

SYNOPSIS

<u>Name of Sponsor/Company</u>	Janssen Pharmaceutical K.K.*
<u>Name of Investigational Product</u>	JNJ-54135419 (esketamine)

* This study was conducted by Janssen Pharmaceutical K.K. in Japan. The term “sponsor” is used to represent Janssen Pharmaceutical K.K.

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Prepared by: Janssen Pharmaceutical K.K.

Protocol No.: 54135419TRD2005

Title of Study: 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

NCT No.: NCT02918318

Clinical Registry No.: CR108227

Principal Investigator: Takatoshi Mori, MD - Arata Clinic, PPD, Japan

Study Centers: The study was conducted in 58 sites in Japan

Publication (Reference): None

Study Period: 14 December 2016 (Date first subject signed informed consent) to 13 December 2019 (Date of last observation for last subject recorded as part of the database)

Phase of Development: 2b

Objectives:Primary Objective:

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

Secondary Objectives:

The secondary objectives were:

- To assess the effect of intranasal esketamine compared with intranasal placebo as an add-on to an oral AD 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

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- 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 AD 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 (HR), blood pressure (BP), 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 AD in Japanese subjects with TRD with attention to:
 - Time to relapse in the posttreatment phase for subjects in remission and for subjects who responded but were not in remission, at the end of the double-blind (DB) induction phase.
 - To evaluate the pharmacokinetics (PK) of intranasally administered esketamine in Japanese subjects with TRD.

Exploratory Objectives:

The exploratory objectives were:

- To assess the comparability of the efficacy and safety of intranasal esketamine as an add-on to an oral AD between the DB 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 polymorphisms (including, but not limited to brain-derived neurotrophic factor [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.

Methodology: This was a randomized, DB, placebo-controlled, multicenter study designed to evaluate the efficacy, safety, and tolerability of fixed dose of intranasal esketamine (28-, 56-, or 84-mg) as an add-on therapy to an oral AD in Japanese subjects with TRD. A total of 183 subjects (72 subjects in the placebo group and 37 subjects in each intranasal esketamine dose group) were planned to be enrolled in this study.

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

The duration of a subject's participation was a maximum of 42 weeks, depending on whether they met phase-specific criteria for response or relapse. The end-of-study (EOS) occurred when the last subject in the study completed his/her last study assessment (ie, last follow-up visit).

Screening Phase:

Japanese men and women, aged 20 to 64 years (both inclusive), who met the 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 International Neuropsychiatric Interview (MINI) were screened according to the inclusion/exclusion criteria.

To confirm eligibility for participation in the prospective lead-in phase, subjects were reviewed for inclusion/exclusion criteria during the screening phase. At the screening visit, subjects who continued to fulfill all inclusion criteria and none of the exclusion criteria were enrolled. The SAFER (state versus trait, Assessability, Face validity, Ecological validity, and Rule of the three Ps [pervasive, persistent, and pathological]) interview was conducted as early as feasible during the screening phase, before down-titration of ADs to avoid change of depressive symptoms because of tapering. The SAFER interview is a tool to facilitate subject selection for MDD clinical studies and was used to ensure enrollment of subjects who have symptoms that reflected the current state of illness, to ensure that these symptoms could be reliably measured with appropriate measurement tools, and to minimize placebo response.

Subject's current AD treatment(s), including adjunctive treatment for MDD was tapered and discontinued in this phase per the local prescribing information. Eligible subjects had their current AD therapies down-titrated and discontinued prior to entering the prospective lead-in. If clinically indicated, cross-tapering was allowed.

Prospective Lead-in Phase:

After enrollment, eligible subjects entered a 6-week OL prospective lead-in phase (Visits 2.1 to 3.1 [prerandomization]), and received a new AD therapy (physician determined) daily for the duration of this phase. The oral AD was to be 1 of the following: selective serotonin reuptake inhibitors or serotonin-specific reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), or mirtazapine (ie, escitalopram, paroxetine controlled-release [CR], sertraline, duloxetine, venlafaxine extended-release [XR], or mirtazapine), which the subject previously had not shown a nonresponse in the current depressive episode or had not been previously intolerant to (lifetime). If clinically indicated, cross-tapering was allowed in the first 2 weeks during the prospective lead-in phase. In the last 4 weeks during the prospective lead-in phase, subjects received a single treatment of switched new oral AD. New oral AD treatment was titrated to the approved maximum dose to optimize the potential for response. The up-titration schedule was based on prescribing information. The dose, which was above the minimum therapeutic dose defined in MGH-ATRQ (Massachusetts General Hospital Antidepressant Treatment Response Questionnaire) was to be kept at last 4 weeks during the prospective lead-in phase, in case they started at lower doses.

The criteria of TRD was defined as nonresponse ($\leq 25\%$ improvement) to at least 1 AD treatment determined retrospectively and 1 AD prospectively in the current episode of depression. After 6 weeks, subjects who were nonresponders to the new oral AD treatment at the end of the prospective lead-in phase were eligible to proceed to the DB induction phase. Nonresponse at the end of the prospective lead-in phase was defined as $\leq 25\%$ improvement in the MADRS total score from Visit 2.1 to each of the Visits 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). An assessment of AD treatment response at the end of the prospective lead-in phase was performed by the investigators. All other subjects who did not proceed to the DB induction phase ended the study participation at this time. No follow-up or further study visits were performed for these subjects. All discontinued subjects were treated with an oral AD after completion of the study, unless it was clinically inappropriate.

MADRS assessment throughout the study was performed by an independent, remote (by phone), blinded rater.

Double-blind Induction Phase:

The 4-week fixed dose DB induction phase was started on Day 1 (Visit 3.1) and ended at Day 28 (Visit 3.10). A total of 183 subjects were randomly assigned in a 2:1:1:1 ratio to receive DB intranasal treatment with either placebo, esketamine 28 mg, esketamine 56 mg, or esketamine 84 mg add-on to the continued stable oral AD initiated in the prospective lead-in phase. Subjects self-administered the intranasal study agent (esketamine 28-, 56-, 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 was on Day 1.

Responders (subjects who had $\geq 50\%$ reduction from baseline in MADRS total score) at the end of the DB induction phase were eligible to proceed to the posttreatment phase; those who did not (ie, nonresponders) proceeded to the 4-week follow-up phase.

Posttreatment Phase:

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

Open-label Induction Phase:

Responders from the DB induction phase who relapsed in the posttreatment phase were eligible for the OL induction phase and received a flexible OL induction treatment course of intranasal esketamine for 4 weeks. The beginning of the OL induction phase was at least 2 weeks (14 calendar days) after the last dose in the DB induction phase. Subjects who met the relapse criteria before 2 weeks after the last dose in the DB induction phase were not eligible to join the OL induction phase. They were withdrawn from the posttreatment phase and entered the follow-up phase.

Subjects who entered the OL induction phase started 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 was increased to 84 mg. On Days 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 was permitted, if required for tolerability; no dose increase was permitted on Day OL15. After Day OL15, the dose was to be stable (unchanged). If needed for tolerability, a dose reduction was permitted from Day OL15 until Day OL25.

The oral AD medication initiated from the prospective lead-in phase, which was continued in the posttreatment phase was also maintained throughout this phase.

Follow-up Phase:

The 4-week follow-up phase included all early withdrawals and nonresponders from DB induction phase, DB induction responders who withdrew in the first 4 weeks of the posttreatment phase and all subjects who received an OL intranasal study agent.

During this phase, further clinical/standard-of-care treatment was provided by the study investigator; however, in order to better assess potential withdrawal symptoms from the intranasal study agent, the oral AD medication was continued for the follow-up phase, unless determined as not clinically appropriate.

Number of Subjects (planned and analyzed):

Planned: A total of 183 subjects [72 subjects in the placebo group and 37 subjects in each intranasal esketamine dose group] were planned to be enrolled in this study.

Analyzed: A total of 202 subjects were analyzed; the number of subjects included in each analysis set during the DB induction, DB follow-up, and posttreatment phases are provided in the table below.

Number of Subjects in Each Analysis Set; Double-blind Induction/Follow-up and Posttreatment Phases

	Esk 28 (N=41)	Esk 56 (N=40)	Esk 84 (N=41)	Placebo (N=80)	Total (N=202)
All randomized	41 (100.0%)	40 (100.0%)	41 (100.0%)	80 (100.0%)	202 (100.0%)
FAS (DB)	41 (100.0%)	40 (100.0%)	41 (100.0%)	80 (100.0%)	202 (100.0%)
FAS (responders)	13 (31.7%)	11 (27.5%)	17 (41.5%)	27 (33.8%)	68 (33.7%)
Safety (DB) (a)	41 (100.0%)	40 (100.0%)	41 (100.0%)	80 (100.0%)	202 (100.0%)
Safety (responders) (a)	13 (31.7%)	11 (27.5%)	17 (41.5%)	27 (33.8%)	68 (33.7%)
Follow-up (DB)	27 (65.9%)	28 (70.0%)	24 (58.5%)	53 (66.3%)	132 (65.3%)

(a) One subject in the safety analysis set who was randomized to the 84 mg group received 56 mg on Day 1, 4 and 28 mg on Day 8 then withdrew due to AE on Day 11. This subject is summarized under Esk 84 treatment group in this table.

The number of subjects in each analysis set of OL induction and OL follow-up phases are shown in table below.

Number of Subjects in Each Analysis Set; Open-label Induction and Open-label Follow-up Phases

	Total (N=68)
FAS (responders)	68 (100.0%)
FAS (OL)	48 (70.6%)
Safety (OL)	48 (70.6%)
Follow-up (OL)	48 (70.6%)

Diagnosis and Main Criteria for Inclusion: The study population included Japanese men and women, 20 to 64 years of age (both inclusive), who met the DSM-5 diagnostic criteria for recurrent or single-episode MDD, without psychotic features, based upon clinical assessment and confirmed by the MINI. In the case of a single-episode MDD, the subject had to be diagnosed with persistent depressive disorder, which met criteria of major depressive episode for a continuous duration of ≥ 2 years, and the same physician from the site had to be examining the subject for ≥ 2 years continuously as a primary care physician of the subject. At the start of the screening phase, the subjects to have had a nonresponse ($\leq 25\%$ improvement) to ≥ 1 but < 5 different oral ADs taken at adequate dosage and for adequate duration, as assessed on the MGH-ATRQ, in the current episode of depression and confirmed by documented medical/pharmacy/prescription records, letter from the treating physician. The subject's current major depressive episode, depression symptom severity (MADRS total score ≥ 28 required), and AD nonresponse in the current depressive episode was confirmed using the "SAFER" criteria interview, which was administered by remote, independent raters.

Test Product, Dose and Mode of Administration, Batch No.: Intranasal esketamine was supplied as a clear and colorless solution containing 16.14% weight/volume (w/v) esketamine hydrochloride (equivalent to 14% w/v esketamine base), in a nasal spray pump (device), which delivered 16.14 mg esketamine hydrochloride (14 mg esketamine base) per 100 μ L spray. Each individual nasal spray device contained a total of 28 mg (ie, 2 sprays). Intranasal esketamine batch numbers were: 502169, 160663, and 170900.

Reference Therapy, Dose and Mode of Administration, Batch No.: Intranasal placebo was supplied as a clear and colorless solution containing water for injection with a bittering agent (denatonium benzoate [Bitrex®]) at a final concentration of 0.001 mg/mL added to simulate the taste of the intranasal esketamine solution. The placebo solution was provided in matching nasal spray devices; each individual

nasal spray device contained 2 sprays. Intranasal placebo batch numbers were: 502264, 160665, and 162284A.

Duration of Treatment: The study had following phases: a 4-week screening phase to taper and discontinued the current AD medication; a 6-week OL prospective lead-in phase to administer new oral AD; a 4-week DB induction phase to receive DB intranasal treatment with either placebo, esketamine 28 mg, esketamine 56 mg, or esketamine 84 mg add-on to the continued stable oral AD initiated in the prospective lead-in phase; a 24-week posttreatment phase comprising of only oral AD therapy, including an optional 4-week OL induction phase to administer intranasal esketamine; and a 4-week follow-up phase. The maximum duration of subject's participation was 42 weeks, depending on whether they met phase-specific criteria for response or relapse.

Criteria for Evaluation:

Pharmacokinetics: Venous blood samples, approximately 4 mL each, were collected for PK analysis at 40-minute, 1-hour, and 2-hour postdose on study Days 4 and 25 in the DB induction phase, and on Day 25 in the OL induction phase. Plasma esketamine and noresketamine concentrations were measured at each PK assessment time point.

Biomarker and Pharmacogenomics (DNA): Blood samples (10 mL for biomarkers and 6 mL for pharmacogenomics, each) for analyses of biomarkers (protein) and DNA were collected on Days 1, 4, 25 prior to intranasal dosing, and at early withdrawal (EW) visit in the DB induction phase.

Efficacy: Efficacy measures included: MADRS (24-hour and 7-day recall), a clinician-rated scale designed to measure depression severity and detect changes due to AD treatment, scored by independent remote blinded raters to ensure an unbiased efficacy evaluation; Clinical Global Impression-Severity (CGI-S), a clinician-rated measure of subject's illness severity; time to relapse; Sheehan Disability Scale (SDS), a subject-reported outcome measure of functional impairment and associated disability; Generalized Anxiety Disorder 7-item Scale (GAD-7), a subject-reported measure of the symptoms of anxiety. Onset of clinical response was defined as 50% reduction in the MADRS total score by the day after taking the first dose of DB medication (Day 2) that was continued through the end of the 4-week DB induction phase with 1 excursion. Subjects were allowed one excursion (nonresponse) on Days 8, 15, or 22. Subjects who discontinued the study prior to the end of the DB induction phase were not considered to have maintained clinical response. A subject was defined as a responder at a given time point if the percent improvement in MADRS total score from baseline was $\geq 50\%$. Subjects who had a MADRS total score of ≤ 12 at a given time point were considered remitters.

Safety: Safety evaluation was based on reported AEs, clinical laboratory tests (hematology, serum chemistry, and urinalysis), vital sign measurements, physical examination, height, body weight, electrocardiograms (ECGs), pulse oximetry, Brief Psychiatric Rating Scale (BPRS+) to assess treatment-emergent psychotic symptoms, Columbia-Suicide Severity Rating Scale (C-SSRS) to assess suicidal ideation and behavior, Clinician Administered Dissociative States Scale (CADSS) to assess treatment-emergent dissociative symptoms, Clinical Global Assessment of Discharge Readiness (CGADR) to assess subject readiness for discharge from the study-site, Modified Observer's Assessment of Alertness/Sedation (MOAA/S) to measure treatment-emergent sedation, Profile of Mood States-Second Edition (POMS-2) to measure abuse-liability, and Physician Withdrawal Checklist 20-item (PWC-20) to assess potential withdrawal symptoms following cessation of intranasal study agent.

Statistical Methods:

Sample Size Determination

The sample size for this study was calculated assuming a treatment difference for the DB induction phase of 4, 4.5, 5 points in the MADRS total score between each dose (28-, 56-, 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 were needed to be randomized to treatment in a 2:1:1:1 ratio (72 subjects on the 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.

Analysis Sets

Subjects were classified into following analysis sets: all randomized, full, safety, PK, and PK/PD.

All Randomized Analysis Set: This analysis set included all subjects who were randomized regardless of whether or not treatment was received.

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

Full Analysis Set (FAS): Efficacy analysis was performed on the following FAS.

- FAS (DB): All randomized subjects who received at least 1 dose of intranasal study agent during the DB induction phase.
- FAS (OL): All subjects who received at least 1 dose of intranasal study agent during the OL induction phase.
- FAS (responders): All randomized subjects who received at least 1 dose of intranasal study agent during the DB induction phase and who were responders at the end of the DB induction phase and entered the posttreatment phase.

Safety Analysis Set: The following safety analysis sets were defined for each phase. Analyses of change from baseline included only those subjects who had baseline and at least 1 postbaseline observation in that phase.

- Safety (DB): All randomized subjects who received at least 1 dose of intranasal study agent in the DB induction phase.
- Safety (OL): All subjects who received at least 1 dose of intranasal study agent in the OL induction phase.
- Safety (responders): All randomized subjects who received at least 1 dose of intranasal study agent during the DB induction phase and who were responders at the end of the DB induction phase and entered the posttreatment phase.

Follow-up Analysis Set: The following follow-up analysis sets were defined for each phase and were used for both safety and efficacy analyses:

- Follow-up (DB): All subjects who did not respond at the end of DB induction phase and entered the DB follow-up phase.
- Follow-up (OL): All safety (OL) subjects who entered the OL follow-up phase.

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

Pharmacokinetic/pharmacodynamic (PK/PD) Analysis Set: Blood pressure (systolic [SBP] and diastolic [DBP]) and QTcF were selected for safety parameters. The PK/PD analysis set included all subjects who received at least 1 dose of intranasal esketamine and had at least 1 time point with nominal time-matched plasma concentration and safety parameter.

Pharmacokinetic Analyses

Plasma esketamine and noresketamine concentrations were listed for all subjects who received at least 1 dose of intranasal esketamine and had at least 1 evaluable concentration data. Descriptive statistics of plasma esketamine and noresketamine concentrations at each PK assessment time points were calculated by dose. Population-PK analysis of plasma concentration-time data of esketamine (and noresketamine, if needed) may be performed with non-linear mixed-effects modeling (NONMEM) approach and may be presented in a separate report.

Pharmacokinetic/Pharmacodynamic Analyses

The PK/PD analysis was based on the PK/PD analysis set for nominal time-matched plasma concentrations and safety parameters. The plots were generated to evaluate the relationship between the safety parameters (absolute value and change [change from predose for SBP, DBP, and CADSS total score and change from baseline for QTcF]) and plasma concentrations of esketamine and noresketamine by phases.

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

Biomarker and Pharmacogenomic Analyses

Details of the analysis plan and results from both biomarker and pharmacogenomic analyses will be reported separately.

Efficacy Analyses

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

As a sensitivity analysis, the change in MADRS total score was analyzed using an analysis of covariance (ANCOVA) model, using last observation carried forward (LOCF) data. In addition to the ANCOVA model based on LOCF method, another sensitivity analysis using the same MMRM model was done, which included the follow-up data from subjects who discontinued the DB induction phase.

Primary Endpoint:

The primary efficacy variable was change from baseline in the MADRS total score at Day 28 in the DB induction phase, was analyzed using a MMRM based on observed case data. The model included baseline MADRS total score as a covariate, and treatment, day, and day-by-treatment interaction as fixed effects. The within-subject covariance between visits was estimated via an unstructured variance-covariance matrix. Comparison of each esketamine dose group with the placebo group was performed with the appropriate contrast using a Dunnett adjustment. The change from baseline in MADRS total score over time in the DB induction phase was analyzed using the same MMRM.

Based on the MMRM, the least-squares (LS) mean estimates for each esketamine dose group and placebo group at Day 28 and the corresponding variances were obtained. The generalized MCP-Mod (multiple comparison procedure - modeling) approach was applied towards the estimates obtained from the MMRM to analyze the dose-response relationship.

The significance of the dose-response signal associated with each candidate model was determined using trend tests with model-specific optimal contrast coefficients. The maximum of the candidate model trend test statistics was used to evaluate the presence of a dose-response signal, properly accounting for

multiplicity at an overall level of 5% (1-sided) using MCP-Mod methodology. If the maximum test statistic was not significant, no dose-response relationship was further explored. Otherwise, the model families corresponding to individual candidate models with significant trend test statistic was used to fit to the observed data and the one with the smallest Akaike Information Criterion (AIC) was selected to represent the dose-response relationship. The corresponding confidence interval (CI) for the response at each dose was computed based on a bootstrap approach.

The sensitivity analysis was based on an ANCOVA model using change from baseline to Day 28 based on the LOCF data. The models included factors for treatment and baseline MADRS total score as a continuous covariate. A 90% CI for the difference in LS means and p-value was calculated based on the contrast test statistic for each esketamine dose level. In addition to the ANCOVA model based on LOCF method, another sensitivity analysis using the same MMRM model was done which included the follow-up data from subjects who discontinued the DB induction phase. For subjects who discontinued from the DB induction phase, the measures on the follow-up visit was treated as the data 'during DB induction phase' and the measure within the visit window for Day 28 and closed to the target date was used. The delta worsening adjustment analysis was to be done only if the dropout rate was >15%.

Secondary Endpoints:

Responders/Remitters: The proportion of subjects who achieved a response/remission was summarized at each time point for each induction phase (DB and OL). The proportion of responders/remitters during the DB induction phase in the esketamine dose group was compared with the placebo group using Fisher's exact test with 90% CIs for the proportion provided by treatment group.

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

- In subjects who remitted (MADRS total score ≤ 12) at the end of the DB induction phase
- In subjects with response ($\geq 50\%$ reduction from baseline in MADRS total score) but who were not in remission at the end of the DB induction phase.

Onset of Clinical response: The proportion of subjects who showed onset of clinical response by Day 2 that was maintained for the duration of the DB induction phase in the esketamine dose group was compared with the placebo group using Fisher's exact test with 90% CIs for the proportion provided by treatment group. The proportion of responders with onset by Day 2 that was maintained to Day 8, Day 15, Day 22, and Day 28 were tested separately.

CGI-S: Descriptive statistics of actual values and changes from baseline by treatment group was provided. Frequency distributions by treatment group were provided at each time point for each analysis phase (DB induction, DB follow-up, posttreatment, OL induction, and OL follow-up). The ranks of the change from baseline for CGI-S in the DB induction phase was analyzed at each time point based on observed case using the same MMRM as described for primary efficacy endpoint.

SDS: Descriptive statistics of actual values and changes from baseline by treatment group were provided at each time point for DB induction and posttreatment phases. The change from baseline in SDS total score at Day 28 in the DB induction phase was analyzed using the same MMRM as described for primary efficacy endpoint.

GAD-7: Descriptive statistics of actual values and changes from baseline by treatment group were provided at each time point during DB induction phase. A frequency distribution was also provided for GAD-7 severity categories at each time point. The change from baseline in GAD-7 total score over time in the DB induction phase was analyzed using the same MMRM as described for primary efficacy endpoint.

MADRS: Descriptive statistics of actual values and changes from baseline were summarized at each time point for each phase (DB induction, DB follow-up, posttreatment, OL induction, and OL follow-up).

Safety Analyses

The number (%) of subjects with TEAEs, serious TEAEs (serious adverse events [SAEs]), and TEAEs that led to study agent discontinuation and/or dose reduction was summarized by system organ class and preferred term (PT). TEAEs were summarized by onset time (4-week intervals). Data listings were generated for deaths, other SAEs, and discontinuations due to AEs. Descriptive statistics for values and changes from baseline were provided for clinical laboratory tests, vital signs, ECG, CADSS, BPRS+, MOAAS, and POMS-2, at each scheduled time point for each induction phase (DB and OL). Frequency distributions at each time point were provided for C-SSRS data. Shifts from the baseline visit to the most severe/maximum score during each analysis phase (DB induction, DB follow-up, posttreatment, OL induction, and OL follow-up) were summarized for C-SSRS data. The proportion of subjects with withdrawal symptoms at the end of induction phases (DB and OL) or during the DB follow-up phase, posttreatment phase and the OL follow-up phase was presented for PWC-20. The proportion of subjects with a response of 'No' on the CGADR at each time point was presented by treatment group during each induction phase (DB and OL).

RESULTS:

STUDY POPULATION:

Of the 460 subjects screened, 308 (67.0%) subjects were enrolled in the prospective lead-in phase, 202 (43.9%) subjects were randomized in the DB induction phase. Of the 202 subjects randomly assigned to intranasal study agent in the DB induction phase, 183 (90.6%) subjects completed the DB induction phase and 19 (9.4%) subjects were withdrawn. The withdrawal rate in the esketamine 28 mg group was 4.9% (2/41 subjects), 17.5% (7/40 subjects) in the esketamine 56 mg group, 4.9% (2/41 subjects) in the esketamine 84 mg group, and 10.0% (8/80 subjects) in the placebo group. The most common reason for withdrawal from the DB induction phase was AEs (5.0% [10/202 subjects]). A total of 132 subjects (ie, including nonresponders and subjects who were withdrawn from the DB induction phase) entered the DB follow-up phase; of these 127 (96.2%) subjects completed the DB follow-up and 5 (3.8%) subjects were withdrawn. A total of 68 subjects were responders at the end of DB induction phase and entered to posttreatment phase. Of these 61 (89.7%) subjects completed the posttreatment phase and 7 (10.3%) subjects were withdrawn from the posttreatment phase. Forty-eight subjects who relapsed within 20 weeks after the start of posttreatment phase entered into the OL induction phase. Of these 47 (97.9%) subjects completed the OL induction phase and 1 (2.1%) subject was withdrawn due to AE. Forty-eight subjects who received at least 1 dose of flexible esketamine in the OL induction phase entered the OL follow-up phase. Of these 47 (97.9%) subjects completed the OL follow-up phase and 1 (2.1%) subject was withdrawn due to AE. A total of 178/202 (88.1%) of randomized subjects in the DB induction phase completed the study and 11 (5.4%) subjects were withdrawn from either the DB, OL, or follow-up phases, or from all phases.

The demographic and baseline characteristics were generally comparable across treatment groups. A higher proportion of subjects were men (52.5%). The median age was 43.0 (range: 20 to 64) years, and over half (54.5%) of the subjects were in the age category 20 to 44 years. The majority (67.8%) of subjects were on oral AD treatment with SSRIs. The mean (SD) baseline MADRS total score 37.5 (5.64). Based on CGI-S scores, the majority of subjects (45.5% [92/202]) were moderately ill (median CGI-S score of 5). At screening, the median (range) duration of the current episode of depression was 34.0 (6; 936) weeks and majority of subjects (40.6% [82/202]) had current episode of depression for ≤ 26 weeks. Approximately 20% (40/202) of subjects had suicidal ideation as assessed using the C-SSRS. In addition, majority of subjects (65.8% [133/202]) had experienced 2 to 3 major depressive episodes, and 51.5% (104/202) and 48.5% (98/202) of subjects had been treated with 2 and ≥ 3 previous AD treatments respectively, in the current episode, including the AD started in the prospective lead-in phase.

Most subjects (95.1% [39/41] of subjects in the esketamine 28 mg group, 80% [32/40] of subjects in the esketamine 56 mg group, 92.7% [38/41] of subjects in the esketamine 84 mg group, and 87.5% [70/80] of subjects in placebo group) received intranasal study medication on all 8 intranasal dosing days during the DB induction phase. In the DB induction phase, most subjects in all the 4 treatment groups were exposed to intranasal study agent for at least 22 days (39/41 [95.1%] subjects in the esketamine 28 mg group, 34/40 [85.0%] subjects in the esketamine 56 mg group, 39/41 [95.1%] subjects in the esketamine 84 mg group, and 72/80 [90.0%] subjects in the placebo group). Most subjects (44/48 [91.7%]) received flexible esketamine (either 28-, or 56-, or 84-mg) on all 8 intranasal dosing days during the OL induction phase. In the OL induction phase, the mean (SD) duration of exposure to flexible intranasal esketamine agent was 24.6 (3.60) days.

EFFICACY RESULTS:

Primary Efficacy Analyses

MMRM Analyses

The mean (SD) change from baseline in the MADRS total score at Day 28 was -15.2 (13.07), -14.5 (10.53), -15.1 (12.21), and -15.3 (11.68) for the esketamine 28-, 56-, 84-mg, and placebo groups, respectively; where decreases from baseline represent improvement. The LS mean differences (SE) of the MADRS total score between each esketamine dose group and the placebo group were -1.0 (2.25), 0.6 (2.33), and -0.9 (2.26) for the esketamine 28-, 56-, and 84-mg groups, respectively. The improvement in the esketamine dose groups (28-, 56-, and 84-mg) compared with the placebo group did not reach statistical significance (1-sided $p=0.475$, $p=0.504$, $p=0.482$, respectively). The decreases in LS mean MADRS total scores were greater in all esketamine dose groups compared with the placebo group at Day 2 of the DB induction phase, with maximum decrease observed in the esketamine 28 mg group. On Day 8, there were some degrees of increases followed by the decreases in the LS mean MADRS total scores in all esketamine and placebo groups until Day 28 of the DB induction phase.

MCP-Mod Analyses

Based on the MCP-Mod analysis, all 5 prespecified models did not show a significant dose-response relationship in the change from baseline in MADRS total score at Day 28.

Sensitivity Analyses

Results of the sensitivity analysis were consistent with primary analysis.

Subgroup Analyses

Overall, no difference was observed between any of the esketamine dose groups and placebo for the subgroups. Subjects with >3 major depressive episodes showed a slight trend for better efficacy in all esketamine dose groups relative to subjects with 2 to 3 major depressive episodes. Subjects with the shortest (≤ 26 weeks) and longest (>104 weeks) duration of current episodes showed a slight trend for better efficacy in all esketamine dose groups relative to subjects with >26 to 52 weeks and >52 to 104 weeks duration.

Secondary Efficacy Analyses

Proportion of Responders

On Day 2, the responder rate for the esketamine 28 mg group (22.0% [9/41 subjects]) was the highest among all esketamine dose groups (esketamine 56 mg: 13.2% [5/38 subjects]; esketamine 84 mg: 10.0% [4/40 subjects]) and numerically much higher than placebo (9.0% [7/78 subjects]) during the DB induction phase. The proportion of responders in all esketamine groups and placebo group decreased at Day 8; thereafter, generally increased over time during the DB induction phase. On Day 28, the

proportion of responders based on the MADRS total score ($\geq 50\%$ improvement in the MADRS total score) was 33.3% (13/39 subjects) in the esketamine 28 mg group, 35.3% (12/34 subjects) in the esketamine 56 mg group, 43.6% (17/39 subjects) in the esketamine 84 mg group, and 37.5% (27/72 subjects) in the placebo group during the DB induction phase.

The percentage of subjects who were responders in the flexible esketamine group at Day 28 OL induction phase was 44.7% (21/47 subjects).

Proportion of Remitters

On Day 2, the proportion of remitters for the esketamine 28 mg group (9.8% [4/41 subjects]) was the highest among all esketamine dose groups (esketamine 56 mg: 0% [0/38 subjects]; esketamine 84 mg: 7.5% [3/40 subjects]), and placebo group (3.8% [3/78 subjects]). On Day 28, the proportion of remitters (MADRS total score ≤ 12) was 23.1% (9/39 subjects) in the esketamine 28 mg group, 11.8% (4/34 subjects) in the esketamine 56 mg group, 23.1% (9/39 subjects) in the esketamine 84 mg group, and 20.8% (15/72 subjects) in the placebo group during the DB induction phase.

The proportion of remitters based on the MADRS total score in the flexible esketamine dose group increased over time and was highest on Day 28 (42.6% [20/47 subjects]) in the OL induction phase.

Onset of Clinical Response

The onset of clinical response (at least 50% improvement from baseline in the MADRS total score by Day 2 that was maintained to Day 28 with 1 excursion on Days 8, 15, or 22) was reported in 2.4% (1/41) of subjects in the esketamine 28 mg group, 2.6% (1/39) of subjects in the esketamine 56 mg group, 7.3% (3/41) of subjects in the esketamine 84 mg group, and 6.3% (5/79) of the subjects in the placebo group during the DB induction phase. The clinical response was maintained from Day 2 to Day 28 in the DB induction phase in the esketamine 28 mg group (0% [0/41 subjects]), esketamine 56 mg group (2.5% [1/40 subjects]), esketamine 84 mg group (7.3% [3/41 subjects]), and the placebo group (2.5% [2/80 subjects]).

CGI-S

In the DB induction phase, the median (range) decreases from baseline to Day 28 of the DB induction phase were -1.0 (-5; 1) in the esketamine 28 mg group, -1.0 (-3; 0) in the esketamine 56 mg group, -1.0 (-5; 0) in the esketamine 84 mg group, and -1.0 (-4; 1) in the placebo group. The severity of the illness improved from OL baseline to OL endpoint and OL follow-up phase endpoint (subjects categorized as mildly ill was $>40\%$ at OL endpoint and OL follow-up endpoint versus 4.2% subjects at OL baseline).

GAD-7

The improvement in mean GAD-7 total scores from baseline to Day 28 of the DB induction phase was generally comparable across all esketamine dose groups and placebo group: mean (SD) changes from baseline were -8.2 (4.94) in the esketamine 28 mg group, -7.8 (5.05) in the esketamine 56 mg group, and -8.1 (5.67) in the esketamine 84 mg group, and -7.7 (5.05) in the placebo group. The LS mean difference (90% CI) between the esketamine 28 mg and placebo groups was -0.4 (-1.91; 1.17), between the esketamine 56 mg and placebo groups was 0.3 (-1.24; 1.93), and between the esketamine 84 mg and placebo groups was -0.4 (-1.94; 1.15).

SDS

In the DB induction phase, the improvement in the mean SDS total scores from baseline to Day 28 of the DB induction phase was generally comparable across all esketamine dose groups and placebo group: the mean (SD) changes from baseline were -8.6 (8.68) in the esketamine 28 mg group, -7.9 (7.94) in the esketamine 56 mg group, -9.5 (8.93) in the esketamine 84 mg group, and -7.0 (7.39) in the placebo group.

Time to Relapse

The median time to relapse for all responders was 37.0 days (90% CI: 26.0; 69.0) and 47.0 days (90% CI: 25.0; 95.0) in the combined esketamine and placebo groups, respectively.

Subjects who remit (MADRS Total Score \leq 12) at the end of the DB induction phase: The median time to relapse was 34.0 days (90% CI: 26.0; 71.0) and 30.0 days (90% CI: 22.0; 50.0) in the combined esketamine and placebo groups, respectively.

Subjects with response (\geq 50% reduction from baseline in MADRS Total Score) but who were not in remission at the end of the DB induction phase: The median time to relapse was 44.0 days (90% CI: 22.0; 100.0) and 91.0 days (90% CI: 22.0; not estimable) in the combined esketamine and placebo groups, respectively. The median time to relapse was 32.0 days (90% CI: 13.0; 44.0) in the esketamine 28 mg group, 26.0 days (90% CI: 9.0; 121.0) in the esketamine 56 mg group, 79.5 days (90% CI: 16.0; 108.0) in the esketamine 84 mg group, and 91.0 days (90% CI: 22.0; not estimable) in the placebo group.

MADRS Total Scores Over Time (After DB Induction Phase)

Overall, a decrease was seen in the MADRS total scores from baseline (OL) to the OL induction phase endpoint; no trend of tolerance was seen after the second induction treatment.

Post hoc Analysis

In the comparison of placebo response by concordance/discordance of MADRS/CGI-S at baseline, a higher placebo response (approximately 2 times) was observed in severe MADRS total score in the moderately-ill population (discordance) on CGI-S at baseline compared with subjects who did not have severe MADRS in the moderately-ill population on CGI-S.

PHARMACOKINETIC RESULTS:

DB induction phase: The plasma esketamine and noresketamine concentrations increased with increasing doses (28-, 56-, and 84-mg). The highest mean plasma esketamine and noresketamine concentrations were observed at 40-minute and 2-hour postdose, respectively. Furthermore, mean plasma esketamine and/or noresketamine concentrations at corresponding time points on Days 4 and 25 were comparable, which suggests that the PK was consistent throughout this period.

OL induction phase: The plasma esketamine concentrations increased with increasing doses (56 mg and 84 mg). The mean plasma esketamine concentrations were highest in samples collected at 40-minute postdose relative to the samples collected at 1- and 2-hour postdose. The mean plasma noresketamine concentration was greater in the esketamine 84 mg dose group compared to the esketamine 56 mg dose group. The mean plasma noresketamine concentrations were highest in samples collected at 1-hour postdose relative to the samples collected at 40-minute and 2-hour postdose. Furthermore, the mean plasma esketamine concentrations on Day 25 were comparable with those at corresponding time points in the DB induction phase.

BIOMARKER AND PHARMACOGENOMIC RESULTS:

The analysis of biomarker and pharmacogenomics data from this study will be reported separately.

SAFETY RESULTS:

TEAEs

Overall 33/41 (80.5%) subjects in the esketamine 28 mg group, 39/41 (95.1%) subjects in the esketamine 56 mg group, 39/40 (97.5%) subjects in the esketamine 84 mg group, and 51/ 80 (63.8%) subjects in the placebo group experienced 1 or more TEAEs during the DB induction phase. The majority of TEAEs reported during the DB induction phase were assessed as mild or moderate in severity. The most common

TEAEs (reported by $\geq 10\%$ of subjects) in the total esketamine group were: BP increased (41.0%), dissociation (37.7%), dizziness (36.1%), somnolence (27.9%), nausea (18.0%), hypoaesthesia (16.4%), vertigo (15.6%), and headache (12.3%). Overall, the TEAE profile was similar between intranasal esketamine dose groups (28-, 56- and 84 mg). The most common TEAEs (reported by $\geq 10\%$ of subjects) in the placebo group were: somnolence (17.5%), and BP increased (10.0%). There were no TEAEs leading to death during the DB induction phase. A total of 3 subjects experienced serious TEAEs during the DB induction phase. One subject in the esketamine 28 mg group experienced a serious TEAE of fracture and 1 subject each in the esketamine 84 mg and placebo groups experienced a serious TEAE of suicidal ideation. All serious TEAEs during the DB induction phase resolved except the event of fracture, which was considered as not related to intranasal study agent. The investigator considered the events of suicidal ideation as doubtful and probably related to intranasal study agent (esketamine 84 mg and placebo groups, respectively). In total, 10 subjects (1/41 [2.4%] subjects in the esketamine 28 mg group, 5/41 [12.2%] subjects in the esketamine 56 mg group, 1/40 [2.5%] subjects in the esketamine 84 mg group, and 3/80 [3.8%] subjects in the placebo group) experienced 1 or more TEAEs leading to discontinuation of intranasal study agent during the DB induction phase. The percentage of subjects reported with TEAEs leading to discontinuation of intranasal study agent was higher in the esketamine 56 mg group compared with the esketamine 28 mg and 84 mg groups. None of the subjects experienced TEAEs leading to discontinuation of oral AD medication during the DB induction phase. During the DB induction phase, 2/41 (4.9%) subjects in the esketamine 28 mg group and 3/41 (7.3%) subjects in the esketamine 56 mg group reduced or interrupted intranasal study agent due to TEAEs.

Overall, 3/27 (11.1%) subjects in the esketamine 28 mg group, 7/29 (24.1%) subjects in the esketamine 56 mg group, 5/23 (21.7%) subjects in the esketamine 84 mg group, and 13/53 (24.5%) subjects in the placebo group experienced 1 or more AEs during the DB follow-up phase. A total of 3/132 (2.3%) subjects experienced SAEs during the DB follow-up phase. One/23 (4.3%) subjects experienced SAEs of muscular weakness and cerebral disorder in the esketamine 84 mg group, which were considered as probably related to intranasal esketamine 84 mg and reported as not resolved. Two/53 (3.8%) subjects experienced SAEs in the placebo group: ankle fracture (n=1) and suicide attempt (n=1), which were considered as not related and probably related to the intranasal study agent, respectively. The outcomes of the events of ankle fracture and suicide attempt were reported as resolving and resolved, respectively. There were no deaths and AEs leading to oral AD discontinuation during the DB follow-up phase.

Overall, 6/13 (46.2%) subjects in the esketamine 28 mg group, 4/11 (36.4%) subjects in the esketamine 56 mg group, 6/17 (35.3%) subjects in the esketamine 84 mg group, and 11/27 (40.7%) subjects in the placebo group experienced 1 or more AEs during the posttreatment phase. The most common AEs (reported by $\geq 10\%$ of subjects) in the esketamine 28-, 56-, 84-mg, and placebo groups was nasopharyngitis (15.4%, 18.2%, 11.8%, and 11.1%, respectively). There were no deaths, SAEs, and AEs leading to oral AD discontinuation during the posttreatment phase.

All 48 (100%) subjects in the intranasal flexible esketamine (28-, 56- or 84 mg) treatment group experienced 1 or more TEAEs during the OL induction phase. The most common TEAEs (reported by $\geq 10\%$ of subjects) were: dissociation (64.6%), BP increased (50.0%), dizziness (43.8%), nausea (25.0%), somnolence (22.9%), headache (16.7%), feeling drunk (14.6%), and hypoaesthesia, vertigo, and sedation (12.5% each). Most TEAEs reported during the OL induction phase were assessed as mild or moderate in severity. Overall, the TEAE incidence profile was similar to that observed in the DB induction phase. There were no TEAEs leading to death during the OL induction phase. A total of 2/48 (4.2%) subjects experienced 1 or more TEAEs that were considered possibly related to the oral AD. One/48 (2.1%) subjects each experienced serious TEAE, TEAE leading to intranasal study agent discontinuation, and TEAE leading to intranasal study agent interruption during the OL induction phase. One subject experienced a serious TEAE of suicide attempt, which was considered as not related to flexible esketamine. The outcome of the event was reported as resolved.

A total of 10/48 (20.8%) subjects in the flexible esketamine group experienced 1 or more AEs during the OL follow-up phase. There were no AEs leading to death during the OL follow-up phase. A total of 2/48

(4.2%) subjects experienced SAEs during the OL follow-up phase: uterine leiomyoma (n=1) and atrioventricular block second degree (n=1), which were considered as not related to the intranasal study agent. The outcome of both events was reported as resolved. One/48 (2.1%) subjects experienced AEs leading to oral AD discontinuation during the OL follow-up phase.

Clinical laboratory Evaluation

In general, the mean changes from baseline in the laboratory values during the DB induction phase in each treatment group were not clinically relevant. The mean changes from baseline in laboratory values during the OL induction phase were not clinically meaningful. There were no SAEs due to laboratory abnormalities, and none of the abnormal laboratory results led to withdrawal of study agent. None of the markedly abnormal laboratory results were considered clinically meaningful.

Vital Signs and Physical Examinations

The mean BP values in the esketamine dose groups (28-, 56-, and 84 mg) increased at 40-minute postdose and subsequently returned close to predose values at the 1.5-hour postdose during the DB induction phase. Overall, increased pulse rate (increase ≥ 15 bpm and value ≥ 100 bpm) was observed in 15 subjects (2/41 [4.9%] in the esketamine 28 mg group, 1/41 [2.4%] subjects in the esketamine 56 mg group, 6/40 [15.0%] subjects in the esketamine 84 mg group, and 6/80 [7.5%] subjects in the placebo group), increased SBP (increase ≥ 20 mm Hg and value of ≥ 180 mm Hg) was observed only in 1/40 (2.5%) subjects in the esketamine 84 mg group, and increased DBP (increase ≥ 15 mm Hg and value of ≥ 105 mm Hg) was observed in 16 subjects (1/41 [2.4%] subjects in the esketamine 28 mg group, 5/41 [12.2%] subjects in the esketamine 56 mg group, 7/40 [17.5%] subjects in the esketamine 84 mg group, and 3/80 [3.8%] subjects in the placebo group) during the DB induction phase. No clinically significant decreases in respiratory rate were observed during the DB induction phase. Within the esketamine dose groups (28-, 56-, or 84 mg), a higher frequency of treatment-emergent abnormal increased vital signs relative to baseline was observed in the esketamine 84 mg group. A higher frequency of treatment-emergent abnormal vital signs relative to predose was observed in the esketamine 84 mg group compared with other treatment groups.

The mean BP values increased at 40-minute postdose by a similar amount and subsequently returned close to predose values at 1.5-hour postdose at each intranasal treatment day during the OL induction phase. Overall, the profile was similar between DB and OL induction phases.

ECG

There were no clinically relevant changes observed for ECG parameters during the DB induction phase and OL induction phase. None of the subjects had changes in QTcB or QTcF interval of ≥ 60 msec in either the DB or OL induction phases. None of the subjects had abnormal QRS or QT duration in either the DB or OL induction phases.

C-SSRS

At each intranasal treatment session during the DB induction phase, the majority of subjects (>75%) in all treatment groups reported a score of 0 on the C-SSRS, indicating no events of suicidal ideation or suicidal behavior. At the end point of the DB induction phase, the percentage of subjects with no suicidal ideation or behavior increased as compared with baseline in the esketamine 28 mg, 56 mg groups, and placebo group (95.1% at end point compared with 80.5% at baseline in the esketamine 28 mg group, 95.0% at end point compared with 82.9% at baseline in the esketamine 56 mg group, and 88.6% at end point compared with 75.0% at baseline in the placebo group). During the DB follow-up phase, posttreatment phase, OL induction phase, and OL follow-up phase, the majority of subjects (>84%, >86%, >79%, and >87%, respectively) reported a score of 0 on the C-SSRS, indicating no events of suicidal ideation or suicidal behavior.

CADSS

Mean total and component CADSS scores in the esketamine dose groups (28-, 56-, and 84-mg) peaked at 40-minute postdose and returned to predose values at 1.5-hour postdose on all treatment days. The results suggesting that the dissociative and perceptual change symptoms measured by the CADSS had an onset shortly after the start of the dose and resolved by 1.5-hour postdose in both the DB or OL induction phases. In DB induction phase, the highest dose of esketamine (84 mg) showed a higher peak value of CADSS. Overall, the peak value and the time course change of CADSS in the OL induction phase was similar to that of esketamine 84 mg group in the DB induction phase.

BPRS+

In the esketamine 84 mg group, the mean BPRS+ total scores peaked at 40-minute postdose and generally returned to predose values at 1.5-hour postdose during the DB induction phase. The mean BPRS+ scores were higher at 40-minute postdose and tended to return to the predose values at 1.5-hour postdose at all treatment days during the OL induction phase. These results suggest that the symptoms assessed by the BPRS+ were limited and had an onset shortly after the start of the dose and resolved by 1.5-hour postdose. The elevation in the esketamine 28 mg and esketamine 56 mg groups was minimum relative to the esketamine 84 mg group.

MOAA/S

A greater proportion of subjects in the esketamine 56 mg (5/41 [12.2%] subjects) and esketamine 84 mg groups (7/40 [17.5%] subjects) had MOAA/S score ≤ 3 at any time during the DB induction phase compared with the esketamine 28 mg (2/41 [4.9%] subjects) and placebo groups (0/80 subjects). A total of 8/48 (16.7%) subjects had MOAA/S score ≤ 3 at any time during the OL induction phase.

CGADR

The proportions of subjects in all treatment groups assessed as not ready for discharge on the CGADR at the 1-, 1.5-, 2-, and 2.5-hour time points were similar on Days 1 and 4 during the DB induction phase.

During the DB induction phase, 37.5% to 51.2%, 24.4% to 41.2%, 15.0% to 28.2%, and 77.0% to 83.1% of subjects in the esketamine 28-, 56-, 84-mg, and placebo groups, respectively, were assessed as ready for discharge (based on the CGADR) by 1-hour after intranasal dose administration. During the DB induction phase 77.5% to 90.2%, 61.0% to 79.4%, 55.0% to 70.0%, and 94.9% to 100.0% of subjects in the esketamine 28-, 56-, 84 mg, and placebo groups, respectively, were assessed as ready for discharge (based on the CGADR) by 1.5-hour after intranasal dose administration.

During the DB induction phase, the number of subjects who were assessed as not ready for discharge decreased to <11 subjects in all treatment groups by 2.5-hour postdose time points.

The proportions of subjects assessed as not ready for discharge on the CGADR at the 1-, 1.5-, 2-, and 2.5-hour time points were similar on Days 1 and 4 during the OL induction phase.

During the OL induction phase, 13.3% to 23.4% and 59.6% to 64.6% of subjects in the flexible esketamine group were assessed as ready for discharge (based on the CGADR) by 1-hour and 1.5-hour, respectively, after intranasal dose administration.

During the OL induction phase, the number of subjects who were assessed as not ready for discharge decreased to <9 subjects in all treatment groups by 2.5-hour postdose time points.

PWC-20

The changes in withdrawal symptoms assessed by the PWC-20 after cessation of treatment with intranasal study agent were consistent with the observed changes in symptoms of depression and anxiety. No clear evidence of withdrawal was observed in both the esketamine (28-, 56-, 84-mg groups) and placebo groups.

POMS-2

There were no clinically meaningful changes in the mean POMS-2 mood disturbance total scores over time in any of the treatment groups after the DB induction phase.

Pharmacokinetic/Pharmacodynamic Relationships

A low positive correlation was observed between BP (SBP and DBP) and plasma concentrations of both esketamine and noresketamine during the DB induction phase.

STUDY LIMITATIONS: As esketamine has known transient dissociative effects that are difficult to blind (the dissociative effects are not possible to mimic adequately using an active placebo), these specific treatment-emergent events could have biased the clinical site staff who observed the intranasal treatment sessions. Therefore, to ensure an unbiased efficacy evaluation, independent, remote (by telephone), blinded MADRS raters were used to assess the treatment response.

CONCLUSIONS:

- The fixed dosed intranasal esketamine (28-, 56-, 84-mg) did not demonstrate significant improvement in depressive symptoms as compared to intranasal placebo as an add-on to a continued oral AD confirmed as nonresponse in the OL prospective lead-in phase in Japanese subjects with TRD as measured by the change in the MADRS total score from baseline to the end of the 4-week DB induction phase.
- The results of secondary efficacy endpoints were consistent with the primary endpoint.
- During the posttreatment phase, approximately 77% and 80% of subjects relapsed who were remitters at the DB endpoint in the combined esketamine and placebo groups, respectively. During the posttreatment phase, approximately 84% and 67% of subjects relapsed who were responders (not in remission) at the DB endpoint in the combined esketamine and placebo groups, respectively.
- Plasma esketamine concentrations exhibited expected dose-dependent increases across the 28-, 56-, and 84-mg doses. Mean plasma esketamine and noresketamine concentrations were consistent on Days 4 and 25.
- Overall, a higher incidence of TEAEs was observed in all esketamine dose groups compared with the placebo group during the DB induction phase. The incidence of TEAEs of increased BP, TEAEs potentially suggestive of abuse, transient dizziness or vertigo during the DB induction phase were higher in the esketamine dose groups (28-, 56-, and 84-mg) as compared with the placebo group. Most of these TEAEs were mild or moderate in severity. None of the subjects experienced TEAEs of dissociation that required concomitant medications during the DB and OL induction phases. Suicidal ideation and behavior measured by C-SSRS improved in all esketamine groups and placebo group in the DB induction phase. Throughout the study, the percentage of subjects reporting suicidal ideation was similar in all esketamine groups and placebo. Transient elevation of CADSS and BP elevation in a dose-response manner immediately after intranasal administration but spontaneously resolved within a short period. Based on a review of AE, BPRS+, and CADSS data, no cases of treatment-emergent psychosis were observed in any subject in either of the intranasal esketamine dose groups during the study. In general, intranasal esketamine doses (28-, 56-, and 84 -mg) evaluated in this study appeared to be safe and tolerated in Japanese subjects with TRD and no new safety concerns were identified.