drug overdose intentional, Poisoning deliberate, Self-injurious behavior, Self-injurious ideation, Suicidal behavior, Suicidal ideation, Suicide attempt)
- hepatic adverse events (Cholecystitis, Cholelithiasis, Hepatic steatosis, Hepatitis, Non-alcoholic steatohepatitis, Primary biliary cholangitis, Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood bilirubin increased, Gamma-glutamyl transferase increased, Hepatic enzyme increased, Liver function test abnormal, Liver function test increased, Transaminases increased, Urine bilirubin increased, Urobilinogen urine increased)
- events related to renal disorders (Cystitis, Pyelonephritis, Urethritis, Urinary tract infection, Blood creatinine increased, Blood urea increased, Blood urine present, Creatinine renal clearance increased, Protein urine present, Urine analysis abnormal, Urine leukocyte esterase positive, Bladder discomfort, Bladder irritation, Bladder outlet obstruction, Cystitis noninfective, Dysuria, Haematuria, Hypertonic bladder, Lower urinary tract symptoms, Micturition urgency, Nephrolithiasis, Nocturia, Pollakiuria, Polyuria, Proteinuria, Renal colic, Renal failure, Semenuria, Stress urinary incontinence, Ureterolithiasis, Urge incontinence, Urinary bladder polyp, Urinary hesitation, Urinary incontinence, Urinary retention)
- symptoms of dissociation persisting beyond the typical ≤2 hour post esketamine administration (dissociation)
- delirium (Post-injection delirium sedation syndrome, Postoperative delirium, Delirium, Intensive care unit delirium)
- psychosis (Acute psychosis, Affective disorder, Alcoholic psychosis, Bipolar I disorder, Epileptic psychosis, Hysterical psychosis, Mania, Parkinson's disease psychosis, Postictal psychosis, Psychosis postoperative, Psychotic disorder, Psychotic disorder due to a general medical condition, Reactive psychosis, Rebound psychosis, Schizoaffective disorder, Substance-induced psychotic disorder, Transient psychosis)
- mania (Hypomania, Mania)

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

Summary statistics for the duration of all episodes of TEAEs associated with discharge readiness (Dissociation, Dizziness, Feeling abnormal, Feeling drunk, Nausea, Somnolence, Vertigo, and Vomiting) with an onset on the day of intranasal study drug administration will be provided for each treatment phase. During the induction phase the summaries are presented for each dosing session and during the optimization/maintenance phase the summaries are presented for the first four dosing sessions and at the Month 3, Month 6 and Month 9 dosing sessions. In addition, the number of occurrences of TEAEs associated with discharge readiness and the number of

occurrences of TEAEs associated with substance dependence is presented by dosing sessions for each treatment phase.

AEs collected at Follow-up phase for France subjects will be provided in a listing.

6.2. 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 in the IND and OP/MA phases. Baseline values (as described in Section 2.2) will be used for change summaries and to determine abnormal values during all treatment phases.

Clinical laboratory tests that meet the criteria for markedly abnormal will be listed by subject for each phase. The incidence of treatment-emergent markedly abnormal (TEMA) laboratory values that occurred at any time during each treatment phase will be presented. Clinical laboratory test values will be considered "TEMA using the criteria defined by the Sponsor (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 (defined above) 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 post-baseline 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. Baseline values are defined in Section 2.2.

The incidence of subjects with ALT values > 3*upper normal limit (ULN) will be presented for each study phase. Additionally, incidence of hepatic toxicity (Hy's Law)[9] defined as ALT values > 3*ULN and total bilirubin values > 2*ULN will be presented for each study 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 the Baseline value is missing) will be eligible for these analyses.

6.3. Vital Signs, Weight, and BMI

Descriptive statistics for values and changes from Baseline values (described in Section 2.2) at each scheduled time-point during the induction and optimization/maintenance phases will be presented for temperature, systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, oxygen saturation, weight, and BMI. Baseline will be used for change summaries and to determine abnormal values during all treatment phases (IND and OP/MA). Graphical presentations will be provided.

In addition, descriptive statistics of pulse rate and blood pressure (systolic and diastolic) values and changes and percent changes from predose will be provided for each intranasal dosing day.

The proportion of subjects who have a treatment-emergent abnormality, as defined in Table 4 below, during each treatment phase will be presented. A listing of subjects meeting any of the following criteria during each treatment phase will also be provided.

Table 4: Treatment-Emergent Abnormality Categories for Vital Signs

Vital Parameter	Post-baseline value outside of normal limit if:	
	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 (mmHg)	A decrease from Baseline of ≥ 20 to a value ≤ 90	An increase from Baseline of ≥ 20 to a value ≥ 180
Diastolic BP (mmHg)	A decrease from Baseline of ≥ 15 to a value ≤ 50	An increase from Baseline of ≥ 15 to a value ≥ 105

BP = blood pressure; Baseline is defined in Section 2.2.

The proportion of subjects who experienced treatment-emergent acute hypertension (systolic BP ≥ 180 or diastolic BP ≥ 110) at any time during each treatment phase will be summarized by hypertension status.

Mean (+/-SE) values for systolic BP, diastolic BP and heart rate will be summarized by hypertension status and presented graphically for each treatment phase. In addition, for subjects with hypertension who receive antihypertensive medication, the same tables and 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.

6.4. 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 values are defined in Section 2.2.

The maximum postbaseline value during each treatment phase (induction and optimization/maintenance phase) will be presented separately and 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 at each scheduled time point during both treatment phases (induction and optimization/maintenance phases).

The frequency of treatment-emergent abnormalities will be tabulated and presented for all treatment phases. The identification of treatment-emergent abnormal ECG values is based on the post-baseline value (a value occurring after the start of the phase) being out of range while the Baseline value (described in Section 2.2) is either missing or within the limits given in Table 5. If postbaseline ECG results are above the upper limits (abnormally high) and the Baseline value is below the lower limits (abnormally low) or missing, 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) or missing. Abnormal ranges for the HR, PR, QRS and QT intervals are given in Table 5.

Table 5: 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, QTcB and QTcF) the incidence of abnormal QTc values and changes from Baseline will be summarized. Criteria for abnormal corrected QT intervals and changes from Baseline are given in Table 6 and are derived from the International Conference on Harmonization (ICH) E14 Guidance[4] (the same criteria apply to all QT corrections).

Table 6: 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 in Section 2.2.

The proportion of subjects with treatment emergent abnormalities will be presented for the IND and OP/MA phases. A listing of subjects with abnormalities will also be provided.

6.5. Nasal Examination

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

Subsequent examinations will consist of a visual inspection of the nostrils, nasal mucosa, and throat for nasal erythema, rhinorrhea, rhinitis, capillary/blood vessel disruption and epistaxis and graded as follows: absent, mild, moderate, or severe.

Changes in findings from Baseline (described in Section 2.2) for each examination (including the upper respiratory tract/throat) will be listed for each treatment phase.

6.6. Other Safety Parameters

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

The C-SSRS[7] is a low-burden measure of the spectrum of suicidal ideation and behavior that was developed in the National Institute of Mental Health Treatment of Adolescent Suicide Attempters Study to assess severity and track suicidal events through any treatment. It is a 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 based on the Full analysis set for subjects who have at least 1 post-baseline C-SSRS measurement and a pre-treatment C-SSRS assessment.

A frequency distribution at each scheduled time point will be provided. Shifts from the Baseline value (described in Section 2.2) to the most severe/maximum score during each phase 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 value (described in Section 2.2) to the maximum category during each phase will be summarized.

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

The MOAA/S will be used to measure treatment-emergent sedation with correlation to levels of sedation defined by the American Society of Anesthesiologists (ASA) continuum. The MOAA/S

scores range from 0 (No response to painful stimulus; corresponds to ASA continuum for general anesthesia) to 5 (Readily responds to name spoken in normal tone [awake]; corresponds to ASA continuum for minimal sedation).

The MOAA/S is measured on each dosing day every 15 minutes from predose to t=+1 hours postdose or longer, if necessary, until the subject has a score of 5.

- If the score is ≤ 3 at any time during the 1 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 hours postdose).
- If a subject does not have a score of 5 at t=+1 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 of the MOAA/S score, changes from predose, and the proportion of subjects experiencing sedation (score less than or equal to 4) will be summarized at each scheduled time point. A bar chart over time for MOAA/S will be provided.

6.6.3. Clinical Global Assessment of Discharge Readiness (CGADR)

The 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 (e.g., sedation, blood pressure, and other adverse events)?"

On each intranasal dosing day, the CGADR will be performed at 30 mins postdose, repeated every 15 minutes if necessary until the response is 'Yes'. On all intranasal treatment session days, subjects must remain at the clinical site until study procedures have been completed and the subject is ready for discharge.

The proportion of subjects with a response of 'No' at each time point will be presented by each of the treatment phases.

6.6.4. Computerized Cognitive Battery and Hopkins Verbal Learning Test-Revised (HVLT-R)

The effect of intranasal esketamine on cognition will be assessed using HVLT-R.

The computerized cognitive battery provides assessment of multiple cognitive domains, including attention, visual learning and memory, and executive function. The tests use culture-neutral stimuli, enabling use in multilingual/multicultural settings. The HVLT-R is a measure of verbal learning and memory and is a 12-item word list recall test. The total number of correct responses are captured for 4 trials as well as the number of true-positive responses and false-positive errors in Trial 4 (Delayed Recall). The Total Recall will be derived as the sum of trials 1, 2 and 3. Retention % will be derived as (the number of correct responses in Trial 4) / (higher score of Trials 2 and 3) * 100. Recognition Discrimination Index will be derived as the total number of true-positives - the total number of false-positives.

See Attachment 2 for details of this analysis.

6.6.5. Physician's Withdrawal Checklist, 20-item (PWC-20)

At the request of the National Agency for the Safety of Medicines and Health Products in France, a 4-week Follow-up Phase was added to assess for potential withdrawal symptoms following cessation of intranasal esketamine using PWC-20 assessment. The PWC-20 will be performed at the Early Withdrawal/ End of Study Visit and every week during the 4-week Follow-up Phase after discontinuation of intranasal esketamine treatment. In order to better assess potential withdrawal symptoms from the intranasal medication it is recommended that any ongoing oral antidepressant medication be continued for the duration of the follow-up phase unless determined as not clinically appropriate.

The PWC-20 is a 20-item simple and accurate method to assess potential development of discontinuation symptoms after stopping of study drug. The PWC-20 is a reliable and sensitive instrument for the assessment of discontinuation symptoms. Discontinuation symptoms occur early and disappear rather swiftly, depending upon speed of taper, daily medication dose, and drug elimination half-life.

The proportion of subjects with withdrawal symptoms at the end of Optimization/Maintenance Phase will be presented for the subjects in France. In addition, symptoms at follow-up will be compared to the end of therapy visit and will be summarized using the following categories: new or worsened symptoms, symptoms present and unchanged, no symptoms, and improved.

7. HEALTH ECONOMICS

7.1. Healthcare Resource Use Questionnaire (HRUQ)

Medical resource utilization data, associated with medical encounters, will be collected using the HRUQ during the optimization/maintenance phase.

The number and percentage of subjects who visited at least one healthcare professional or had a hospital emergency room visit because of their depression in the 4 weeks preceding each time point will be summarized for each type of healthcare professional. The total number of visits to each type of healthcare professional, total number of visits to any healthcare professional, and the total number of hospital emergency room visits related to depression in the 4 weeks preceding each time point will be summarized at each time point with descriptive statistics.

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ATTACHMENTS

♦ **Attachment 1: Criteria of Markedly Abnormal Laboratory Values**

Laboratory Parameter	Markedly Abnormal Limits 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
Erythrocytes (RBC) [$x10^{12}$/L] - female	3.0	5.5
- male	3.0	6.4
Leukocytes(WBC) [$x10^9$/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 gender is indicated;
N/A = Not applicable.

Attachment 2: Statistical Analysis Plan for COGSTATE (dated of 07 Mar 2019)

NCT02782104

Statistical Analysis Plan

AN OPEN-LABEL LONG-TERM EXTENSION SAFETY STUDY OF INTRANASAL ESKETAMINE IN TREATMENT-RESISTANT DEPRESSION

SAFETY AND SUSTENANCE OF ESKETAMINE TREATMENT RESPONSE WITH REPEATED DOSES AT INTERVALS DETERMINED BY SYMPTOM SEVERITY (SUSTAIN-3)

Protocol Number: 54135419TRD3008

Sponsor: Janssen Research & Development, LLC

Address: Cogstate, Inc.
Level 4, 195 Church Street
New Haven, CT, USA, 06510

SAP Version: 1
SAP Date: 07 Mar 2019
Protocol Version: Approved; Amendment 2, Date: 9 May 2018

1. Note

Cogstate has prepared a Statistical Analysis Plan (SAP) for the Sponsor to review and sign-off for study 54135419TRD3008. Analyses will be provided after this document has been finalized and officially signed. Anything in italics is taken directly from the protocol. For more details, please refer to the study protocol.

2. Version History

Version Number	Date	Author	Reason for Revision
1.0	07 MAR 2019	PPD	Initial Version

Cogstate

3. Signature Page for SAP Approval

The following signatures indicate the approval of the statistical analysis plan for the data Cogstate is responsible for analysing in study 54135419TRD3008.

Cogstate

Name (print): PPD

Position:

Signature:

Date (DD-MMM-YYYY):

Janssen Research & Development, LLC

Name (print): PPD

Position:

Signature:

Date (DD-MMM-YYYY):

Name (print): PPD

Position:

Signature:

Date (DD-MMM-YYYY):

4. Table of Contents

5. Abbreviations

Abbreviation	Description
DET	Detection Test
EW	Early Withdrawal
GML	Groton Maze Learning Test
HVLT-R	Hopkins Verbal Learning Test-Revised
IDN	Identification Test
ISD	Intra-Subject Standard Deviation
OCL	One Card Learning
ONB	One Back Test
RCI	Reliable Change Index
RT	Reaction Time
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
TLF	Tables, Listings and Figures
TRD	Treatment-Resistant Depression

6. Introduction

This Statistical Analysis Plan (SAP) contains a more technical and detailed elaboration of the principal features of the analysis described in the 54135419TRD3008 Study Protocol related to Cogstate computerized battery and the Hopkins Verbal Learning Test – Revised (HVLT-R) and includes detailed procedures for executing the statistical analysis of the Cogstate battery data.

The SAP is finalized and signed prior to database lock. If needed, revisions to the approved SAP may be made prior to database lock. Revisions will be version controlled.

Any changes from the analyses planned in the SAP will be justified in the Cogstate statistical report.

Prior to database lock, a review of all tables, listings, and figures will occur. This requires the sponsor to send Cogstate SDTM FT and SUPPFT datasets for both the computerized tests as well as the Hopkins Verbal Learning Test – Revised (HVLT-R), in addition to an ADSL dataset. The same datasets will be requested again immediately after database lock (for both the interim and final analyses) to perform the statistical analyses.

7. Study Objectives Related to Cogstate

The primary objective of this study is to assess the safety and tolerability of intranasal esketamine in subjects with Treatment-Resistant Depression (TRD), with special attention to potential long-term effects on cognitive function.

8. Study Design

8.1. General Description

This is a multicenter, open-label long term extension study to evaluate the safety, tolerability, and efficacy of intranasal esketamine in subjects with TRD. This study has 2 open label phases:

- *A 4-week induction phase*
- *A variable duration optimization/maintenance phase*

Induction Phase

Subjects will self-administer open-label intranasal esketamine as a flexible dose regimen twice a week for 4 weeks [as outlined in Study Protocol Section 6.1.1].

At the end of the induction phase, subjects may be eligible to proceed to the optimization/maintenance phase, according to the investigator's clinical assessment of the benefit versus risk for the subject.

If a subject withdraws from the study before the end of the induction phase for reasons other than withdrawal of consent or is not eligible to proceed to the optimization/maintenance phase, an Early Withdrawal (EW) visit will be conducted within 1 week of the last intranasal dose.

Subjects who are currently in the induction phase at the time the 54135419TRD3008 study is completed will conduct an "End of Study" visit as their final study visit within 1 week of the last intranasal dose.

Optimization/Maintenance Phase

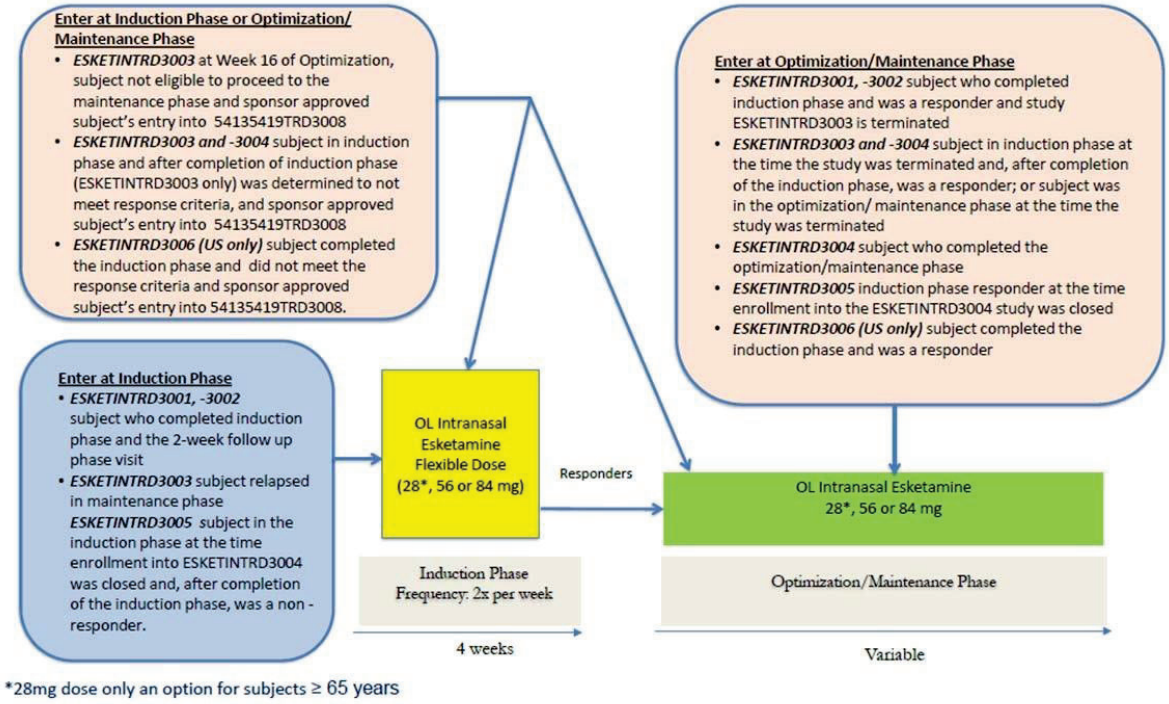
During this phase, the dose and intranasal treatment session frequency can be adjusted based on the criteria outlined in [Study Protocol Section 6.1.2].

If a subject withdraws from the study before the end of the optimization/maintenance phase for reasons other than withdrawal of consent, an EW visit will be conducted within 1 week of the last intranasal dose.

Subjects who are currently in the optimization/maintenance phase at the time the 54135419TRD3008 study is completed will conduct an "End of Study" visit as their final study visit within 1 week of the last intranasal dose.

8.2. Schematic Design

Figure 1: Schematic Overview of Study 54135419TRD3008



8.3. Scheduled Visits

Table 1: Visit Schedule for Cogstate Computerized Cognitive Battery and HVLT-R

Analysis Phase	Scheduled Day[a]	Time Interval[a] (label on output)	Time Interval[a] (Day)	Target Time Point[a] (Day)	Analysis Visit
IND	1	Baseline	≤ 1	1	Yes
	28	Day 28 (IND)	2 to end of IND	28	Yes
	IND final visit	End Point (IND)	2 to end of IND		Yes
OP/MA i = 1, 2, 3…	15	Week 3 (OP/MA)	1-60	15	Yes
	106	Week 16 (OP/MA)	16 – 148	106	Yes
	106 + i*84	Week (16 + i*12) (OP/MA)	65 + i*84 to 148 + i*84	106 + i*84	Yes
	OP/MA final visit	End Point (OP/MA)	1 to end of OP/MA		Yes

[a] For IND phase, time interval is relative to the first day of the induction phase.
For OP/MA phase, time interval is relative to the first day of the optimization/maintenance phase.

9. Analysis Set and Population

9.1. Unblinding Procedure

As this study is open-label, blinding procedures are not applicable.

9.2. Analysis Set

9.2.1. All Enrolled Analysis Set

All subjects who were eligible to enter this study and received at least one dose of intranasal esketamine.

9.3. Sample Size and Analysis Population

No formal sample size calculation was performed. The study population will include adult and elderly men and women who previously participated in studies ESKETINTRD3001, ESKETINTRD3002, ESKETINTRD3003, ESKETINTRD3004, or ESKETINTRD3005, or ESKETINTRD3006 (US sites only).

9.4. Handling of missing data

No imputations will be performed in the event of missing data due to dropouts or omitted visits. All incomplete subject profiles will be retained in the analysis. In view of issues of reliability, all analyses will be conducted with completion failures removed.

10. Analysis Endpoints, Baseline Definition, and Outcome Measures

10.1. Analysis Endpoints

The analysis endpoint for each of the tests in the Cogstate computerized cognitive battery and for the Hopkins Verbal Learning Test-Revised (HVLT-R) is change from baseline scores over time.

10.2. Baseline Definitions

10.2.1. First Baseline (i.e., Comparison to Pre-Drug Exposure)

For all subjects enrolled in 54135419TRD3008 (except for those subjects entering from ESKETINTRD3006), baseline is defined as Baseline (IND) (i.e., Study Day 1) of the first study from which they have entered. For example, if a subject participated in study TRD3005 and went to TRD3004 and then finally joined 3008, the first baseline will be the Baseline (IND) from study TRD3005.

10.2.2. Study Baseline (i.e., Comparison Pre-Drug Exposure Within 54135419TRD3008)

For subjects who enter the study at the Induction Phase, study baseline is defined as the last observation prior to or on the start date of the Induction Phase. For subjects who enter the study at the Optimization/Maintenance Phase, study baseline is defined as the last observation prior to or on the start date of the Optimization/Maintenance Phase.

10.3. Outcome Measures Related to Cogstate Analysis

The cognitive tests administered include computerized tests from the Cogstate Battery as well as the HVLT-R.

Detection (DET; Psychomotor Function)
The Detection test is a measure of psychomotor function and uses a well-validated simple reaction time paradigm with playing card stimuli. In this test, the playing cards all depict the same joker. The subject is asked to press the **Yes** key as soon as the card in the center of the screen turns face up. The software records the mean reaction time (log10 ms).
Duration of Test: 2 minutes

Identification (IDN; Attention)
The Identification test is a measure of visual attention and uses a well-validated choice reaction time paradigm with playing card stimuli. In this test, the playing cards are all either red or black jokers. The subject is asked whether the card displayed in the center of the screen is red. The subject responds by pressing the **Yes** key when the joker card is red and **No** when it is black. The software records the mean reaction time (log10 ms).
Duration of Test: 2 minutes

One Card Learning (OCL; Visual Learning)
The One Card Learning test is a measure of visual learning and uses a well-validated pattern separation paradigm with playing card stimuli. In this test, the playing cards are identical to those found in a standard deck of 52 playing cards (without the joker cards). The subject is asked whether the card displayed in the center of the screen was seen previously in this test. The subject responds by pressing the **Yes** or **No** key. The software measures the accuracy across all responses (arcsine sqrt % correct).
Duration of Test: 5 minutes

One Back (ONB; Working Memory)

The One Back test is a measure of working memory and uses a well-validated n-back paradigm with playing card stimuli. In this test, the playing cards are identical to those found in a standard deck of 52 playing cards (without the joker cards). The subject is asked whether the card displayed in the center of the screen is the same as the card presented immediately previously. The subject responds by pressing the **Yes** or **No** key. Because no card has been presented yet on the first trial, a correct first response is always **No**. The software records the mean reaction time (log10 ms).

Duration of Test: 3 minutes

Groton Maze Learning Test (GML; Executive Function)

The Groton Maze Learning test is a measure of problem solving and reasoning and uses a well-validated maze learning paradigm. In this test, the subject is shown a 10 x 10 grid of boxes on a computer screen. A 28-step pathway is hidden among these 100 possible locations. Each box represents move locations, and the grid refers to the box array (i.e., 10 × 10). Subjects are required to find the hidden pathway guided by [four] search rules. These rules are: do not move diagonally, do not move more than one box (i.e., do not jump), do not move back on the pathway, and return to the last correct location after an error. At each step only the most recently selected box is shown. Feedback is given with visual and auditory cues (green check marks and red crosses) to indicate whether the selected box is correct or incorrect. The head of path, or the last correct location, flashes with a green check when two errors are made in succession to indicate to the subject that they must return to this location. There are [20] well-matched alternate pathways available. The software records counts of total errors made across all learning trials.

Duration of Test: 5 minutes

Hopkins Verbal Learning Test-Revised (HVLT-R)

The HVLT-R, a measure of verbal learning and memory, is a 12-item word list recall test. Administration includes 3 learning trials, a delayed recall (20-minute) trial, and a 24-word recognition list (including 12 target and 12 foil words) (Benedict et al., 1998). The test administrator reads instructions and word lists aloud, and records words recalled/recognized by the subject. Scores include learning, delayed recall, and recognition. The HVLT-R is a well-validated and widely used measure of verbal episodic memory.

The tests will be administered in the following order: HVLT-R, computerized cognitive test battery, and HVLT-R Delayed.

Although each of the Cogstate computerized cognitive tests yields multiple outcome measures, research by Cogstate has identified a set of measures that are optimal for the detection of cognitive change in clinical trials at both the group and individual level (Falleti et al., 2006; Maruff et al., 2009; Bland & Altman, 1996a; Bland & Altman, 1996b).

For each Cogstate computerized cognitive test, a single primary outcome measure was selected prior to data analysis from each test in the battery to minimize experiment-wise error rates. Each primary outcome measure was selected because it has been shown to be optimal for the detection of change because:

a) It is drawn from a data distribution that contains only a small probability of floor or ceiling effects and no restriction in the range of possible performance values (Falleti et al., 2006; Bland & Altman, 1996a; Bland & Altman, 1996b).
b) It is drawn from a normal distribution or a distribution which can be corrected to normal through the use of appropriate mathematical transformation (e.g., logarithmic base 10, or arcsine) (Falleti et al., 2006; Bland & Altman, 1996a; Bland & Altman, 1996b).

Table 2 below summarizes the outcome measures for the Cogstate computerized battery and HVLT-R, with the tests from which they were derived, the operational definition, and the variable code.

Table 2: Cogstate and HVLT-R Tests Administered in Study 54135419TRD3008, the Cognitive Domains they Assess, and their Primary Outcome Measures

Test Type	Test	Cognitive Domain Assessed	Primary Outcome Measure	Interpretation of Primary Outcome Score
Cogstate Battery	Detection Test (DET)	Psychomotor Function	Speed of performance; mean of the log_{10} transformed reaction times for correct responses	Lower score = better performance
	Identification Test (IDN)	Attention	Speed of performance; mean of the log_{10} transformed reaction times for correct responses	Lower score = better performance
	One Card Learning Test (OCL)	Visual Learning	Accuracy of performance; arcsine transformation of the square root of the proportion of correct responses	Higher score = better performance
	One Back Test (ONB)	Working Memory	Speed of performance; mean of the log_{10} transformed reaction times for correct responses	Lower score = better performance
	Groton Maze Learning Test (GML)	Executive Function	Total number of errors made while attempting to learn the same hidden pathway across the consecutive learning trials performed at a single assessment	Lower score = better performance
HVLT-R	Total Recall	Verbal Learning	Total number of words recalled across trials 1-3	Higher score = better performance
	Delayed Recall	Delayed Verbal Memory	Total number of words recalled after a 20-minute delay	Higher score = better performance

Test Type	Test	Cognitive Domain Assessed	Primary Outcome Measure	Interpretation of Primary Outcome Score
	True Positives	Recognition Memory	Total number of true positives (words recognized) after a 20-minute delay	Higher score = better performance
	Recognition Discrimination Index	Recognition Memory	Total number of true positives (words recognized) minus total number of false positives after a 20-minute delay	Higher score = better performance

10.4. The Reliable Change Index (RCI): Comparison of Individual Scores to Baseline

To evaluate the magnitude of change for individual subjects relative to expected variation over repeated assessments, Reliable Change Index (RCI) scores are calculated for each test. The equation is as follows:

$$RCI_2 = \frac{(x_2 - x_1) * Multiplicand}{\sigma_1 * \sqrt{2(1-r)}}$$

Where:

- x_2 = subject's current score
- x_1 = subject's baseline
- σ_1 = Standard Deviation of the age-matched normative sample
- r = normative test-retest reliability

As RCI scores will only be computed for the DET and IDN tests, the multiplicand will equal -1 as a lower score on these tests is indicative of better cognitive performance.

Clinically meaningful change occurs when the RCI scores are less than or equal to -1.65. This threshold was chosen based on existing literature which states that an RCI score—an established measure of meaningful cognitive change—of ≤ -1.65 is often considered significant at a 90% confidence level (Hinton-Bayre, 2010).

11. Data Quality Assurance

Cogstate Computerized Tests

Data from the Cogstate Battery will be collected on computers at sites and uploaded to the Cogstate database for processing. Cogstate data management staff will query any data discrepancies. Queries will be confirmed and resolved with the sponsor.

HVLT-R

Before raters can administer the test to subjects, they are required to become certified as an HVLT-R rater by completing online training requirements (i.e., didactic training video and a demonstration video showing proper administration of the HVLT-R) and successfully complete an audio recorded HVLT-R practice/assessment administration. After viewing the online training videos, the rater is instructed to practice the administration of the HVLT-R several times to become proficient in the procedures before audio recording the final practice administration and submitting it to Cogstate for review. A neuropsychologist at Cogstate then evaluates the completed source

document and audio recording from the final practice administration and issues corrective feedback, if necessary. During the study, Cogstate monitors the HVLT-R data for clinically unusual patterns in test performance data, including test scores outside the expected range for the study population based on published data at any given timepoint or unusual score changes from one timepoint to the next, which may be indicative of an error made by the rater when deriving one or more of the scores for the test. The Cogstate Data Management team notifies the site if there are any outliers or other unusual values identified in the data, so that the rater can confirm that the obtained values were derived correctly or make any changes to the data if any errors had been made.

11.1. Test Completion Criteria

For each of the Cogstate tests, subjects must provide sufficient responses to allow computation of reliable performance measures. For the majority of Cogstate tests, the term “sufficient” has been defined as a Test Completion criterion. The number of trials required for Test Completion is unique to each test. They do not vary for different patient groups or study samples.

The completion criteria set forth a priori for each test were as follows:

Adult Tests:

- DET: The number of responses provided by the subject is ≥ 75% of the desired number of trials (responses ≥ 27)
- IDN: The number of responses provided by the subject is ≥ 75% of the desired number of trials (responses ≥ 23)
- OCL: 75% of the desired number of trials were displayed to the subject (trials ≥ 60)
- ONB: The number of responses provided by the subject is ≥ 75% of the desired number of trials (responses ≥ 24)
- GML: The subject provided 28 correct moves in each of the 5 learning trials

12. Statistical Methodology

12.1. Analysis Overview

Cogstate is responsible for reporting the results from the Cogstate Battery and HVLT-R tests to assess the safety and tolerability of intranasal esketamine in subjects with TRD, with special attention to potential long-term effects on cognitive function.

A subject listing including scores and change from baseline scores on each test will also be generated.

All analyses will be done in SAS (v9.4).

Mock shells of the tables, listings, and figures will be provided in a supplementary document.

12.2. Analysis of Cogstate Computerized Battery and HVLT-R

12.2.1. Primary Analyses

Note: For both comparisons of interest (i.e., against First Baseline and Study Baseline), all analyses summarized in this section will be conducted for all subjects as well as by age group (i.e., <65 years old and ≥ 65 years old).

Score and change from baseline scores for the Cogstate Battery and HVLT-R tests will be tabulated descriptively (n, mean, median, SD, min, max) by timepoint across the induction phase and optimization/maintenance phases. Intra-subject standard deviation, which is the standard deviation across all log10 transformed reaction times for correct responses made within a given test administration, will also be summarized across timepoints for the Detection and Identification tests.

Line plots will be generated for the Cogstate Battery and HVLT-R tests, reflecting the Mean (+/-SE) of the scores at each timepoint for each dose level.

12.2.2. Exploratory Analyses

Note: For both comparisons of interest (i.e., against First Baseline and Study Baseline), all analyses summarized in this section will be conducted for the Detection and Identification tests in the ≥ 65 years old age group.

The exploratory analyses that will be conducted are as follows:

- Spaghetti plots reflecting RCI scores across timepoints including each subject
- Line plots evaluating the relationship between the changes in RT and the clinical/treatment parameters listed below. Note: these plots will be generated by Janssen.
    - Age at Diagnosis
    - Duration of Current Depressive Episode
    - Concomitant Benzodiazepine Use
    - Modal Esketamine Dose in OP/MA
    - Baseline MADRS Total Score
    - Baseline PHQ-9 Total Score
    - Total MADRS Score Over Time
    - Total PHQ-9 Score Over Time

13. References

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Falleti, M. G., Maruff, P., Collie, A., & Darby, D. G. (2006). Practice effects associated with the repeated assessment of cognitive function using the CogState battery at 10-minute, one week and one month test-retest intervals. *Journal of Clinical and Experimental Neuropsychology*, *28*(7), 1095-1112.

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