Janssen Pharmaceutical K.K.*

Clinical Protocol

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

Protocol 54135419TRD2005; Phase 2b
AMENDMENT 5

JNJ-54135419 (esketamine)

*This study is being conducted by Janssen Pharmaceutical K.K. in Japan. The term "sponsor" is used throughout the protocol to represent Janssen Pharmaceutical K.K.

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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

TABLE OF CONTENTS

TABLE OF CONTENTS **2**

LIST OF ATTACHMENTS **5**

LIST OF IN-TEXT TABLES AND FIGURES **5**

PROTOCOL AMENDMENTS **6**

SYNOPSIS **15**

TIME AND EVENTS SCHEDULE 1 [-SCREENING PHASE, PROSPECTIVE LEAD-IN PHASE AND DOUBLE-BLIND INDUCTION PHASE] **26**

TIME AND EVENTS SCHEDULE 2 [-POSTTREATMENT PHASE AND FOLLOW-UP PHASE] **32**

TIME AND EVENTS SCHEDULE 3 [-OPEN-LABEL INDUCTION PHASE] **34**

ABBREVIATIONS **36**

1. INTRODUCTION **38**
1.1. Background 39
1.1.1. Nonclinical Studies 39
1.1.2. Clinical Studies 42
1.1.2.1. Pharmacokinetics and Product Metabolism 42
1.1.2.2. Pharmacodynamics and Efficacy 44
1.1.2.3. Safety and Tolerability 49
1.1.3. Marketing Experience 53
1.2. Overall Rationale for the Study 53

2. OBJECTIVES AND HYPOTHESIS **57**
2.1. Objectives 57
2.2. Hypothesis 58

3. STUDY DESIGN AND RATIONALE **58**
3.1. Overview of Study Design 58
3.2. Study Design Rationale 64
3.2.1. Study Population 64
3.2.2. Study Phases 64
3.2.3. Blinding and Randomization 66
3.2.4. Treatment Groups and Dose Selection 66
3.2.5. Selection of Efficacy Scales and Safety Evaluations 68
3.2.5.1. Efficacy Scales 68
3.2.6. Safety Evaluations 69
3.2.7. Pharmacokinetic Evaluations 69
3.2.8. Biomarker and Pharmacogenomic (DNA) Evaluations 69

4. SUBJECT POPULATION **70**
4.1. Inclusion Criteria 70
4.2. Exclusion Criteria 74
4.3. Criteria for Double-blind and Open-label Induction Phases and Posttreatment Phase 78
4.3.1. Criteria to Enter Double-blind Induction Phase 78
4.3.2. Criteria to Enter Posttreatment Phase 79
4.3.3. Criteria to Enter Open-label Induction Phase 79
4.4. Prohibitions and Restrictions 79

5. TREATMENT ALLOCATION AND BLINDING **80**

5.1. Treatment Allocation 80
5.2. Blinding 80

6. DOSAGE AND ADMINISTRATION 81
6.1. Screening Phase 81
6.2. Prospective Lead-in Phase 81
6.3. Double-blind Induction Phase 82
6.3.1. Guidance on Blood Pressure Monitoring on Intranasal Treatment Session Days 84
6.4. Posttreatment Phase 85
6.4.1. Open-label Induction Phase 85
6.5. Follow-up Phase 85

7. TREATMENT COMPLIANCE 85

8. PRESTUDY AND CONCOMITANT THERAPY 86

9. STUDY EVALUATIONS 87
9.1. Study Procedures 87
9.1.1. Overview 87
9.1.2. Informed Consent Procedure 89
9.1.3. Screening Phase 90
9.1.4. Prospective Lead-in Phase 91
9.1.5. Double-blind Induction Phase 91
9.1.6. Posttreatment Phase 92
9.1.7. Open-label Induction Phase 93
9.1.8. Follow-up Phase 94
9.2. Efficacy 94
9.2.1. Evaluations 94
9.2.1.1. Primary Efficacy Evaluation 95
9.2.1.1.1. MADRS (7-day Recall) 95
9.2.1.2. Secondary Efficacy Evaluation (Clinician-completed) 95
9.2.1.2.1. MADRS (24-hour Recall) 95
9.2.1.2.2. CGI-S 95
9.2.1.2.3. Time to Relapse 96
9.2.1.3. Secondary Efficacy Evaluations (Patient-reported Outcomes) 96
9.2.1.3.1. SDS 96
9.2.1.3.2. GAD-7 96
9.2.2. Endpoints 96
9.2.2.1. Primary Endpoint 96
9.2.2.2. Secondary Endpoints 97
9.3. Pharmacokinetics 97
9.3.1. Evaluations 97
9.3.2. Analytical Procedures 98
9.3.3. Pharmacokinetic Parameters 98
9.4. Pharmacokinetic/Pharmacodynamic Evaluations 98
9.5. Biomarker and Pharmacogenomic (DNA) Evaluations 98
9.6. Safety Evaluations 99
9.7. Other Evaluations 104
9.8. Sample Collection and Handling 105

10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY TREATMENT/ WITHDRAWAL FROM THE STUDY 105
10.1. Completion 105
10.2. Withdrawal From the Study 106
10.3. Withdrawal From the Use of Research Samples 107

11. STATISTICAL METHODS 107
11.1. Subject Information 107
11.2. Sample Size Determination 108

11.3. Interim Analysis 108
11.4. Efficacy Analyses 108
11.5. Pharmacokinetic Analyses 109
11.6. Biomarker and Pharmacogenomic Analyses 109
11.7. Pharmacokinetic/Pharmacodynamic Analyses 109
11.8. Safety Analyses 110

12. ADVERSE EVENT REPORTING 111
12.1. Definitions 112
12.1.1. Adverse Event Definitions and Classifications 112
12.1.2. Attribution Definitions 113
12.1.3. Severity Criteria 113
12.2. Special Reporting Situations 114
12.3. Procedures 114
12.3.1. All Adverse Events 114
12.3.2. Serious Adverse Events 115
12.3.3. Pregnancy 116
12.4. Contacting Sponsor Regarding Safety 116

13. PRODUCT QUALITY COMPLAINT HANDLING 116
13.1. Procedures 117
13.2. Contacting Sponsor Regarding Product Quality 117

14. STUDY DRUG INFORMATION 117
14.1. Physical Description of Study Drugs 117
14.2. Packaging 117
14.3. Labeling 118
14.4. Preparation, Handling, and Storage 118
14.5. Drug Accountability 118

15. STUDY-SPECIFIC MATERIALS 119

16. ETHICAL ASPECTS 119
16.1. Study-Specific Design Considerations 119
16.2. Regulatory Ethics Compliance 122
16.2.1. Investigator Responsibilities 122
16.2.2. Independent Ethics Committee or Institutional Review Board 122
16.2.3. Informed Consent 124
16.2.4. Privacy of Personal Data 124
16.2.5. Long-Term Retention of Samples for Additional Future Research 125

17. ADMINISTRATIVE REQUIREMENTS 125
17.1. Protocol Amendments 125
17.2. Regulatory Documentation 126
17.2.1. Regulatory Approval/Notification 126
17.2.2. Required Prestudy Documentation 126
17.3. Subject Identification, Enrollment, and Screening Logs 127
17.4. Source Documentation 127
17.5. Case Report Form Completion 128
17.6. Data Quality Assurance/Quality Control 128
17.7. Record Retention 129
17.8. Monitoring 129
17.9. Study Completion/Termination 130
17.9.1. Study Completion/End of Study 130
17.9.2. Study Termination 130
17.10. On-Site Audits 130
17.11. Use of Information and Publication 131

REFERENCES 133

INVESTIGATOR AGREEMENT **142**

LIST OF ATTACHMENTS

Attachment 1: Prohibited Concomitant Medications 137
Attachment 2: New York Heart Association Classification of Cardiac Disease 140
Attachment 3: Example of the Up-titration Schedule for a New Oral Antidepressant Therapy (Physician Determined) in Prospective Lead-in Phase 141

LIST OF IN-TEXT TABLES AND FIGURES

TABLES

Table 1: Adverse Reactions Listed as Very Common, Common, or Frequent Occurrences in the Product Information of Anesthetic Ketamine and Esketamine 50
Table 2: Intranasal Treatment Administration During the Double-blind Induction Phase 83
Table 3: Approximate Volume of Blood to be Collected From Each Subject 89

FIGURES

Figure 1: Study 54135419TRD2005 Flowchart 63

PROTOCOL AMENDMENTS

Protocol Version	Date
Original Protocol	20 June 2016
Amendment 1	20 September 2016
Amendment 2	17 March 2017
Amendment 3	31 August 2017
Amendment 4	30 August 2018
Amendment 5	21 December 2018

Amendments below are listed beginning with the most recent amendment.

Amendment 5 (21 December 2018)

The overall reason for the amendment: The subject exclusion criteria were amended to improve recruitment and for clarification.

Applicable Section(s)	Description of Change(s)
Rationale: Revised the exclusion criterion regarding alanine aminotransferase and aspartate aminotransferase values in the screening phase of the study because elevation in liver enzymes were reported at low rates in Phase 1, 2 and 3 esketamine studies to date.	
4.2 Exclusion Criteria	A part of exclusion criteria no.13 was revised as follows (bold text revised): "Subject has a history of, or symptoms and signs suggestive of, liver cirrhosis (eg, esophageal varices, ascites, and increased prothrombin time) OR alanine aminotransferase or aspartate aminotransferase values ≥**~~32~~**× the upper limit of normal or total bilirubin >1.5×ULN in the screening phase."
Rationale: Revised the exclusion criterion to delete the exclusion for complete right bundle branch block as the analyses of PR intervals from subjects in Phase 1, 2, and 3 esketamine studies to date showed no impact of esketamine on PR interval.	
4.2 Exclusion Criteria	A part of exclusion criteria no.11 was revised as follows (bold text revised): "Evidence of 2nd and 3rd degree atrioventricular (AV) block, **or** complete left bundle branch block (LBBB)**~~, or complete right bundle branch block (RBBB)~~**."
Rationale: Clarified that any potential subject with cluster A personality disorders will be excluded from the study.	
4.2 Exclusion Criteria	Exclusion criteria no. 4 was revised as follows (bold text revised): "Subject has a current or prior DSM-5 diagnosis of a psychotic disorder or MDD with psychotic features bipolar or related disorders (confirmed by the MINI), obsessive compulsive disorder (current only), intellectual disability (DSM-5 diagnostic codes 317, 318.0, 318.1, 318.2, 315.8, and 319), autism spectrum disorder, borderline personality disorder, antisocial personality disorder, histrionic personality disorder,**~~ or~~** narcissistic personality disorder**, paranoid personality disorder, schizoid personality disorder, or schizotypal personality disorder**."

Amendment 4 (30 August 2018)

The overall reason for the amendment: The subject inclusion criteria were amended to improve recruitment. Also, the protocol contents were updated and clarified.

Applicable Section(s)	Description of Change(s)
Rationale: To improve recruitment, inclusion criteria was amended to allow enrollment of subjects who meet the diagnostic criteria for single episode major depressive disorder.	
4.1 Inclusion Criteria	Inclusion criterion no. 3 was revised as follows (bold text revised): "At the start of the screening phase, subject must meet the DSM-5 diagnostic criteria for **single-episode MDD or** recurrent MDD, without psychotic features, based upon clinical assessment and confirmed by MINI. **In the case of single-episode MDD, the subject must be diagnosed with persistent depressive disorder, which meets criteria of major depressive episode for a continuous duration of ≥2 years, and the same physician from the site must be examining the subject for ≥2 years continuously as a primary care physician of the subject.**"
Synopsis Overview of Study Design;	To align with the inclusion criterion, the bold text has been revised as follows: "Japanese men and women aged 20 to 64 years old (both inclusive), who meet Diagnostic and Statistical Manual of Mental Disorders (fifth edition) (DSM-5) diagnostic criteria for **single-episode major depressive disorder (MDD) or** recurrent ~~**major depressive disorder (**~~MDD~~**)~~ without psychotic features, based upon clinical assessment, and confirmed by the MINI will be screened according to the inclusion/exclusion criteria. **In the case of single-episode MDD, the subject must be diagnosed with persistent depressive disorder, which meets criteria of major depressive episode for a continuous duration of ≥2 years, and the same physician from the site must be examining the subject for ≥2 years continuously as a primary care physician of the subject.**"
Synopsis Subject Population	To align with the inclusion criterion, the bold text has been revised as follows: "Japanese men or women aged between 20 and 64 years (both inclusive) must meet the DSM-5 diagnostic criteria for **single-episode MDD or** recurrent MDD, without psychotic features, based upon clinical assessment and confirmed by the MINI will be enrolled. **In the case of single-episode MDD, the subject must be diagnosed with persistent depressive disorder, which meets criteria of major depressive episode for a continuous duration of ≥2 years, and the same physician from the site must be examining the subject for ≥2 years continuously as a primary care physician of the subject.**"
3.1 Overview of Study Design	To align with the inclusion criterion, the bold text has been revised as follows: "Japanese men and women aged 20 to 64 years old (both inclusive), who meet Diagnostic and Statistical Manual of Mental Disorders (fifth edition) (DSM-5) diagnostic criteria for **single-episode MDD or** recurrent MDD without psychotic features, based upon clinical assessment and confirmed by the Mini International Neuropsychiatric Interview (mental status questionnaire) (MINI) will be screened according to the inclusion/exclusion criteria. **In the case of single-episode MDD, the subject must be diagnosed with persistent depressive disorder, which meets criteria of major depressive episode for a continuous duration of ≥2 years, and the same physician from the site must be examining the subject for ≥2 years continuously as a primary care physician of the subject.**

Applicable Section(s)	Description of Change(s)
3.2.1 Study Population	To align with the inclusion criterion, the bold text has been revised as follows: "Subjects will meet DSM 5 diagnostic criteria for **single-episode MDD or** recurrent MDD, without psychotic features, based upon clinical assessment and confirmed by the MINI. **In the case of single-episode MDD, the subject must be diagnosed with persistent depressive disorder, which meets criteria of major depressive episode for a continuous duration of ≥2 years, and the same physician from the site must be examining the subject for ≥2 years continuously as a primary care physician of the subject.**"
Rationale: Revised exclusion criteria to exclude subjects with a history (lifetime) of psilocybin and psilocin.	
4.2 Exclusion Criteria	Exclusion criterion no. 6 was revised as follows (bold text revised): "Subject has a history of moderate or severe substance or alcohol use disorder according to DSM-5 criteria, except nicotine or caffeine, within 6 months before the start of the screening phase. A history (lifetime) of ketamine, phencyclidine, lysergic acid diethylamide (LSD), ~~**or**~~ 3, 4-methylenedioxy-methamphetamine (MDMA)**, or psilocybin/psilocin** hallucinogen-related use disorder is exclusionary."
Rationale: Added definition about going out during hospitalization.	
4.1 Inclusion Criteria	Inclusion criterion no. 2.1 was revised as follows (bold text revised): "In this study, outpatients and inpatients are allowed for enrollment. Hospitalization for the study is allowed, subject must remain hospitalized from the beginning of the prospective lead-in phase to the end of the double-blind induction phase, maintaining the stable environment for 10 weeks. Temporary discharge is not permitted basically during the 10-week hospitalization. **As a general rule, going out from the hospital (leaving the site during hospitalization for reasons other than temporary discharge regardless of the attendant's presence) is to be within 6 hours at a time and not to exceed twice in 7 contiguous days.**"
9.1.3 Screening Phase	To be consistent with the inclusion criteria, the bold text has been added as follows: "In this study, outpatients and inpatients are allowed for enrollment. Hospitalization for the study is allowed, subject must remain hospitalized from the beginning of the prospective lead-in phase to the end of the double-blind induction phase, maintaining the stable environment for 10 weeks. Temporary discharge is not permitted basically during the 10-week hospitalization. **As a general rule, going out from the hospital (leaving the site during hospitalization for reasons other than temporary discharge regardless of the attendant's presence) is to be within 6 hours at a time and not to exceed twice in 7 contiguous days.**"
Rationale: Clarified that intranasal treatment sessions should not take place on consecutive days in the open-label induction phase.	
Synopsis Dosage and Administration; 6.4.1 Open-label Induction Phase	The bold statement has been added as follows: "**Intranasal treatment sessions should not take place on consecutive days.**"

Applicable Section(s)	Description of Change(s)
Rationale: Clarifications made regarding the usage of antidepressant treatments for indications other than depression, and the use of corticosteroids, pseudoephedrine, and dopamine agonists.	
Attachment 1	Changes were as follows (bold text revised): – Antidepressant: "Even if used ~~**primarily for sleep, trazodone used is not permitted.**~~ **for indication other than MDD (eg, trazodone or low dose tricyclic antidepressants for sleep), the use of any medication listed on the ATRQ, is not permitted during the treatment phase.**" – Corticosteroids: changed from "oral" to "systemic"; episodic use permitted (previously prohibited); the following text added: "**intermittent IM/IV corticosteroids are permitted (chronic use prohibited)**". – Pseudoephedrine: clarified that it is an "orally" administered agent (not intranasal). – Dopamine agonists: "**Subjects who were taking these medications at the start of the screening phase, can continue them throughout the study; however, dose increases or starting new dopamine agonists are not permitted. The dopamine agonists must be continued at a stable dose for 1 month prior to the beginning of the screening phase.**"
Rationale: Minor errors were noted.	
Time and Events Schedule 1	The bold text has been deleted from footnote p as follows: – Footnote p: "MADRS interview should not be conducted on the same day with the ~~**MADRS**~~ assessment at Visit 3.9."
Time and Events Schedule 3	The bold text has been deleted from footnote j as follows: – Footnote j: "MADRS interview should not be conducted on the same day with the ~~**MADRS**~~ assessment at Visit 5.9."

Amendment 3 (31 August 2017)

The overall reason for the amendment: The subject entry process is being clarified and revised to improve recruitment, based on feedback received from Investigators involved in the study.

Applicable Section(s)	Description of Change(s)
Rationale: Clarify the informed consent procedure is the independent procedure and obtaining informed consent is not required at the same day of the Screening Visit 1.1.	
9.1.2 Informed Consent Procedure	The following text has been added as a new section: "**Informed consent must be obtained prior to the subject entering the study, and before any protocol-directed procedures (eg, washout of prohibited medications) are performed. Signing ICF is not required at the same day of the Screening Visit 1.1. Investigators can observe the subjects until Screening Visit 1.1 after obtaining IC, if clinically indicated (eg, washout of prohibited medications). If Screening Visit 1.1 is on more than 28 days after singing ICF, investigators must obtain informed consent again, to confirm their willingness.**"
Time and Events schedule 1	"Informed Consent" was added in the Screening/ Administrative row to clarify the independence of the procedure. The following new footnote o has been added to Informed consent (ICF): – Footnote o: "Informed consent must be obtained prior to the initiation of any study procedure including washout of prohibited therapies."

Applicable Section(s)	Description of Change(s)
Synopsis Overview of Study Design; 3.1 Overview of Study Design;	To align with the study procedure, the bold text has been deleted as follows: "SAFER interview will be conducted as early as feasible during the screening period, ~~**preferably in the first week after signing of informed consent form (ICF)**~~ before down-titration of antidepressants to avoid change of depressive symptoms because of tapering."
8 Prestudy and Concomitant Therapy	To align with the study procedure, the bold text has been revised as follows: "Prestudy non-antidepressant therapies administered up to 30 days before **obtaining IC** ~~**the start of the screening phase**~~ must be recorded at the start of this phase. All antidepressant treatments, including adjunctive treatment for MDD, taken during the current depressive episode (ie, including those taken more than 30 days prior to **obtaining IC** ~~**the start of the screening phase**~~) will be recorded at the start of the screening phase."
Rationale: To improve recruitment, revised the criteria of the hospitalization for the study.	
4.1. Inclusion Criteria	Inclusion criterion no. 2 was revised as follows (bold text revised): "In this study, outpatients and inpatients are allowed for enrollment. ~~**However, hospitalization**~~ Hospitalization for the study is ~~**not**~~ allowed, **subject must remain hospitalized from the beginning of the prospective lead-in phase to the end of the double-blind induction phase, maintaining the stable environment for 10 weeks. Temporary discharge is not permitted basically during the 10-week hospitalization.**~~**which means inpatients who has already hospitalized before signing ICF can be enrolled.**~~"
9.1.3 Screening Phase	The bold text has been revised as follows: "In this study, outpatients and inpatients are allowed for enrollment. ~~**However, hospitalization**~~ Hospitalization for the study is ~~**not**~~ allowed, **subject must remain hospitalized from the beginning of the prospective lead-in phase to the end of the double-blind induction phase, maintaining the stable environment for 10 weeks. Temporary discharge is not permitted basically during the 10-week hospitalization.**~~**which means inpatients who has already hospitalized before signing ICF can be enrolled.**~~"
Rationale: Revise the remote MADRS interview window for Day 28 of the double-blind and Day OL 28 of the open-label induction phase to allow more flexibility for conducting the visit	
Time and Events schedule 1; Time and Events schedule 3	For Visit 3.10 during the double-blind induction phase and Visit 5.10 during the open-label induction phase, the visit window was revised to -2 days (rather than -1 day).
Time and Events schedule 1	The following text has been added to the remote MADRS interview window at Visit 3.10 as Footnote p: - Footnote p: "MADRS interview should not be conducted on the same day with the MADRS assessment at Visit 3.9."
Time and Events schedule 3	The following text has been added to the remote MADRS interview window at Visit 5.10 as Footnote j: - Footnote j: "MADRS interview should not be conducted on the same day with the MADRS assessment at Visit 5.9."

Applicable Section(s)	Description of Change(s)
Rationale: Revised exclusion criterion no. 11, because ESKETINTRD1013 study, which evaluated the effects of esketamine on cardiac repolarization in healthy subjects, showed no impact of esketamine on QT/QTc interval.	
4.2. Exclusion Criteria	Exclusion criterion no. 11 was revised as follows (bold text revised): "Subject has clinically significant ECG abnormalities at the start of the screening phase or on Day 1 prior to randomization, defined as: – During screening, a QT interval corrected according to Fridericia's formula (QTcF): ≥~~**450**~~ **470** msec **in males and ≥480 msec in females**; if the QTcF is prolonged on the initial ECG, the average QTcF of 3 ECGs recorded 4 minutes apart must not be ≥450 msec. – On Day 1 (predose), a QTcF: ≥~~**450**~~ **470** msec **in males and ≥480 msec in females** based on the site-evaluated ECG; if the QTcF is prolonged on the initial ECG, the average QTcF of 3 ECGs recorded 4 minutes apart must not be ≥450 msec. – Evidence of 2nd and 3rd degree atrioventricular (AV) block, complete left bundle branch block (LBBB), or complete right bundle branch block (RBBB). – Features of new ischemia. – Arrhythmia (except premature atrial contractions [PACs] and premature ventricular contractions [PVCs])."
Rationale: Clarify the rule of rescreening.	
4.2. Exclusion Criteria	The bold text has been added after "NOTE" as follows: The sponsor will evaluate and approve/reject requests to rescreen an individual subject on a case by-case basis. **Rescreening will be allowed only once basically.**
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 2 (17 March 2017)

The overall reason for the amendment: To add a new inflammatory biomarker assessment and to update and/or clarify protocol content based on ongoing feedback received from Investigators during study initiation activities.

Applicable Section(s)	Description of Change(s)
Rationale: Add IL-17A as a new biomarker to assess the potential relationship with inflammation more clearly.	
9.1 Study Procedures, Table 3	IL-17A has been added: – Footnote f: "This sample will provide serum for all of the following assays: IL-10, IL-1b, IL-6, TNFa, Adiponectin, Cortisol, hs-CRP (non-cardiac), IL-6R, BDNF, IGF-1~~**, and**~~ Leptin **and IL-17A**."
Rationale: Clarification of intranasal esketamine dose adjustments which are permitted on Day OL8 and OL11 in the open-label induction phase.	

Applicable Section(s)	Description of Change(s)
Synopsis Overview of Study Design, Dosage and Administration; 3.1 Overview of Study Design; 6.4.1 Open-label Induction Phase; 9.1.6 Open-label Induction Phase	The bold text has been revised as follows: "On Day OL8 and OL11, the dose ~~**may**~~ **could be maintained,** ~~**remain the same as 84 mg or**~~ **increased** or ~~**could be**~~ reduced by 28 mg as determined by the investigator based on efficacy and tolerability."
Rationale: Revise the visit window for Day 32 of the post treatment phase to prevent overlapping the visit window of Day 28.	
Time and Events schedule 2	For Visit 4.1 during the post treatment phase, the visit window was revised to +3 day (rather than ±3 days).
Rationale: Clarify the restrictions of benzodiazepines.	
3.1 Overview of Study Design; 8. Prestudy and Concomitant Therapy	The bold text has been revised as follows: "Subjects receiving benzodiazepines (at dosages equal to or less than the equivalent of 6 mg/day of lorazepam) or permitted non-benzodiazepine sleep medications (eg, zolpidem, eszopiclone, and zopiclone) or both during the screening phase can continue these medications throughout the study~~**, provided the doses of these medications remain unchanged or no new benzodiazepine medications or both are initiated during the study**~~**; however, dose increases or starting new benzodiazepine medications are not permitted.**"
Rationale: Clarify protocol text, where required.	
Time and Events schedule 1	Footnote "e" has been added to the PWC-20 and POMS-2 to align with the study procedure in the double-blind induction phase.
Time and Events schedule 1	For the following items, footnote "e" has been added and deleted footnote "c" to align with the study procedure in the double-blind induction phase: CGI-S, SDS, GAD-7, Hematology, Chemistry, Urinalysis, Urine drug screen, Urine pregnancy test, Blood sample collection (Protein) and Blood sample collection (DNA)
4.3 Criteria for Double-blind and Open-label Induction Phases and Posttreatment Phase	The following has been delated to align with the study procedure: "Subjects who do not meet the predetermined criteria as defined below will be discontinued from the study, undergo EOS/EW Withdrawal Visit procedures, and treated according to an accepted standard-of-care. "
9.1 Study Procedures	The order of administration has been revised and clarified: "PRO: GAD-7, SDS, POMS-2 Clinician-administered: CGI-S, C-SSRS, **PWC-20,** BPRS+, CADSS, MOAA/S, CGADR~~**, PWC-20**~~
Attachment 1	A new row was added for dopamine agonists.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.
Time and Events schedule 1	Day P14, P28 and P42 were corrected to Day P15, P29 and P43, respectively.

Amendment 1 (20 September 2016)

The overall reason for the amendment: Based on the feedback received from Investigators from the study, recording of remote MADRS interview is clarified from the perspective of protecting subject privacy.

Applicable Section(s)	Description of Change(s)
Rationale: Provide clarification in the recording of the remote MADRS interview from the perspective of protecting subject privacy.	
Synopsis Overview of Study Design; 9.2.1. Evaluations	The following text has been added: "**The remote MADRS interviews will be recorded to assess accuracy and thoroughness of the interviews and measure overall quality assurance.**"
Rationale: Provide clarification of antidepressants which should be washed out in the screening phase.	
Synopsis Overview of Study Design, Dosage and Administration; 3.1 Overview of Study Design; 6.1 Screening Phase; 9.1.2 Screening Phase	The bold text has been added as follows : "Subject's current antidepressant treatment(s)**, including adjunctive treatment for MDD,** should be tapered and discontinued in this phase per the local prescribing information."
Rationale: Clarify the handling of exacerbation of primary disease.	
12.1.1. Adverse Event Definitions and Classifications	The following text has been added: "**Exacerbation of primary disease is not defined as AE.**"
Rationale: Clarify protocol text, where required.	
Time and Events schedule 1	The following text has been added to Visit 3.10 as Footnote m: – Footnote m: "Visit 3.10 will be identical to the start day of the posttreatment phase."
Time and Events schedule 1	The "x^n" at Visit 2.1 and 3.1 was added to the MOAA/S and pulse oximetry row to align with the exclusion criteria 10 and the following was added. – Footnote n: "Pulse oximetry only."
Time and Events schedule 3	The following text has been added to Day OL 1 as Footnote i: – Footnote i: "If the assessment on Day OL 1 is conducted on the same day as a scheduled visit in the posttreatment phase, duplicate assessments are not required."
Synopsis Overview of Study Design, Dosage and Administration; 3.1 Overview of Study Design; 6.4.1 Open-label Induction Phase; 9.1.6 Open-label Induction Phase	The period between the double-blind induction phase and the open-label induction phase has been clarified by calendar day: "The beginning of the OL induction phase should be at least 2 weeks **(14 calendar days)** after the last dose in the double-blind induction phase."
4.2 Exclusion Criteria	Transcranial magnetic stimulation has been clarified in Exclusion Criteria 3: "Subject has received vagal nerve stimulation, **has received transcranial magnetic stimulation** or has received deep brain stimulation in the current episode of depression."

Applicable Section(s)	Description of Change(s)
9.1 Study Procedures, Table 3	IGF-1 has been added and C reactive protein has been deleted: – Footnote f: "This sample will provide serum for all of the following assays: IL-10, IL-1b, IL-6, TNFa, Adiponectin, Cortisol, hs-CRP (non-cardiac), IL-6R, BDNF, **IGF-1 and** Leptin ~~and C-reactive protein~~."
9.1 Study Procedures	The order of administration has been revised and clarified: "PRO: GAD-7, **SDS**, POMS-2 Clinician-administered: ~~**MADRS,**~~ CGI-S, C-SSRS, BPRS+, CADSS, MOAA/S, CGADR, PWC-20 **Remote MADRS interview should be conducted at predose on intranasal dosing days during the double blind induction phase and the open label induction phase**."
9.6 Safety Evaluations	The recall period of POMS-2 has been clarified: "The recall period for this study is 7 days."
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.
Time and Events schedule 3	An "x" has been deleted from Drug Accountability at EW Visit.
17.4 Source Documentation	The following has been delated because each source data will be recorded in separate documents: "~~• Blood pressure and heart rate~~ ~~• Height and weight~~ ~~• Details of physical examination~~ ~~• Some subject- and clinician- reported scales and assessments designated by the sponsor~~"
9.1 Study Procedures, Table 3	An "h" has been added to the Approximate total blood volume for the study row to align with the footnote.
Attachment 1	Corrected the number of predefined oral antidepressant treatment options: "Only 1 of the **6** predefined oral antidepressant treatment options are permitted"

SYNOPSIS

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

Ketamine and esketamine (S-ketamine, the S enantiomer of ketamine) are approved medications and widely used for the induction and maintenance of anesthesia via intramuscular (IM) or intravenous (IV) administration. The desired analgesic-anesthetic effects of ketamine and esketamine are attributed to the blockade of ionotropic N-methyl-D-aspartate (NMDA) glutamate receptors. The antidepressive mechanism of action of ketamine and esketamine is distinct from conventional monoaminergic treatments. Ketamine profoundly affects fast excitatory glutamate transmission, increases brain-derived neurotrophic factor (BDNF) release, and stimulates synaptogenesis.

Due to the higher NMDA receptor affinity of esketamine over arketamine (R-ketamine), Janssen Research & Development (JRD) is developing esketamine for antidepressant therapy, thereby requiring a lower volume which can be administered via a non-invasive and rapidly absorbed route.

The study 54135419TRD2005 is a randomized, double-blind, placebo-controlled, multicenter study designed to evaluate the efficacy, safety and tolerability of fixed dosed intranasal esketamine (28 mg, 56 mg or 84 mg) as an add-on therapy to an oral antidepressant in Japanese subjects with treatment-resistant depression (TRD).

OBJECTIVES

Primary Objective

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

Secondary Objectives

- To assess the effect of intranasal esketamine compared with intranasal placebo as an add-on to an oral antidepressant in Japanese subjects with TRD, including the following parameters:
  - Dose response;
  - Depression response rates;
  - Depression remission rates;
  - Onset of clinical response;
  - Overall severity of depressive illness;
  - Anxiety symptoms;
  - Functioning and associated disability.
- To investigate the safety and tolerability of intranasal esketamine compared with intranasal placebo as an add-on to an oral antidepressant in Japanese subjects with TRD, including the following parameters:
  - Treatment-emergent adverse events (TEAEs), including adverse events (AEs) of special interest;
  - Potential withdrawal or rebound symptoms or both following cessation of intranasal esketamine treatment;

  - Perceptual changes (dissociative symptoms);
  - Effects on alertness and sedation;
  - Effects on heart rate, blood pressure, respiratory rate, and blood oxygen saturation;
  - Potential effects on suicidal ideation/behavior;
  - Potential abuse-liability;
  - Potential psychosislike effects.
- To evaluate the durability of intranasal esketamine as an add-on to an oral antidepressant in Japanese subjects with TRD, with attention to:
  - Time to relapse in the posttreatment phase for subjects in remission and for subjects who respond but are not in remission, at the end of the double-blind induction phase.
- To evaluate the pharmacokinetics (PK) of intranasally administered esketamine in Japanese subjects with TRD.

Exploratory Objectives

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

Hypothesis

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

OVERVIEW OF STUDY DESIGN

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

The study consists of the following phases: a screening phase (up to 4 weeks); a 6-week prospective oral antidepressant lead-in phase; a 4-week double-blind induction phase; a posttreatment phase (up to 24 weeks comprising of only oral antidepressant therapy), including an optional 4-week OL induction phase; and a 4-week follow-up phase. The 4-week OL induction phase will be applicable for subjects who relapse during the posttreatment phase.

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

Screening Phase

Japanese men and women aged 20 to 64 years old (both inclusive), who meet Diagnostic and Statistical Manual of Mental Disorders (fifth edition) (DSM-5) diagnostic criteria for single-episode major depressive disorder (MDD) or recurrent MDD without psychotic features, based upon clinical assessment, and confirmed by the MINI will be screened according to the inclusion/exclusion criteria. In the case of single-episode MDD, the subject must be diagnosed with persistent depressive disorder, which meets criteria of major depressive episode for a continuous duration of ≥2 years, and the same physician from the site must be examining the subject for ≥2 years continuously as a primary care physician of the subject.

To confirm eligibility for participation in the prospective lead-in phase, subjects will have a review of the inclusion/exclusion criteria in the screening phase. Subjects must not have responded to ≥1 but <5 different oral antidepressants taken at adequate dosage and for adequate duration, as assessed on the Massachusetts General Hospital – Antidepressant Treatment Response Questionnaire (MGH-ATRQ) and documented by medical history/prescription records, for the current episode of depression. The subject's current major depressive episode, depression symptom severity (MADRS total score ≥28 required), and treatment response to antidepressant medication used in the current episode (retrospectively assessed) must be deemed valid for participation in the clinical study based on the SAFER interview, which is administered by a remote, independent rater. At the screening visit, subjects who continue to fulfill all inclusion criteria and none of the exclusion criteria will be enrolled.

SAFER interview will be conducted as early as feasible during the screening period, before down-titration of antidepressants to avoid change of depressive symptoms because of tapering.

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

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

Prospective Lead-in Phase

After enrollment, eligible subjects will enter the 6-week OL prospective lead-in phase (Visits 2.1 to 3.1 [prerandomization]) during which, subjects will receive a new antidepressant therapy (physician determined) daily for the duration of this phase.

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

In the last 4 weeks during the prospective lead-in phase, 'oral antidepressant' must be single treatment of switched new oral antidepressant. New oral antidepressant treatment should be titrated to the approved maximum dose, to optimize the potential for response. The up-titration schedule should be per prescribing

information. The dose, which is above the minimum therapeutic dose defined in MGH-ATRQ should be kept at last 4 weeks during the prospective lead-in phase, in case they start at lower doses.

The criteria of TRD is defined as nonresponse (≤25% improvement) to at least 1 antidepressant treatment determined retrospectively and 1 antidepressant prospectively in the current episode of depression. After 6 weeks, subjects who are nonresponders to the new oral antidepressant treatment at the end of the prospective lead-in phase can be eligible to proceed to the double-blind induction phase. Nonresponse at the end of the prospective lead-in phase is defined as ≤25% improvement in the MADRS total score from Visits 2.1 to each of Visit 2.3 and 3.1 (prerandomization) respectively, and a MADRS total score of ≥28 on each of the Visits 2.1, 2.3, and 3.1 (prerandomization). Assessment of antidepressant treatment response at the end of the prospective lead-in phase will be performed by investigators. All other subjects who do not proceed to the double-blind induction phase will end study participation at this time. No follow-up or further study visits will be performed for these subjects. All subjects who are discontinued must be treated with an oral antidepressant after completion of the study, unless it is clinically inappropriate.

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

Double-blind Induction Phase

The 4-week fixed dose double-blind induction phase will start on Day 1 (Visit 3.1) and end at Day 28 (Visit 3.10). A total of 183 subjects will be randomly assigned in a 2:1:1:1 ratio to receive double-blind intranasal treatment with either placebo, esketamine 28 mg, esketamine 56 mg, or esketamine 84 mg add-on to the continued stable oral antidepressant initiated in the prospective lead-in phase. The intranasal treatment sessions (esketamine or placebo) will occur twice weekly. Subjects will self-administer the intranasal study drug (esketamine 28 mg, 56 mg, 84 mg, or placebo) at treatment sessions occurring twice a week for 4 weeks at the clinical site under clinical supervision. The first treatment session will be on Day 1. Responders (subjects who have ≥50% reduction from baseline in MADRS total score) at the end of the double-blind induction phase will be eligible to proceed to the posttreatment phase; those who do not (ie, nonresponders) will proceed to the 4-week follow-up phase. Given the potential for treatment-emergent transient elevation in SBP and DBP, the guidance on Blood Pressure Monitoring should be followed on intranasal dosing days during the double-blind induction phase.

Posttreatment Phase

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

Open-label Induction Phase

Subjects who relapsed in the posttreatment phase will receive a 4-week open-label induction treatment course of intranasal esketamine. The beginning of the OL induction phase should be at least 2 weeks (14 calendar days) after the last dose in the double-blind induction phase. Subjects who meet the relapse criteria before 2 weeks after the last dose in the double-blind induction phase will not have an option for joining open label induction phase. They will withdraw from the posttreatment phase and move forward to the follow up phase.

Subjects who enter the OL induction phase will start treatment sessions with 56 mg of intranasal esketamine on the first day of OL induction phase (Day OL1). On the fourth day (Day OL4), the dose will be increased to 84 mg. On Day OL8 and OL11, the dose could be maintained, increased or reduced by

28 mg as determined by the investigator based on efficacy and tolerability. On Day OL15, a dose reduction is permitted if required for tolerability; no dose increase is permitted on Day OL15. After Day OL15, the dose should be stable (unchanged). If needed for tolerability, a dose reduction is permitted from Day OL15 until Day OL25.

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

Follow-up Phase

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

SUBJECT POPULATION

Main Criteria for Inclusion

Japanese men or women aged between 20 and 64 years (both inclusive) must meet the DSM-5 diagnostic criteria for single-episode MDD or recurrent MDD, without psychotic features, based upon clinical assessment and confirmed by the MINI will be enrolled. In the case of single-episode MDD, the subject must be diagnosed with persistent depressive disorder, which meets criteria of major depressive episode for a continuous duration of ≥2 years, and the same physician from the site must be examining the subject for ≥2 years continuously as a primary care physician of the subject. At the start of the screening phase, subject must have had nonresponse (≤25% improvement) to ≥1 but <5 oral antidepressant treatments in the current episode of depression, assessed using the MGH-ATRQ and confirmed by documented medical/pharmacy/prescription records, letter from treating physician etc. The subject's current major depressive episode, depression symptom severity (MADRS total score ≥28 required), and antidepressant treatment response in the current depressive episode, must be confirmed using the SAFER interview.

DOSAGE AND ADMINISTRATION

Intranasal esketamine will be made available as an aqueous solution of esketamine hydrochloride (16.14% weight/volume [w/v]; equivalent to 14% w/v of esketamine base) containing ethylenediaminetetraacetic acid (EDTA) and citric acid. The solution will consist of 161.4 mg/mL esketamine hydrochloride (equivalent to 140 mg of esketamine base) in water for injection. It will be provided in a nasal spray pump, which delivers 16.14 mg esketamine hydrochloride (14 mg esketamine base) per 100-µL spray. Each device contains sufficient volume for 2 sprays.

The placebo solution will be provided as a clear, colorless intranasal solution of water for injection, with a bittering agent (denatonium benzoate [Bitrex®] at a final concentration of 0.001mg/mL) added to simulate the taste of the intranasal solution with active drug.

Screening Phase

Benzodiazepines or permitted non-benzodiazepine sleep medications or both, which have been taken and are ongoing before the start of screening phase will be continued throughout the study. Subject's current antidepressant treatment(s), including adjunctive treatment for MDD, should be tapered and discontinued in this phase per the local prescribing information.

Prospective Lead-in Phase

All subjects will initiate a physician determined new OL oral antidepressant daily for the duration of this phase. The oral antidepressant will be 1 oral antidepressant medication of SSRIs, SNRIs or Mirtazapine (eg, escitalopram, paroxetine controlled-release [CR], sertraline, duloxetine, venlafaxine extended-release [XR], or mirtazapine), that the subject has not previously had a nonresponse to in the current depressive episode has not been previously intolerant to (lifetime). If clinically indicated, cross-tapering is allowed in the first 2 weeks during the prospective lead-in phase. In the last 4 weeks during the prospective lead-in phase, 'oral antidepressant' must be single treatment of switched new oral antidepressant. New oral antidepressant treatment should be titrated to the approved maximum dose, to optimize the potential for response. Up-titration of the antidepressant may be performed per investigator's discretion based on prescribing information in the prospective lead-in phase. The dose, which is above the minimum therapeutic dose defined in MGH ATRQ, should be kept at last 4 weeks during the prospective lead-in phase, in case they start at lower doses.

Double-blind Induction Phase

Eligible and randomized TRD subjects will self-administer double-blind intranasal treatment either placebo, esketamine 28 mg, esketamine 56 mg, or esketamine 84 mg add-on to continued stable oral antidepressant.

Prior to the first intranasal dose on Day 1, subjects will practice spraying (into the air, not intranasally) with a demonstration intranasal device that is filled with placebo solution.

The following table describes how each intranasal treatment session will be administered in the double-blind induction phase.

	Time of Intranasal Device Administration[a]		
Intranasal Treatment	0 minute[b]	5 minutes	10 minutes
Intranasal device [c]	1st	2nd	3rd
Placebo	1 spray of placebo to each nostril	1 spray of placebo to each nostril	1 spray of placebo to each nostril
Esketamine 28 mg	1 spray of esketamine to each nostril	1 spray of placebo to each nostril	1 spray of placebo to each nostril
Esketamine 56 mg	1 spray of esketamine to each nostril	1 spray of esketamine to each nostril	1 spray of placebo to each nostril
Esketamine 84 mg	1 spray of esketamine to each nostril	1 spray of esketamine to each nostril	1 spray of esketamine to each nostril

a. The 3 intranasal devices for each intranasal treatment session should be administered in the medication kit order provided by the interactive web response system (IWRS)
b. Time 0 is defined as the time of administration of the first intranasal spray to 1 nostril from the first intranasal device.
c. One device will be used at each time point. Each individual intranasal device contains 2 sprays. The intranasal devices containing esketamine deliver 14 mg per spray, for a total of 28 mg per individual device (ie, 2 sprays)

The first treatment session will be on Day 1. Intranasal treatment sessions should not take place on consecutive days. To improve tolerability, subjects who will be randomly assigned to esketamine 84 mg will start at 56 mg on Day 1 and then the dose will increase to 84 mg on Day 4 as a forced titration and stay at 84 mg for all subsequent intranasal treatment sessions. Starting with a lower dose may therefore reduce the number of subjects discontinuing the study treatment because of intolerability in the 84 mg dose group. Subjects who are randomly assigned to 28 mg or 56 mg will remain on that dose for all subsequent intranasal treatment sessions. No adjustment to the intranasal esketamine dose is permitted for the duration of the double-blind induction phase.

Food will be restricted for at least 2 hours before each administration of study drug. Drinking of any fluids will be restricted for at least 30 minutes before the first nasal spray. A new oral antidepressant treatment which is ongoing and stable from the prospective lead-in phase will also be maintained throughout the study.

Posttreatment Phase

Subjects who relapse within 20 weeks after the start of the posttreatment phase will transit to an OL induction phase and receive 4 weeks of OL treatment course with intranasal esketamine. Subjects who relapse more than 20 weeks after the start of the posttreatment phase will withdraw from the study and clinical/standard-of-care treatment will be arranged by the study investigator after relapse. Subjects who have no relapse throughout this 24-week posttreatment phase will complete this study without 4-week follow-up phase. The oral antidepressant must be continued at a stable dose during post treatment phase.

Open-label Induction Phase

Subjects who relapsed in the posttreatment phase will receive a 4-week OL induction treatment course of intranasal esketamine. During this phase, subjects will continue to receive their switched oral antidepressant medication. The beginning of the OL induction phase should be at least 2 weeks (14 calendar days) after the last dose in the double-blind induction phase.

Eligible TRD subjects will start treatment sessions with 56 mg of intranasal esketamine on the first day of OL induction phase (Day OL1). On Day OL4, the dose must be increased to 84 mg. On Day OL8 and OL11, the dose could be maintained, increased or reduced by 28 mg as determined by the investigator based on efficacy and tolerability. On Day OL15, a dose reduction is permitted, if required for tolerability; no dose increase is permitted on Day OL15. After Day OL15, the dose should be stable (unchanged). If needed for tolerability, a dose reduction is permitted from Day OL15 until Day OL25. Intranasal treatment sessions should not take place on consecutive days.

Follow-up Phase

During this phase, further clinical/standard-of-care treatment will be arranged by the study investigator however, in order to better assess potential withdrawal symptoms from intranasal study drug, the oral antidepressant medication must be continued for the follow-up phase unless determined as not clinically appropriate.

EFFICACY EVALUATIONS/ENDPOINTS

Primary Efficacy Evaluation and Endpoint

The primary efficacy evaluation will be the MADRS total score. The MADRS will be performed by independent remote raters during the study, using the Structured Interview Guide for the MADRS. The MADRS is a clinician-rated scale designed to measure depression severity and detects changes due to antidepressant treatment.

The primary efficacy endpoint is the change in the MADRS total score as measured by the change from baseline (prior to randomization) to the end of the 4-week double-blind induction phase.

Secondary Efficacy Evaluations and Endpoints

1. Proportion of responders (≥50% reduction from baseline in MADRS total score) in the double-blind induction phase.
2. Proportion of remitters (MADRS total score ≤12) in the double-blind induction phase.
3. Proportion of subjects showing onset of clinical response in the double-blind induction phase.

4. Severity of depressive illness, using the Clinical Global Impression – Severity (CGI-S). Endpoint: Change from baseline in CGI-S in the double-blind induction phase.
5. The 7-item subject-reported Generalized Anxiety Disorder 7-item scale (GAD-7) will be used to measure the secondary objective of symptoms of anxiety. Endpoint: Change from baseline in GAD-7 in the double-blind induction phase.
6. Sheehan Disability Scale (SDS): The SDS is a subject-reported outcome measure that will be used to assess functional impairment and associated disability. Endpoint: Change from baseline in SDS total score in the double-blind induction phase.
7. Time to relapse:
    a. In subjects who remit (MADRS total score ≤12) at the end of the double-blind induction phase.
    b. In subjects with response (≥50% reduction from baseline in MADRS total score) but who are not in remission at the end of the double-blind induction phase.

       Relapse is defined as any of the following:

        1) MADRS total score ≥22 for 2 consecutive assessments. The date of the second MADRS assessment will be used for the date of relapse.
        2) Hospitalization for worsening depression or any other clinically relevant event determined per clinical judgment to be suggestive of a relapse of depressive illness such as suicide attempt, completed suicide, or hospitalization for suicide prevention. If hospitalized for any of these events, the start date of hospitalization will be used for the date of relapse. Otherwise the date of the event will be used if the subject is not hospitalized.
        3) In case both relapse criteria are met, the earlier date will be defined as the date of relapse for this subject.
8. Change from baseline in SDS total score in the posttreatment phase.
9. Change from baseline (prior to the first dose of OL induction phase) in MADRS total score in the OL induction phase.
10. Proportion of responders (≥50% reduction from baseline in MADRS total score) in the OL induction phase.
11. Proportion of remitters (MADRS total score ≤12) in the OL induction phase.
12. Change from baseline (prior to the first dose of OL induction phase) in CGI-S in the OL induction phase.

Pharmacokinetic Evaluations

Whole blood samples will be used to evaluate the PK of esketamine (and noresketamine or additional metabolites, if warranted). The plasma concentration-time data of esketamine (and noresketamine or additional metabolites, if warranted) will be analyzed using population PK modeling. Typical population values of basic PK parameters (eg, esketamine clearance, distribution volume) will be estimated together with the inter-individual variability. Effects of subject demographics, laboratory parameter values, and other covariates on the PK of esketamine will be explored. The results of the population PK analyses may be reported separately.

Pharmacokinetic/Pharmacodynamic Evaluations

The PK/PD relationship of intranasal esketamine and MADRS total score (and possibly selected AEs as additional PD parameters) may be evaluated. If there is any visual trend in graphical analysis, suitable models will be applied to describe the exposure-effect relationships. The results of the PK/PD evaluations will be presented in a separate report.

Biomarker Evaluations

During the study, blood will be collected for the assessment of biomarkers at the time points indicated in the TIME AND EVENTS SCHEDULE 1. The biomarker blood samples should be collected prior to dosing.

Pharmacogenomic (DNA) Evaluations

A pharmacogenomic blood sample will be collected to allow for pharmacogenomic research, as necessary.

A pharmacogenomic blood sample will be collected to allow for the assessment of genetic and epigenetic variation in genes in pathways relevant to the effect of esketamine.

SAFETY EVALUATIONS

Physical examination, height, and body weight, vital signs (including temperature, heart rate, blood pressure measurements, and respiratory rate), 12-lead electrocardiogram (ECG), pulse oximetry, clinical laboratory tests, evaluation of concomitant therapies, and TEAEs including TEAEs of special interest will be performed throughout the study to monitor subject safety.

The Columbia Suicide Severity Rating Scale (C-SSRS) will be performed to assess suicidal ideation and behavior, the Clinician-Administered Dissociative States Scale (CADSS) will be administered to assess treatment-emergent dissociative symptoms, the four-item Positive Symptom Subscale of the Brief Psychiatric Rating Scale (BPRS+) will be administered to assess treatment-emergent psychotic symptoms, the Modified Observer's Assessment of Alertness/Sedation (MOAA/S will) be used to measure treatment-emergent sedation, the Clinical Global Assessment of Discharge Readiness (CGADR) will be used to measure the subject's readiness for discharge based on parameters including sedation, blood pressure and AEs, and the 20-item Physician Withdrawal Checklist (PWC-20) will be administered to assess potential withdrawal symptoms after cessation of esketamine treatment, and Profile of Mood States 2nd edition (POMS-2) will be used to evaluate the abuse-liability of intranasal esketamine treatment.

On all intranasal dosing days, subjects will remain at the site until study procedures have been completed and the subject is ready for discharge. Subjects should be accompanied by a responsible adult when released from the clinical site. Subjects must not drive a car or work with machines for 24 hours after receiving the intranasal study drug.

STATISTICAL METHODS

Subject Information

The primary efficacy (full analysis set [FAS]) and safety analysis sets are defined below.

- **Full Analysis Set:** All randomized subjects who receive at least 1 dose of intranasal study drug in the double-blind induction phase.
- **Open-label Analysis Set:** All subjects who receive at least 1 dose of intranasal study drug in the OL induction phase.
- **Safety Analysis Set:** All randomized subjects who receive at least 1 dose of intranasal study drug in the double-blind induction phase.

Sample Size Determination

The sample size for this study was calculated assuming a treatment difference for the double-blind induction phase of 4, 4.5, 5 points in MADRS total score between each dose (28 mg, 56 mg, 84 mg) of esketamine and the placebo respectively, a SD of 10 for each treatment group, a 1-sided significance level of 0.05 and a drop-out rate of 12.5%. A total of 183 subjects will need to be randomized to treatment in a

2:1:1:1 ratio (72 subjects on placebo group and 37 subjects per intranasal esketamine dose group) to achieve 80% power to detect difference for at least one dose group of intranasal esketamine to placebo using a Dunnett adjustment. The treatment difference and SD used in this calculation were assumed based on results of Panel B of the ESKETINTRD2003 study with clinical consideration.

Efficacy Analyses

Efficacy analysis will be performed on the FAS, which will include all randomized subjects who receive at least 1 dose of intranasal study drug in the double-blind induction phase. Unless otherwise specified, a 1-sided significance level of 0.05 will be used. For the primary efficacy analysis, change from baseline in MADRS total score at Week 4 in the double-blind induction phase will be analyzed using a mixed-effects model for repeated measures. The model will include baseline MADRS total score as a covariate, and treatment, day, and day-by-treatment interaction as fixed effects. An unstructured variance-covariance matrix will be used. Comparison of each esketamine dose groups with the placebo group will be performed with the appropriate contrast using a Dunnett adjustment.

The impact of the missing data on the efficacy results will be assessed using sensitivity analyses. The follow-up data from subjects who discontinued the double-blind induction phase will be incorporated in the sensitivity analyses. Methods of sensitivity analyses will be specified in the statistical analysis plan (SAP).

For the secondary efficacy analysis, the dose-response relationship will be investigated using the MCP-Mod procedure. Details will be provided in the SAP.

The other secondary efficacy endpoints, the endpoints with continuous values will be analyzed by using mixed-effects model for repeated measures similar to the primary endpoint. Comparison of each esketamine group versus placebo group will be performed using the appropriate contrast. Binary endpoints will be analyzed using Fisher's exact test with 90% confidence intervals (CIs) for the proportion provided for each treatment group.

Time to relapse will be defined as the time between the end of the double-blind induction phase and the first documentation of a relapse event during the posttreatment phase. This will be analyzed separately either remitters or responders (but who are not remitters) at the end of the double-blind induction phase. Summary statistics (eg, number of relapses, number of censored subjects, median 25th and 75th percentile) will be provided from the Kaplan-Meier method.

Additionally, scores and the changes from baseline of all efficacy endpoints will be summarized for all visits in the each induction phase. Data from the OL induction phase will be summarized based on subjects who received treatment during the OL induction phase.

Pharmacokinetic Analyses

Plasma esketamine (and noresketamine, if needed) concentrations will be listed for all subjects. Descriptive statistics of plasma esketamine (and noresketamine, if needed) concentration at each PK assessment time points will be calculated by dose. All concentrations below the lowest quantifiable sample concentration of the assay (BQL) or missing data will be labeled as such in the concentration data listing.

Population PK analysis of plasma concentration-time data of esketamine (and noresketamine, if needed) will be performed with non-linear mixed-effects modeling (NONMEM) approach.

Biomarker and Pharmacogenomic (DNA) Analyses

Baseline biomarker values and changes from baseline biomarker values to the time points specified in the TIME AND EVENTS SCHEDULE 1 will be assessed. Biomarker values will be tabulated by treatment group over time points and summary statistics will be calculated. Associations between biomarkers and clinical endpoints will be explored. Correlations between baseline values and change in baseline values with efficacy and other clinical evaluations will be assessed, including the relation with response, maintenance of response, illness relapse, and nonresponse.

Pharmacogenomic analyses may include candidate gene analyses or genome-wide association analyses in relation to treatment response, maintenance/stabilization of response, relapse, and nonresponse.

Details of the analysis plan and summary of results from both biomarker and pharmacogenomics analyses will be provided in a separate report.

Pharmacokinetic/Pharmacodynamic Analyses

The PK/PD relationship of intranasal esketamine and MADRS total score (and possibly selected AEs as additional PD parameters) may be evaluated. If there is any visual trend in graphical analysis, suitable models will be applied to describe the exposure-effect relationships. The results of the PK/PD evaluation will be presented in a separate report.

Safety Analyses

Safety analysis set will consist of all randomized subjects who receive at least 1 dose of intranasal study drug in the double-blind induction phase. Safety data for the double-blind period will be analyzed for this population. For the analysis of safety data in the OL induction phase, all subjects who received at least 1 dose of intranasal study drug in this period will be analyzed.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). For each AE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. Subjects who discontinue treatment due to an AE and serious adverse events (SAEs) will be summarized separately.

The TEAEs of special interest will be examined separately grouped in the following categories: Drug abuse, dependence and withdrawal (standardized MedDRA queries [SMQ]), increased blood pressure, increased heart rate, transient dizziness/vertigo, impaired cognition, anxiety, and cystitis. AEs of special interest will be further listed in the SAP.

Body weight, vital signs, 12-lead ECG, pulse oximetry, and clinical laboratory test results, and changes from baseline will be presented over time by treatment group, using descriptive statistics. Any treatment-emergent abnormalities will be presented.

PWC-20 rating scale, dissociative data from the CADSS, alertness data from the CGADR, sedation data from the MOAA/S, suicide-related thoughts and behaviors based on C-SSRS, Abuse-liability data from POMS-2, and psychosislike effect data from the BPRS+ will be summarized descriptively at each scheduled visit by treatment group.

TIME AND EVENTS SCHEDULE 1 [-SCREENING PHASE, PROSPECTIVE LEAD-IN PHASE AND DOUBLE-BLIND INDUCTION PHASE]

	Screening Phase	Prospective Lead-in Phase			Double-blind Induction Phase										
Visit number	1.1 [b]	2.1 [b]	2.2	2.3	3.1 [a]		3.2	3.3	3.4	3.5	3.6	3.7	3.8	3.9	3.10 [m]	EW [c]
Study Week	Within 4 weeks of Day P1	-6	-4	-2	1				2		3		4			—
Study day	-70 (P-28 to P-1)	-42 (P1)	-28 (P15)	-14 (P29)	1 (P43) Prerandomization	1 (P43) Postrandomization	2	4	8	11	15	18	22	25	28	EW
Clinic visit window (days)		-3	±3	±3	—	—	—	±1	±1	±1	±1	±1	±1	±1	±1	—
Remote MADRS interview window (in days; relative to Study day [not including visit window])		-3	±3	±3	—	—	—	—	-2 [d]	—	-2 [d]	—	-2 [d]	—	-2 [d, p]	—
Clinic visit (C) or remote MADRS interview only (RM)		C	C	C	C		RM	C	C	C	C	C	C	C	C	C
Informed Consent/Screening/Administrative																
Informed consent (ICF)	X [o]															
Medical history, psychiatric history, demographics, employment status	X															
MINI	X															
MGH-ATRQ	X															
SAFER interview	X															
Height	X															
Inclusion/exclusion criteria	X	X			X											
Study Drug and Oral Antidepressants (Base Therapy)																
Randomization						X										
Dispensing of new oral antidepressant		X	X	X		X			X				X			
Practice session for use of intranasal device						X [e]										

	Screening Phase	Prospective Lead-in Phase			Double-blind Induction Phase										
Visit number	1.1 [b]	2.1 [b]	2.2	2.3	3.1 [a]		3.2	3.3	3.4	3.5	3.6	3.7	3.8	3.9	3.10 [m]	EW [c]
Study Week	Within 4 weeks of Day P1	-6	-4	-2	1				2		3		4			—
Study day	-70 (P-28 to P-1)	-42 (P1)	-28 (P15)	-14 (P29)	1 (P43) Prerandomization	1 (P43) Postrandomization	2	4	8	11	15	18	22	25	28	EW
Clinic visit window (days)		-3	±3	±3	—	—	—	±1	±1	±1	±1	±1	±1	±1	±1	—
Remote MADRS interview window (in days; relative to Study day [not including visit window])		-3	±3	±3	—	—	—	—	-2 [d]	—	-2 [d]	—	-2 [d]	—	-2 [d, p]	—
Clinic visit (C) or remote MADRS interview only (RM)		C	C	C	C		RM	C	C	C	C	C	C	C	C	C
Intranasal esketamine or placebo						X		X	X	X	X	X	X	X		
Drug accountability (intranasal study drug)						X		X	X	X	X	X	X	X		
Oral antidepressant compliance check			X	X	X	X		X	X	X	X	X	X	X	X	X
Safety Assessments (Clinician)																
Physical examination	X				X				X		X			X	X	X
Vital signs: blood pressure, pulse, respiratory rate, temperature [e]	X	X	X		X			X	X	X	X	X	X	X		X
Vital signs (postdose): blood pressure, pulse, respiratory rate [f]						X		X	X	X	X	X	X	X		
Weight	X				X						X				X	X
12-lead ECG [g]	X				X	X			X		X			X		X
C-SSRS: Baseline/Screening version	X															

	Screening Phase	Prospective Lead-in Phase			Double-blind Induction Phase										
Visit number	1.1 [b]	2.1 [b]	2.2	2.3	3.1 [a]		3.2	3.3	3.4	3.5	3.6	3.7	3.8	3.9	3.10 [m]	EW [c]
Study Week	Within 4 weeks of Day P1	-6	-4	-2	1				2		3		4			—
Study day	-70 (P-28 to P-1)	-42 (P1)	-28 (P15)	-14 (P29)	1 (P43) Prerandomization	1 (P43) Postrandomization	2	4	8	11	15	18	22	25	28	EW
Clinic visit window (days)		-3	±3	±3	—	—	—	±1	±1	±1	±1	±1	±1	±1	±1	—
Remote MADRS interview window (in days; relative to Study day [not including visit window])		-3	±3	±3	—	—	—	—	-2 [d]	—	-2 [d]	—	-2 [d]	—	-2 [d, p]	—
Clinic visit (C) or remote MADRS interview only (RM)		C	C	C	C		RM	C	C	C	C	C	C	C	C	C
C-SSRS: Since last visit version		X	X	X	X			X	X	X	X	X	X	X	X	X
MOAA/S and pulse oximetry [h]		X [n]			X [n]	X		X	X	X	X	X	X	X		
BPRS+ [i]						X		X	X	X	X	X	X	X		
CADSS [i]						X		X	X	X	X	X	X	X		
CGADR [j]						X		X	X	X	X	X	X	X		
PWC-20 [e]														X		X
Subject-completed Assessments (Safety)																
POMS-2 [e]														X		X
Efficacy Assessments (Clinician)																
MADRS (7-day recall; performed by independent, remote raters)		X	X	X	X				X		X		X		X	X
MADRS (24-hr recall; performed by independent, remote raters)							X									
CGI-S [e]		X	X	X	X				X		X		X		X	X

	Screening Phase	Prospective Lead-in Phase			Double-blind Induction Phase										
Visit number	1.1 [b]	2.1 [b]	2.2	2.3	3.1 [a]		3.2	3.3	3.4	3.5	3.6	3.7	3.8	3.9	3.10 [m]	EW [c]
Study Week	Within 4 weeks of Day P1	-6	-4	-2	1				2		3		4			—
Study day	-70 (P-28 to P-1)	-42 (P1)	-28 (P15)	-14 (P29)	1 (P43) Prerandomization	1 (P43) Postrandomization	2	4	8	11	15	18	22	25	28	EW
Clinic visit window (days)		-3	±3	±3	—	—	—	±1	±1	±1	±1	±1	±1	±1	±1	—
Remote MADRS interview window (in days; relative to Study day [not including visit window])		-3	±3	±3	—	—	—	—	-2 [d]	—	-2 [d]	—	-2 [d]	—	-2 [d, p]	—
Clinic visit (C) or remote MADRS interview only (RM)		C	C	C	C		RM	C	C	C	C	C	C	C	C	C
Subject-completed Assessments																
SDS [e]					X										X	X
GAD-7 [e]					X						X				X	X
Clinical Laboratory Assessments																
TSH, HbA1c	X															
Lipid panel (fasting)		X														
Hematology, chemistry [e]	X				X										X	X
Urinalysis [e]	X				X						X				X	X
Urine drug screen [e]	X															
Alcohol breath test	X															
Serum pregnancy test	X														X	X
Urine pregnancy test [e]					X						X					
Pharmacokinetics																
Blood collection [k]								X						X		
Biomarker and Pharmacogenomic (DNA) Evaluations																
Blood sample collection (Protein) [e, l]						X		X						X		X
Blood sample collection (DNA) [e, l]						X		X						X		X

	Screening Phase	Prospective Lead-in Phase			Double-blind Induction Phase										
Visit number	1.1 [b]	2.1 [b]	2.2	2.3	3.1 [a]		3.2	3.3	3.4	3.5	3.6	3.7	3.8	3.9	3.10 [m]	EW [c]
Study Week	Within 4 weeks of Day P1	-6	-4	-2	1				2		3		4			—
Study day	-70 (P-28 to P-1)	-42 (P1)	-28 (P15)	-14 (P29)	1 (P43) Prerandomization	1 (P43) Postrandomization	2	4	8	11	15	18	22	25	28	EW
Clinic visit window (days)		-3	±3	±3	—	—	—	±1	±1	±1	±1	±1	±1	±1	±1	—
Remote MADRS interview window (in days; relative to Study day [not including visit window])		-3	±3	±3	—	—	—	—	-2 [d]	—	-2 [d]	—	-2 [d]	—	-2 [d, p]	—
Clinic visit (C) or remote MADRS interview only (RM)		C	C	C	C		RM	C	C	C	C	C	C	C	C	C
Ongoing Subject Review																
Concomitant therapy	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X

Footnotes:

Note: On intranasal dosing days, time 0 is defined as the time of the first intranasal spray. Therefore, postdose time points are referenced from this.

a. Visit 3.1 Prerandomization must coincide exactly on the same day as Visit 3.1 Postrandomization. All subjects who will be randomized and enrolled in the double-blind induction phase must meet all of the inclusion criteria and none of the exclusion criteria at Visit 3.1 Prerandomization. After randomization, all subjects will proceed to Visit 3.1 Postrandomization.
b. If clinically indicated, cross tapering is allowed.
c. If a subject withdraws before the end of the double-blind induction phase (ie, before completing Visit 3.10/Day 28) for reasons other than withdrawal of consent, an EW Visit should be conducted within 1 week of the date of discontinuation, followed by the follow-up phase. If the EW Visit is conducted on the same day as a scheduled visit, duplicate assessments are not required.
d. MADRS assessment should be conducted at predose.
e. Predose (if/when performed on intranasal dosing days). With the exception of postdose assessments, subject-reported outcome assessments should be administered before all other study-related procedures during a clinic visit.
f. Postdose vital signs will be performed at 40 minutes, 1 hour, and 1.5 hours postdose. Please refer to Section 6.3.1 for guidance for blood pressure monitoring on intranasal dosing days.

g. Twelve-lead ECG will be performed at t=1 hour postdose at Visit 3.1 Postrandomization. Twelve-lead ECG will be performed at t=1 hour postdose at Visits 3.4 to 3.9 (only at the time points indicated), but no predose ECGs are required at Visits 3.4 to 3.9. A time window of ±15 minutes is permitted.
h. The MOAA/S will be performed every 15 minutes from predose to t=+1.5 hours postdose. Pulse oximetry will be performed every 15 minutes from predose to t=1.5 hours postdose.
i. The BPRS+ and CADSS to be performed predose and at 40 minutes and 1.5 hours postdose.
j. CGADR to be performed at 1 hour and 1.5 hour postdose; if the response is not "Yes" at 1.5 hour postdose, the assessment will be repeated every 15 minutes until a "Yes" response is achieved or until the subject is referred for appropriate medical care if clinically indicated. A subject should not be discharged prior to the 1.5 hour time point.
k. PK blood collection will be performed at t=40 minutes, t=1 hour and t=2 hours postdose (where time=0 is defined as the time of the first intranasal spray on PK blood collection Day).
l. Blood samples should be collected prior to dosing. It is preferred that subjects adhere to a low fat diet on the day of sample collection. Subjects also should refrain from strenuous exercise for 24 hours prior to sample collection.
m. Visit 3.10 will be identical to the start day of the posttreatment phase.
n. Pulse oximetry only.
o. Informed consent must be obtained prior to the initiation of any study procedure including washout of prohibited therapies.
p. MADRS interview should not be conducted on the same day with the assessment at Visit 3.9.

TIME AND EVENTS SCHEDULE 2 [-POSTTREATMENT PHASE AND FOLLOW-UP PHASE]

Visit number	Posttreatment Phase											Follow-up Phase [a]	
	4.1	4.2	4.3	4.4	4.5	4.6	4.7	4.8	4.9, 4.10, 4.11, 4.13, 4.14, 4.15, 4.17, 4.18, 4.19, 4.21, 4.22, 4.23	4.12 4.16 4.20 4.24	EW	6.1 6.2	6. 3
Study week	5	6	7	8	9	10	11	12	13, 14, 15, 17, 18, 19, 21, 22, 23, 25, 26, 27	16 20 24 28	-	F1 F2	F4
Study day	32	39	46	53	60	67	74	81	88, 95, 102, 116, 123, 130, 144, 151, 158, 172, 179, 186	109 137 165 193	-	F7 F14	F28
Clinic visit or remote MADRS window (days)	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3	-	±3	±3
Clinic (C) or remote MADRS interview only (RM)	C	C	C	C	RM	C	RM	C	RM	C	C	C	C
Safety Assessments (Clinician-completed)													
C-SSRS: Since last visit version	X	X	X	X		X		X		X	X	X	X
PWC-20	X	X	X	X								X	X
Safety Assessments (Subject-completed)													
POMS-2	X	X		X		X		X		X	X	X	X
Efficacy Assessments (Clinician-completed)													
MADRS (7-day recall)	*Performed weekly* [b, c]											X	X
CGI-S	X	X	X	X		X		X		X	X	X	X
Efficacy Assessments (Subject-completed)													
SDS		X		X		X		X		X	X		
Clinical Laboratory Assessments													
Urine pregnancy test				X				X			X		X
Oral antidepressant													
Oral antidepressant compliance check	X	X	X	X		X		X		X	X	X	X
Dispensing of oral antidepressant	X	X	X	X		X		X		X		X	X

Visit number	Posttreatment Phase											Follow-up Phase [a]	
	4.1	4.2	4.3	4.4	4.5	4.6	4.7	4.8	4.9, 4.10, 4.11, 4.13, 4.14, 4.15, 4.17, 4.18, 4.19, 4.21, 4.22, 4.23	4.12 4.16 4.20 4.24	EW	6.1 6.2	6. 3
Study week	5	6	7	8	9	10	11	12	13, 14, 15, 17, 18, 19, 21, 22, 23, 25, 26, 27	16 20 24 28	-	F1 F2	F4
Study day	32	39	46	53	60	67	74	81	88, 95, 102, 116, 123, 130, 144, 151, 158, 172, 179, 186	109 137 165 193	-	F7 F14	F28
Clinic visit or remote MADRS window (days)	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3	-	±3	±3
Clinic (C) or remote MADRS interview only (RM)	C	C	C	C	RM	C	RM	C	RM	C	C	C	C
Ongoing Subject Review													
Concomitant therapy	X	X	X	X		X		X		X	X	X	X
Adverse events	X	X	X	X		X		X		X	X	X	X

Footnotes:

a. All subjects who are discontinued must be treated with an oral antidepressant after completion of the study, unless it is clinically inappropriate.

b. MADRS assessments will be performed weekly through Week 24 or relapse, whichever occurs first. In the posttreatment phase, subjects who relapse within 20 weeks after the start of the posttreatment phase will receive an open-label treatment course of esketamine. The beginning of the open-label induction phase should be at least 2 weeks after the last dose in the double-blind induction phase.

c. Relapse based on MADRS assessment is defined as MADRS total score ≥22 for 2 consecutive visits.

TIME AND EVENTS SCHEDULE 3 [-OPEN-LABEL INDUCTION PHASE]

	Open-label Induction Phase (Visit number; 5.1-5.10, Study week; OL1-OL4, Study day; OL1-OL28)									
Visit number	**5.1**	**5.3**	**5.4**	**5.5**	**5.6**	**5.7**	**5.8**	**5.9**	**5.10**	**EW** [a]
Study Week	**OL 1**		**OL 2**		**OL 3**		**OL 4**			**—**
Study day	**OL 1** [i]	**OL 4**	**OL 8**	**OL 11**	**OL 15**	**OL 18**	**OL 22**	**OL 25**	**OL 28**	**EW**
Clinic visit window (days)	—	±1	±1	±1	±1	±1	±1	±1	±1	—
Remote MADRS interview window (in days; relative to Study day [not including visit window])	—	—	-2	—	-2	—	-2	—	-2 [j]	—
Clinic visit (C) or remote MADRS interview only (RM)	C	C	C	C	C	C	C	C	C	C
Study Drug and Oral Antidepressants (Base Therapy)										
Dispensing of new oral antidepressant	X		X				X			
Intranasal esketamine	X	X	X	X	X	X	X	X		
Drug accountability (intranasal study drug)	X	X	X	X	X	X	X	X		
Oral antidepressant compliance check	X	X	X	X	X	X	X	X	X	X
Safety Assessments (Clinician)										
Physical examination [b]	X		X		X			X	X	X
Vital signs: blood pressure, pulse, respiratory rate, temperature [b]	X	X	X	X	X	X	X	X		X
Vital signs (postdose): blood pressure, pulse, respiratory rate [c]	X	X	X	X	X	X	X	X		
Weight [b]	X				X				X	X
12-lead ECG [d]	X				X			X		X
C-SSRS: Since last visit version [b]	X	X	X	X	X	X	X	X	X	X
MOAA/S and pulse oximetry [e]	X	X	X	X	X	X	X	X		
BPRS+ [f]	X	X	X	X	X	X	X	X		
CADSS [f]	X	X	X	X	X	X	X	X		
CGADR [g]	X	X	X	X	X	X	X	X		
PWC-20 [b]								X		X
Efficacy Assessments (Clinician)										
MADRS (7-day recall; performed by independent, remote raters)	X		X		X		X		X	X
CGI-S [b]	X		X		X		X		X	X

	Open-label Induction Phase (Visit number; 5.1-5.10, Study week; OL1-OL4, Study day; OL1-OL28)									
Visit number	**5.1**	**5.3**	**5.4**	**5.5**	**5.6**	**5.7**	**5.8**	**5.9**	**5.10**	**EW** [a]
Study Week	**OL 1**		**OL 2**		**OL 3**		**OL 4**			**—**
Study day	**OL 1** [i]	**OL 4**	**OL 8**	**OL 11**	**OL 15**	**OL 18**	**OL 22**	**OL 25**	**OL 28**	**EW**
Clinic visit window (days)	—	±1	±1	±1	±1	±1	±1	±1	±1	—
Clinical Laboratory Assessments										
Hematology, chemistry [b]	X								X	X
Urinalysis [b]	X				X				X	X
Serum pregnancy test	X								X	X
Urine pregnancy test [b]					X					
Pharmacokinetics										
Blood collection [h]								X		
Ongoing Subject Review										
Concomitant therapy	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X

Footnotes:

Note: On intranasal dosing days, time 0 is defined as the time of the first intranasal spray. Therefore, postdose time points are referenced from this.

a. If a subject withdraws before the end of the open-label induction phase (ie, before completing Visit 5.10/Day OL28) for reasons other than withdrawal of consent, an EW Visit should be conducted within 1 week of the date of discontinuation, followed by the follow-up phase. If the EW Visit is conducted on the same day as a scheduled visit, duplicate assessments are not required.
b. Predose (if/when performed on intranasal dosing days).
c. Postdose vital signs will be performed at 40 minutes, 1 hour, and 1.5 hours postdose. Please refer to Section 6.3.1 for guidance for blood pressure monitoring on intranasal dosing days.
d. Twelve-lead ECG will be performed at t=1 hour postdose at Visit 5.1 to 5.10 (only at the time points indicated), but no predose ECGs are required at Visits 5.1 to 5.10. A time window of ±15 minutes is permitted.
e. The MOAA/S will be performed every 15 minutes from predose to t=+1.5 hours postdose. Pulse oximetry will be performed every 15 minutes from predose to t=1.5 hours postdose.
f. The BPRS+ and CADSS to be performed predose and at 40 minutes and 1.5 hours postdose.
g. CGADR to be performed at 1 hour and 1.5 hour postdose; if the response is not "Yes" at 1.5 hour postdose, the assessment will be repeated every 15 minutes until a "Yes" response is achieved or until the subject is referred for appropriate medical care if clinically indicated. A subject should not be discharged prior to the 1.5 hour time point.
h. PK blood collection will be performed at t=40 minutes, t=1 hour and t=2 hours postdose (where time=0 is defined as the time of the first intranasal spray on PK blood collection Day).
i. If the assessment on Day OL 1 is conducted on the same day as a scheduled visit in the posttreatment phase, duplicate assessments are not required.
j. MADRS interview should not be conducted on the same day with the assessment at Visit 5.9.

ABBREVIATIONS

AE	adverse event
ASA	American Society of Anesthesiologists
AUC	area under curve
BDNF	brain-derived neurotrophic factor
BPRS+	four-item positive symptom subscale of the Brief Psychiatric Rating Scale
CADSS	Clinician-Administered Dissociative Symptom Scale
CGADR	Clinical Global Assessment of Discharge Readiness
CGI-S	Clinical Global Impression – Severity
Cmax	maximum plasma concentration
CI	confidence interval
CR	controlled-release
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	hepatic cytochrome P450
DBP	diastolic blood pressure
DBS	deep brain stimulation
DNA	deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders (fifth edition)
ECG	electrocardiogram
eCRF	electronic case report form
ECT	electroconvulsive therapy
eDC	electronic data capture
EOS	end-of-study
EW	early withdrawal
FAS	full analysis set
FT4	free thyroxine
GAD-7	Generalized Anxiety Disorder 7-item scale
GCP	good clinical practice
HbA1c	glycated hemoglobin
HPA	hypothalamic pituitary-adrenal
HRUQ	Healthcare Resource Use Questionnaire
HVLT-R	Hopkins Verbal Learning Test-Revised
IC	informed consent
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IM	intramuscular
IP	investigational product
IRB	Institutional Review Board
IV	intravenous
IWRS	interactive web response system
MADRS	Montgomery-Asberg Depression Rating Scale
MDD	major depressive disorder
MGH-ATRQ	Massachusetts General Hospital – Antidepressant Treatment Response Questionnaire
MINI	Mini International Neuropsychiatric Interview
MOAA/S	Modified Observer's Assessment of Alertness/Sedation
MMRM	mixed-effects model for repeated measures
NMDA	N-methyl-D-aspartate
OL	open-label
PD	pharmacodynamics
PK	pharmacokinetic
POMS-2	Profile of Mood States 2nd edition
PQC	product quality complaint
PWC-20	Physician Withdrawal Checklist; 20-item
QTc	corrected QT
QTcF	QT interval corrected according to Fridericia's formula

RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SDS	Sheehan Disability Scale
SE	standard error
SNPs	single nucleotide polymorphisms
SSRI	selective serotonin re-uptake inhibitor
SNRI	serotonin–norepinephrine reuptake inhibitor
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TRD	treatment-resistant depression
TSH	thyroid-stimulating hormone
XR	extended-release

1. INTRODUCTION

Major depressive disorder (MDD) is a serious, recurrent, and disabling psychiatric illness.[67] It is the second leading cause of years lost to disability worldwide and is associated with excess mortality; and the estimated median years of potential life lost is 10 years.[68,71] About 30% of subjects fail to achieve remission despite treatment with multiple antidepressant medications, and are considered to have treatment-resistant MDD (TRD).[26,58] In subjects who respond to antidepressant treatments, the time to onset of effect is typically 4 to 7 weeks, during which time subjects continue to suffer from their symptoms and continue to be at risk of self-harm, as well as being impacted by the associated harm to their personal and professional lives.[58,61] Therefore, there is a significant need to develop novel treatments based upon relevant pathophysiologic pathways underlying MDD for the rapid relief of depressive symptoms, especially in subjects with TRD.[22,23]

Ketamine and esketamine (S-ketamine, the S-enantiomer of ketamine) are approved and widely used for the induction and maintenance of anesthesia via intramuscular (IM) or intravenous (IV) administration. The desired analgesic-anesthetic effects of ketamine and esketamine are attributed to the blockade of ionotropic N-methyl-D-aspartate (NMDA) glutamate receptors. The mechanism of action of ketamine and esketamine are distinct from conventional monoaminergic antidepressant treatments, in that they profoundly affect fast excitatory glutamate transmission, increases in brain-derived neurotrophic factor (BDNF) release, and stimulate synaptogenesis.

Monoamines (serotonin, norepinephrine, or dopamine) are only modulatory transmitters; therefore, conventional monoaminergic antidepressant treatments would not be expected to robustly affect synaptic transmission, activity-dependent release of BDNF, or synaptogenesis.[23] In contrast, the mechanism of action of ketamine is distinct from conventional antidepressant treatments by profoundly affecting fast excitatory glutamate transmission, increasing BDNF release, and stimulating synaptogenesis.[23]

Most literature reports of the antidepressant effects of ketamine describe studies using IV administration of the racemate, with a few exceptions.[20,45] Janssen Research & Development is developing intranasal esketamine because of the higher NMDA receptor affinity of esketamine in contrast to its racemate arketamine (R-ketamine), which would require administration of a lower volume of medication via the intranasal route.[38,46,51]

For the most comprehensive nonclinical and clinical information regarding esketamine, refer to the latest version of the Investigator's Brochure[32] for esketamine.

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Background

1.1.1. Nonclinical Studies

Safety Pharmacology

The following text, quoted from the United States (US) prescribing information for anesthetic Ketalar® (ketamine hydrochloride [HCl] injection)[33]: Intravenous Ketalar produces a fall in arterial blood pressure in the Rhesus monkey and a rise in arterial blood pressure in the dog. In this respect, the dog mimics the cardiovascular effect observed in man. The pressor response to Ketalar injected into intact, unanesthetized dogs is accompanied by a tachycardia, rise in cardiac output, and a fall in total peripheral resistance. The pressor response to Ketalar is reduced or blocked by chlorpromazine (central depressant and peripheral α-adrenergic blockade), by β-adrenergic blockade, and by ganglionic blockade.

Findings from animal studies suggest that the increase in blood pressure produced by ketamine/esketamine is due to selective activation of central cardiac stimulating mechanisms leading to an increase in cardiac output.

In a 3-month repeat-dose toxicity study with intranasally administered esketamine in dogs, no relevant electrocardiogram (ECG) changes were noted up to the highest dose tested, ie, 72 mg/day. Heart rate was slightly increased. The cardiovascular safety of racemic ketamine and esketamine in humans and animals is summarized in the Investigator's Brochure.[32]

Toxicology

Repeat-dose Toxicity Studies

In repeat-dose toxicity studies with intranasally administered esketamine in rats up to 9 mg/day for 6 months, and dogs up to 72 mg/day for 3 months of duration, the clinical observations mainly related to the central nervous system (eg, changes in activity and gait). No adverse effects were noted up to the highest dose tested, ie, 9 mg/day in rats and 72 mg/day in dogs. These observations reflected the (exaggerated) pharmacology of the test compound. Minor histologic findings were noted in the nasal cavity. These tissue changes were not considered adverse.

In 3- and 9-month repeat-dose toxicity studies with intranasally administered esketamine in dogs, no relevant electroencephalographic changes were noted up 72 mg/day. Heart rate was slightly increased.[32]

Genetic Toxicity

A series of in vitro and in vivo genotoxicity studies was conducted with ketamine and esketamine. The weight of evidence indicates that esketamine poses no genotoxic risk to humans.[32]

Neurotoxicity

Racemic ketamine has been reported to induce neurotoxicity in animal fetuses, and in juvenile, adolescent, and adult animals, as evidenced by histopathologic brain lesions and functional

sequelae. The precise thresholds for dose and duration of exposure causing neurotoxicity in animals remain to be established. The relevance to humans of ketamine's neurotoxic action in animals is unknown.

In studies exploring neurotoxic effects of ketamine on juvenile and prenatal monkeys, neuroapoptosis was observed to be more widespread in fetal brains than in neonatal brains, after administration of ketamine anesthesia IV for 5 hours. In fetal brains, the cerebellum, caudate nucleus, putamen, and nucleus accumbens were most severely affected. In neonatal brains, the cerebellum was not affected; the strongest neuroapoptotic response was noted in the basal ganglia and several thalamic areas.

In juvenile rodents, ketamine-induced apoptotic neurodegeneration was observed that was more widespread than in adult rodents, with the developing brain affected in several major regions. Neuronal cell death was induced in the dorsolateral thalamus at blood levels of ketamine of 14 µg/mL (7 times the human anesthetic blood level of approximately 2 µg/mL).

No significant neurotoxic effects occurred in juvenile Rhesus monkeys if the anesthesia was administered as IM induction followed by IV maintenance. Ketamine infusion for 9 or 24 hours increased neuronal cell death in the frontal cortex, but no significant changes were noted in the hippocampus, thalamus, striatum, or amygdala. Cognitive impairments were observed beginning around 10 months of age and persisted at 3.5 years of age.

The clinical studies will exclude neonates, infants, children, pregnant women, and breastfeeding women. Therefore, ketamine's neurotoxicity in juvenile animals does not represent a safety risk to eligible elderly subjects. Moreover, the large dosages and prolonged treatment durations associated with neurotoxicity in juvenile animals do not suggest a concern.

Chronic treatment with ketamine at high dose levels affected the brain of adolescent monkeys, as evidenced by histopathologic lesions and functional impairment.

The neurotoxicity of ketamine in adult animals is also associated with high dose levels, in contrast to the relatively low dose levels of esketamine associated with antidepressant efficacy in humans. In single-dose and 14-day repeated-neurotoxicity studies with intranasally administered esketamine in rats, no histopathologic brain lesions were noted even upon high exposures, as achieved at 54 mg/day in the 14-day study. In the 6-month rat and 9-month dog repeat-dose toxicology studies with intranasally administered esketamine, where the animals were of adolescent age at initiation of treatment, and in the pre- and postnatal developmental toxicity study in rats, no evidence of neurotoxicity was found. Consequently, the risk of neurotoxicity associated with intranasal administration of esketamine to adult and adolescent subjects is considered low.[32]

Abuse Potential

Animal studies with ketamine suggest that it would have abuse potential in humans. These studies included self-administration and withdrawal experiments in several species.[32]

Reproductive Toxicity

In a rat fertility and early embryonic developmental toxicity study with intranasally administered esketamine, no adverse effects on fertility or reproductive capacity or performance were found.

Rat and rabbit embryo-fetal developmental toxicity studies with intranasally administered racemic ketamine did not reveal evidence of reproductive toxicity. However, when monkey fetuses were exposed in utero to high dose levels of racemic ketamine, neurotoxicity was observed.

Intranasally administered esketamine did not affect pre- and postnatal development in rats. However, high dose levels of racemic ketamine-induced neurotoxicity in early postnatal rat pups.[32]

Considering the neurotoxic potential of ketamine and esketamine; and the fact that no threshold for these effects has been demonstrated, female subjects of childbearing potential should be adequately protected from becoming pregnant and pregnant women should not be enrolled.

Cardiovascular Toxicity

In guinea pig tissues, ketamine-induced negative inotropic effects and shortening of action potential duration at the 0-mV level was observed, likely as a result of the suppression of inward calcium current whereas in rat left atria and ketamine-induced positive inotropic effects and prolongation of action potential duration at the 0-mV level was observed, likely as a result of a decrease in calcium-insensitive transient outward current.[25] The inhibitory action on membrane currents may partly explain the species and tissue differences in inotropic responses to ketamine.

Blood pressure responses to ketamine also vary with the laboratory species and with experimental conditions. Blood pressure is increased in normotensive and renal hypertensive rats with and without adrenalectomy and under pentobarbital anesthesia.[33]

These observations support the hypothesis that the hypertension produced by Ketalar is due to selective activation of central cardiac stimulating mechanisms leading to an increase in cardiac output.

The dog would be considered the most predictive species in terms of ketamine's cardiovascular effects in humans, but the antidepressant effects of ketamine were studied only in rodent models. The myocardial contractility effects and blood pressure responses to ketamine vary between species.[32] Consequently, a margin of safety could not be reliably derived from the available animal data.

Overall Conclusion

The currently available nonclinical safety studies support chronic intranasal administration of esketamine in human subjects up to a dosage of 84 mg/day.

1.1.2. Clinical Studies

1.1.2.1. Pharmacokinetics and Product Metabolism

Ketamine (and esketamine) undergoes extensive metabolism by hepatic cytochrome P450 (CYP). In humans, N-demethylation to norketamine is the major route of metabolism, which can undergo further metabolism to form hydroxynorketamine. Ketamine and norketamine are extensively hydroxylated to a series of 6-hydroxynorketamine metabolites and 2-hydroxyketamine metabolites.[70] Like ketamine, norketamine is a noncompetitive antagonist at the NMDA receptor. Norketamine has a half-life in plasma of approximately 5 hours.[24,31] The major human hepatic CYPs that catalyze ketamine N-demethylation in vitro are CYP2B6 and CYP3A4.[52] The CYP enzymes responsible for the formation of norketamine metabolites include CYP2A6 and CYP2B6.[52] Published results of a clinical pharmacokinetic (PK) study indicate that esketamine does not invert to the R-enantiomer.[28]

Racemic ketamine and its metabolites have been previously shown to be predominantly excreted in the urine. An average of 91% and 3% of a tritium-labeled dose (1 mg/kg) administered to 6 healthy subjects was recovered in urine and feces, respectively.[3] Less than 3% of an administered dose was excreted in urine as parent drug.[69]

A PK summary of esketamine administered by the IV and intranasal routes is provided below.

Intravenous Esketamine

Subjects with TRD received 0.2 mg/kg or 0.4 mg/kg esketamine as a 40-minute IV infusion during Study ESKTIVTRD2001.[17] Maximum concentrations of esketamine were observed at the end of the infusion. Mean maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) values increased with an increase in the esketamine dose administered (80.9 and 135 ng/mL, respectively, and 150 and 218 ng*h/mL, respectively, for 0.2 mg/kg and 0.4 mg/kg esketamine). The mean plasma clearance of esketamine was high (109 L/h and 141 L/h for the 0.2 mg/kg and 0.4 mg/kg doses, respectively), as it was similar to or exceeded hepatic blood flow in humans. The large volume of distribution suggests that esketamine distributes widely into tissues (236 L and 303 L, respectively). The half-life of esketamine in plasma was 2.14 and 2.65 hours, respectively, for the 2 doses.

Intranasal Esketamine

Plasma esketamine PK results from Studies ESKETINTRD1001, ESKTINTRD1002, ESKETINTRD1003, ESKETINTRD1012, and ESKETINTRD2003 are described below.[12, 13, 14, 15, 16] The results demonstrate that plasma esketamine concentrations produced by effective IV regimens (0.2 mg/kg and 0.4 mg/kg as 40-minute infusions) may be achieved by the intranasal route.

Study ESKETINTRD1001 included 3 cohorts of subjects who were healthy male and female subjects.[12] The intranasal esketamine treatments were self-administered under the direct supervision of the investigator or designee. Subjects in Cohorts 1 and 3 received esketamine doses from 28 to 112 mg. The regimens were self-administered by subjects in the upright

position. No instructions were given with regards to sniffing after administration. The reported median T_{max} of esketamine ranged from 0.37 to 0.83 hours from the time the first spray was administered (ie, 0.33 to 0.5 hours after the last spray was administered). The doses of 28 to 112 mg produced mean C_{max} values ranging from 63.3 to 151 ng/mL, whereas mean AUC_{∞} values ranged from 164 to 565 ng*h/mL. Mean C_{max} and AUC values of esketamine increased in a less than dose-proportional manner across the dose regimens. Furthermore, there was substantial overlap in the range of individual C_{max} and AUC values among the 3 doses. The mean terminal half-life of esketamine ranged from 5.86 to 9.83 hours across all treatments.

Subjects in Cohort 2 received 84 mg in a semi-reclined position and were instructed to sniff after each spray. Higher mean C_{max} and AUC_{∞} values were observed in this cohort (174 ng/mL and 437 ng*h/mL, respectively) compared with the same esketamine dose self-administered by subjects in Cohort 1 (107 ng/mL and 363 ng*h/mL, respectively). The semi-reclined position of the head and the instruction to subjects to sniff gently following intranasal dosing are believed to be the cause for the increase in exposure observed in Cohort 2 compared with Cohort 1. As a result, the instructions for self-administration of intranasal esketamine were adapted to include the semi-reclined position of the head and sniffing following dosing for all future studies.

During the Phase 1 Study ESKETINTRD1002, 15 healthy Japanese and 14 healthy Caucasian subjects received single intranasal doses of esketamine 28 mg, 56 mg, and 84 mg in a crossover manner.[13] The mean body mass index (BMI) were 21.98 kg/m^2 and 23.49 kg/m^2 in Japanese and Caucasian subjects, respectively. On average, plasma esketamine C_{max} and AUC values were up to 48% higher in Japanese subjects compared with Caucasian subjects. The incidence of the treatment-emergent adverse events (TEAEs) was higher in Japanese subjects (80% [12/15]) as compared to Caucasian subjects (50% [7/14]). The most commonly reported TEAEs by preferred term (>10%) in Japanese subjects were headache (26.7% [4/15] of subjects), vertigo (46.7% [7/15] of subjects), vomiting (26.7% [4/15] of subjects), derealization (20.0% [3/15] of subjects), nausea (20.0% [3/15] of subjects), depressed level of consciousness (13.3% [2/15] of subjects), somnolence (13.3% [2/15] of subjects), and confusional state (13.3% [2/15] of subjects). Though TEAEs were seen in majority of subjects, they were transient, mild or moderate in severity and were consistent with previously reported TEAEs for esketamine. Hence, a single intranasal dose of esketamine (28 mg, 56 mg, and 84 mg) was observed to be safe and well tolerated in Japanese subjects with no new safety findings of clinical concern.

Study ESKETINTRD1003 compared the PK, safety, and tolerability of intranasally administered esketamine in healthy elderly (≥65 years of age) and younger adult subjects (18 to 55 years of age, both inclusive).[14] Subjects received a single intranasal treatment of esketamine 28 mg. Median time to reach the maximum plasma concentration (t_{max}) of esketamine was approximately 30 minutes for both age groups. The geometric means of the C_{max} and area under the plasma concentration-time curve from time 0 to infinite time, AUC_{∞}, for esketamine were approximately 21% and 17% higher, respectively, in the elderly compared with younger adult subjects.[14]

Another Study, ESKETINTRD1012, compared the PK, safety, and tolerability of intranasally administered esketamine in elderly subjects (≥75 years of age) and healthy younger adult

subjects (18 to 55 years of age, both inclusive). On average, the plasma C_{max}, AUC_{last}, and AUC_{∞} of esketamine produced by a single, 84 mg intranasal dose were approximately 67%, 34%, and 38% higher, respectively, in subjects who are ≥75 years of age, relative to younger adult subjects. A small difference was observed in the mean half-life of esketamine in plasma between elderly subjects (8.8 hours) and younger adults (7.5 hours).[15]

Study ESKETINTRD2003 is a 2-panel, doubly randomized, double-blind, placebo-controlled, multicenter study.[16] Panel A was conducted in the United States and Belgium and Panel B in Japan. Panel A assessed the efficacy and safety of 3 dose strengths of intranasal esketamine (28, 56, and 84 mg) administered twice a week in subjects with TRD. Panel B was designed to assess the efficacy and safety of 14-mg and 56-mg dose strengths. A limited PK sampling strategy was included in Study ESKETINTRD2003.[16] The esketamine concentrations in plasma samples collected at 40 minutes postdose on Days 1 and 11 (Panels A and B) were compared. For each panel, a dose-dependent increase in esketamine concentrations was evident. Plasma esketamine concentrations in subjects from Panel B who received 56 mg of esketamine were higher relative to the corresponding concentrations produced by the same esketamine dose administered in Panel A, consistent with results from Phase 1 Study ESKETINTRD1002.[13]

1.1.2.2. Pharmacodynamics and Efficacy

The efficacy of subanesthetic doses (0.5 mg/kg IV administered over 40 minutes) of IV ketamine has been evaluated in approximately 192 subjects with MDD (cases and controls), and 2 studies in bipolar depressed subjects (meta-analysis).[27] This recently published meta-analysis of studies suggests that ketamine has a rapid onset (within 1 day) of antidepressant efficacy, including in those who have not benefitted from other antidepressant treatments, used as monotherapy or in combination with oral antidepressant treatments.

Esketamine (0.2 and 0.4 mg/kg administered IV over 40 minutes) has similar, rapid, and robust antidepressant effect as that seen with IV ketamine. A double-blind, double-randomization, placebo-controlled study (ESKETIVTRD2001) enrolled 30 adult subjects with TRD: 10 in the IV placebo group, 9 in the IV esketamine 0.20-mg/kg group, and 11 in the IV esketamine 0.40-mg/kg group (based on Day 1 randomization).[17] The full analysis set (FAS) of the primary efficacy variable (change in Montgomery-Asberg Depression Rating Scale [MADRS] total score from baseline Day 1 to Day 2) indicated that the improvement in both esketamine dose groups was statistically significant (1-sided p=0.001 in both dose groups) compared with the placebo group. The mean (standard deviation [SD]) change from baseline Day 1 to Day 2 in MADRS total score was -4.9 (4.72) in the placebo group, -16.8 (10.12) in the esketamine 0.20 mg/kg group, and -17.8 (9.45) in the esketamine 0.40 mg/kg group.

The studies listed above assessed the efficacy of ketamine or esketamine after a single dose as the primary endpoint. The average duration of response to a single-dose of ketamine (0.5 mg/kg) was approximately 5 days. An open-label (OL) study demonstrated that the response to the first dose could be maintained by multiple infusions 3 times a week over 2 weeks. The duration of response lasted for approximately 19 days.[1]

Study KETIVTRD2002 assessed whether multiple doses of ketamine given twice a week would also maintain the antidepressant response; the data from this study suggest that ketamine (0.50 mg/kg IV over 40 minutes) administered twice a week was sufficient for maintaining the initial effect over a 4-week treatment period.[18]

As noted above, Study ESKETINTRD2003 is a 2-panel, doubly-randomized, double-blind, placebo-controlled, multicenter study.[16] Panel A was conducted in the US and Belgium and Panel B in Japan. Panel A assessed the efficacy and safety of 3 dose strengths of intranasal esketamine (28, 56, and 84 mg) administered twice a week in subjects with TRD. Panel B is designed to assess the efficacy and safety of 14-mg and 56-mg dose strengths. In Panel A, subjects in Period 1 (1-week duration) were randomly assigned in a 3:1:1:1 ratio to placebo (33 subjects), esketamine 28 mg (11 subjects), esketamine 56 mg (11 subjects), or esketamine 84 mg (12 subjects). An initial analysis of the data from the double-blind phase of Panel A indicates that of the 67 subjects randomized in Period 1, 63 entered Period 2 (1-week duration), in which 28 placebo subjects who were eligible for re-randomization at the end of Period 1, were randomly assigned in a 1:1:1:1 ratio to placebo (n=6), esketamine 28 mg (n=8), esketamine 56 mg (n=9), or esketamine 84 mg (n=5). Subjects eligible for re-randomization had to have a Quick Inventory of Depressive Symptomatology - Self Report ($QIDS\text{-}SR_{16}$) total score of >11 at the end of Period 1.[16]

In Panel A, the improvement (with respect to change in MADRS total score from baseline [Day 1] to Day 8) in all 3 esketamine dose groups reached statistical significance ($p=0.021$, $p=0.001$, and $p<0.001$ for esketamine 28, 56, and 84 mg, respectively) compared with placebo. The results of the 2 periods were consistent. The mean differences from placebo on Day 8 (after 1 week of treatment), estimated using data from the combined periods, were:

- Esketamine 28 mg: -4.2 (standard error [SE] 2.09);
- Esketamine 56 mg: -6.3 (SE 2.07);
- Esketamine 84 mg: -9.0 (SE 2.13).

The effect sizes (confidence interval [CI]) in Period 1 for esketamine, compared with placebo, were:

- Esketamine 28 mg: 0.43 (-0.259-1.118);
- Esketamine 56 mg: 0.92 (0.201-1.621);
- Esketamine 84 mg: 1.19 (0.473-1.883).

The duration of effect with the 28-mg dose appears to be shorter, with the MADRS total score higher on Day 8 than on Day 2. The duration of effect for the 56- and 84-mg doses appears to support twice-a-week dosing.[16]

These data with intranasal esketamine support the hypotheses that intranasal esketamine is effective as a treatment for depression, that it has rapid onset of effect within 2 hours, and that multiple repeated sessions dose-dependently show sustained response throughout the study duration. A clear dose response was seen in the double-blinded data in Panel A, and the point

estimates and CIs suggest a high effect size (Cohen's D) with the 56-mg and 84-mg dose groups, supporting further development.[16]

In Panel B, 41 Japanese subjects entered Period 1 and were randomly assigned in a 2:1:1 ratio to placebo (21 subjects), esketamine 14 mg (11 subjects) or esketamine 56 mg (9 subjects). All 41 subjects in Period 1 entered Period 2, where 13 subjects initially randomized to placebo were eligible for re-randomization at the end of Period 1 and were randomized to receive placebo, esketamine 14 mg, or esketamine 56 mg in Period 2 in a 1:1:1 ratio. The remaining placebo subjects of Period 1 who were not eligible for re-randomization at the end of Period 1 (8 subjects) and subjects who were randomized to esketamine 14 mg (11 subjects), or esketamine 56 mg (9 subjects) continued to receive the same treatment in Period 2. Subjects eligible for re-randomization had to have a QIDS-SR_{16} total score ≥11 at the end of Period 1.[16]

In Period 1, greater improvements in MADRS total score were observed in the esketamine 56 mg group compared with the placebo group (least squares mean treatment difference [SE]: -3.7 [2.81]; p=0.096). Smaller improvements in MADRS total score were observed in the esketamine 14 mg group compared with the placebo group (least squares mean treatment difference [SE]: +1.8 [2.62]). Although there was a statistically significant difference at the one-sided 0.10 level between the esketamine 56 mg and placebo groups in Period 1, this result should be interpreted with caution because there was a significant treatment by baseline MADRS total score interaction (p=0.052), where results favored the placebo group for subjects with higher baseline MADRS total scores and the esketamine groups for subjects with lower baseline MADRS total scores. In addition, there was a high placebo response rate for subjects in Panel B in Period 1. In Period 2, greater improvements in MADRS score were observed in both esketamine groups compared with the placebo group (least squares mean treatment differences [SE]: -5.9 [5.58] for esketamine 14 mg and -0.5 [6.25] for esketamine 56 mg). However, the results for Period 2 must be interpreted with caution due to the small number of subjects in each treatment group. A consistency test showed that the results for Period 1 were not consistent with Period 2 in Panel B; therefore, the data from each period were not combined to assess the treatment differences using the weighted combination test.[16]

A dose response was detected in Period 1 (p=0.097); however this should be interpreted with caution given the significant treatment by baseline MADRS total score interaction that was observed in Period 1 (see above). No dose response was detected in Period 2, which may be due to the small number of subjects included in the analysis in Period 2 (n=13). Because of the observed inconsistency between the two periods, the combination test was not performed.[16]

In Panel B, the decrease in MADRS total score was greater in the esketamine 56-mg treatment group compared with the placebo group at the double-blind endpoint (Study Day 15). Adjusted treatment differences between the esketamine groups and the placebo group (estimate for placebo group adjusted to account for subjects who received placebo in Period 1 and esketamine in Period 2) after 2 weeks of treatment for subjects who received the same treatment for both periods and completed the double-blind phase were -1.0 for esketamine 14 mg and -7.4 for esketamine 56 mg.[16]

MADRS total score decreased from OL baseline (Study Day 15) to Study Day 25; mean (SE) change from OL baseline was -2.4 (1.33) for all subjects. Mean (SE) change from OL baseline was -4.5 (2.30) in the placebo/placebo/OL esketamine group, -1.3 (4.67) in the placebo/esketamine/OL esketamine group, and -1.4 (1.48) in the esketamine/esketamine/OL esketamine group.[16]

The results from subjects in Panel B who received the same treatment during both periods suggested that after 2 weeks of treatment, subjects who received esketamine 56-mg in both periods had greater improvements in mean MADRS score, response rates, and remission rates compared with those who received placebo. Furthermore, evaluation of response rates and remission rates in Panel B over time during the double-blind and OL phases suggested that improvements in symptoms of depression resulting from esketamine treatment could be sustained over 25 days with repeated dosing.[16]

At the time of protocol writing, there are 6 ongoing Phase 3 studies of intranasal esketamine formulation: ESKETINTRD3001, ESKETINTRD3002, ESKETINTRD3003, ESKETINTRD3004, ESKETINTRD3005, and ESKETINTRD3008.[32, 5]

ESKETINTRD3001 is a randomized, double-blind, multicenter, active-controlled study to evaluate the efficacy, safety, and tolerability of fixed doses of intranasal esketamine plus an oral antidepressant in adult subjects with TRD (TRANSFORM-1).[7] Subjects will be randomly assigned at a 1:1:1 ratio to receive double-blind intranasal treatment with either esketamine 56 mg, esketamine 84 mg, or placebo twice weekly. Subjects will self-administer the drug at 0-, 5-, and 10 minutes. In addition, all subjects will initiate a new OL oral antidepressant on Day 1 that will be taken daily until 4 weeks. Subjects assigned to 84 mg will receive 56 mg on Day 1; thereafter 84 mg on subsequent dosing days. Responders (subjects with ≥50% reduction in the MADRS total score) may be eligible to participate in the subsequent study ESKETINTRD3003.[9]

ESKETINTRD3002 is a randomized, double-blind, multicenter, active-controlled study to evaluate the efficacy, safety, and tolerability of flexible doses of intranasal esketamine plus an oral antidepressant in adult subjects with TRD (TRANSFORM-2).[8] Subjects will be randomly assigned in a 1:1 ratio to receive intranasal esketamine (flexible dose, 56 mg or 84 mg) or placebo twice weekly. Subjects will self-administer the drug at 0-, 5-, and 10 minutes. In addition, all subjects will be initiated on a new OL oral antidepressant on Day 1 that will be taken daily until 4 weeks. Responders (subjects with ≥50% reduction in the MADRS total score) may be eligible to participate in the subsequent Study ESKETINTRD3003.[9]

ESKETINTRD3003 is a randomized, double-blind, multicenter, active-controlled study of intranasal esketamine plus an oral antidepressant for relapse prevention in TRD (SUSTAIN-1).[9] This study includes following phases: 4 weeks OL Induction Phase, Optimization Phase, Maintenance Phase and Follow-up Phase. During OL Induction Phase, eligible direct-entry subjects will receive intranasal esketamine, flexible dose: 56 mg or 84 mg, twice weekly. In addition, all subjects will initiate a new OL oral antidepressant on Day 1 daily until 4 weeks. Responders (≥50% reduction in the MADRS total score) may be eligible to proceed to the optimization phase. During the 12-week optimization phase, eligible direct-entry subjects from

the OL induction phase and transferred-entry subjects will receive intranasal esketamine dose weekly for first 4 weeks followed by either once weekly or once every other week (based on total MADRS score) and same oral antidepressant treatment initiated during the induction phase. Subjects in stable remission and those with stable response at the end of optimization phase may be eligible to continue into the maintenance phase. Maintenance Phase has a variable duration, until 84 relapses occur in subjects with stable remission, or earlier based on interim analysis results. Approximately 211 subjects in stable remission with stable response will be randomized in a 1:1 ratio (each using a separate randomization list) to either continue with intranasal esketamine (same dose) and the same oral antidepressant or to continue with the same oral antidepressant (active comparator) but switch to intranasal placebo. Transferred-entry subjects who achieve stable remission or stable response at the end of optimization phase after treatment with an oral antidepressant plus intranasal placebo will continue to receive the same treatment.

The frequency of intranasal treatment sessions will be further individualized once weekly or once every other week (based on MADRS score) during the maintenance phase.[9]

Study ESKETINTRD3005 is a randomized, double-blind, multicenter, active-controlled study to evaluate the efficacy, safety, and tolerability of intranasal esketamine plus an oral antidepressant in elderly subjects with TRD (TRANSFORM-3).[11] During the double-blind induction phase (4 weeks), approximately 148 eligible subjects will be randomly assigned at a 1:1 ratio to receive double-blind intranasal treatment with either esketamine (flexible dose 28 mg, 56 mg, or 84 mg), or placebo, starting with an initial dose of 28 mg on Day 1 to be taken twice weekly. In addition, all subjects will initiate a new, OL oral antidepressant on Day 1 to be taken daily until 4 weeks. After completing the double-blind induction phase, subjects may be eligible to participate in the subsequent Study ESKETINTRD3004 if they meet all other study entry criteria or else will be followed by 2-week follow-up phase.

Study ESKETINTRD3004 is an OL, long-term, safety and efficacy study of intranasal esketamine in TRD (SUSTAIN-2).[10] Approximately, 750 direct-entry subjects will be enrolled in this study, plus transferred-entry subjects from Study ESKETINTRD3005.[11] A total of at least 100 subjects who are 65 years or older (who are either direct-entry subjects or transferred-entry subjects from the Study ESKETINTRD3005) will be enrolled. During an OL induction phase (4 weeks), direct-entry subjects will receive intranasal esketamine (flexible dose: 28 mg [dose option for elderly subjects only], 56 mg, or 84 mg twice weekly) with dose adjusted based on the age and efficacy and tolerability. In addition, all subjects will initiate a new OL oral antidepressant on Day 1 daily until 4 weeks. Transferred-entry nonresponder subjects will start intranasal esketamine with an initial dose of 28 mg on Day 1, with the dose adjusted based on efficacy and tolerability (28, 56, or 84 mg) and continue to take the same oral antidepressant at same dose as taken in the last week of double-blind induction phase of Study ESKETINTRD3005. Responders (subjects with ≥50% reduction in the MADRS total score) may be eligible to proceed to the optimization phase of 12 weeks.

Study ESKETINTRD3008 is an OL, long-term, extension safety study of intranasal esketamine in TRD (SUSTAIN-3).[5] This study provides an opportunity for subjects who have participated in select Phase 3 studies (ESKETINTRD3001, ESKETINTRD3002, ESKETINTRD3003,

ESKETINTRD3004, and ESKETINTRD3005) to receive open label intranasal esketamine until: it is commercially available or a preapproval access program is made available to the subject in the subject's respective country; the subject does not benefit from further treatment (based on the investigator's clinical judgment), or withdraws consent; or the company terminates clinical development of intranasal esketamine for TRD.[7, 8, 9, 10, 11]

In addition, 2 Phase 1 studies related to Japanese, Study 54135419TRD1008[6] and 54135419TRD1018[4,] are ongoing. Study 54135419TRD1008 is a single-dose study to assess the PK, safety, and tolerability of intranasally administered esketamine in healthy Han Chinese, Korean, Japanese, and Caucasian Subjects. Study 54135419TRD1018 is a single-ascending dose study to compare the PK, safety, and tolerability of intranasally administered esketamine in elderly Japanese subjects and healthy younger adult Japanese subjects.[4]

1.1.2.3. Safety and Tolerability

Ketamine is a rapidly acting general anesthetic that is approved and widely used IV or IM for the induction and maintenance of anesthesia in children and adults at a dose of 1 to 3 mg/kg given as a bolus. Ketamine is marketed as a racemic mixture and in Europe also as the S-enantiomer, esketamine. Ketamine was first introduced as an anesthetic in 1963 and is considered to have an excellent medical safety profile.[30,34,64,54]

In the US prescribing information for ketamine HCl for injection and the Summary of Product Characteristics (SmPC) for esketamine HCl for injection, the following adverse reactions are listed as very common, common, or frequent occurrences: Emergence or recovery reactions, elevated blood pressure and heart rate, stimulation of respiration, nausea, and vomiting.[33] See Table 1 for details.

Table 1: Adverse Reactions Listed as Very Common, Common, or Frequent Occurrences in the Product Information of Anesthetic Ketamine and Esketamine

System Organ Class	"Frequent" Adverse Reactions Per Anesthetic Ketamine USPI[33,a]	"Very Common" or "Common" Reactions Per Anesthetic Esketamine SmPC[34,b]
Psychiatric disorders	Frequency: Emergence reactions occurred in approximately 12% of subjects. Characteristics: Severity varied from pleasant dreamlike states, vivid imagery, hallucinations, and emergence delirium. Some states were accompanied by confusion, excitement, and irrational behavior, which some subjects recalled as an unpleasant experience.	Frequency: Recovery reactions were common. When esketamine was the sole anesthetic, up to 30% of subjects displayed dose-dependent recovery reactions. Characteristics: Reactions included vivid dreams (including nightmares), nausea and vomiting, increased salivation, blurred vision, dizziness, and motor restlessness[c].
Cardiac disorders	Blood pressure and pulse rate were frequently elevated after administration. However, hypotension and bradycardia have been observed. Arrhythmia has also occurred.	Common occurrences were temporary tachycardia and increase in blood pressure and heart rate (approximately 20% of the initial value was typical).
Respiratory, thoracic, and mediastinal disorders	Although stimulation of respiration was a frequently observed effect, severe depression of respiration or apnea also could occur after rapid intravenous administration of high doses.	Common effects were increase in vascular resistance in pulmonary circulation and increase in mucus secretion. Increased oxygen consumption, laryngospasms, and temporary respiratory depression were common; the risk of respiratory depression was noted to depend on dose and injection speed.
Gastrointestinal disorders	No gastrointestinal effects were listed as frequent, but the USPI stated that anorexia, nausea, and vomiting have been observed.	Common effects included nausea and vomiting.

SmPC = Summary of Product Characteristics; USPI = United States Prescribing Information

[a] "Frequent" was not defined numerically, except in the case of emergence reactions (12%). The terms "very common" and "common" did not appear in the adverse effects section of the USPI.

[b] "Very common" was defined in the SmPC as ≥1/10 and "common" was defined as ≥1/100 to <1/10.

[c] The incidence of these events can be greatly reduced by the administration of a benzodiazepine

Source: Investigator's Brochure for esketamine (JNJ-54135419).[32]

Adverse Events Associated with Short-term Use of Intranasal Esketamine in Subjects With MDD

Administration of esketamine is associated with a number of adverse events (AEs), which are transient in nature and typically resolve in 2 hours or less from the start of drug administration. The phase 1 study ESKETINTRD1003 evaluated the PK and safety of a single intranasal esketamine 28 mg in 14 healthy elderly subjects (≥65 years of age, with 3 subjects ≥75 years of age) and 20 healthy younger adult subjects (18 to 55 years of age, inclusive). The incidences of the TEAEs were slightly higher in young subjects (100% [20 subjects]) as compared with elderly subjects (85.7% [12 subjects]). The most commonly reported TEAEs by preferred term (>20%) in elderly subjects were dysgeusia and vertigo (9 [64%] of 14 subjects each).[14]

No deaths were reported in the double-blind or OL phases of Study ESKETINTRD2003 in Panel A. One subject experienced a serious adverse event (SAE) of esophagitis in Panel A (double-blind phase, placebo/placebo treatment group). A total of 3 subjects withdrew during the double blind phase because of AEs. One subject in esketamine 28 mg group experienced a TEAE of syncope of severe intensity on Day 2 of Period 1, 1 day after receiving the first dose of study

medication. The subject was discontinued from the study and the study drug was permanently withdrawn due to this event, which resolved on the same day. The investigator considered the event to be possibly related to the study drug. Another subject in the placebo/esketamine 56 mg group experienced a TEAE of headache of moderate intensity on Day 11 of Period 2 and the study drug was permanently withdrawn due to this event, which resolved on the same day. The investigator considered the event to be very likely related to the study drug. A third subject in the esketamine group (84 mg/esketamine 84 mg) experienced a TEAE of dissociative disorder (verbatim term: Dissociative syndrome) of moderate intensity on Day 8 of Period 2 (day of the third esketamine 84 mg dose in the study). The subject was discontinued from the study and the study drug was permanently withdrawn due to the event of dissociative disorder, which resolved on the same day. The investigator considered the event to be very likely related to the study drug.[59]

Dissociative symptoms measured on the Clinician-Administered Dissociative States Scale (CADSS) were dose-dependent and were observed to reduce significantly with multiple doses over 2 weeks. No psychotic symptoms were seen. Transient increases in mean blood pressure (systolic and diastolic) were observed post dose following the intranasal esketamine administration.[59]

The mean (SD) peak systolic blood pressure (SBP) after the first administration in each dose group was:

- Placebo: 124.2 (11.51) mm Hg (mean [SD] increase of 5.4 [7.84] mm Hg);
- 28 mg: 131.8 (15.49) mm Hg (mean [SD] increase of 10.4 [10.44] mm Hg);
- 56 mg: 130.4 (18.64 mm Hg (mean [SD] increase of 11.2 [15.01] mm Hg);
- 84 mg: 146.1 (19.9) mm Hg (mean [SD] increase of 17.1 [15.5] mm Hg).

Mean (SD) peak diastolic blood pressure (DBP) after the first administration in each dose group was:

- Placebo: 81.2 (8.36) mm Hg (mean [SD] increase of 3.8 [7.99] mm Hg);
- 28 mg: 85.7 (9.16) mm Hg (mean [SD] increase of 6.5 [7.00] mm Hg);
- 56 mg: 86.5 (11.34) mm Hg (mean [SD] increase of 7.2 [9.67] mm Hg);
- 84 mg: 87.8 (10.62) mm Hg (mean [SD] increase of 8.1 [9.12] mm Hg).

The blood pressure increase typically resolved within 2 hours. Unlike dissociative symptoms, the blood pressure changes observed do not appear to attenuate over time with multiple doses. Transient increases in heart rate were also observed in parallel with blood pressure change. There was no clinically meaningful change in blood oxygen level.[59]

In Panel B of Study ESKETINTRD2003 the most common TEAEs during the double-blind phase (≥10% of subjects in any treatment group) were somnolence, hypoesthesia, dizziness, headache, dysgeusia, feeling abnormal, nausea, dissociation, dizziness postural, and hyperhidrosis.[59]

There were no deaths or other SAEs during the double-blind or OL phase of the study. However, there was one death by completed suicide in the follow-up phase of the study. The investigator considered the event to be not related to study medication.

The dissociative and perceptual change symptoms measured by the CADSS, suggest these symptoms had an onset shortly after the start of the dose, with a peak by 40 minutes and resolved by 2 hours post dose.[59]

The mean (SD) peak SBP after the first administration in each dose group was:

- Placebo: 116.4 (14.84) mm Hg (mean [SD] increase of 1.7 [1.74] mm Hg);
- 14 mg: 124.9 (13.46) mm Hg (mean [SD] increase of 6.5 [3.33] mm Hg);
- 56 mg: 125.4 (10.11) mm Hg (mean [SD] increase of 7.2 [3.04] mm Hg).

The mean (SD) peak DBP after the first administration in each dose group was:

- Placebo: 75.3 (11.30) mm Hg (mean [SD] increase of 3.6 [1.81] mm Hg);
- 14 mg: 80.6 (14.42) mm Hg (mean [SD] increase of 5.4 [3.02] mm Hg);
- 56 mg: 82.6 (9.33) mm Hg (mean [SD] increase of 8.3 [3.13] mm Hg).

Adverse Events Associated With Chronic Use of Ketamine

There are no controlled studies of long-term use with esketamine/ketamine in subjects with MDD. Much of the literature on chronic use of ketamine comes from data gathered from street/illegal use of the drug, rather than systematically conducted clinical studies. Data therefore should be interpreted with caution, as in many cases, no baseline pre-drug data are available and drug exposure is poorly documented.

In a 1-year longitudinal study, 150 subjects were divided into 5 groups of 30 subjects each. Frequent ketamine users (more than 4 times per week), infrequent ketamine users (at least once a month), abstinent users (abstinent for at least 1 month), polydrug controls, and non-users of illicit drugs.[43] Eighty percent of the participants were retested at the end of 1 year. Cognitive deficits (including impairment in spatial working memory, pattern recognition memory and category fluency) were mainly observed in frequent users and not with the infrequent users. Short-lasting, dose-dependent effects of psychosis were associated with ketamine users. There was no increase in symptoms over time, and symptoms were completely reversible upon stopping use of ketamine. As noted, these data should be interpreted with caution, as baseline data predating drug use were not available. Furthermore, in their recent review, Morgan and Curran report that there is little evidence of any link between chronic, heavy use of ketamine and diagnosis of a psychotic disorder.[42]

The principal action of ketamine is at the NMDA receptor, and the consequences of ketamine use on cognition have been fairly widely investigated. Several studies have examined cognitive function in infrequent and frequent ketamine users.[42,43] Overall, infrequent or recreational ketamine use does not appear to be associated with long-term cognitive impairment.[43] The most robust

findings are that frequent ketamine users (more than 5 times a week) exhibit impairments in both short- and long-term memory.[41] Although dosages have varied, dosages reported by ketamine users in this study were much higher than the dosages of ketamine or equivalent doses of esketamine intended for use in treating TRD. Memory impairments may be reversible when individuals stop using the drug, as they were not found in a group of 30 ex-ketamine users who had been abstinent for at least a year. [42, 43]

Ketamine-induced ulcerative cystitis is a recently identified complication.[42] The most common symptoms are frequency and urgency of urination, dysuria, urge incontinence, and occasionally painful hematuria (blood in urine). Computerized tomography scans of these subjects revealed a marked thickening of the bladder wall, a small bladder capacity, and perivesicular stranding consistent with severe inflammation. At cystoscopy, all subjects had severe ulcerative cystitis. Biopsies in 4 of these cases found denuded urothelial mucosa with thin layers of reactive and regenerating epithelial cells, and ulcerations with vascular granulation tissue and scattered inflammatory cells. Cessation of ketamine use provided some relief of symptoms. Most of the described cases are in near-daily users of ketamine for recreational purposes. The prevalence is difficult to determine, as it is seen in recreational users who often do not seek help.

The majority of cases resolve after stopping ketamine use, one-third remaining static.

Abuse-liability, Dependence, and Withdrawal

There are a number of reports of ketamine dependence in the literature but no large-scale studies, and so the incidence of ketamine dependence is largely unknown.[43,49] An interview study of 90 ketamine users found that 57% of frequent users, 43% of infrequent users, and 60% of ex-users expressed concerns about ketamine addiction.[44] The majority of frequent users in that study reported using the drug without stopping until supplies ran out, so compulsive patterns of behavior are also a concern. Oral ketamine has also been evaluated as a positive control in human abuse potential studies, with dosages of 65 mg and 110 mg reported as appropriate for use as positive controls for future abuse potential studies of compounds with a similar mechanism of action or with possible perception-altering effects.[63] There is conflicting evidence of the existence of a "withdrawal syndrome" after cessation of ketamine use. Cravings seem to be a key problem in frequent users: 28 of the 30 daily users in 1 study reported having tried to stop taking the drug but failed; all reported ketamine cravings as the reason for failure.[43] The same study found that 12 of the 30 daily users reported withdrawal symptoms characterized by anxiety, shaking, sweating, and palpitations when they stopped using. A few published case studies also show craving and somatic and psychologic aspects of anxiety as withdrawal symptoms.[19] However, a specific ketamine withdrawal syndrome has not yet been described.

1.1.3. Marketing Experience

No intranasal formulation of esketamine is currently marketed.

1.2. Overall Rationale for the Study

Converging lines of evidence suggest that the glutamatergic system may play a role in the pathophysiology and treatment of depression, and that drugs modulating glutamatergic

neurotransmission, and therefore synaptic plasticity, may represent a novel class of antidepressants. Esketamine/ketamine is an antagonist of the NMDA receptor (a subtype of glutamatergic ion channel receptor), for which there is both preclinical and clinical data supporting its potential for the treatment of depression. Preclinical studies demonstrate that the rapid antidepressant actions of ketamine are mediated by the induction of synaptic proteins and increased number and function of new spine synapses in the prefrontal cortex.[23]

A range of pilot studies with esketamine/ketamine suggests that it is a paradigm-shifting breakthrough for the treatment of MDD and TRD. The sponsor has completed clinical conduct of a Phase 2 study with IV esketamine (Clinical Study Report ESKETIVTRD2001)[17] in Europe, which demonstrated the efficacy of 0.2 mg/kg and 0.4 mg/kg (both as 40-minute IV infusions) of esketamine in a TRD population. The efficacy of esketamine appears similar to the efficacy seen in studies with ketamine. A second Phase 2 study with IV ketamine in the US (Clinical Study Report KETIVTRD2002)[18] was done to demonstrate the minimal dosing frequency necessary for the short-term induction phase. This study demonstrated that ketamine (0.5 mg/kg IV over 40 minutes) administered twice a week is sufficient for maintaining the initial effect over a 4-week treatment period. In parallel to the studies done with IV esketamine and ketamine, a Phase 1 study in healthy subjects with intranasal esketamine (Clinical Study Report ESKETINTRD1001)[12] has demonstrated that plasma levels equivalent to those achieved after 0.2 to 0.4 mg/kg IV administration can be achieved after intranasal administration of doses of 28 to 84 mg esketamine.

A 2-panel Phase 2, ESKETINTRD2003,[16] in which the primary objective was to assess the efficacy and dose-response of intranasal esketamine (Panel A: 28 mg, 56 mg, 84 mg; Panel B: 14 mg and 56 mg) compared with placebo in improving depressive symptoms in subjects with TRD, as assessed by a change from baseline in the MADRS total score for the combined periods in the double-blind induction phase. Non-Japanese subjects in Panel A demonstrated the statistically significant efficacy of 56-mg and 84-mg doses of intranasal esketamine, as measured by a change in MADRS total score after 1 week of treatment. The 28-mg dose, which was administered in Panel A only, showed also statistically significant efficacy compared to placebo, however did not demonstrate sufficient clinically meaningful efficacy. Japanese subjects in Panel B showed a statistically significant improvement in symptoms of depression in the 56-mg dose of intranasal esketamine, however there was no statistically significant difference at 1 week postdose between the esketamine 14 mg group and the placebo group in Period 1. The distribution of plasma esketamine concentrations in Japanese subjects treated at 14 mg was comparable with that in non-Japanese subjects treated at 28 mg. Overall, Panel B showed higher response to placebo than Panel A, with smaller changes from baseline and smaller differences from placebo. In addition, the distribution of plasma esketamine concentrations in Japanese subjects treated at 56 mg was comparable with that in non-Japanese subjects treated at 84 mg. In this study, the PK/pharmacodynamic (PD) analysis suggested the efficacy of esketamine 28 mg in Japanese Panel. Meanwhile, from the pooled dose-response analyses of non-Japanese Panel and Japanese Panel, the efficacy of esketamine 28 mg was considered low. But as this analysis only included 28 mg from non-Japanese Panel, the efficacy of esketamine 28 mg could not clearly be excluded in Japanese subjects with TRD. On the other hand, esketamine 84 mg has not

been evaluated in the Japanese subjects with TRD in Phase 2 studies. It was well tolerated in Japanese subjects in the Phase 1 study, however, considering the PK results of this study and no treatment experience at 84 mg in Japanese subjects with TRD, safety and tolerability of 84 mg with fixed dose for 4 weeks in Japanese subjects with TRD needs to be carefully assessed. Hence, this Phase 2 study will be conducted to investigate the appropriate doses from esketamine 28 mg to esketamine 84 mg in Japanese subjects with TRD, to proceed to the confirmatory Phase 3 study.

The randomized, double-blind, multicenter, 54135419TRD2005 study is being conducted to evaluate the efficacy, safety, and tolerability of 28 mg, 56 mg and 84 mg fixed doses of intranasal esketamine add-on to an oral antidepressant in Japanese subjects with TRD.

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

Screening Phase

A screening phase of up to 4 weeks was chosen to allow adequate time for completion of all screening procedures with results available to the investigator before the first dose of the new antidepressant in the prospective lead-in phase, and to allow sufficient time for tapering and washout of prohibited medications to occur.

Prospective Lead-in Phase

Implementation of a prospective lead-in phase before randomization and active treatment will allow the use of a new antidepressant treatment which will contribute to standardize the base therapy in the population and the 6-week duration will allow for a prospective confirmation of nonresponse to the new antidepressant treatment that is continued for the duration of this phase.

Double-blind Induction Phase

Subjects must meet the predefined criteria of nonresponse to antidepressant therapy at the end of the prospective lead-in phase for eligibility to enter the randomized, double-blind induction phase. The determination of nonresponse in prospective manner is necessary to enroll qualified TRD patients.

Subjects who fulfill all inclusion criteria and none of the exclusion criteria will be randomized to 4-week double-blind intranasal treatment with either placebo, esketamine 28 mg, esketamine 56 mg, or esketamine 84 mg.

The primary endpoint will be assessed in the 4-week double blind induction phase, as the change from baseline in the MADRS total score at Week 4.

At the end of the 4-week double-blind induction phase, responders will be eligible to proceed to the posttreatment phase; those who do not (ie, nonresponders) will proceed to the 4-week follow-up phase.

Posttreatment Phase

Responders who completed the double-blind induction phase will enter the 24-week posttreatment phase. The 24-week duration of the posttreatment phase will allow sufficient time to evaluate sustained efficacy after cessation of add-on intranasal esketamine treatment while continuing the oral antidepressant medication regimen, as assessed by the following efficacy endpoints: 1) the time to relapse; and 2) proportion of responders and remitters at each visit in this phase. In the first 4 weeks of the posttreatment phase, withdrawal or rebound symptoms or both and potential abuse-liability will be evaluated. Subjects who relapse within 20 weeks after the start of the posttreatment phase will transit to an open-label induction phase and receive 4 weeks of open-label treatment with intranasal esketamine (28, 56, or 84 mg).

Subjects who relapse more than 20 weeks after the start of the posttreatment phase will withdraw from the study and clinical/standard-of-care treatment will be arranged by the study investigator after relapse.

Subjects who do not experience relapse throughout this 24-week posttreatment phase will complete study without the 4-week follow-up phase.

Open-label Induction Phase

The 4-week OL induction phase will be conducted for subjects who relapse in the posttreatment phase. This will evaluate if subjects will respond again to a second induction treatment course without any new safety signal compared to the double-blind induction treatment course. The beginning of the open-label induction phase should be at least 2 weeks after the last dose in the double-blind induction phase.

Subjects who meet the relapse criteria before 2 weeks after the last dose in the double-blind induction phase will not have an option for joining open label induction phase. They will withdraw from the posttreatment phase and move forward to the follow up phase.

Follow-up Phase

Following subjects will have follow-up Visits; subjects who withdraw from double blind induction phase, nonresponders after double-blind induction phase, responders who withdraw within 4 weeks after the last dose of double blind intranasal drug and all subjects who receive open label intranasal drug. During this phase, further clinical/standard-of-care treatment will be arranged by the study investigator.

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

Primary Objective

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

Secondary Objectives

- To assess the effect of intranasal esketamine compared with intranasal placebo as an add-on to an oral antidepressant in Japanese subjects with TRD, including the following parameters:
  - Dose response;
  - Depression response rates;
  - Depression remission rates;
  - Onset of clinical response;
  - Overall severity of depressive illness;
  - Anxiety symptoms;
  - Functioning and associated disability.
- To investigate the safety and tolerability of intranasal esketamine compared with intranasal placebo as an add-on to an oral antidepressant in Japanese subjects with TRD, including the following parameters:
  - TEAEs, including AEs of special interest;
  - Potential withdrawal or rebound symptoms or both following cessation of intranasal esketamine treatment;
  - Perceptual changes (dissociative symptoms);
  - Effects on alertness and sedation;
  - Effects on heart rate, blood pressure, respiratory rate, and blood oxygen saturation;
  - Potential effects on suicidal ideation/behavior;
  - Potential abuse-liability;
  - Potential psychosislike effects.
- To evaluate the durability of intranasal esketamine as an add-on to an oral antidepressant in Japanese subjects with TRD, with attention to:
  - Time to relapse in the posttreatment phase for subjects in remission and for subjects who respond but are not in remission, at the end of the double-blind induction phase.
- To evaluate the PK of intranasally administered esketamine in Japanese subjects with TRD.

Exploratory Objectives

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

2.2. Hypothesis

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

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

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

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

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

Screening Phase

Japanese men and women aged 20 to 64 years old (both inclusive), who meet Diagnostic and Statistical Manual of Mental Disorders (fifth edition) (DSM-5) diagnostic criteria for single-episode MDD or recurrent MDD without psychotic features, based upon clinical assessment and confirmed by the Mini-International Neuropsychiatric Interview (mental status questionnaire) (MINI) will be screened according to the inclusion/exclusion criteria. In the case of single-episode MDD, the subject must be diagnosed with persistent depressive disorder, which meets

criteria of major depressive episode for a continuous duration of ≥2 years, and the same physician from the site must be examining the subject for ≥2 years continuously as a primary care physician of the subject. Subjects receiving benzodiazepines (at dosages equal to or less than the equivalent of 6 mg/day of lorazepam) or permitted non-benzodiazepine sleep medications (eg, zolpidem, eszopiclone and zopiclone) or both during the screening phase can continue these medications throughout the study; however, dose increases or starting new benzodiazepine medications are not permitted.

To confirm eligibility for participation in the prospective lead-in phase, subjects will have a review of the inclusion/exclusion criteria in the screening phase. Subjects must not have responded to ≥1 but <5 different oral antidepressants taken at adequate dosage and for adequate duration, as assessed on the Massachusetts General Hospital – Antidepressant Treatment Response Questionnaire (MGH-ATRQ) and documented by medical history/prescription records, for the current episode of depression. The subject's current major depressive episode, depression symptom severity (MADRS total score ≥28 required), and treatment response to antidepressant medication used in the current episode (retrospectively assessed) must be deemed valid for participation in the clinical study based on the SAFER interview, which is administered by a remote, independent rater. At the screening visit, subjects who continue to fulfill all inclusion criteria and none of the exclusion criteria will be enrolled.

SAFER interview will be conducted as early as feasible during the screening period, before down-titration of antidepressants to avoid change of depressive symptoms because of tapering.

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

Prospective Lead-in Phase

After enrollment, eligible subjects will enter the 6-week OL prospective lead-in phase (Visits 2.1 to 3.1 [prerandomization]) during which, subjects will receive a new antidepressant therapy (physician determined) daily for the duration of this phase.

All subjects will initiate a physician-determined new OL oral antidepressant daily for the duration of this phase. The oral antidepressant will be 1 of the following: selective serotonin re-uptake inhibitors or serotonin-specific reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), or mirtazapine (ie, escitalopram, paroxetine controlled-release [CR], sertraline, duloxetine, venlafaxine extended-release [XR], or mirtazapine), which the subject has not previously had a nonresponse to in the current depressive episode or has not been previously intolerant to (lifetime). If clinically indicated, cross-tapering is allowed in the first 2 weeks during the prospective lead-in phase. In the last 4 weeks during the prospective lead-in phase,

'oral antidepressant' must be single treatment of switched new oral antidepressant. New oral antidepressant treatment should be titrated to the approved maximum dose, to optimize the potential for response. The up-titration schedule should be per prescribing information. The dose, which is above the minimum therapeutic dose defined in MGH-ATRQ should be kept at last 4 weeks during the prospective lead-in phase, in case they start at lower doses. Refer Attachment 3 (Example of the Up-titration Schedule for a New Oral Antidepressant Therapy (Physician Determined) in Prospective Lead-in Phase) for further information on up-titration.

The criteria of TRD is defined as nonresponse (≤25% improvement) to at least 1 antidepressant treatment determined retrospectively and 1 antidepressant prospectively in the current episode of depression. After 6 weeks, subjects who are nonresponders to the new oral antidepressant treatment at the end of the prospective lead-in phase can be eligible to proceed to the double-blind induction phase. Nonresponse at the end of the prospective lead-in phase is defined as ≤25% improvement in the MADRS total score from Visits 2.1 to each of Visit 2.3 and 3.1 (prerandomization) respectively, and a MADRS total score of ≥28 on each of the Visits 2.1, 2.3, and 3.1 (prerandomization). Assessment of antidepressant treatment response at the end of the prospective lead-in phase will be performed by investigators. All other subjects who do not proceed to the double-blind induction phase will end study participation at this time. No follow-up or further study visits will be performed for these subjects. All subjects who are discontinued must be treated with an oral antidepressant after completion of the study, unless it is clinically inappropriate.

MADRS assessment throughout the study will be performed by an independent, remote, blinded rater.

Double-blind Induction Phase

The 4-week fixed dose double-blind induction phase will start on Day 1 (Visit 3.1) and end at Day 28 (Visit 3.10). A total of 183 subjects will be randomly assigned in a 2:1:1:1 ratio to receive double-blind intranasal treatment with either placebo, esketamine 28 mg, esketamine 56 mg, or esketamine 84 mg add-on to the continued stable oral antidepressant initiated in the prospective lead-in phase. The intranasal treatment sessions (esketamine or placebo) will occur twice weekly. Subjects will self-administer the intranasal study drug (esketamine 28 mg, 56 mg, 84 mg, or placebo) at treatment sessions occurring twice a week for 4 weeks at the clinical site under clinical supervision. The first treatment session will be on Day 1.

Subjects assigned to esketamine 84 mg dosing will start treatment sessions with 56 mg of intranasal esketamine on Day 1 to improve tolerability. On Day 4 (Visit 3.3), the dose will be increased to 84 mg as a forced titration and remain at 84 mg for all subsequent intranasal treatment sessions. Subjects who are randomly assigned to 28 mg and 56 mg on Day 1 will remain on that dose for all subsequent intranasal treatment sessions. No adjustment to the intranasal esketamine dose is permitted during the double-blind induction phase.

Use of benzodiazepines and non-benzodiazepine sleeping medications (eg, zolpidem, eszopiclone, and zopiclone) is prohibited within 12 hours prior to the start of each intranasal treatment session.

Responders (subjects who have ≥50% reduction from baseline in MADRS total score) at the end of the double-blind induction phase will be eligible to proceed to the posttreatment phase; those who do not (ie, nonresponders) will proceed to the 4-week follow-up phase.

If a subject withdraws before the end of the double-blind induction phase for reasons other than withdrawal of consent, the Early Withdrawal (EW) Visit should be conducted within 1 week of the date of discontinuation, followed by a 4-week follow-up phase. MADRS information will be collected during the 4 week follow-up phase. If the EW Visit occurs on the same day as a scheduled visit, the EW Visit can be performed on the same day; duplicate assessments are not required.

Given the potential for treatment-emergent transient elevation in SBP and DBP, the guidance on Blood Pressure Monitoring (see Section 6.3.1) should be followed on intranasal dosing days during the double-blind induction phase.

Posttreatment Phase

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

Relapse is defined as any of the following:

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

In case both relapse criteria are met, the earlier date will be defined as the date of relapse for this subject.

Subjects who relapse within 20 weeks after the start of the posttreatment phase will transit to an OL induction phase and receive 4 weeks of OL treatment with intranasal esketamine (28, 56, or 84 mg). Subjects who relapse more than 20 weeks after the start of the posttreatment phase will withdraw from the study and clinical/standard-of-care treatment will be arranged by the study investigator after relapse. Subjects who do not experience relapse throughout this 24-week posttreatment phase will complete study without the 4-week follow-up phase (see Section 9.2.1.2.3).

Subjects who meet the criteria of relapse, they need to join OL induction phase before next remote MADRS assessment.

In the first 4 weeks of the posttreatment phase, withdrawal or rebound symptoms or both and potential abuse-liability will be evaluated using Physician's Withdrawal Checklist, 20-item (PWC-20) and Profile of Mood States, 2nd Edition (POMS-2).

The oral antidepressant medication initiated from the prospective lead-in phase, which will continue to be ongoing and stable during the double-blind induction phase will also be maintained throughout this phase.

Open-label Induction Phase

Subjects who relapsed in the posttreatment phase will receive a 4-week OL induction treatment course of intranasal esketamine. The beginning of the OL induction phase should be at least 2 weeks (14 calendar days) after the last dose in the double-blind induction phase. Subjects who meet the relapse criteria before 2 weeks after the last dose in the double-blind induction phase will not have an option for joining open label induction phase. They will withdraw from the posttreatment phase and move forward to the follow up phase.

Subjects who enter the OL induction phase will start treatment sessions with 56 mg of intranasal esketamine on the first day of OL induction phase (Day OL1). On the fourth day (Day OL4), the dose will be increased to 84 mg. On Day OL8 and OL11, the dose could be maintained, increased or reduced by 28 mg as determined by the investigator based on efficacy and tolerability. On Day OL15, a dose reduction is permitted if required for tolerability; no dose increase is permitted on Day OL15. After Day OL15, the dose should be stable (unchanged). If needed for tolerability, a dose reduction is permitted from Day OL15 until Day OL25.

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

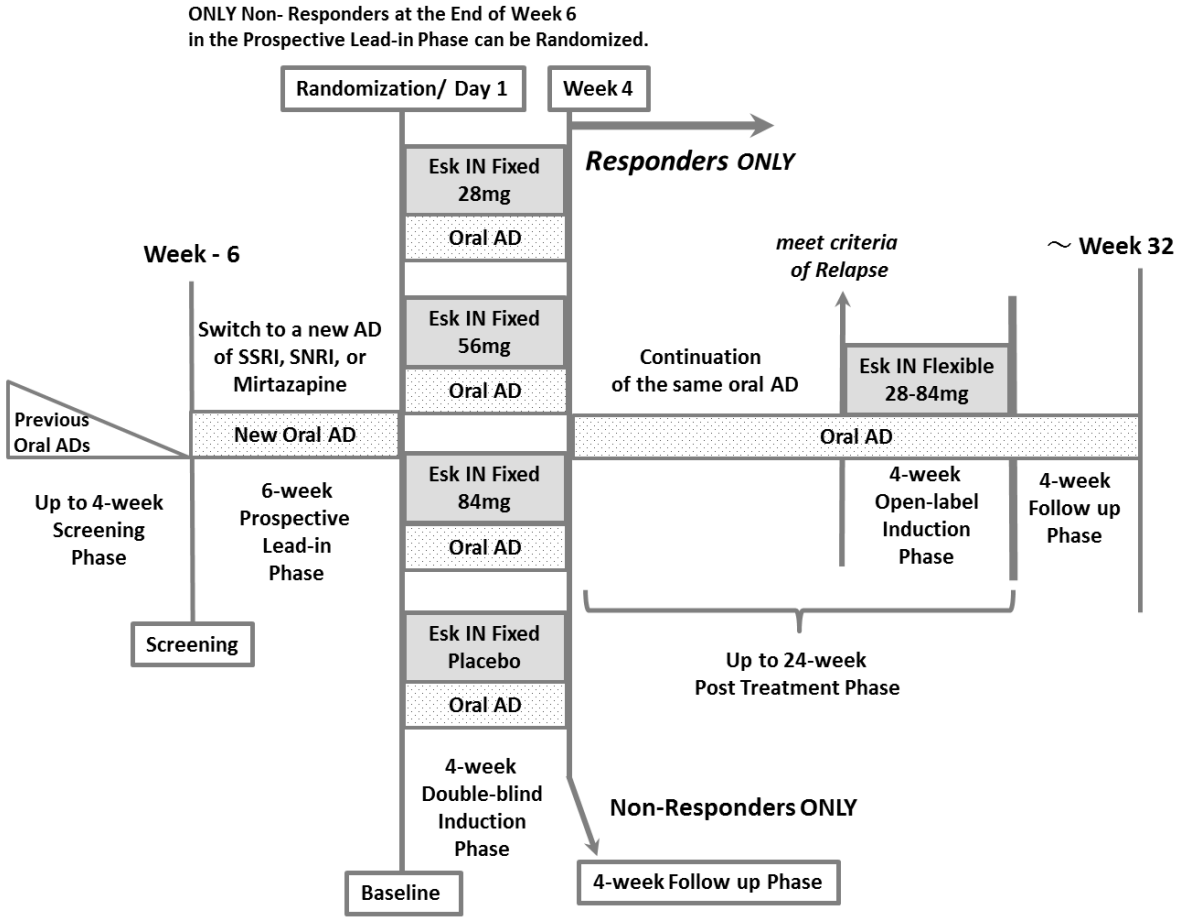
Guidance on Blood Pressure Monitoring (Section 6.3.1) as indicated for intranasal treatment sessions during the double-blind induction phase should also be followed on intranasal dosing days in the OL induction phase.

Follow-up Phase

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

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

Figure 1: Study 54135419TRD2005 Flowchart



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

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

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

Blood samples will be collected from all subjects to further explore the PK of esketamine. The total volume of blood to be drawn for laboratory evaluations, pharmacogenomics, biomarker analyses, and PK sampling throughout this study is approximately 112.5 mL for each subject.

Pharmacogenomic blood samples will be collected to allow for genetic and/or epigenetic research related to esketamine.

The study assessments will be performed at timepoints shown in the Time and Events Schedules for the respective study phases (see Section 9).

3.2. Study Design Rationale

3.2.1. Study Population

The study will include Japanese men and women 20 to 64 years old (both inclusive). This age range is selected because it includes the adults in the conventional age range of 20 to 64 years, thereby facilitating the evaluation of safety and tolerability of add-on esketamine in adults with TRD.

Subjects will meet DSM-5 diagnostic criteria for single-episode MDD or recurrent MDD, without psychotic features, based upon clinical assessment and confirmed by the MINI. In the case of single-episode MDD, the subject must be diagnosed with persistent depressive disorder, which meets criteria of major depressive episode for a continuous duration of ≥2 years, and the same physician from the site must be examining the subject for ≥2 years continuously as a primary care physician of the subject.

Treatment-resistant depression is defined as a lack of clinically meaningful improvement after treatment with at least 2 different antidepressant agents prescribed in adequate dosages for adequate duration. At the start of the prospective lead-in phase, subjects must not have responded to ≥1 but <5 different oral antidepressants taken at adequate dosage and for adequate duration, as assessed on the MGH-ATRQ and documented by medical history/prescription records, for the current episode of depression. The use of historical data to define nonresponse to treatment prior to patient enrollment in a treatment study is considered practical and valid. The MGH-ATRQ is a validated tool assessing treatment response. Additionally, in the prospective lead-in phase, all subjects will start a new switched antidepressant to confirm nonresponse to ≥2 antidepressants in their current episode.

Nonresponders to the new oral antidepressant treatment can be eligible to proceed to the double-blind induction phase. Nonresponse at the end of the prospective lead-in phase is defined as ≤25% improvement in the MADRS total score from Visits 2.1 (beginning of the prospective lead-in phase) to each of Visit 2.3 (Week 4 of the prospective lead-in phase) and Visit 3.1 (prerandomization [Week 6 of the prospective lead-in phase]) respectively, and a MADRS total score of ≥28 on each of the Visits 2.1, 2.3 and 3.1 (prerandomization).

The subject's current major depressive episode and antidepressant nonresponse in the current depressive episode will be confirmed using the SAFER criteria interview, which will be administered by remote, independent raters. SAFER criteria interview is a tool to facilitate subject selection for MDD clinical studies, with a goal to ensure enrollment of subjects who have symptoms that reflect the current state of illness and that these symptoms can be reliably measured.

3.2.2. Study Phases

Screening Phase

A screening phase of up to 4 weeks was chosen to allow adequate time for completion of all screening procedures with results available to the investigator before the first dose of the new

antidepressant in the prospective lead-in phase, and to allow sufficient time for tapering and washout of prohibited medications to occur.

Prospective Lead-in Phase

Implementation of a 6-week prospective lead-in phase before randomization and active treatment will allow the following:

- Use of a new antidepressant therapy will contribute to standardize the base therapy in the population.
- Use of an antidepressant prior to randomization and active treatment will be used to enrich the population in the treatment phase and minimize the impact of the expectation bias on the part of subjects and investigators on treatment effect. Because the add-on effects of esketamine are yet to be established, the prospective lead-in phase will assist in determining an ideal antidepressant medication, which would be combined with esketamine as an add-on treatment.
- The 6-week duration of the prospective lead-in phase will allow for a prospective confirmation of nonresponse to the new antidepressant treatment that is continued for the duration of this phase.

Double-blind Induction Phase

Subjects must meet the predefined criteria of nonresponse to antidepressant therapy at the end of the prospective lead-in phase for eligibility to enter the double-blind induction phase. The determination of nonresponse in prospective manner is necessary to enroll qualified TRD patients.

Randomization and blinding is necessary only in the double-blind induction phase of this study. The randomized design will allow the comparison of intranasal esketamine (3 doses to be evaluated) and placebo and provides a method of unambiguous assignment to study groups.

As described in Section 1.1.2, the duration of the 4 week double-blind induction phase was selected based upon the onset of effect of typical antidepressant treatments and the duration is considered to be sufficiently long to show the antidepressant effects of the oral antidepressants. Preliminary findings from an analysis of antidepressant treatments were presented recently, as well as a completed analysis of 24 recent MDD studies that compared study durations of 4, 6, and 8 weeks. Exploratory analyses were conducted for each of the study durations using mixed-effects model for repeated measures (MMRM), but excluding data beyond the duration of interest. These preliminary findings suggest that it is plausible to shorten the study duration down to 4 weeks.[36,72] Similarly, it has been demonstrated that improvement of ≥25% on the Hamilton Depression 17-item rating scale on Day 14 was a significant cutoff value to predict response after 5 weeks of treatment and a lack of improvement (ie, <25%) by Day 14 predicted poor response after 5 weeks of treatment.[47] All together, these results suggest that a 4 week duration should be adequate to assess antidepressant response.

Posttreatment Phase

The 24-week duration of the posttreatment phase will allow sufficient time to evaluate sustained efficacy after cessation of add-on intranasal esketamine treatment while continuing the oral antidepressant medication regimen, as assessed by the following efficacy endpoints: 1) the time to relapse; and 2) proportion of responders and remitters at each visit in this phase. In the first 4 weeks of the posttreatment phase, withdrawal or rebound symptoms or both and potential abuse-liability will be evaluated.

Open-label Induction Phase

The 4-week OL induction phase will be conducted for subjects who relapse in the posttreatment phase. This will evaluate if subjects will respond again to a second induction treatment course without any new safety signal compared to the double-blind induction treatment course.

Follow-up Phase

Following subjects will have follow-up Visits; subjects who withdraw from double blind induction phase, nonresponders after double-blind induction phase, responders who withdraw within 4 weeks after the last dose of double blind intranasal drug and all subjects who receive open label intranasal drug. During this phase, further clinical/standard-of-care treatment will be arranged by the study investigator.

3.2.3. Blinding and Randomization

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

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

3.2.4. Treatment Groups and Dose Selection

The 4 treatment groups in the double-blind induction phase are:

- Intranasal placebo;
- Intranasal esketamine (28 mg);
- Intranasal esketamine (56 mg);
- Intranasal esketamine (84 mg).

In all treatment groups, subjects must have been switched to a new, oral antidepressant, initiated during prospective lead-in phase, which will continue throughout the study, except follow-up phase.

The treatment groups will allow for an evaluation of the efficacy, safety and tolerability of 3 fixed doses of intranasal esketamine in addition to an oral antidepressant compared with intranasal placebo in addition to an oral antidepressant medication in adult subjects with TRD.

Intranasal Study Drug (Esketamine)

The dose selection (28, 56, and 84 mg) and administration interval (2 treatment sessions per week for 4 weeks) for this study were based on the results from Studies ESKETIVTRD2001, KETIVTRD2002, ESKETINTRD1001, and ESKETINTRD2003, described above in Section 1.1.2. [17, 18, 12, 16]

The data from PK/PD analysis of study ESKETINTRD2003 suggested the efficacy of esketamine 28 mg in Japanese subjects with TRD.[16] Results of the pooled dose-response analyses of non-Japanese Panel (Panel A) and Japanese Panel (Panel B) of the Study ESKETINTRD2003 showed the efficacy of esketamine 28 mg to be low. However, as this analysis included only the 28-mg esketamine dose from the non-Japanese panel, the efficacy of esketamine 28 mg could not clearly be excluded in Japanese subjects with TRD.

The data from Study ESKETINTRD2003 Panel A support the hypothesis that both 56 mg and 84 mg doses of esketamine are effective in treatment for depression in subjects with TRD, that they have a rapid onset of effect, and that 2 treatment sessions per week can sustain the response throughout the 4-week duration of the double-blind induction phase. In addition, the 56 mg and 84 mg doses were generally well-tolerated by subjects. The exposure is expected to be higher at each esketamine dose in Japanese subjects compared with non-Japanese subjects.[16]

To improve tolerability, subjects who will be randomly assigned to esketamine 84 mg will start at 56 mg on Day 1 and then, in a blinded manner, the dose will be increased to 84 mg on Day 4. By the lower dose (56 mg) initially and then increasing to 84 mg, may allow subjects to adjust to the effects of the lower dose before going to the higher dose (84 mg). Thereafter, no dose adjustments will be permitted. For example, internal data from the CADSS suggest a dose-response, with the greatest effect seen initially on the 84 mg dose (Study ESKETINTRD2003).[16] However, on subsequent repeated dosing, dissociative symptoms lessen. Starting with a lower dose may therefore limit the number of subjects discontinuing the study treatment because of intolerability in the 84-mg dose group.

Oral Antidepressant

A new, OL oral antidepressant medication will be initiated for all subjects in the prospective lead-in phase. Each subject will be assigned to receive 1 oral antidepressant medication of SSRIs, SNRIs, or mirtazapine (ie, escitalopram, paroxetine CR, sertraline, duloxetine, venlafaxine XR, or mirtazapine), that the subject has not previously had a nonresponse to in the current depressive episode, has not been previously intolerant to (lifetime).

The antidepressant medication will be assigned by the investigator based on review of the MGH-ATRQ and relevant prior antidepressant medication information.

The SSRIs and SNRIs were selected because they are the most commonly prescribed antidepressant classes in this population and are generally well tolerated. Mirtazapine was selected because >50% of Japanese subjects used mirtazapine in the Study ESKETINTRD2003.[16] If clinically indicated, subjects can join the prospective lead-in phase and initiate a new oral antidepressant before discontinuation of current oral antidepressants; therefore, cross-tapering is allowed. Dosing of the oral antidepressant will begin from prospective lead-in phase. New oral antidepressant treatment should be titrated to the approved maximum dose, to optimize the potential for response. The up-titration schedule should be per prescribing information. The dose, which is above the minimum therapeutic dose defined in MGH-ATRQ should be kept at last 4 weeks during the prospective lead-in phase, in case they start at lower doses.

The new oral antidepressant medication initiated during the prospective lead-in phase will be ongoing and at a stable dose during the double-blind induction phase. The treatment will be maintained at the same dose throughout the posttreatment phase.

3.2.5. Selection of Efficacy Scales and Safety Evaluations

The full lists of efficacy and safety assessments for this study are described in Sections 9.2 and 9.6, respectively.

3.2.5.1. Efficacy Scales

The 10-item clinician-administered MADRS is designed to be used in subjects with MDD to measure the overall severity of depressive symptoms.[40] The MADRS scale has been selected as the primary efficacy measure for this study because it is validated, reliable, and acceptable to regulatory health authorities as a primary scale to determine efficacy in major depression.

The Clinical Global Impression – Severity (CGI-S) is included to rate the severity of the subject's illness at the time of assessment, relative to the clinician's past experience with subjects who have the same diagnosis and improvement with treatment.[29]

The Sheehan Disability Scale (SDS) is a subject-reported outcome measure and is included as an assessment of functional impairment and associated disability.[37,62]

Generalized Anxiety Disorder 7-item scale (GAD-7) is included as a brief and validated measure of overall anxiety.[65]

The relapse criteria used in this study (see Section 9.2.1.2.3) are identical to the criteria that have been used in the previous and ongoing esketamine clinical studies.

3.2.6. Safety Evaluations

Physical examination, body weight, vital signs (including blood pressure measurements), 12-lead ECG, pulse oximetry, clinical laboratory tests, and evaluation of TEAEs and concomitant therapies will be performed throughout the study to monitor subject safety.

The TEAEs of special interest will be examined separately grouped in the following categories: Drug abuse, dependence and withdrawal (standardized Medical Dictionary for Regulatory Activities [MedDRA] queries [SMQ]), increased blood pressure, increased heart rate, transient dizziness/vertigo, impaired cognition, anxiety, and cystitis.

Given the potential for treatment-emergent transient elevation in SBP and DBP, increased oxygen consumption, laryngospasms, and temporary respiratory depression following will be monitored throughout the study and at multiple time points on dosing days: heart rate, blood pressure, respiratory rate, and SpO_2. Specific guidance to be followed on intranasal dosing days is provided in Section 6.3.1.

Safety scales will include the Columbia Suicide Severity Rating Scale (C-SSRS) for assessing suicidal ideation and behavior, CADSS for assessing treatment-emergent dissociative symptoms, four-item positive symptom subscale of the brief psychiatric rating scale (BPRS+) for assessing treatment-emergent psychotic symptoms, Modified Observer's Assessment of Alertness/Sedation (MOAA/S) for measuring treatment-emergent sedation, Clinical Global Assessment of Discharge Readiness (CGADR) for measuring the subject's readiness for discharge based on parameters including sedation, blood pressure, and AEs, PWC-20 for assessing potential withdrawal symptoms after cessation of esketamine treatment, and POMS-2 to evaluate the abuse-liability of intranasal esketamine treatment. These safety scales are widely accepted scales for the rating of extrapyramidal side effects.

3.2.7. Pharmacokinetic Evaluations

Pharmacokinetic samples will be obtained during the study for measurement of the plasma concentrations of esketamine and if warranted, noresketamine or additional metabolites.

The purpose of PK/PD modeling is to evaluate relationship of intranasal esketamine and MADRS total score (and possibly selected AEs as additional PD parameters) in Japanese subjects with TRD.

3.2.8. Biomarker and Pharmacogenomic (DNA) Evaluations

Assessment of biomarkers (protein) and their potential relationship to the different treatment groups and to maintenance/stabilization of response, nonresponse, and relapse will be explored. Blood samples will be collected to measure genetic and epigenetic markers (including but not limited to BDNF allelic variants) and protein markers (including but not limited to growth factors, inflammation, endocrine, or metabolic). Samples of deoxyribonucleic acid (DNA) and biomarkers may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

Genetic variation can be an important contributory factor to inter-individual differences in drug distribution and response and can also serve as a marker for disease susceptibility and prognosis. Pharmacogenomic research may help to explain inter-individual variability in clinical outcomes and may help to identify population subgroups that respond differently to a drug or subgroups that are more susceptible to relapse. In addition, pharmacogenomics research may allow for the identification of genetic factors that influence the PK, PD, efficacy, safety, or tolerability of the different treatment groups.

Protein biomarkers may aid in the elucidation of the mechanism of action of the different treatment groups or help to explain inter-individual variability in clinical outcomes or may help to identify population subgroups that respond differently to a drug or may help to identify subgroups that are more susceptible to relapse. The goal of the biomarker analyses is to evaluate the PD of the different treatment groups, and aid in evaluating the drug-clinical response relationship.

For the 24 hour period prior to sample collection, participants should refrain from strenuous exercise as this increases levels of inflammatory biomarkers. On the day of biomarker sample collection, it is preferred that subjects adhere to low fat diet (as an alternative to fasting) to reduce the level of postprandial lipemia in blood samples because moderately or grossly lipemic specimens may interfere with assay results.

4. SUBJECT POPULATION

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

For a discussion of the statistical considerations of subject selection, refer to Section 11.2, Sample Size Determination.

4.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study:

1. Subject must be a Japanese man or woman aged between 20 and 64 years (both inclusive) at the time of signing the ICF.

2. Criterion modified per amendment 3

   2.1 Criterion modified per amendment 4

   2.2 In this study, outpatients and inpatients are allowed for enrollment. Hospitalization for the study is allowed, subject must remain hospitalized from the beginning of the prospective lead-in phase to the end of the double-blind induction phase, maintaining the stable environment for 10 weeks. Temporary discharge is not permitted basically during the 10-week hospitalization. As a general rule, going out from the hospital

(leaving the site during hospitalization for reasons other than temporary discharge regardless of the attendant's presence) is to be within 6 hours at a time and not to exceed twice in 7 contiguous days.

3. Criterion modified per amendment 4

   3.1 At the start of the screening phase, subject must meet the DSM-5 diagnostic criteria for single-episode MDD or recurrent MDD, without psychotic features, based upon clinical assessment and confirmed by the MINI. In the case of single-episode MDD, the subject must be diagnosed with persistent depressive disorder, which meets criteria of major depressive episode for a continuous duration of ≥2 years, and the same physician from the site must be examining the subject for ≥2 years continuously as a primary care physician of the subject.

4. The subject's current major depressive episode, depression symptom severity (MADRS total score ≥28 required), and antidepressant treatment response in the current depressive episode, must be confirmed using the SAFER interview.

5. The reported duration of the current major depressive episode is at least 12 weeks at Day 1 of the double-blind induction phase.

6. At the start of the screening phase, subject must have had a nonresponse (≤25% improvement) to ≥1 but <5 oral antidepressant treatments in the current episode of depression, assessed using the MGH-ATRQ and confirmed by documented medical/pharmacy/prescription records or letter from treating physician. For specific tricyclic antidepressants, which are being taken at a dose below the MGH-ATRQ minimum therapeutic dose, a blood level that is within the therapeutic (antidepressant) range, is acceptable to establish the adequacy of the antidepressant treatment.

   Subjects who are nonresponders to a new oral antidepressant medication from the prospective lead-in phase (as assessed by independent, remote raters) may be eligible for randomization if all other entry criteria are met. Nonresponse at the end of the prospective lead-in phase is defined as ≤25% improvement in the MADRS total score from Visits 2.1 to each of Visit 2.3 and 3.1 (prerandomization) respectively, and a MADRS total score of ≥28 on each of the Visits 2.1, 2.3 and 3.1 (prerandomization).

7. Subject must be medically stable on the basis of clinical laboratory tests performed at screening. If the results of the serum chemistry panel hematology, or urinalysis are outside the normal reference ranges, the subject may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable for the population under study. This determination must be recorded in the subject's source documents and initialed by the investigator.

   - Subjects with a preexisting-history of thyroid disease/disorder who are treated with thyroid hormones must be on a stable dosage for 3 months

prior to the start of the screening phase.

- For any subject (regardless of thyroid history), if the thyroid-stimulating hormone (TSH) value is out of range, a free thyroxine (FT4) will be conducted. If the FT4 value is abnormal and considered to be clinically significant (after discussion with the medical monitor), the subject is not eligible.

8. Subject must be medically stable on the basis of physical examination, medical history, vital signs (including blood pressure), pulse oximetry, and 12-lead ECG performed in the screening phase. If there are any abnormalities that are not specified in the inclusion and exclusion criteria, the determination of their clinical significance must be determined by the investigator and recorded in the subject's source documents and initialed by the investigator.

9. Subject must be comfortable with self-administration of intranasal medication and be able to follow the intranasal administration instruction.

10. Each subject must sign an ICF indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.

11. A woman of childbearing potential must have a negative highly sensitive serum β-human chorionic gonadotropin [β-hCG] test at the start of the screening phase and a negative urine pregnancy test must be obtained before the first dose of study drug on Day 1 of the double-blind induction phase prior to randomization.

12. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for subject participating in clinical studies.

    Before randomization, a woman must be either:

    a. Not of childbearing potential defined as:

       - Postmenopausal
         A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy, however in the absence of 12 months of amenorrhea, a single follicle stimulating hormone measurement is insufficient.
       - Permanently sterile
         Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

    b. Of childbearing potential and

       - practicing a highly effective method of contraception (failure rate of <1%

per year when used consistently and correctly)

Examples of highly effective contraceptives include
- user-independent methods:
  implantable progestogen-only hormone contraception associated with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); vasectomized partner; sexual abstinence (sexual abstinence is considered a highly effective method **only** if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject);
- user-dependent methods:
  combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, and transdermal; progestogen-only hormone contraception associated with inhibition of ovulation: oral and injectable;

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method.

- agrees to remain on a highly effective method throughout the study and for at least 6 weeks after the last dose of study drug.

13. During the study and for a minimum of 1 spermatogenesis cycle (defined as approximately 90 days) after receiving the last dose of study drug, in addition to the highly effective method of contraception, a man

- who is sexually active with a woman of childbearing potential must be practicing a highly effective method of contraception with his female partner from those listed above (see examples of highly effective methods of contraception provided for female subjects);
- who is sexually active with a woman who is pregnant must use a condom;
- must agree not to donate sperm.

14. Subject must be willing and able to adhere to the prohibitions and restrictions specified in this protocol (see Section 4.3).

4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study:

1. The subject's depressive symptoms have previously demonstrated nonresponse to:

    - All of the oral antidepressant treatment options available in the prospective lead-in phase (ie, escitalopram, paroxetine CR, sertraline, duloxetine, venlafaxine XR or, mirtazapine) in the current major depressive episode (based on MGH-ATRQ); or

    - An adequate course of treatment with electroconvulsive therapy (ECT) in the current major depressive episode, defined as at least 7 treatments with unilateral/bilateral ECT.

2. Subject previously received esketamine or ketamine as treatment for their MDD.

3. Subject has received vagal nerve stimulation, has received transcranial magnetic stimulation or has received deep brain stimulation in the current episode of depression.

4. Criterion modified per amendment 5

    4.1 Subject has a current or prior DSM-5 diagnosis of a psychotic disorder or MDD with psychotic features bipolar or related disorders (confirmed by the MINI), obsessive compulsive disorder (current only), intellectual disability (DSM-5 diagnostic codes 317, 318.0, 318.1, 318.2, 315.8, and 319), autism spectrum disorder, borderline personality disorder, antisocial personality disorder, histrionic personality disorder, narcissistic personality disorder, paranoid personality disorder, schizoid personality disorder, or schizotypal personality disorder.

5. Subject has homicidal ideation/intent, per the investigator's clinical judgment, or has suicidal ideation with some intent to act within 6 months prior to the start of the screening phase, per the investigator's clinical judgment or based on the C-SSRS, corresponding to a response of "Yes" on Item 4 (active suicidal ideation with some intent to act, without specific plan) or Item 5 (active suicidal ideation with specific plan and intent) for suicidal ideation on the C-SSRS, or a history of suicidal behavior within the past year prior to the start of the screening phase. Subjects reporting suicidal ideation with intent to act or suicidal behavior prior to the start of the double-blind induction phase should be excluded.

6. Criterion modified per amendment 4

    6.1 Subject has a history of moderate or severe substance or alcohol use disorder according to DSM-5 criteria, except nicotine or caffeine, within 6 months before the

start of the screening phase.

A history (lifetime) of ketamine, phencyclidine, lysergic acid diethylamide (LSD), 3, 4-methylenedioxy-methamphetamine (MDMA), or psilocybin/psilocin hallucinogen-related use disorder is exclusionary.

7. Subject has a current or past history of seizure disorder (uncomplicated childhood febrile seizures with no sequelae are not exclusionary).

8. Subject has 1 of the following cardiovascular-related conditions:

    - Cerebrovascular disease with a history of stroke or transient ischemic attack;
    - Aneurysmal vascular disease (including intracranial, thoracic, or abdominal aorta, or peripheral arterial vessels);
    - Coronary artery disease with myocardial infarction, unstable angina, or revascularization procedure (eg, coronary angioplasty or bypass graft surgery) within 12 months before the start of the screening phase. Subjects who have had a revascularization performed >12 months prior to screening and are clinically stable and symptom-free, per investigator's clinical judgment, can be included;
    - Hemodynamically significant valvular heart disease such as mitral regurgitation, aortic stenosis, or aortic regurgitation;
    - New York Heart Association (NYHA) Class III-IV heart failure of any etiology.

9. Subject has a history of uncontrolled hypertension despite diet, exercise, or antihypertensive therapy at the start of the screening phase or any past history of hypertensive crisis or ongoing evidence of uncontrolled hypertension defined as a supine SBP >140 mm Hg or DBP >90 mm Hg during screening phase, which continues to be above this range with repeated testing during this phase. Note: On Day 1 prior to randomization a supine SBP >140 mm Hg or DBP >90 mm Hg is exclusionary.

   A potential subject may have his/her current antihypertensive medication(s) adjusted during the screening phase and be reevaluated to assess their blood pressure control. The subject must be on a stable regimen for at least 2 weeks before Day 1 of the double-blind induction phase.

10. Subject has a current or past history of significant pulmonary insufficiency/condition or with an arterial blood oxygen saturation (SpO2) of <93% at the start of the prospective lead-in phase or Day 1 prior to randomization.

11. Criterion modified per amendment 3

11.1 Criterion modified per amendment 5

11.2 Subject has clinically significant ECG abnormalities at the start of the screening phase or on Day 1 prior to randomization, defined as:

- During screening, a QT interval corrected according to Fridericia's formula (QTcF): ≥470 msec in males and ≥480 msec in females; if the QTcF is prolonged on the initial ECG, the average QTcF of 3 ECGs recorded 4 minutes apart must not be ≥450 msec.
- On Day 1 (predose), a QTcF: ≥470 msec in males and ≥480 msec in females based on the site-evaluated ECG; if the QTcF is prolonged on the initial ECG, the average QTcF of 3 ECGs recorded 4 minutes apart must not be ≥450 msec.
- Evidence of 2nd and 3rd degree atrioventricular (AV) block, or complete left bundle branch block (LBBB).
- Features of new ischemia.
- Arrhythmia (except premature atrial contractions [PACs] and premature ventricular contractions [PVCs]).

12. Subject has a history of additional risk factors for Torsades des Pointes (eg, heart failure, hypokalemia, family history of Long QT Syndrome).

13. Criterion modified per amendment 5

13.1 Subject has a history of, or symptoms and signs suggestive of, liver cirrhosis (eg, esophageal varices, ascites, and increased prothrombin time) OR alanine aminotransferase or aspartate aminotransferase values ≥3× the upper limit of normal or total bilirubin >1.5×ULN in the screening phase.

- Repeat of screening test for abnormal alanine aminotransferase and aspartate aminotransferase is permitted once during the screening phase per investigator discretion and provided there is an alternative explanation for the out of range value.
- For elevations in bilirubin, if in the opinion of the investigator and agreed upon by the sponsor's medical officer, the elevation in bilirubin is consistent with Gilbert's disease, the subject may participate in the study.

14. Subject has positive test result(s) for drugs of abuse (including barbiturates, methadone, opiates, cocaine, phencyclidine, and amphetamine/methamphetamine) at the start of the screening phase.

- Subjects who have a positive test result at screening due to prescribed opiates, barbiturates, or amphetamines may be permitted to continue in the screening/prospective lead-in phase if the medication is discontinued

at least 1 week or 5 half-lives, whichever is longer, before Day 1 of randomization. They need to have an additional test for drugs of abuse on Day 1 (prior to randomization). The result of the Day 1 (prior to randomization) test for drugs of abuse must be negative for the subject to be randomized.

- Retesting is not permitted for positive test result(s), except for reasons stated above.

15. Subject has uncontrolled diabetes mellitus, as evidenced by glycated hemoglobin (HbA1c) >9% in the prospective lead-in phase or history in the prior 3 months prior to the start of the prospective lead-in phase of diabetic ketoacidosis, hyperglycemic coma, or severe hypoglycemia with loss of consciousness.

16. Subject has untreated glaucoma, current penetrating or perforating eye injury, brain injury, hypertensive encephalopathy, intrathecal therapy with ventricular shunts, or any other condition associated with increased intracranial pressure or increased intraocular pressure or planned eye surgery.

17. Subject has any anatomical or medical condition that, per the investigator's clinical judgment based on assessment, may impede delivery or absorption of intranasal study drug.

18. Subject has a history of malignancy within 5 years before screening phase (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy that, in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence).

19. Subject has known allergies, hypersensitivity, or intolerance contraindications to esketamine/ketamine or its excipients (refer to Investigator's Brochure).[32]

20. Subject has taken any prohibited therapies that would not permit dosing on Day 1.

21. Subject is taking a total daily dose of benzodiazepines greater than the equivalent of 6 mg/day of lorazepam at the start of the screening phase.

22. Subject has an obstructive sleep apnea, which must be ruled out (eg, apnea-hypopnea index [AHI] must be <30). A subject with obstructive sleep apnea can be included if he or she is using a positive airway pressure device or other treatment/therapy that is effectively treating (ie, AHI<30) his or her sleep apnea.

23. Subject has received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 90 days before the start of the screening phase, or has participated in 2 or more MDD or other psychiatric condition clinical interventional studies (with different investigational medication) in the previous 1 year before the start of the screening phase, or is currently enrolled in an

investigational interventional study.

24. Subject is a woman who is pregnant, breastfeeding, or planning to become pregnant while enrolled in this study or within 6 weeks after the last dose of intranasal study drug.

25. Subject has a diagnosis of acquired immunodeficiency syndrome (AIDS). Human immunodeficiency virus (HIV) testing is not required for this study.

26. Subject has any condition or situation/circumstance for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

27. Subject has had major surgery, (eg, requiring general anesthesia) within 12 weeks before the start of the screening phase, or will not have fully recovered from surgery or has surgery planned during the time the subject is expected to participate in the study.

    Note: Subjects with planned surgical procedures to be conducted under local anesthesia may participate in the study.

28. Subject has severe renal impairment (creatinine clearance <30 mL/min).

29. Subject has taken any disallowed therapies before the planned first dose of study drug.

30. Subject is an employee of the investigator or study-site, with direct involvement in the proposed study or other studies under the direction of that investigator or study-site, as well as family members of the employees or the investigator.

NOTE: Investigators should ensure that all study enrollment criteria have been met. If a subject's status changes (including laboratory results or receipt of additional medical records) before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

The sponsor will evaluate and approve/reject requests to rescreen an individual subject on a case-by-case basis. Rescreening will be allowed only once basically.

4.3. Criteria for Double-blind and Open-label Induction Phases and Posttreatment Phase

4.3.1. Criteria to Enter Double-blind Induction Phase

After treatment with OL new oral antidepressant for 6 weeks during the prospective lead-in phase, subjects must have a nonresponse to the oral antidepressant medication. Nonresponse at

the end of the prospective lead-in phase is defined as ≤25% improvement in the MADRS total score from Visits 2.1 to each of Visit 2.3 and 3.1 (prerandomization) respectively, and a MADRS total score of ≥28 on each of the Visits 2.1, 2.3 and 3.1 (prerandomization). Only nonresponders at the end of the prospective lead-in phase will be eligible to proceed to the double-blind induction phase.

4.3.2. Criteria to Enter Posttreatment Phase

Subjects must be responders (≥50% reduction from baseline in MADRS total score) to the study treatment at the end of the 4-week induction phase to enter the posttreatment phase; nonresponders will proceed to the 4-week follow-up phase.

4.3.3. Criteria to Enter Open-label Induction Phase

Subjects who relapse within 20 weeks after the start of the posttreatment phase will transit to an OL induction phase and receive 4 weeks of OL treatment course with intranasal esketamine. See Section 9.2.1.2.3 for details on relapse criteria.

4.4. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

1. Agree to follow all requirements that must be met during the study as noted in the Section 4.1 (Inclusion Criteria) and Section 4.2 (Exclusion Criteria) (eg, contraception requirements).

2. Refer to Section 8 (Prestudy and Concomitant Therapy) and Attachment 1 (Prohibited Concomitant Medications for Intranasal Study Medication [Esketamine or Placebo]) for further information on prohibited therapies.

3. Subjects who were taking benzodiazepines (at doses equal to or less than the equivalent of 6 mg/day of lorazepam) or permitted non-benzodiazepine sleep medications (eg, zolpidem, eszopiclone and zopiclone) or both during the screening phase, can continue these medications throughout the study; however, dose increases or starting new benzodiazepine medications are not permitted. Benzodiazepines and non-benzodiazepine sleeping medications (eg, zolpidem, zaleplon, eszopiclone, and ramelteon) are prohibited within 12 hours prior to the start of each intranasal treatment session.

4. Subjects must abstain from using alcohol within 24 hours before and after each intranasal treatment session. If a subject appears intoxicated, dosing should not occur (delayed per the permitted visit window; see the TIME AND EVENTS SCHEDULE 1 and TIME AND EVENTS SCHEDULE 3).

5. On all intranasal study treatment sessions, all subjects must remain at the clinical study-site until study procedures have been completed and the subject is ready for

discharge. Subjects should be accompanied by a responsible adult when released from the clinical study-site. Subjects must not drive a car or work with machines for 24 hours after study drug dosing.

6. Subjects must adhere to prohibitions of the new oral antidepressants which are shown in their prescribing information.

7. Electroconvulsive therapy, deep brain stimulation, transcranial magnetic stimulation, and vagal nerve stimulation are prohibited from study entry through the end of the double-blind induction phase.

5. TREATMENT ALLOCATION AND BLINDING

5.1. Treatment Allocation

Procedures for Randomization

Randomization will be employed only in the double-blind induction phase of the study. Central randomization will be implemented in this study. Subjects will be randomly assigned to 1 of 4 treatment groups in a 2:1:1:1 ratio based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. Randomization will be balanced by using randomly permuted blocks across the 4 treatment groups.

The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed.

5.2. Blinding

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

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

Under normal circumstances, the blind should not be broken until all subjects have completed the study and the database is finalized. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may in an emergency determine the identity of the

treatment by contacting the IWRS. It is recommended that the investigator contact the sponsor or its designee if possible to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented in the appropriate section of the electronic case report form (eCRF), and in the source document.

Subjects who have had their treatment assignment unblinded should continue to return for scheduled evaluations.

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

To maintain the blinding of intranasal study drug, the esketamine and placebo intranasal devices will be indistinguishable. Please refer to Section 14 (Study Drug Information) for information on the physical characteristics of the study drugs and devices.

6. DOSAGE AND ADMINISTRATION

6.1. Screening Phase

As described in Section 3.1, unless prohibited per protocol, subjects taking benzodiazepines (at dosages equal to or less than the equivalent of 6 mg/day of lorazepam) or permitted non-benzodiazepine sleep medications (eg, zolpidem, eszopiclone and zopiclone) or both during screening phase, can continue these medications throughout the study, but dose increases or starting new benzodiazepine medications are not permitted. Subject's current antidepressant treatment(s), including adjunctive treatment for MDD, should be tapered and discontinued in this phase per the local prescribing information.

6.2. Prospective Lead-in Phase

All subjects will initiate a physician-determined new OL oral antidepressant daily for the duration of this phase. If clinically indicated, cross-tapering is allowed. Cross-tapering is defined as discontinuation of previous antidepressant treatment(s) by lowering the dose(s) per the local prescribing information and simultaneously increasing the dose of single new antidepressant treatment within the first 2 weeks of the prospective lead-in phase. New oral antidepressant treatment should be titrated to the approved maximum dose, to optimize the potential for response. The up-titration schedule should be per prescribing information.

Oral Antidepressant Medication

At the start of the prospective lead-in phase, all enrolled subjects will be switched to a new single-agent oral antidepressant therapy determined by the investigator. The oral antidepressant will be 1 of the following: selective serotonin reuptake inhibitors or SSRIs, SNRIs, or mirtazapine (ie, escitalopram, paroxetine CR, sertraline, duloxetine, venlafaxine XR, or

mirtazapine), which the subject has not previously had a nonresponse to in the current depressive episode or has not been previously intolerant to (lifetime). If clinically indicated, cross-tapering is allowed in the first 2 weeks during the prospective lead-in phase. In the last 4 weeks during the prospective lead-in phase, 'oral antidepressant' must be single treatment of switched new oral antidepressant. New oral antidepressant treatment should be titrated to the approved maximum dose, to optimize the potential for response. Up-titration of the antidepressant may be performed per investigator's discretion based on prescribing information in the prospective lead-in phase. The dose, which is above the minimum therapeutic dose defined in MGH-ATRQ should be kept at last 4 weeks during the prospective lead-in phase, in case they start at lower doses. Refer Attachment 3 (Example of the Up-titration Schedule for a New Oral Antidepressant Therapy [Physician Determined] in Prospective Lead-in Phase) for further information on up-titration. Following completion of this phase, subjects entering the subsequent phases of the study will continue to receive the oral antidepressant at a stable dose through EOS/study discontinuation.

Subjects must continue the new antidepressant throughout the study, except follow up phase. In follow-up phase, standard of care is allowed. However, oral antidepressant medication must be continued in the follow-up phase unless determined as not clinically appropriate. Study-site personnel will instruct subjects on how to take and store the oral antidepressant medications during this study for at-home use. A subject diary to capture oral antidepressant use will be provided. Missing >2 days of the new antidepressant medication per consecutive 7 days from the beginning of the prospective lead-in phase, will be considered as inadequate adherence and the subject should withdraw from the study.

Subjects will be instructed not to consume their assigned oral antidepressant until at least 3 hours after an intranasal treatment session.

6.3. Double-blind Induction Phase

During this phase, subjects will self-administer double-blind intranasal treatment either placebo, esketamine 28 mg, esketamine 56 mg, or esketamine 84 mg add-on to the continued oral antidepressant from the prospective lead-in phase. The oral antidepressant must be administered at a stable dose during this phase and through EOS/study discontinuation.

Intranasal Study Drug

On all intranasal treatment session days, a medical doctor or nurse of a site must be present with the subject during the intranasal treatment session and the postdose observation period. In addition, equipment for supportive ventilation and resuscitation needs to be present.

The subjects must be upright, in a semi-reclining position when intranasal study drug is administered. Table 2 describes how each intranasal treatment session will be administered in the double-blind induction phase. Please refer to Section 6.3.1 for guidance on Blood Pressure Monitoring on intranasal dosing days.

Table 2: Intranasal Treatment Administration During the Double-blind Induction Phase

	Time of Intranasal Device Administration[a]		
Intranasal Treatment	0 minute[b]	5 minutes	10 minutes
Intranasal device [c]	1st	2nd	3rd
Placebo	1 spray of placebo to each nostril	1 spray of placebo to each nostril	1 spray of placebo to each nostril
Esketamine 28 mg	1 spray of esketamine to each nostril	1 spray of placebo to each nostril	1 spray of placebo to each nostril
Esketamine 56 mg	1 spray of esketamine to each nostril	1 spray of esketamine to each nostril	1 spray of placebo to each nostril
Esketamine 84 mg	1 spray of esketamine to each nostril	1 spray of esketamine to each nostril	1 spray of esketamine to each nostril

a. The 3 intranasal devices for each intranasal treatment session should be administered in the medication kit order provided by the interactive web response system (IWRS)
b. Time 0 is defined as the time of administration of the first intranasal spray to 1 nostril from the first intranasal device.
c. One device will be used at each time point. Each individual intranasal device contains 2 sprays. The intranasal devices containing esketamine deliver 14 mg per spray, for a total of 28 mg per individual device (ie, 2 sprays)

Instructions for use documents (healthcare provider versions) for intranasal study drug administration will be provided as separate documents. Details regarding study drug administration will be recorded in the source documents and the eCRF. In the event of a missed dose, ensure to contact to sponsor immediately.

Prior to the first intranasal dose on Day 1, subjects will practice spraying (into the air, not intranasally) with a demonstration intranasal device that is filled with placebo solution.

The intranasal treatment sessions (esketamine or placebo) will occur twice weekly. Subjects will self-administer the intranasal study drug (esketamine 28 mg, 56 mg, 84 mg, or placebo) at treatment sessions occurring twice a week for 4 weeks at the study-site. The first treatment session will be on Day 1. Intranasal treatment sessions should not take place on consecutive days.

To improve tolerability, subjects who will be randomly assigned to esketamine 84 mg will start at 56 mg on Day 1 and then the dose will increase to 84 mg on Day 4 as a forced titration and remain at 84 mg for all subsequent intranasal treatment sessions. Subjects who are randomly assigned to 28 mg and 56 mg dose groups will remain on that dose for all subsequent intranasal treatment sessions. No adjustment to the intranasal esketamine dose is permitted for the duration of the double-blind induction phase.

Food will be restricted for at least 2 hours before each administration of study drug. Drinking of any fluids will be restricted for at least 30 minutes before the first nasal spray.

If the subject has nasal congestion on the dosing day, an intranasal decongestant can be used to reduce congestion or the dosing day be delayed (per the permitted visit window; see the Time and Events Schedules). If an intranasal decongestant is used to reduce congestion, it cannot be used within 1 hour prior to intranasal study drug administration.

On all intranasal treatment sessions, subjects must remain at the clinical site until study procedures have been completed and the subject is ready for discharge. Subjects should be

accompanied by a responsible adult when released from the clinical study site. Subjects must not drive a car or work with machines for 24 hours after the intranasal treatment session.

6.3.1. Guidance on Blood Pressure Monitoring on Intranasal Treatment Session Days

Given the potential for treatment-emergent transient elevation in SBP and DBP, the following guidance should be followed on intranasal dosing days:

- If subsequent to fulfilling the inclusion and exclusion criteria on Day 1 (ie, applicable for all other intranasal treatment session days after Day 1), a subject's predose SBP is >140 mm Hg or DBP is >90 mm Hg or both, it is recommended to repeat the blood pressure measurement after subject rests in sitting or recumbent position. If after rest and repeated measurements, predose SBP is >140 mm Hg or DBP is >90 mm Hg or both (except for Day 1), then dosing should be postponed and the subject must be scheduled to return on the following day or within the given visit window (if it is shown on Day 1, the subject should be excluded from the study). If the blood pressure elevation still persists on the next visit, the subject will be scheduled for a consultation by cardiologist, other specialist, or primary care physician, prior to further dosing.
- If at any postdose time point on the dosing day, the SBP is ≥180 mm Hg but <200 mm Hg or the DBP is ≥110 mm Hg but <120 mm Hg or both, further intranasal dosing should be interrupted and the subject should be referred to a cardiologist, other specialist, or primary care physician for a follow-up assessment.
  - After the assessment by a cardiologist, other specialist, or primary care physician, if recommended by the referring doctor and considered appropriate according to the clinical judgment for the subject to continue in the study, the subject may continue with intranasal dosing if the predose blood pressure at the next scheduled visit is within the acceptable range (see bullet point above).
- If at any postdose time point on the dosing day the SBP is ≥200 mm Hg or the DBP is ≥120 mm Hg or both, the subject must discontinue from further dosing and the subject should be referred to a cardiologist, other specialist, or primary care physician for a follow-up assessment.

During the double-blind induction phase, at 1.5 hours postdose, if the SBP is ≥160 mm Hg or the DBP ≥100 mm Hg or both, assessments should continue every 30 minutes until:

- Blood pressure is <160 mm Hg SBP and <100 mm Hg DBP, or
- In the investigator's clinical judgment, the subject is clinically stable and can be discharged from the study-site, or
- Subject is referred for appropriate medical care, if clinically indicated.
- If the blood pressure remains ≥180 mm Hg SBP or ≥110 mm Hg DBP or both, 2 hours after dosing, the subject should be referred for immediate medical treatment.

6.4. Posttreatment Phase

Subjects who relapse within 20 weeks after the start of the posttreatment phase will transit to an OL induction phase and receive 4 weeks of OL treatment course with intranasal esketamine. Subjects who meet the criteria of relapse, they need to join OL induction phase before next remote MADRS assessment. Subjects who relapse more than 20 weeks after the start of the posttreatment phase will withdraw from the study and clinical/standard-of-care treatment will be arranged by the study investigator after relapse. Subjects who have no relapse throughout this 24-week posttreatment phase will complete this study without 4-week follow-up phase. The oral antidepressant must be continued at a stable dose during post treatment phase.

6.4.1. Open-label Induction Phase

Subjects who relapsed in the posttreatment phase will receive a 4-week OL induction treatment course of intranasal esketamine. During this phase, subjects will continue to receive their switched oral antidepressant medication. The beginning of the OL induction phase should be at least 2 weeks (14 calendar days) after the last dose in the double-blind induction phase. Subjects who meet the relapse criteria before 2 weeks after the last dose in the double-blind induction phase will not have an option for joining open label induction phase. They will withdraw from the post treatment phase and move forward to the follow up phase.

Eligible subjects will start treatment sessions with 56 mg of intranasal esketamine on the first day of OL induction phase (Day OL1). On Day OL4, the dose must be increased to 84 mg. On Day OL8 and OL11, the dose could be maintained, increased, or reduced by 28 mg as determined by the investigator based on efficacy and tolerability. On Day OL15, a dose reduction is permitted, if required for tolerability; no dose increase is permitted on Day OL15. After Day OL15, the dose should be stable (unchanged). If needed for tolerability, a dose reduction is permitted from Day OL15 until Day OL25. Intranasal treatment sessions should not take place on consecutive days.

6.5. Follow-up Phase

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

7. TREATMENT COMPLIANCE

The investigator or designated study-site personnel will maintain a log of all intranasal study drug. Supplies of intranasal study drug for each subject will be inventoried and accounted for throughout the study.

Subjects will receive instructions on compliance with the oral antidepressant medication. During the course of the study, the investigator or designated study-site personnel will be responsible for

providing additional instruction to re-educate any subject to ensure compliance with taking the oral antidepressant. A subject diary will be provided to capture oral antidepressant use.

Antidepressant treatment adherence during the entire study will be assessed using subject diary.

All doses of intranasal study drug will be self-administered by the subjects at the investigative site under the direct supervision of the investigator or designee, and will be recorded in the eCRF.

8. PRESTUDY AND CONCOMITANT THERAPY

Prestudy non-antidepressant therapies administered up to 30 days before obtaining IC must be recorded at the start of this phase.

All antidepressant treatments, including adjunctive treatment for MDD, taken during the current depressive episode (ie, including those taken more than 30 days prior to obtaining IC) will be recorded at the start of the screening phase. Information will also be obtained regarding any history of intolerance to any of the following antidepressant choices: SSRIs, SNRIs, or mirtazapine (ie, escitalopram, paroxetine CR, sertraline, duloxetine, venlafaxine XR, or mirtazapine). Antidepressant treatments, which are not listed on the MGH-ATRQ but were used, or are currently being used in the current depressive episode must be recorded in 'Concomitant Therapy' section of the eCRF.

Concomitant therapies must be recorded throughout the study, beginning with signing of the informed consent and continuing up to the last visit. Information on concomitant therapies should also be obtained beyond this time only in conjunction with new or worsening AEs until resolution of the event.

Subjects receiving benzodiazepines (at dosages equal to or less than the equivalent of 6 mg/day of lorazepam) or permitted non-benzodiazepine sleep medications (eg, zolpidem, eszopiclone, and zopiclone) or both during the screening phase can continue these medications throughout the study; however, dose increases or starting new benzodiazepine medications are not permitted. Benzodiazepines and non-benzodiazepine sleeping medications (eg, zolpidem, eszopiclone, and zopiclone) are prohibited within 12 hours prior to the start of each intranasal treatment session.

Subjects should continue to take their permitted concomitant medications (eg, antihypertensive medications) at their regular schedule; however, restrictions as outlined in Section 4.4 should be taken into account. Of note, if a subject has routinely taken his/her oral antihypertensive medications in the morning on dosing days, the morning dose should be taken prior to intranasal dosing. For any concomitant medication given as a treatment for a new or worsening condition, the condition must be documented in the Adverse Event section of the eCRF.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies, such as psychotherapy, electrical stimulation, acupuncture, special diets, and exercise regimens) different from the study drug must be recorded in the eCRF. Modification of an effective preexisting therapy should not be made for the explicit

purpose of entering a subject into the study, unless permitted by protocol (eg, adjustment of blood pressure medications).

Rescue Medications

Rescue medications will not be supplied by the sponsor. In case of TEAEs that cannot be resolved by stopping further administration of intranasal esketamine/placebo, the following rescue medications may be considered:

- For agitation or anxiety: As required, midazolam (maximum dose 2.5 mg orally or IM) or short-acting benzodiazepine
- For nausea: As required, ondansetron 8 mg sublingually, metoclopramide (10 mg orally or IV or IM) or dimenhydrinate (25 to 50 mg, IV or IM)
- Unless clinically indicated, it is recommended that transient increases in blood pressure not be treated, as the blood pressure typically returns to predose values in 2 hours. The effect of any treatment may result in hypotension.

Prohibited Medications

A list of prohibited medications is provided in Attachment 1 as a general guidance for the investigator (but is not all inclusive).

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The TIME AND EVENTS SCHEDULE 1 summarizes the frequency and timing of efficacy, PK, biomarker, pharmacogenomic, and safety measurements applicable to screening, prospective lead-in and double-blind induction phases of this study.

The TIME AND EVENTS SCHEDULE 2 summarizes the frequency and timing of efficacy and safety measurements applicable to posttreatment and follow-up phases of this study.

The TIME AND EVENTS SCHEDULE 3 summarizes the frequency and timing of efficacy, PK, ongoing subject review and safety measurements applicable to OL induction phase of this study.

With the exception of postdose assessments, visit-specific assessments for subject-reported outcomes should be conducted or completed before any tests, procedures, or other consultations for that study-site visit to prevent influencing subject perceptions. When multiple patient-reported outcomes (PRO) and clinician-administered assessments are scheduled for the same time point, it is recommended they be performed in the following sequence. Actual dates and times of assessments will be recorded in the source documentation and eCRF.

PRO: GAD-7, SDS, POMS-2

Clinician-administered: CGI-S, C-SSRS, PWC-20, BPRS+, CADSS, MOAA/S, CGADR

Remote MADRS interview should be conducted at predose on intranasal dosing days during the double blind induction phase and the open label induction phase.

The maximum total blood volume to be collected from each subject will be approximately 112.5 mL (Table 3).

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Table 3: Approximate Volume of Blood to be Collected From Each Subject

Type of Sample	Volume per Sample (mL)	No. of Samples per Subject	Total Volume of Blood (mL)[a]
Screening Phase			
TSH, FT4 and FT3[d]	3.5	1	3.5
Hematology[b]	2	1	2
Chemistry panel[c]	2.5	1	2.5
Approximate total blood volume for screening phase			*8*
Prospective Lead-in Phase			
Chemistry panel[e]	2.5	1	2.5
Approximate total blood volume for Prospective Lead-in Phase			*2.5*
Double-blind Induction Phase			
Hematology	2	2	4
Chemistry panel	2.5	2	5
Pharmacokinetics	4	6	24
Biomarkers: protein[f]	10	3	30
Pharmacogenomic (DNA)	6	3	18
Approximate total blood volume for double-blind induction treatment phase			*81*
Double-blind Early Withdrawal Visit (if applicable)			
Hematology	2	1	2
Chemistry panel	2.5	1	2.5
Biomarkers: protein[f]	10	1	10
Pharmacogenomic (DNA)	6	1	6
Approximate total blood volume for double-blind early withdrawal			*20.5*
Open-label Induction Treatment Phase[g]			
Hematology	2	2	4
Chemistry panel	2.5	2	5
Pharmacokinetics	4	3	12
Approximate total blood volume for open-label induction treatment phase			*21*
Open-label Early Withdrawal Visit (if applicable)			
Hematology	2	1	2
Chemistry panel	2.5	1	2.5
Approximate total blood volume for open-label early withdrawal			*4.5*
Retest (if applicable)			
TSH	3.5	1	3.5
Hematology	2	1	2
Chemistry panel	2.5	1	2.5
Biomarkers: protein[f]	10	1	10
			18
Approximate total blood volume for the study[g], [h]			**112.5**

DNA-deoxyribonucleic acid; FT3-free triiodothyronine; FT4-free thyroxine; TSH-thyroid-stimulating hormone.

a. Calculated as number of samples multiplied by volume of blood per sample.
b. HbA1c will be measured from the sample collected for hematology.
c. Serum chemistry including serum β-hCG pregnancy tests (for women of childbearing potential).
d. For any subject (regardless of thyroid history), if the TSH value is out of range, a free thyroxine (FT4) will be conducted
e. Serum chemistry including lipid panel.
f. This sample will provide serum for all of the following assays: IL-10, IL-1b, IL-6, TNFa, Adiponectin, Cortisol, hs-CRP (non-cardiac), IL-6R, BDNF, IGF-1, Leptin and IL-17A.
g. The second induction treatment phase is optional.
h. Blood volume of the following visits is not included in the total volume: Double-blind Early Withdrawal, Open-label Early Withdrawal, and Retest.

9.1.2. Informed Consent Procedure

Informed consent must be obtained prior to the subject entering the study, and before any protocol-directed procedures (eg, washout of prohibited medications) are performed. Signing ICF is not required at the same day of the Screening Visit 1.1. Investigators can observe the subjects until Screening Visit 1.1 after obtaining IC, if clinically indicated (eg, washout of

prohibited medications). If Screening Visit 1.1 is on more than 28 days after singing ICF, investigators must obtain informed consent again, to confirm their willingness.

9.1.3. Screening Phase

Up to 4 weeks before entry into the prospective lead-in phase, all subjects will undergo screening procedures. After signed informed consent has been obtained, the inclusion and exclusion criteria will be reviewed to verify the subjects' eligibility.

After signing the ICF, subjects who are 20 to 64 years of age (inclusive) will be screened to determine eligibility for study participation (please refer to the study entry criteria listed in Section 4).

At the start of this phase, subjects must have had nonresponse (≤25% improvement) to ≥1 but <5 oral antidepressant medications taken at adequate dosage and for adequate duration, as assessed using the MGH-ATRQ and documented by records (eg, medical/pharmacy/prescription records or a letter from treating physician, etc), for the current episode of depression. In this study, outpatients and inpatients are allowed for enrollment. Hospitalization for the study is allowed, subject must remain hospitalized from the beginning of the prospective lead-in phase to the end of the double-blind induction phase, maintaining the stable environment for 10 weeks. Temporary discharge is not permitted basically during the 10-week hospitalization. As a general rule, going out from the hospital (leaving the site during hospitalization for reasons other than temporary discharge regardless of the attendant's presence) is to be within 6 hours at a time and not to exceed twice in 7 contiguous days.

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

The subject's current major depressive episode, depression symptom severity (MADRS total score ≥28 required), and treatment response to antidepressant medication used in the current episode (retrospectively assessed) must be deemed valid for participation in the clinical study based on the SAFER interview, which is administered by remote, independent raters.

Clinical safety assessments including physical examination, examination of vital signs, recording of weight, ECG, C-SSRS scale, as well as clinical laboratory assessments will be performed as outlined in the TIME AND EVENTS SCHEDULE 1. Prestudy and concomitant therapies and ongoing antidepressant therapy will be recorded in the eCRF.

Subjects taking benzodiazepines or permitted non-benzodiazepine sleep medications or both during screening phase, can continue these medications throughout the study, but dose increases or starting new benzodiazepine medications are not permitted.

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study visit.

At the screening visit, subjects who continue to fulfill all inclusion criteria and none of the exclusion criteria will be able to proceed to the prospective lead-in phase.

9.1.4. Prospective Lead-in Phase

All subjects will initiate a physician-determined new OL oral antidepressant daily for the duration of this phase. The oral antidepressant will be 1 oral antidepressant medication of SSRIs, SNRIs or mirtazapine (ie, escitalopram, paroxetine CR, sertraline, duloxetine, venlafaxine XR, or mirtazapine), that the subject has not previously had a nonresponse to in the current depressive episode, has not been previously intolerant to (lifetime). If clinically indicated, cross-tapering is allowed in the first 2 weeks during the prospective lead-in phase. In the last 4 weeks during the prospective lead-in phase, 'oral antidepressant' must be single treatment of switched new oral antidepressant to keep the same condition to compare the MADRS throughout the period. New oral antidepressant treatment should be titrated to the approved maximum dose, to optimize the potential for response. The up-titration schedule should be per prescribing information. The dose, which is above the minimum therapeutic dose defined in MGH-ATRQ should be kept at last 4 weeks during the prospective lead-in phase, in case they start at lower doses at the start the prospective lead-in phase.

After 6 weeks, subjects who are nonresponders to the new oral antidepressant medication at the end of the prospective lead-in phase can be eligible to proceed to the double-blind induction phase. Nonresponse at the end of the prospective lead-in phase is defined as ≤25% improvement in the MADRS total score from Visits 2.1 to each of Visit 2.3 and 3.1 (prerandomization) respectively, and a MADRS total score of ≥28 on each of the Visits 2.1, 2.3 and 3.1 (prerandomization).

Efficacy assessments including MADRS (7-day recall) assessment by an independent, remote, blinded rater and CGI-S will be performed. Clinical safety assessments including examination of vital signs, lipid panel (fasting) and C-SSRS (baseline/screening version) assessments will be performed as outlined in the TIME AND EVENTS SCHEDULE 1. Concomitant therapies and antidepressant therapy will be recorded in the eCRF.

At the baseline visit, subjects who continue to fulfill all inclusion criteria and none of the exclusion criteria will be enrolled and randomized. All other subjects who do not proceed to the double-blind induction phase will end study participation at this time. No further study visits or follow-up is required.

9.1.5. Double-blind Induction Phase

Approximately 183 subjects will be randomly assigned at a 2:1:1:1 ratio to receive double-blind intranasal treatment with either placebo, esketamine 28 mg, esketamine 56 mg, or esketamine 84 mg add-on to continued stable oral antidepressant.

Safety, efficacy, and PK evaluations to be performed at each visit during this phase are described in the TIME AND EVENTS SCHEDULE 1. All assessments performed prior to the first dose of intranasal esketamine in the double-blind induction treatment phase will be considered baseline assessments.

Prior to the first intranasal dose on Day 1, subjects will practice spraying (into the air, not intranasally) with a demonstration intranasal device that is filled with placebo solution.

During this phase, subjects will self-administer (under clinical supervision) intranasal study drug (esketamine 28 mg, 56 mg, or 84 mg, or placebo) at treatment sessions occurring twice a week for 4 weeks at the clinical site (see Section 6.3, Dosage and Administration for details).

The new oral antidepressant medication, which is ongoing and stable from prospective lead-in phase, will be continued throughout the study.

Benzodiazepines and non-benzodiazepine sleeping medications (eg, zolpidem, eszopiclone and zopiclone) are prohibited within 12 hours prior to the start of each intranasal treatment session.

Clinic visits and remote assessment visits will be performed as specified in the TIME AND EVENTS SCHEDULE 1.

Early Withdrawal

If a subject withdraws before the end of the 1st induction treatment phase for reasons other than withdrawal of consent, the EW Visit should be conducted within 1 week of the date of discontinuation, followed by the 4-week follow-up phase. If the EW Visit occurs on the same day as a scheduled visit, the EW Visit can be performed on the same day and duplicate assessments are not required.

Further clinical/standard-of-care for the treatment of depression will be arranged by the study investigator. The study investigator will determine whether or not the current oral antidepressant medication will continue. All subjects who are discontinued must be treated with an oral antidepressant after completion of the study, unless it is clinically inappropriate.

9.1.6. Posttreatment Phase

Responders (subjects with ≥50% reduction from baseline in MADRS total score) at the end of the intranasal esketamine double-blind induction phase will enter this 24-week posttreatment phase.

During this phase, subjects will be evaluated for sustained efficacy after cessation of add-on intranasal esketamine treatment while continuing the oral antidepressant medication regimen, as assessed by the time to relapse and proportion of responders and remitters at each visit in this phase. Clinic visits and remote assessment visits will be performed as specified in the TIME AND EVENTS SCHEDULE 2.

MADRS assessments will be performed weekly through Week 24 or relapse, whichever occurs first. Relapse based on MADRS assessment is defined as MADRS total score ≥22 for 2 consecutive visits (See Section 9.2.1.2.3). Other efficacy assessments during the posttreatment phase include CGI-S and SDS.

Safety assessments includes C-SSRS scoring, evaluation of withdrawal or rebound symptoms or both using PWC-20 and evaluation of potential abuse-liability using POMS-2.

9.1.7. Open-label Induction Phase

Subjects who relapse in the posttreatment phase will receive a 4-week induction treatment course of intranasal esketamine (OL this time) add-on to continued stable oral antidepressant. The beginning of the 2nd induction treatment phase should be at least 2 weeks (14 calendar days) after the last dose in the double-blind induction treatment phase. Subjects who meet the relapse criteria before 2 weeks after the last dose in the double-blind induction phase will not have an option for joining open label induction phase. They will withdraw from the posttreatment phase and move forward to the follow-up phase.

Safety, efficacy, and PK evaluations to be performed at each visit are described in the TIME AND EVENTS SCHEDULE 3. All assessments performed prior to the first dose of intranasal esketamine in the OL induction treatment phase will be considered baseline (prior to the first dose of OL induction phase) assessments.

Eligible TRD subjects will start treatment sessions with 56 mg of intranasal esketamine on the first day of OL induction phase (Day OL1). On Day OL4, the dose must be increased to 84 mg. On Day OL8 and OL11, the dose could be maintained, increased or reduced by 28 mg as determined by the investigator based on efficacy and tolerability. On Day OL15, a dose reduction is permitted, if required for tolerability; no dose increase is permitted on Day OL15. After Day OL15, the dose should be stable (unchanged). If needed for tolerability, a dose reduction is permitted from Day OL15 until Day OL25. This phase will evaluate if subjects will respond again to a second induction treatment course without any new safety signal compared to the double-blind induction treatment course.

During this phase, eligible subjects will receive intranasal esketamine as per the details provided in Dosage and Administration section (Refer Section 6.4.1).

After completion of this phase, a follow-up phase will be scheduled for 4 weeks.

If a subject withdraws before the end of the OL induction phase (ie, before completing Visit 5.10/Day OL28) for reasons other than withdrawal of consent, an EW Visit should be conducted within 1 week of the date of discontinuation, followed by the follow-up phase. If the EW Visit is conducted on the same day as a scheduled visit, duplicate assessments are not required.

9.1.8. Follow-up Phase

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

During this period subjects will have 3 clinic visits to evaluate the safety, as specified in the TIME AND EVENTS SCHEDULE 2.

During this phase, further clinical/standard-of-care treatment will be arranged by the study investigator. The decision to continue the oral antidepressant medication in this phase will be at the discretion of the investigator, however, in order to better assess potential withdrawal symptoms from intranasal study drug, the oral antidepressant medication must be continued for the follow-up phase unless determined as not clinically appropriate.

Any clinically significant abnormalities persisting at the end of the study will be followed by the investigator until resolution or until a clinically stable endpoint is reached. All AEs and special reporting situations, whether serious or non-serious, will be reported until completion of the subject's last study-related procedure.

9.2. Efficacy

9.2.1. Evaluations

The primary efficacy endpoint is the change in the MADRS total score from baseline (Day 1 prior to randomization) to the end of the 4-week double-blind induction phase.

In addition to being the primary efficacy measure, the MADRS will also be used to evaluate the following secondary efficacy endpoints of the double-blind induction phase: proportion of responders (≥50% reduction from baseline in MADRS total score), proportion of remitters (MADRS total score ≤12); time to relapse (in subjects who remit [MADRS total score ≤12] and in subjects with response but not remit); and proportion of subjects showing onset of clinical response (ie, antidepressant effect) by Day 2 that is maintained for the duration of the double-blind induction phase. Onset of clinical response is defined as 50% reduction in the MADRS total score by the day after taking the first dose of double-blind medication (Day 2) that continued through the end of the 4-week double-blind induction phase with one excursion. Subjects are allowed one excursion (nonresponse) on Days 8, 15 or 22. Subjects who discontinue the study prior to the end of the double-blind induction phase will not be considered to have maintained clinical response. Other secondary evaluations include CGI-S, SDS and GAD-7.

Every effort should be made to ensure that all clinician-administered efficacy assessments are completed by a qualified assessor at the baseline and subsequent assessments are performed by the same individual. It is recommended that the various subject-reported outcome assessments be completed prior to other procedures.

9.2.1.1. Primary Efficacy Evaluation

9.2.1.1.1. MADRS (7-day Recall)

The primary efficacy evaluation will be the MADRS total score. The MADRS will be performed by independent remote raters during the study, using the Structured Interview Guide for the Montgomery-Asberg Depression Rating Scale (SIGMA: Williams 2008). The remote MADRS interviews will be recorded to assess accuracy and thoroughness of the interviews and measure overall quality assurance.

The MADRS is a clinician-rated scale designed to measure depression severity and detects changes due to antidepressant treatment.[39] The scale consists of 10 items, each of which is scored from 0 (item not present or 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, inability to feel (interest level), pessimistic thoughts, and suicidal thoughts. The test exhibits high inter-rater reliability.

The typical recall period for the MADRS is 7 days and will be used for the primary efficacy evaluation. In this study, the MADRS will also be administered using modified recall period of 24 hours (see Section 9.2.1.2.1).

9.2.1.2. Secondary Efficacy Evaluation (Clinician-completed)

9.2.1.2.1. MADRS (24-hour Recall)

The MADRS will also be administered using a modified recall period of 24 hours for the key secondary efficacy evaluation related to onset of clinical response by Day 2 that is maintained for the duration of the double-blind induction phase.

The MADRS with a 24-hour recall period will be used on Day 2. The feasibility of this shortened recall period has been confirmed with subjects, and physicians, and there are data supporting the psychometric properties of this shortened recall period (data on file). The MADRS with a 7-day recall will be used for all subsequent MADRS assessments used for the key secondary efficacy evaluation (maintenance of clinical response achieved on Day 2 for duration of double-blind induction phase).

9.2.1.2.2. CGI-S

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.[29] 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 subjects. The CGI-S permits a global evaluation of the subject's condition at a given time.

9.2.1.2.3. Time to Relapse

Relapse is defined as any of the following:

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

9.2.1.3. Secondary Efficacy Evaluations (Patient-reported Outcomes)

9.2.1.3.1. SDS

The SDS will be used to assess the secondary objective of functional impact and associated disability. 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.[37,62] The first 3 items assess disruption of (1) work/school, (2) social life, and (3) family life/home responsibilities using a 0 to 10 rating scale. The score for the first 3 items are summed to create a total score of 0 to 30 where a higher score indicates greater impairment. It also has 1 item on days lost from school or work and 1 item on days when underproductive. The recall period for this study is 7 days.

9.2.1.3.2. GAD-7

The 7-item subject-reported GAD-7 will be used to measure the secondary objective of symptoms of anxiety. The GAD-7 is a brief and validated measure of overall anxiety. Each item is rated on a 4-point scale (0=not at all; 1=several days; 2=more than half the days; 3=nearly every day). [65] Item responses are summed to yield a total score (range of 0 to 21), with higher scores indicating more anxiety. The recall period is 2 weeks.

9.2.2. Endpoints

9.2.2.1. Primary Endpoint

The primary efficacy endpoint is the change in the MADRS total score as measured by the change from baseline (prior to randomization) to the end of the 4-week double-blind induction phase.

9.2.2.2. Secondary Endpoints

The secondary endpoints include the following:

1. Proportion of responders (≥ 50% reduction from baseline in MADRS total score) in the double-blind induction phase.
2. Proportion of remitters (MADRS total score ≤ 12) in the double-blind induction phase.
3. Proportion of subjects showing onset of clinical response in the double-blind induction phase.
4. Change from baseline in CGI-S in the double-blind induction phase.
5. Change from baseline in GAD-7 in the double-blind induction phase.
6. Change from baseline in SDS total score in the double-blind induction phase.
7. Time to relapse:
    a. In subjects who remit (MADRS total score ≤12) at the end of the double-blind induction phase.
    b. In subjects with response (≥50% reduction from baseline in MADRS total score) but who are not in remission at the end of the double-blind induction phase.
8. Change from baseline in SDS total score in the posttreatment phase.
9. Change from baseline (prior to the first dose of OL induction phase) in MADRS total score in the OL induction phase.
10. Proportion of responders (≥50% reduction from baseline in MADRS total score) in the OL induction phase.
11. Proportion of remitters (MADRS total score ≤12) in the OL induction phase.
12. Change from baseline (prior to the first dose of OL induction phase) in CGI-S in the OL induction phase.

9.3. Pharmacokinetics

Whole blood samples will be used to evaluate the PK of esketamine (and noresketamine or additional metabolites, if warranted). Plasma collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these plasma samples. Subject confidentiality will be maintained.

9.3.1. Evaluations

Venous blood samples of approximately 4 mL will be collected for measurement of plasma concentrations of esketamine and if warranted, noresketamine or additional metabolites at the time points specified in the TIME AND EVENTS SCHEDULE 1 and TIME AND EVENTS SCHEDULE 3. The exact dates and times of PK blood sampling must be recorded. Additional information about the collection, handling, and shipment of biological samples can be found in the Laboratory Manual.

9.3.2. Analytical Procedures

Plasma samples will be analyzed to determine concentrations of esketamine (and noresketamine or additional metabolites, if warranted) using a validated, specific, achiral, and sensitive liquid chromatography-tandem mass spectrometry (LC-MS/MS) method by or under the supervision of the sponsor. If required, some plasma samples may be analyzed to document the presence of other analytes (eg, circulating metabolites or denatonium) using a qualified research method. In addition, plasma PK samples may be stored for future analysis of the metabolite profile.

The bioanalytical report, including a description of the assay and a summary of the assay performance data, will be included in the final clinical study report as an addendum.

9.3.3. Pharmacokinetic Parameters

The plasma concentration-time data of esketamine (and noresketamine or additional metabolites, if warranted) will be analyzed using population PK modeling. Typical population values of basic PK parameters (eg, esketamine clearance, distribution volume) will be estimated together with the inter-individual variability. Effects of subject demographics, laboratory parameter values, and other covariates on the PK of esketamine will be explored. The results of the population PK analyses may be reported separately.

9.4. Pharmacokinetic/Pharmacodynamic Evaluations

The PK/PD relationship of intranasal esketamine and MADRS total score (and possibly selected AEs as additional PD parameters) may be evaluated. If there is any visual trend in graphical analysis, suitable models will be applied to describe the PK/PD relationships. The results of the PK/PD evaluations will be presented in a separate report.

9.5. Biomarker and Pharmacogenomic (DNA) Evaluations

During the study, blood will be collected for assessment of biomarkers at the time points indicated in the TIME AND EVENTS SCHEDULE 1. The biomarker blood samples should be collected prior to dosing. It is preferred that subjects adhere to a low fat diet on the day of sample collection. Participants also should avoid strenuous exercise for 24 hours prior to sample collection.

In blood, biomarkers (protein) related to (but not limited to) the immune system activity, hypothalamic HPA axis activation, neurotrophic factors, and metabolic factors will be investigated. Biomarkers may be added or deleted based on scientific information or technical innovations under the condition that the total volume of blood collected will not be increased.

Blood samples for DNA analyses will be collected at the time points indicated in the TIME AND EVENTS SCHEDULE 1 for the assessment of genetic and epigenetic variation in genes in pathways relevant to the effect of esketamine (eg, HPA axis, inflammation, growth factors, monoamine transporters, ion channels, and circadian rhythm).

Genotyping will be conducted only on a single sample; pharmacogenomics and epigenetic evaluations may be performed on any/all collected samples.

DNA samples will be used for research related to esketamine. They may also be used to develop tests/assays related to esketamine. Pharmacogenomic research may consist of the analysis of 1 or more candidate genes or of the analysis of genetic and epigenetic markers throughout the genome (as appropriate) in relation to esketamine.

The biomarker data obtained from this study may also be included in an ongoing cross-study analysis to investigate the relationship between depression severity and phenotypes and biomarkers.

Further information regarding handling, shipment, and labeling of biological samples will be provided in a separate laboratory manual.

9.6. Safety Evaluations

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF.

Any clinically significant abnormalities persisting at the EOS/EW will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the TIME AND EVENTS SCHEDULE 1, TIME AND EVENTS SCHEDULE 2, and TIME AND EVENTS SCHEDULE 3. Where clinician-administered efficacy assessments are concerned, every effort should be made to ensure that all assessments are completed by a qualified assessor at the baseline and subsequent assessments are performed by the same individual.

Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

The TEAEs of special interest will be examined separately (please refer to Section 3.2.6 and Section 11.8).

Clinical Laboratory Tests

Blood samples for serum chemistry and hematology and a random urine sample for urinalysis will be collected. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the Adverse Event section of the eCRF. The laboratory reports must be filed with the source documents.

The use of local laboratories is allowed in cases where initiation of treatment or safety follow-up is time-critical and the central laboratory results are not expected to be available before the need to begin dosing or if actions need to be taken for safety reasons.

The following tests will be performed by the central laboratory, unless noted otherwise:

- Hematology Panel

  -hemoglobin
  -hematocrit
  -red blood cell count
  -white blood cell count with differential
  -platelet count

- Serum Chemistry Panel

  -sodium
  -potassium
  -chloride
  -bicarbonate
  -blood urea nitrogen
  -creatinine
  -glucose
  -aspartate aminotransferase
  -alanine aminotransferase
  -gamma-glutamyltransferase
  -total bilirubin
  -alkaline phosphatase
  -creatine phosphokinase
  -calcium
  -phosphate
  -albumin
  -total protein

- Urinalysis

  Dipstick
  -specific gravity
  -pH
  -glucose
  -protein
  -blood
  -ketones
  -bilirubin
  -urobilinogen
  -nitrite
  -leukocyte esterase

  Sediment (if dipstick result is abnormal)
  -red blood cells
  -white blood cells
  -epithelial cells
  -crystals
  -casts
  -bacteria

  If dipstick result is abnormal, flow cytometry or microscopy will be used to measure sediment. In case of discordance between the dipstick results and the flow cytometric results, the sediment will be examined microscopically.

The following tests will be done at time points specified in the TIME AND EVENTS SCHEDULE 1, TIME AND EVENTS SCHEDULE 2, and TIME AND EVENTS SCHEDULE 3.

- Lipid panel: total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, and triglycerides
- Serum and urine pregnancy testing (for women of childbearing potential only)
- Urine Drug Screen: barbiturates, methadone, opiates, cocaine, phencyclidine, and amphetamine/methamphetamine
  - The central laboratory will analyze the urine drug screen performed at screening.
- TSH (screening only)
- HbA1c test (screening only)

Electrocardiogram (ECG)

The 12-lead ECG will be collected at time points specified in the TIME AND EVENTS SCHEDULE 1 and TIME AND EVENTS SCHEDULE 3.

During the collection of ECGs, subjects should be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs.

If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

All ECG tracings will be sent to a central ECG laboratory. The ECGs will be read at the scheduled time points and summarized by a central ECG laboratory. The central ECG laboratory will send the sponsor an electronic copy of the data for inclusion in the clinical database. In addition, the investigator or sub-investigator is required to review all ECGs at the study visit to assess for any potential safety concerns or evidence exclusionary conditions prior to dosing.

Vital Signs (Temperature, Heart Rate, Respiratory Rate, Blood Pressure)

Blood pressure and heart rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available. For further details regarding blood pressure, please see Guidance for Blood Pressure Monitoring on Intranasal Dosing Days (Section 6.3.1).

Blood pressure and heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

Tympanic temperature is recommended, but axillary temperature is also allowed. Throughout the study, the tempreture condition should be same.

Pulse Oximetry

Pulse oximetry will be used to measure arterial oxygen saturation.

On each dosing day, the device will be attached to the finger, toe, or ear before the first nasal spray of esketamine. Pulse oximetry will be performed every 15 minutes from predose to 1.5 hours postdose. If <93% at any time during the 1.5-hour postdose interval, pulse oximetry will be performed every 5 minutes until returns to ≥93% or until the subject is referred for appropriate medical care, if clinically indicated. Any arterial blood oxygen saturation <93% and lasting for more than 2 minutes, and confirmed by an additional manual measurement on another part of the body, will be reported as an AE.

Physical Examination, Height, and Body Weight

Physical examinations, body weight, and height will be performed or measured as per the TIME AND EVENTS SCHEDULE 1 and TIME AND EVENTS SCHEDULE 3.

BPRS+

Four items of the BPRS will be administered to assess treatment-emergent psychotic symptoms.

The BPRS[48] is an 18-item rating scale, which is used to assess a range of psychotic and affective symptoms rated from both observation of the subject and the subject's own report. It reportedly provides a rapid and efficient evaluation of treatment response in clinic drug studies and in clinical settings.[57]

Only the 4-item positive symptom subscale (consisting of: suspiciousness, hallucinations, unusual thought content and conceptual disorganization) will be used in this study. It is highly sensitive to change, and excellent inter-rater reliability can be achieved with training and a standard interview procedure.

C-SSRS

The C-SSRS will be performed to assess suicidal ideation and behavior.

The C-SSRS is a low-burden measure of the spectrum of suicidal ideation and behavior that was developed in the National Institute of Mental Health Treatment of Adolescent Suicide Attempters Study to assess severity and track suicidal events through any treatment.[53] It is a clinical interview providing a summary of both ideation and behavior that can be administered during any evaluation or risk assessment to identify the level and type of suicidality present. The C-SSRS can also be used during treatment to monitor for clinical worsening.

Two versions of the C-SSRS will be used in this study, the baseline/screening version, and the Since last visit version. The baseline/screening version of the C-SSRS will be used in the screening phase. In this version, suicidal ideation will be assessed at 2 time points (“lifetime” and “in the past 6 months”) and suicidal behavior will be assessed at 2 time points (“lifetime” and “in the past year”). All subsequent C-SSRS assessments in this study will use the Since Last Visit version, which will assess suicidal ideation and behavior since the subject’s last visit.

CADSS

The CADSS will be administered to assess treatment-emergent dissociative symptoms.

The CADSS is an instrument for the measurement of present-state dissociative symptoms. The CADSS comprises 23 subjective items, divided into 3 components: depersonalization (Items 3 to 7, 20, 23), derealization (Items 1, 2, 8 to 13, 16 to 19, 21) and amnesia (Items 14 and 15, 22). Participant's responses are coded on a 5-point scale (0="Not at all" through to 4="Extremely"). CADSS has excellent inter-rater reliability and internal consistency.

CGADR

The CGADR will be used to measure the subject's current clinical status and is the clinician's assessment of the readiness to be discharged from the study-site.

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

On intranasal treatment session days, the CGADR will be performed at 1 hour, and 1.5 hours postdose; if the response is not "Yes" at 1.5 hours postdose, the assessment will be repeated every 15 minutes until a "Yes" response is achieved or until the subject is referred for appropriate medical care if clinically indicated. A subject should not be discharged prior to the 1.5-hour time point.

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.

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).[50]

The MOAA/S scores range from 0 (no response to painful stimulus; corresponds to ASA continuum for general anesthesia) to 5 (readily responds to name spoken in normal tone [awake]; corresponds to ASA continuum for minimal sedation).

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

- If the score is ≤3 at any time during the 1.5-hour postdose interval, the MOAA/S will be performed every 5 minutes until a score of 4 is reached (at which point a frequency of every 15 minutes can be resumed until 1.5-hour postdose).
- If a subject does not have a score of at least 5 at 1.5-hour postdose, he/she should continue to be monitored. For subjects with a score of 4, the assessment should be repeated every 15 minutes. And for subjects with a score of ≤3, the assessment should be repeated every 5 minutes until the score returns to 5 or the subject is referred for appropriate medical care, if clinically indicated.

POMS-2

The POMS-2 will be used to measure the abuse-liability of intranasal esketamine administered twice a week for 4 weeks, at time points outlined in TIME AND EVENTS SCHEDULE 1 and TIME AND EVENTS SCHEDULE 2.

The POMS-2 is a self-report measure that allows for the quick assessment of transient, fluctuating feelings, and enduring affect states. Full-length versions (65 items) yield several scale scores: Anger-Hostility, Confusion- Bewilderment, Depression-Dejection, Fatigue-Inertia, Tension-Anxiety, and Vigor-Activity. Total Mood Disturbance is a function of these 6 scale scores. The recall period for this study is 7 days.

PWC-20

The PWC-20 will be administered to assess potential withdrawal symptoms following cessation of intranasal esketamine treatment at time points outlined in TIME AND EVENTS SCHEDULE 1, TIME AND EVENTS SCHEDULE 2, and TIME AND EVENTS SCHEDULE 3.

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.[55] Discontinuation symptoms occur early and disappear rather swiftly, depending upon speed of taper, daily medication dose, and drug elimination half-life.

9.7. Other Evaluations

MINI

The MINI is a short structured diagnostic interview for DSM-5. It has an administration time of approximately 15 minutes to provide accurate structured psychiatric interview for multicenter clinical trials. Subjects will undergo MINI (a brief, structured diagnostic interview) to confirm the diagnosis of MDD and to determine if there are other psychiatric conditions present.

MGH-ATRQ

The MGH-ATRQ is used to determine treatment resistance in MDD.[21] Information regarding all antidepressant therapies used in the current depressive episode will be recorded on the ATRQ.

The MGH-ATRQ evaluates the adequacy of duration and dosage of all antidepressant medications used for the current major depressive episode. In addition, the MGH-ATRQ assesses the degree of improvement on a scale from 0% (not improved at all) to 100% (completely improved). The MGH-ATRQ will be completed by the clinician, in collaboration with the subject.

SAFER Criteria Interview

Remote, independent psychiatrists/psychologists will perform the SAFER Interview[66] for all subjects to assess the validity of a diagnosis of depression and eligibility for the study.

SAFER refers to:

S	State versus trait	The identified symptoms must reflect the current state of illness and not longstanding traits. Traits do not generally change in 4–12 weeks.
A	Assessibility	The patient's symptoms are measurable with standard, reliable rating instruments. The symptoms of valid subjects can be reliably assessed with standardized measurement tools
F	Face validity	The patient's presentation is consistent with our knowledge of the illness (symptoms map to the nosological entity; clear change from previous level of function; similar to previous episodes if recurrent)
E	Ecological validity	The patient's symptoms reflect the characteristics of the illness in a real-world setting (frequency, intensity, duration, course, impact over at least 4 weeks)
R	Rule of the 3 P's	Identified symptoms must be pervasive, persistent, and pathologic and interfere with function and quality of life

9.8. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form. If blood samples are collected via an indwelling cannula, an appropriate amount (1 mL) of serosanguineous fluid slightly greater than the dead space volume of the lock will be removed from the cannula and discarded before each blood sample is taken. After blood sample collection, the cannula will be flushed with 0.9% sodium chloride, United States Pharmacopeia (USP) (or equivalent) and charged with a volume equal to the dead space volume of the lock.

Refer to the TIME AND EVENTS SCHEDULE 1, TIME AND EVENTS SCHEDULE 2, and TIME AND EVENTS SCHEDULE 3 for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY TREATMENT/ WITHDRAWAL FROM THE STUDY

10.1. Completion

A subject will be considered to have completed the study:

- If he or she do not respond at the end of 4-week double-blind induction phase;
- If he or she relapse during posttreatment phase and complete the OL phase;
- If he or she complete 24-week posttreatment phase without relapse.

Subjects who prematurely discontinue study treatment for any reason before completion of the double-blind induction phase will not be considered to have completed the double-blind induction phase of the study. In addition, subjects who prematurely discontinue study treatment

for any reason before completion of the posttreatment or OL phases, will not be considered to have completed the posttreatment phase of the study.

10.2. Withdrawal From the Study

Withdrawal From the Study

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent (Note: See "Withdraw of Consent" section below; this should only be selected as a reason for withdrawal if the subject does not agree to any further study assessments or procedures. If the subject is agreeable to participating in the EW visit and the follow-up phase, another reason for withdrawal should be selected.)
- Violation of protocol procedures (determined on a case-by-case basis)
- Blind is broken (double-blind induction phase)
- Lack of efficacy
- The investigator or sponsor believes (eg, that for safety or tolerability reasons such as an AE) it is in the best interest of the subject to discontinue the study. See also guidance on blood pressure monitoring on intranasal dosing days (Section 6.3.1).
- At any time point after baseline (Day 1, predose), the subject has a:
  - QTcF change from baseline ≥60 msec and QTcF >480 msec, or
  - QTcF >500 msec.
- Noncompliance to switched oral antidepressant therapy (missing >2 days per consecutive 7 days)
- Subject becomes pregnant
- Study is terminated by sponsor for futility
- Death

If the subject withdraws from the study before the end of the double-blind induction phase, an EW visit is to be performed.

If a subject is lost to follow-up, every reasonable effort must be made by the study-site personnel to contact the subject and determine the reason for discontinuation/withdrawal. This should include at least 3 telephone calls, certified letters, email requests, etc. To ensure access to follow-up subjects, the study-sites should attempt to obtain both primary and secondary telephone contact numbers (eg, home, work, and mobile phone numbers), as well as other contact information (eg, email addresses) from subjects before randomization. In addition, the study-site should emphasize the importance of follow-up information to the subject before randomization. The measures taken to follow up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Subjects who withdraw will not be replaced.

Withdrawal of Consent

Every effort will be made in the study to ensure withdrawal of consent is not selected as a reason for discontinuation when in fact the subject withdrew for an identifiable reason (eg, due to an AE or lack of efficacy).

Subjects who wish to withdraw from the study should be asked if they are agreeable to be contacted to collect follow-up information. Subjects who are not agreeable to follow-up contact will be withdrawn from the study as "withdrawal of consent." Subjects who no longer wish to take study drug but agree to provide follow-up information will be withdrawn from the double-blind induction phase with the reason noted as "Other" and will specify the reason why.

For a subject who "withdraws consent", it is recommended that the subject withdraw consent in writing; if the subject refuses or is physically unavailable, the study-site should document and sign the reason for the subject's failure to withdraw consent in writing and maintain it with the subjects source records.

The investigator will be responsible for making all required notifications to the Institutional Review Board (IRB).

10.3. Withdrawal From the Use of Research Samples

Withdrawal From the Use of Samples in Future Research

The subject may withdraw consent for use of samples for research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the ICF.

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

11.1. Subject Information

The primary efficacy (FAS) and safety analysis sets are defined below.

- **Full Analysis Set:** All randomized subjects who receive at least 1 dose of intranasal study drug in the double-blind induction phase.
- **Open-label Analysis Set:** All subjects who receive at least 1 dose of intranasal study drug in the OL induction phase.

- **Safety Analysis Set:** All randomized subjects who receive at least 1 dose of intranasal study drug in the double-blind induction phase.

11.2. Sample Size Determination

The sample size for this study was calculated assuming a treatment difference for the double-blind induction phase of 4, 4.5, 5 points in MADRS total score between each dose (28 mg, 56 mg, 84 mg) of esketamine and the placebo respectively, a SD of 10 for each treatment group, a 1-sided significance level of 0.05 and a drop-out rate of 12.5%. A total of 183 subjects will need to be randomized to treatment in a 2:1:1:1 ratio (72 subjects on placebo group and 37 subjects per intranasal esketamine dose group) to achieve 80% power to detect difference for at least one dose group of intranasal esketamine to placebo using a Dunnett adjustment. The treatment difference and SD used in this calculation were assumed based on results of Panel B of the ESKETINTRD2003 study with clinical consideration.[16]

11.3. Interim Analysis

No interim analysis is planned. The first database lock will occur after that all subjects will complete the double-blind induction phase.

11.4. Efficacy Analyses

Efficacy analysis will be performed on the FAS, which will include all randomized subjects who receive at least 1 dose of intranasal study drug in the double-blind induction phase. Unless otherwise specified, a 1-sided significance level of 0.05 will be used. For the primary efficacy analysis, change from baseline in MADRS total score at Week 4 in the double-blind induction phase will be analyzed using a MMRM. The model will include baseline MADRS total score as a covariate, and treatment, day, and day-by-treatment interaction as fixed effects. An unstructured variance-covariance matrix will be used. Comparison of each esketamine dose groups with the placebo group will be performed with the appropriate contrast using a Dunnett adjustment.

The impact of the missing data on the efficacy results will be assessed using sensitivity analyses. The follow-up data from subjects who discontinued the double-blind induction phase will be incorporated in the sensitivity analyses. Methods of sensitivity analyses will be specified in the SAP.

For the secondary efficacy analysis, the dose-response relationship will be investigated using the MCP-Mod procedure. Details will be provided in the SAP.

The other secondary efficacy endpoints, the endpoints with continuous values will be analyzed by using MMRM similar to the primary endpoint. Comparison of each esketamine group versus placebo group will be performed using the appropriate contrast. Binary endpoints will be analyzed using Fisher's exact test with 90% CIs for the proportion provided for each treatment group.

Time to relapse will be defined as the time between the end of the double-blind induction phase and the first documentation of a relapse event during the posttreatment phase. This will be analyzed separately either remitters or responders (but who are not remitters) at the end of the double-blind induction phase. Summary statistics (eg, number of relapses, number of censored subjects, median 25th and 75th percentile) will be provided from the Kaplan-Meier method.

Additionally, scores and the changes from baseline of all efficacy endpoints will be summarized for all visits in the each induction phase. Data from the OL induction phase will be summarized based on subjects who received treatment during the OL induction phase.

11.5. Pharmacokinetic Analyses

Plasma esketamine (and noresketamine and other metabolites, if needed) concentrations will be listed for all subjects. Descriptive statistics of plasma esketamine (and noresketamine or other metabolites, if needed) concentration at each PK assessment time points will be calculated by dose.

All concentrations below the lowest quantifiable sample concentration of the assay (BQL) or missing data will be labeled as such in the concentration data listing. All subjects and samples excluded from the analysis will be clearly documented in the study report.

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

11.6. Biomarker and Pharmacogenomic Analyses

Baseline biomarker values and changes from baseline to the time points specified in the TIME AND EVENTS SCHEDULE 1 will be assessed. Biomarker values will be tabulated by treatment group over time points and summary statistics will be calculated. Associations between biomarkers and clinical endpoints will be explored. Correlations between baseline values and change in baseline values with efficacy and other clinical evaluations will be assessed, including the relation with response, maintenance of response, illness relapse, and nonresponse.
Pharmacogenomic analyses may include candidate gene analyses or genome-wide association analyses in relation to treatment response, maintenance/stabilization of response, relapse, and nonresponse.
Details of the analysis plan and summary of results from both biomarker and pharmacogenomics analyses will be provided in a separate report.

11.7. Pharmacokinetic/Pharmacodynamic Analyses

The PK/PD relationship of intranasal esketamine and MADRS total score (and possibly selected AEs as additional PD parameters may be evaluated. If there is any visual trend in graphical analysis, suitable models will be applied to describe the PK/PD relationships. The results of the PK/PD evaluation will be presented in a separate report.

11.8. Safety Analyses

Safety analysis set will consist of all randomized subjects who receive at least 1 dose of intranasal study drug in the double-blind induction phase. Safety data for the double-blind period will be analyzed for this population. For the analysis of safety data in the OL induction phase, all subjects who received at least 1 dose of intranasal study drug in this period will be analyzed.

Adverse Events

For each AE, the number of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group.

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The TEAEs are AEs with onset during the treatment phase or that are a consequence of a preexisting condition that has worsened since baseline. All reported AEs will be included in the analysis. For each AE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. In addition, comparisons between treatment groups will be provided if appropriate.

The TEAEs of special interest will be examined separately (please refer to Section 3.2.6). The AEs of special interest will be further listed in the SAP.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an AE, or who experience a severe or an SAE.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Markedly abnormal results (specified in the SAP) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at each respective scheduled time point in each phase of the study. Changes from baseline results will be presented. Frequency tabulations of the abnormalities will be made. A listing of subjects with any markedly abnormal laboratory results will also be provided.

Electrocardiogram (ECG)

The effects on cardiovascular variables will be evaluated by means of descriptive statistics and frequency tabulations. These tables will include observed values and changes from baseline values.

Electrocardiogram data will be summarized by ECG parameter. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

The ECG variables that will be analyzed are heart rate, PR interval, QRS interval, QT interval, and corrected QT (QTc) interval using the following correction methods: QT corrected according to Bazett's formula (QTcB) and QTcF.[2,31,60]

Descriptive statistics of QTc intervals and changes from baseline will be summarized at each scheduled time point. The percentage of subjects with QTc interval >450 milliseconds, >480 milliseconds, or >500 milliseconds will be summarized, as will the percentage of subjects with QTc interval increases from baseline >30 milliseconds or >60 milliseconds.

All clinically relevant abnormalities in ECG waveform that are changes from the baseline readings will be reported (eg, changes in T-wave morphology or the occurrence of U-waves).

Vital Signs

Descriptive statistics of temperature, heart rate, pulse oximetry, respiratory rate, and blood pressure (systolic and diastolic) (supine) values and changes from baseline will be summarized at each scheduled time point. The percentage of subjects with values beyond clinically important limits will be summarized.

Physical Examination

Results of physical examinations (abnormalities) will be listed.

C-SSRS

Suicide-related thoughts and behaviors based on the C-SSRS will be summarized by treatment group in incidence and shift tables. Separate endpoints for suicidal ideation and suicidal behavior will be defined and summarized descriptively by treatment group. Missing scores will not be imputed.

PWC-20, CADSS, CGADR, MOAA/S, BPRS+, and POMS-2

Physician Withdrawal Checklist; 20-item (PWC-20) rating scale, dissociative data from the CADSS, alertness data from the CGADR, sedation data from the MOAA/S, psychosislike effect data from the BPRS+ and abuse-liability data from POMS-2 will be summarized descriptively at each scheduled visit by treatment group.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

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

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

Note: The sponsor collects AEs starting with the signing of the ICF (refer to Section 12.3.1, All AEs, for time of last AE recording). Exacerbation of primary disease is not defined as AE.

Serious Adverse Event

An SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent 1 of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study drug and the event (eg, death from anaphylaxis), the event must

be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For esketamine, the expectedness of an AE will be determined by whether or not it is listed in the Investigator's Brochure.

Adverse Event Associated With the Use of the Drug

An AE is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2, Attribution Definitions.

12.1.2. Attribution Definitions

Not Related

An AE that is not related to the use of the drug.

Doubtful

An AE for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An AE that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An AE that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

12.2. Special Reporting Situations

Safety events of interest on a sponsor study drug that may require expedited reporting or safety evaluation or both include, but are not limited to:

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Accidental or occupational exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject exposure to the sponsor study drug, eg, name confusion)
- Exposure to a sponsor study drug from breastfeeding

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the SAE page of the eCRF.

12.3. Procedures

12.3.1. All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure, which may include contact for follow-up of safety. Serious AEs, including those spontaneously reported to the investigator until completion of the subject's last study-related procedure, must be reported using the SAE Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

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

All AEs, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute

where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

For all studies with an outpatient phase, including OL studies, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number
- Any other information that is required to do an emergency breaking of the blind

12.3.2. Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding SAEs will be transmitted to the sponsor using the SAE Form, which must be completed and signed by a physician from the study-site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be made by facsimile (fax).

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as an SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the

course of a subject's participation in a study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility).
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.

The cause of death of a subject in a study, whether or not the event is expected or associated with the study drug, is considered an SAE.

12.3.3. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the SAE Form. Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with an SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drugs

Intranasal Study Drug

Esketamine will be supplied as a clear, colorless intranasal solution of esketamine hydrochloride (16.14% weight/volume [w/v]; equivalent to 14% w/v of esketamine base) in a nasal spray pump. The solution will consist of 161.4 mg/mL esketamine hydrochloride (equivalent to 140 mg/mL of esketamine base) formulated in 0.12 mg/mL ethylenediaminetetraacetic acid (EDTA) and 1.5 mg/mL citric acid at a pH of 4.5 in water for injection. It is provided in a nasal spray pump, which delivers 16.14 mg esketamine hydrochloride (14 mg esketamine base) per 100 µL spray. Each individual nasal spray pump (device) contains a total of 28 mg (ie, 2 sprays).

The placebo solution will be supplied as a clear, colorless intranasal solution of water for injection, with a bittering agent (denatonium benzoate [Bitrex®] at a final concentration of 0.001mg/mL) added to simulate the taste of the intranasal solution with active drug. The placebo solution will be provided in matching nasal spray pump devices. Benzalkonium chloride is added as a preservative at a concentration of 0.3 mg/mL. Each individual nasal spray pump (device) contains 2 sprays.

Esketamine and placebo will be manufactured and provided under the responsibility of the sponsor. Please refer to the Investigator's Brochure for a list of excipients.[32]

14.2. Packaging

Intranasal Study Drug

Study drug (ie, intranasal esketamine and placebo solution) will be supplied by the sponsor in a bi-dose nasal spray device. The devices will contain 200 µL. Each device delivers 16.14 mg esketamine hydrochloride (14 mg esketamine base) or 0.1 µg of denatonium benzoate per 100 µL spray.

Each nasal spray device will be individually packaged in a blister tray and subsequently put into a carton box. Each carton box constitutes a non-child-resistant subject kit, labeled with a unique medication kit number.

Device for Practicing Intranasal Study Drug Administration

The demonstration intranasal device will also be supplied by the sponsor and will contain placebo solution. Subjects will practice spraying into the air and will not spray intranasally.

14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements.

14.4. Preparation, Handling, and Storage

Study drug will be stored at the study-site in a secure area with restricted access until dispensed to the subjects.

All study drugs must be stored at controlled temperatures as indicated on the product-specific labeling.

Please refer to the pharmacy manual/study-site investigational product (IP) manual and instructions for use documents for additional guidance on study drug preparation, handling, and storage.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study.

The dispensing of study drug to the subject, and the return of study drug from the subject (if applicable), must be documented on the drug accountability form. Subjects must be instructed to return all original containers, whether empty or containing study drug.

The study drug administered to the subject must be documented on the drug accountability form. All study drugs will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers.

Study drug must be handled in strict accordance with the protocol and the container label, and must be stored at the study-site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug, and study drug returned by the subject, must be available for verification by the sponsor's study-site monitor during on-site monitoring visits. The return to the sponsor of unused study drug, or used returned study drug for destruction, will be documented on the drug return form. When the study-site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Potentially hazardous materials such as used ampoules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject.

Whenever a subject brings his or her study drug to the study-site for pill count, this is not seen as a return of supplies. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study-sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Practice intranasal devices
- Investigator's Brochure for esketamine
- IP Binder, including the IP Procedures Manual
- Laboratory manual and materials
- Clinician-administered and subject-reported outcome assessments (paper versions, as applicable)
- IWRS Manual
- ECG equipment and associated materials (eg, manual)
- Instructions for Use documents (healthcare provider versions) for intranasal study drug
- Rater qualifications/requirements for select clinician-administered assessments
- Procedural documents for SAFER interview
- Procedural documents for remote MADRS interviews
- MGH-ATRQ Guidance document
- Sample ICF
- CRF completion guideline
- Subject diary

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Clinical Study in Treatment-resistant Major Depression

Major depressive disorder is a common, severe, chronic, and often life-threatening illness. It is now the leading cause of disability worldwide. There is a clear need to develop novel and improved therapeutics for TRD.

Studies with esketamine have shown robust antidepressant effects in several clinical studies and it has been well-tolerated in these clinical studies.

Selection of Subjects

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

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation.

They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

Justification for Using Placebo

Intranasal placebo is being used as a double-blind for intranasal esketamine to maintain study blinding. All subjects will also receive an oral antidepressant from the prospective lead-in phase. Subjects will not be on placebo alone. Assessment of the potential efficacy of a new compound for the treatment of treatment-resistant major depression requires adequate and well-controlled clinical studies. This superiority study will compare intranasal esketamine to intranasal placebo, as an add-on to an oral antidepressant.

Recent analyses have shown response to placebo varies considerably, from 10% to 55%. Therefore, there is a concern that randomized, controlled studies that rely on comparison with standard antidepressant treatments alone will generate unreliable results with limited assay sensitivity. However, some have considered it unethical to do placebo-controlled studies in major depression due to the potential risk of irreversible harm.[56] In a meta-analysis of drug studies conducted in MDD, it was reported that adult subjects did not have higher rates of suicide behaviors or attempts in the placebo group compared with those receiving an active antidepressant.[35] These studies showed annual suicide rates of 0.8% on the investigational drug, 0.7% on the active comparator, and 0.4% on placebo. Thus, the risk of irreversible harm was not higher in the placebo arm compared with the active control arms.

Some subjects may decide to not participate in a placebo-controlled study due to the potential for increased distress and dysfunction from prolonged depression.

Therefore, the use of an active-controlled study allows for assessment of efficacy of a new compound to allow for scientifically meaningful results.

Moreover, the duration of the double-blind induction phase is relatively short (4-week duration). Subjects will visit the study-site at least twice a week during the double-blind induction phase, and their symptoms will be carefully monitored during each study visit. Safety evaluations will

include evaluation of suicidal ideation/behavior at each clinic visit. At any point in the study, the subject may withdraw consent or be removed from the study by the investigator if there are any clinical concerns.

Subjects who relapsed in the posttreatment phase will receive a 4-week OL induction treatment course of intranasal esketamine.

During follow-up phase further clinical/standard-of-care treatment will be arranged by the study investigator.

Precautions to Ensure Subject Safety in the Study

Subjects may participate in the study only if they have adequate capacity to give consent and after fully understanding the potential risks and giving an informed consent. Determination of capacity will be made by the study investigator. Subjects may discontinue the study at any time. The probability of receiving placebo and the concept of random assignment will be explained to the subject. The duration of the study is short, minimizing the time on intranasal placebo (which is being administered with an oral antidepressant). Potential disadvantages and AEs of participating in the study and alternative treatment options will be discussed. For subjects who do not meet predefined response criteria during the study, clinical care will be arranged between the study investigator and their physician.

The primary ethical concerns of this study is that exposure to esketamine in Japanese subjects may be higher compared with non-Japanese populations at the same dose. Plasma esketamine C_{max} and AUC values were up to 48% higher in Japanese subjects compared with Caucasian subjects following intranasal doses of 28 mg, 56 mg, and 84 mg of esketamine (ESKETINTRD1002).[13] In Phase 2 Study, plasma esketamine concentrations in Japanese patients who received 56 mg of esketamine were higher relative to the corresponding concentrations produced by the same esketamine dose administered in non-Japanese patients, consistent with results from Phase 1 Study ESKETINTRD1002.[13] Assuming the increase in exposure due to an increase in ethnicity is observed, exposure to esketamine may be up to 48% higher than non-Japanese patients for the 84 mg dose. However, this exposure to esketamine is still expected to be lower than the exposure typically used to induce and maintain anesthesia.

Dosing of subjects within a treatment group will be staggered to provide sufficient time for adequate safety monitoring. Vital signs will be assessed before and repeatedly following study drug administration, particularly to monitor transient increases in blood pressure. If blood pressure exceeds predefined limits before dosing, study drug administration may be postponed or the subject may be withdrawn from the study after repeated predose blood pressure exceeds the predefined limits. Refer Section 6.3.1 for guidance on blood pressure monitoring on intranasal treatment session days.

Compensation for any procedure will be fair per local standards and approved by the participating sites IEC/IRB in order to not offer any undue incentive to participate in the study.

Subjects will be carefully monitored during the study and subjects who are unable to tolerate study drug during the double-blind induction phase will be discontinued from the study. If the investigator judges it to be necessary to immediately stop study drug, he or she has the option to do so. Specific guidance is provided regarding blood pressure monitoring on intranasal dosing days (Section 6.3.1).

Only subjects who had nonresponse to their current oral antidepressant medication, where a clinician would consider changing it in the future due to lack of response, will be enrolled.

Only qualified and trained investigators will participate in the study.

The total volume of blood collected is considered to be a clinically acceptable volume of blood to be collected over this time period for biomarkers, PK, pharmacogenomic and safety tests in this study and is less than the standards of the Japan Red Cross for blood donations.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects

- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required. The reapproval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data, or study conduct).

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

16.2.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the subject agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed.

The subject will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

Where local regulations require, a separate ICF may be used for the required DNA component of the study.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory DNA and biomarker research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

16.2.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand esketamine to understand differential drug responders, and to develop tests/assays related to esketamine. The research may begin at any time during the study or the poststudy storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.3, Withdrawal From the Use of Samples in Future Research.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate

document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug to the study-site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator.
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all sub-investigators
- Documentation of sub-investigator qualifications (eg, curriculum vitae)

- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth. In cases where the subject is not randomized into the study, the date seen and date of birth will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study-site as a basis for standard medical care must be available for the following: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

In addition, the author of an entry in the source documents should be identifiable.

At a minimum, the type and level of detail of source data available for a subject should be consistent with that commonly recorded at the study-site as a basis for standard medical care. Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The following data will be recorded directly into the eCRF and will be considered source data:

- Race

The minimum source documentation requirements for Section 4.1, Inclusion Criteria and Section 4.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or

- Complete history of medical notes at the site
- Discharge summaries
- Antidepressant treatment in the current episode of depression

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by subject interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If the electronic source system is utilized, references made to the eCRF in the protocol include the electronic source system but information collected through the electronic source system may not be limited to that found in the eCRF. Data in this system may be considered source documentation.

17.5. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each subject in electronic format. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

Electronic Data Capture (eDC) will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an eCRF. Study-specific data will be transmitted in a secure manner to the sponsor within the timeframe agreed upon between the sponsor and the study-site. The electronic file will be considered to be the eCRF.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subject's source documents. Data must be entered into eCRF in English. The eCRF must be completed as soon as possible after a subject visit and the forms should be available for review at the next scheduled monitoring visit.

If necessary, queries will be generated in the eDC tool. If corrections to a eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study-sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by the sponsor, uploading data

transfers from external service providers into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided.

The sponsor will review eCRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.8. Monitoring

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study-site visit log that will be kept at the study-site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare data entered into the eCRF with the source documents (eg, hospital/clinic/physician’s office medical records); a sample may be reviewed. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are

accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study-site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the data recorded are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The study is considered completed with the last scheduled study assessment for the last subject participating in the study. The final data from the study-site will be sent to the sponsor (or designee) after completion of the final subject assessment at that study-site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

The sponsor reserves the right to close the study-site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study-sites will be closed upon study completion. A study-site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study-site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study drug development

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study-site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study

records, including source documents, for inspection and comparison with the eCRFs. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding esketamine or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic or exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of esketamine, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study-sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of pharmacogenomic or exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study-site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow

for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study-site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law.

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10. Clinical Study Protocol ESKETINTRD3004 (Amendment 2). An Open-label, Long-term, Safety and Efficacy Study of Intranasal Esketamine in Treatment-resistant Depression. Document No. EDMS-ERI-93094730 (in preparation)
11. Clinical Study Protocol ESKETINTRD3005 (Amendment 2). A Randomized, Double-blind, Multicenter, Active-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Intranasal Esketamine Plus an Oral Antidepressant in Elderly Subjects with Treatment-resistant Depression. Document No. EDMS-ERI-93094734, 3.0 (10 January 2016).
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Attachment 1: Prohibited Concomitant Medications

This list of medications is **not all-inclusive**; if necessary, please contact the medical monitor for any questions regarding a medication(s).

Please refer to the prescribing information of the subject's oral antidepressant medication for information regarding prohibited concomitant medications (if subjects don't have the follow up phase, they are prohibited until end of study).

Except where specifically noted, the prohibited medications listed in the following table are prohibited from 1 week (or 5 half-lives, whichever is longer) prior to the first dose of intranasal study drug until the beginning of the follow up phase.

Note in the following table: N, Prohibited; Y, Permitted, with restrictions (please refer to the column labeled "Comments" for additional guidance).

Drug Class	Episodic Use (as needed)	Continuous Use	Comments	Reason for Prohibition
Amantadine	N	N		PD interaction
Anorexiants (eg, phentermine, phendimetrazine)	N	N		Safety
Anticholinesterase inhibitors	N	N		Subject population is excluded
Anticonvulsants	N	N	Subjects with seizures are excluded. Use as adjunctive treatment for major depressive disorder (MDD) is prohibited. – Note: Anticonvulsants used for indications other than seizures may be allowed (eg valproate for migraine; pregabalin)	Safety and PD interaction
Antidepressants (*other than the specific antidepressant started in the prospective lead-in phase of the study*)	N	N	– Only 1 of the 6 predefined oral antidepressant treatment options are permitted – If a subject is taking a monoamine oxidase inhibitor (MAOI), there must be a minimum washout interval of 2 weeks prior to the first dose of intranasal study drug. – Even if used for indication other than MDD (eg, trazodone or low dose tricyclic antidepressants for sleep), the use of any medication listed on the ATRQ, is not permitted during the treatment phase.	Safety and PD interaction
Antipsychotics (including sulpiride)	N	N		PD interaction

Drug Class	Episodic Use (as needed)	Continuous Use	Comments	Reason for Prohibition
Benzodiazepines (at dosages equal to or less than the equivalent of 6 mg/day lorazepam) and non-benzodiazepine sleeping medication (including: zolpidem, zaleplon, eszopiclone, and ramelteon)	N	Y	Subjects who were taking these during the screening phase, can continue them throughout the study; however, dose increases or starting new benzodiazepine medications are not permitted. Prohibited within 12 hours prior to the start of each intranasal treatment session	Safety and PD interaction
Benztropine	Y	N		Safety and PD interaction.
Chinese herbal medicine, which are psychoactive	N	N		PD interaction
Chloral hydrate, melatonin, valerian	N	N		Safety and PD interaction
Clonidine	N	N		Safety and PD interaction
Corticosteriods (systemic)	Y	N	Inhaled, intranasal, topical, and ophthalmic steroids are not prohibited. Intermittent IM/IV corticosteroids are permitted (chronic use prohibited).	PD interaction
Cough/cold preparations/nasal solutions containing vasoconstrictors, decongestants	Y	Y	Intranasally-administered decongestants (vasoconstrictors) should not be used from 1 hour prior to each intranasal study drug administration. Pseudoephedrine- containing oral products should not be used within 12 hours prior to an intranasal treatment session.	Safety and PD interaction
CYP3A4 inducers - Potent	N	N	Subjects may not take a known potent inducer of hepatic CYP3A activity within 2 weeks of the first administration of intranasal study drug until at least 24 hours after the last intranasal dose of study drug. Examples (not all-inclusive): Efavirenz, nevirapine, barbiturates, carbamazepine, glucocorticoids, modafinil, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort	PK
Dextromethorphan	N	N		PD interaction
Diphenhydramine	Y	N	Prohibited within 12 hours prior to the start of each intranasal treatment session	Safety

Drug Class	Episodic Use (as needed)	Continuous Use	Comments	Reason for Prohibition
Dopamine agonists	N	Y	Subjects who were taking these medications at the start of the screening phase, can continue them throughout the study; however, dose increases or starting new dopamine agonists are not permitted. The dopamine agonists must be continued at a stable dose for 1 month prior to the beginning of the screening phase.	PD interaction
Ketanserin	N	N		Safety
Lithium	N	N		PD interaction
Memantine	N	N		PD interaction
Methyldopa	N	N		Safety and PD Interaction
Metyrosine	N	N		Safety and PD interaction
Non-vitamin K antagonist oral anticoagulation agents (eg, dabigatran, rivaroxaban, apixaban	N	N		Safety
Opioids	N	N		PD interaction
Psychostimulants (eg, amphetamines, methylphenidate, and modafanil, armodafinl)	N	N		Cardiovascular safety
ADHD medications (eg, atomoxetine, guanfacine)	N	N	See also “Psychostimulants” row.	Safety
Reserpine	N	N		PD interaction
Scopolamine	N	N		PD interaction
St. John’s Wort	N	N		PD interaction and PK
Thyroid hormone supplement for treatment of thyroid condition only (not for depression)	N	Y		Safety
Thyroxine/ triiodothyronine (T3), thyroid hormone prescribed for depression	N	N		PD interaction
Warfarin	N	N		Primary condition where used is excluded

Abbreviations: N, Prohibited; PD, pharmacodynamics; PK, pharmacokinetics; Y, Permitted, with restrictions (please refer to the column labeled “Comments” for additional guidance).

Attachment 2: New York Heart Association Classification of Cardiac Disease

New York Heart Association Classification of Cardiac Disease

Category	Description
Functional Capacity	
Class I	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.
Objective Assessment	
A	No objective evidence of cardiovascular disease.
B	Objective evidence of minimal cardiovascular disease.
C	Objective evidence of moderately severe cardiovascular disease.
D	Objective evidence of severe cardiovascular disease.

Source: Criteria Committee of the New York Heart Association. Functional capacity and objective assessment. In: Dolgin M, ed. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels, 9th ed. Boston, MA: Little, Brown & Co; 1994, 253-255.

Attachment 3: Example of the Up-titration Schedule for a New Oral Antidepressant Therapy (Physician Determined) in Prospective Lead-in Phase

Antidepressant		Approved Dose in Japan (Min./ Max.)	Example of Up-titration Schedule in Prospective Lead-in Phase					
Class	Drug		Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
SSRI	Escitalopram	10/ 20 mg	10 mg[a]	20 mg	20 mg	20 mg	20 mg	20 mg
	Paroxetine CR	12.5/ 50 mg	12.5 mg	25 mg[a]	37.5 mg	50 mg	50 mg	50 mg
	Sertraline	25/ 100 mg	25 mg	50 mg[a]	100 mg	100 mg	100 mg	100 mg
SNRI	Duloxetine	20/ 60 mg	20 mg	40 mg[a]	60 mg	60 mg	60 mg	60 mg
	Venlafaxine XR	37.5/ 225 mg	37.5 mg	75 mg	150 mg[a]	225 mg	225 mg	225 mg
NaSSA	Mirtazapine	15/ 45 mg	15 mg[a]	30 mg	45 mg	45 mg	45 mg	45 mg

Note: New oral antidepressant treatment should be titrated to the approved maximum dose, to optimize the potential for response. The uptitration schedule should follow respective prescribing information in Japan. The dose, which is above the minimum therapeutic dose defined in MGH-ATRQ should be kept at last 4 weeks during the prospective lead-in phase, in case they start at lower doses.

[a.] Minimum effective dose for oral antidepressant drug which is defined in MGH-ATRQ.

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Takuto Tokudome

Signature: electronic signature appended at the end of the protocol Date: _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

SIGNATURES

Signed by	Date	Justification
Takuto Tokudome	21Dec2018, 07:38:07 AM, UTC	Document Approval