SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Finished Product	To be determined
Name of Active Ingredient(s)	JNJ-54135419 (esketamine)

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Status: Approved

Date: 1 May 2014

Prepared by: Janssen Research & Development, LLC

Protocol No.: ESKETIVTRD2001

Title of Study: A Double-blind, Double-randomization, Placebo-controlled Study of the Efficacy of Intravenous Esketamine in Adult Subjects With Treatment-resistant Depression

EudraCT Number: 2011-005992-17

NCT No.: NCT01640080

Clinical Registry No.: CR100843

Coordinating Investigator: Geert De Bruecker, MD - Psych. Instituut Zoete Nood Gods; Lede, Oost-Vlaanderen, Belgium, 9340.

Study Centers: Subjects were enrolled at 8 sites in Europe (3 in Belgium, 4 in Germany, and 1 in Poland).

Publication (Reference): None.

Study Period: 15 June 2012 to 03 June 2013

Phase of Development: 2a

Objectives:

The primary objectives of this study were:

1. To assess the efficacy of esketamine at 24 hours after dosing on Day 1, administered as a 0.40 mg/kg and 0.20 mg/kg intravenous (IV) infusion, compared with placebo in improving symptoms of depression in subjects with treatment-resistant depression (TRD), using the Montgomery-Asberg Depression Rating Scale (MADRS).
2. To investigate the safety and tolerability of esketamine IV infusion in subjects with TRD with a special attention to:
    a. Effects on dissociative symptoms using the Clinician Administered Dissociative States Scale (CADSS);
    b. Psychosis-like side effects by using a 4-item positive symptom subscale (consisting of suspiciousness, hallucinations, unusual thought content, and conceptual disorganization) of the Brief Psychiatric Rating Scale (BPRS);

c. Effects on suicidal ideation/behavior using the Columbia Suicide Severity Rating Scale (C-SSRS);

d. Effects on ventilation, heart rate, and blood pressure by continuous monitoring during the first hour after the start of the infusion;

e. Effects on cognition using the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (MGH-CPFQ).

The secondary objectives of this study were:

1. To assess the efficacy, using the MADRS, of esketamine:
   a. 0.40 mg/kg IV infusion in subjects who do not respond to esketamine 0.20 mg/kg IV infusion;
   b. 0.20 mg/kg and 0.40 mg/kg IV infusion in subjects who do not respond to placebo;
   c. 0.40 mg/kg IV infusion when administered on both Day 1 and Day 4;
   d. 0.20 mg/kg IV infusion when administered on both Day 1 and Day 4.
2. To assess the impact of esketamine IV infusion on:
   a. The change in major depressive disorder (MDD) symptoms using the Quick Inventory of Depressive Symptomatology - Self Report (QIDS-SR), 14-item ($QIDS\text{-}SR_{14}$) with a 24-hour recall period, administered once daily, and the QIDS-SR, 16-item ($QIDS\text{-}SR_{16}$) administered weekly;
   b. The severity of illness using the Clinical Global Impression - Severity (CGI-S) and the global change in MDD based on the Clinical Global Impression - Improvement (CGI-I);
   c. The severity of illness using Patient Global Impression - Severity (PGI-S);
   d. Subject perspective of global change in MDD since start of study treatment, as measured by the Patient Global Impression of Change (PGI-C).
3. To assess the proportion of responders (subjects who have a reduction in MADRS total score of >50% vs baseline on Day 2, 3, or 4 [prior to dosing]) in each of the esketamine dose groups compared to placebo.
4. To evaluate the pharmacokinetics of esketamine, administered as an IV infusion, in subjects with TRD.

Methodology: This was a multicenter, double-blind, double-randomization, placebo-controlled, multiple-dose study of esketamine IV in adults with TRD. The study consisted of 3 phases: a screening phase of up to 2 weeks, a 7-day double-blind treatment phase (Day 1 to Day 7), and a 4-week posttreatment phase (comprising an optional open-label phase lasting up to 2 weeks and a follow-up phase making up the remainder).

On Day 1 of the double-blind treatment phase (first dose), a target of 30 adults with TRD were to be enrolled and randomized at a ratio of 1:1:1 to treatment (esketamine 0.40 mg/kg, esketamine 0.20 mg/kg, or placebo IV infusion). Subjects who had a reduction in MADRS total score of >50% vs baseline on Day 2, 3, or 4 (prior to the second dose) were defined as responders. Subjects who were responders after the dose on Day 1 received the same treatment again on Day 4. For subjects who were not responders after the dose on Day 1, the following rules were applied for treatment on Day 4:

- Placebo on Day 1: re-randomization at a ratio of 1:1 to esketamine 0.40 mg/kg or esketamine 0.20 mg/kg IV infusion on Day 4.
- Esketamine 0.20 mg/kg on Day 1: treatment with esketamine 0.40 mg/kg IV infusion on Day 4.

- Esketamine 0.40 mg/kg on Day 1: treatment with esketamine 0.40 mg/kg IV infusion again on Day 4.

One week (7 days) after the end of the double-blind treatment phase (Day 14), subjects returned to the clinical site for a follow-up visit. Visits (telephone or clinic) were conducted 3 days (ie, at Day 10), 10 days (ie, at Day 17), 14 days (ie, at Day 21), 21 days (ie, at Day 28), and 28 days (ie, at Day 35) after the end of the double-blind treatment phase.

For subjects who chose it, and when agreed with the investigator, optional open-label treatment of esketamine 0.40 mg/kg (or lower when required) on Days 7, 10, 14, and 17 was made available by the sponsor. If esketamine was not well tolerated by a subject on Day 1 and/or Day 4, the dose for the optional open-label treatment could start at 0.30 mg/kg.

The interval between the first and last dose of study medication during the double-blind treatment period was 3 days. The last dose of optional open-label esketamine treatment was to be administered on or before Day 21. The total study duration for each subject was a maximum of 7 weeks. The end of study was defined as the date of the last study assessment of the last subject in the trial. An interim analysis was to be performed as needed.

Number of Subjects (Planned and Analyzed): Subjects were randomly assigned in a 1:1:1 ratio to the following Day 1 treatment groups: placebo (n=10 planned; 10 randomized and analyzed), esketamine 0.20 mg/kg (n=10 planned; 9 randomized and analyzed), and esketamine 0.40 mg/kg (n=10 planned; 11 randomized and analyzed).

Diagnosis and Main Criteria for Inclusion: Subjects eligible for this study were men and women ages 18 to 64 years (inclusive), who were medically stable and met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) diagnostic criteria for recurrent MDD, without psychotic features (DSM-IV, 296.22, 296.23, 296.32, or 296.33), based upon clinical assessment and confirmed by the Mini International Neuropsychiatric Interview (MINI). In addition, their depressive episode was required to be deemed "valid" using the State vs Trait, Assessability, Face Validity, Ecological Validity, and Rule of 3 P's (SAFER) criteria interview, which was conducted by telephone by remote, independent raters. Subjects were required to have had an inadequate response to at least 1 antidepressant in their current episode of depression and at least 1 other inadequate treatment response to an antidepressant either in their current episode or in a previous episode (ie, the subject took the antidepressant at an adequate dose and for an adequate duration), assessed using the Massachusetts General Hospital - Antidepressant Treatment Response Questionnaire (MGH-ATRQ). Subjects also had to have an Inventory of Depressive Symptomatology - Clinician-rated, 30-item ($IDS\text{-}C_{30}$) total score $\geq$34 at Screening and Day -1.

Test Product, Dose and Mode of Administration, Batch No.: Esketamine was supplied by the sponsor in a commercially available package. The vials contained 20 mL solution for injection of esketamine hydrochloride, corresponding to 5 mg free esketamine base per mL. The appropriate volume of esketamine (determined from body weight) was diluted with 0.9% sodium chloride for injection, which was supplied by the site, to achieve doses of 0.20 mg/kg or 0.40 mg/kg. Lot numbers for liquid in vial were 366065 and 366711.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo was supplied by the clinical sites as 0.9% sodium chloride injection.

Duration of Treatment: A 7-day double-blind treatment phase, and a 4-week posttreatment phase that includes an optional open-label treatment.

Criteria for Evaluation:

Efficacy: Efficacy measures included MADRS (7-day, 24-hour, 2-hour, and since last assessment recall periods), CGI-S and CGI-I, $QIDS\text{-}SR_{16}$ (7-day recall), $QIDS\text{-}SR_{14}$ (24-hour recall), QIDS-SR, 10-item

(QIDS-SR_{10}) (2-hour recall), PGI-C, PGI-S, and Safety, Tolerability, and Efficacy Preview (STEP) Interview.

Safety: Safety assessment was based on reported adverse events (AEs), clinical laboratory tests, vital sign measurements, physical examinations, electrocardiogram (ECG) assessments, pulse oximetry, C-SSRS, CADSS, BPRS, and MGH-CPFQ.

Pharmacokinetics: Venous blood samples (4 mL each to obtain approximately 1.8 mL of plasma) for measurement of plasma concentrations of esketamine and noresketamine (an esketamine metabolite) were collected on Day 1 (1 sample prior to dosing and 10 samples over 6 hours after the start of the esketamine infusion) and Day 4 (1 sample at 40 minutes after the start of the infusion). The pharmacokinetics samples were to be collected from the arm opposite to the arm being used for esketamine administration (ie, separate arms were to be used for esketamine infusion and pharmacokinetic sampling). Key analysis variables based on plasma esketamine and noresketamine concentration-time data on Day 1 included the maximum plasma concentration (C_{max}) and its observed time (t_{max}), as well as the area under the plasma concentration-time curve (AUC) from time zero to the time of the last quantifiable concentration (AUC_{last}) and the AUC from time zero extrapolated to infinite time (AUC_{∞}).

Pharmacogenomics: An optional pharmacogenomic blood sample (10 mL) was collected to allow for pharmacogenomic research, as necessary (where local regulations permitted).

Statistical Methods:

General: In addition to providing descriptive statistics (N, mean, median and range) for continuous measurements and frequency distribution for discrete measurements, model based statistical analyses were also provided. Graphical data displays and subject listings were used to summarize data. Due to the exploratory nature of this study, no adjustments for multiple testing were applied.

Sample size determination: Sample sizes of 10 per group were calculated to achieve 90% power to detect a difference of 60% in response rate (>50% reduction in MADRS total score) between each esketamine group and placebo (1-sided Fisher's exact test; 0.10 significance level), assuming 20% placebo response rate. Similarly, 10 subjects per group were calculated to achieve 90% power to detect a 40% difference in MADRS total score reduction between each esketamine group and placebo (2-sample t-test, 0.10 significance level), assuming a standard deviation (SD) of 32%.

Interim analysis: A preliminary efficacy analysis of the primary endpoint only was performed after all randomized subjects completed the double-blind treatment phase. This preliminary analysis was based on all 30 subjects planned for the study, was limited to the primary efficacy endpoint, and was performed before the final database lock was completed. The purpose of this preliminary analysis was to provide the team with the primary efficacy endpoint results in order to make an informative dose selection decision for the program.

Efficacy analysis: All the efficacy analyses were performed on the intent-to-treat analysis set. Analyses of change from baseline included only subjects who had both baseline and at least 1 postbaseline data assessment during the double-blind phase. Subjects who received an incorrect treatment (n=4) were analyzed under the planned treatment sequence. The primary efficacy analysis was also analyzed by excluding subjects who received an incorrect esketamine dose as a sensitivity analysis. Missing data (visit) were not imputed in efficacy analyses. Imputation of missing individual item scores was applied only to the MADRS.

The primary endpoint was the change in the MADRS total score from Day 1 to Day 2 (24 hours after the first infusion). A mixed-effects model using repeated measures was performed on the change from baseline in MADRS total score up to the second infusion on Day 4 (prior to dosing). The model included baseline score as covariate, and day, treatment, center and day-by-treatment interaction as fixed effects, and a random subject effect and used a unstructured variance-covariance matrix. Appropriate contrasts

were used to determine the estimated differences between each esketamine dose and placebo. The contrast on Day 2 changes was of primary interest, and tested at a 1-sided alpha level of 0.10.

Subjects who had a reduction in MADRS total score of >50% vs baseline on Day 2, Day 3, or Day 4 (prior to dosing) were considered responders. Regarding comparisons between esketamine and placebo in response rate, it may be useful and relevant to take the baseline MADRS score into consideration. Thus, the response rate in each esketamine group was compared with that in the placebo group using a logistic regression model including baseline MADRS score and treatment, although the protocol calls for exact Cochran-Mantel-Haenszel test.

RESULTS:

STUDY POPULATION:

Thirty subjects entered the double-blind phase. Placebo doses were administered to 10 subjects on Day 1; none responded to placebo, and therefore no subjects received placebo on Day 4. Esketamine doses were administered to 20 subjects on Day 1 and 30 subjects on Day 4. One subject chose to withdraw from the double-blind phase after experiencing a treatment-emergent AE (TEAE) on Day 4. Of the 29 subjects who entered the posttreatment phase, 28 completed the study (1 subject failed to return for the last 2 follow-up visits). Of the 29 subjects who entered the posttreatment phase, 26 subjects opted for open-label treatment (with all 26 participating subjects receiving at least 2 open-label esketamine doses and 21 [80.8%] of these 26 subjects receiving 4 open-label esketamine doses).

Baseline demographic characteristics (such as age, body mass index [BMI], sex, race, and ethnicity) were generally balanced among placebo, esketamine 0.20 mg/kg, and esketamine 0.40 mg/kg groups. The subjects had a mean (SD) age of 43.0 (11.59) years. The majority were women (18 [60%] of 30 subjects) and of white race (29 [96.7%] of 30 subjects).

Due to errors by the site staff, incorrect (double) doses of esketamine were administered to 4 subjects at 1 or more visits, as follows:

- 1 subject received 1 doubled active dose (the assigned esketamine 0.40 mg/kg [resulting in 0.80 mg/kg] on Day 4);
- 1 subject received 2 doubled active doses (the assigned esketamine 0.20 mg/kg [resulting in 0.40 mg/kg] on Day 1, and the assigned 0.40 mg/kg [resulting in 0.80 mg/kg] on Day 4);
- 1 subject received 3 doubled active doses (the assigned esketamine 0.20 mg/kg [resulting in 0.40 mg/kg] on both double-blind dosing days, as well as the assigned esketamine 0.40 mg/kg [resulting in 0.80 mg/kg] at 1 open-label visit);
- 1 subject received 6 doubled active doses (the assigned esketamine 0.40 mg/kg [resulting in 0.80 mg/kg] on both double-blind dosing days and at all 4 open-label visits).

Because of these dosing errors, the numbers of subjects randomized and dosed on Day 1 were as follows: placebo, 10 randomized and 10 dosed; esketamine 0.20 mg/kg, 9 randomized but 7 dosed; esketamine 0.40 mg/kg, 11 randomized but 12 dosed; esketamine 0.80 mg/kg, 0 randomized but 1 dosed. Similarly, the numbers of subjects assigned and dosed on Day 4 were as follows: placebo, 0 assigned and 0 dosed; esketamine 0.20 mg/kg, 9 assigned but 8 dosed; esketamine 0.40 mg/kg, 21 assigned but 19 dosed (of whom 1 did not complete the dose); esketamine 0.80 mg/kg, 0 assigned but 3 dosed.

For tolerability reasons, open-label doses of esketamine were lowered to 0.30 mg/kg in 1 case and 0.20 mg/kg in 2 cases.

PHARMACOKINETIC RESULTS:

The pharmacokinetics of esketamine and the metabolite noresketamine were characterized in subjects with TRD who received 0.20 mg/kg (n=7 subjects) or 0.40 mg/kg (n=12 subjects) of esketamine as a 40-minute IV infusion on Day 1. Maximum concentrations (C_{max}) of esketamine were observed at the end of the infusion (median, 0.65 or 0.67 hours). The C_{max} of noresketamine was observed later (median, 0.77 to 1 hour). All of the following mean pharmacokinetic parameters increased with an increase in the esketamine dose (0.20 and 0.40 mg/kg): esketamine C_{max} (80.9 and 135 ng/mL, respectively), esketamine AUC_{last} (126 and 196 ng·h/mL, respectively), esketamine AUC_{∞} (150 and 218 ng·h/mL, respectively), noresketamine C_{max} (29.6 and 46.2 ng/mL, respectively), and noresketamine AUC_{last} (97.2 and 178 ng·h/mL, respectively). The mean ratio of noresketamine to esketamine C_{max} was 0.36 and 0.38 for the 0.20-mg/kg and 0.40-mg/kg doses, respectively. For AUC_{last}, the mean ratios were 0.78 and 0.88, respectively.

The mean clearance of esketamine was 109 L/h and 141 L/h for the 0.20-mg/kg and 0.40-mg/kg doses, respectively. The mean volume of distribution of esketamine was 236 L and 303 L, respectively. The mean half-life of esketamine in plasma was 2.14 hours and 2.65 hours for the 0.20-mg/kg and 0.40-mg/kg doses, respectively. The mean half-life of noresketamine was 4.02 hours and 6.05 hours for the 0.20-mg/kg and 0.40-mg/kg doses, respectively.

The mean esketamine concentrations at 40 minutes after the start of the 0.20-mg/kg IV infusion were 78.5 ng/mL and 53.1 ng/mL on Days 1 and 4, respectively (n=7 subjects for each dose). The mean concentrations were 139 ng/mL (n=10 subjects) and 152 ng/mL (n=16 subjects), respectively, for the 0.40-mg/kg IV infusion.

PHARMACOGENOMIC RESULTS:

Pharmacogenomics will be reported separately.

EFFICACY RESULTS:

Efficacy analyses were performed for the 30 intent-to-treat subjects, all of whom received at least 1 dose of study medication during the double-blind phase. The 4 subjects who received incorrect esketamine doses on any study days were analyzed under the planned treatment sequence. The primary efficacy analysis was also analyzed as a sensitivity analysis by excluding the 3 subjects who received an incorrect esketamine dose on Day 1 (ie, the sensitivity analysis set represented 27 subjects).

Primary Efficacy

At Day 1 baseline, the mean (SD) score for MADRS with 7-day recall for the 30 subjects was 33.6 (4.54) out of a possible 60 (with a score of 0 representing no symptoms and a score of 60 representing the worst possible depression). That mean baseline score represents depression approximately near the moderate/severe borderline (though classifications for MADRS severity categories can vary). Baseline MADRS scores were qualitatively similar among randomization groups.

On Day 2, results for MADRS with 24-hour recall were as shown in the table below. The improvement in both esketamine dose groups was statistically significant (p=0.001 for both) when compared with the placebo group. Alternate statistical analyses of the primary efficacy outcome supported the main findings. The results also were clinically significant; they approximately represented outcomes of moderate depression for placebo but mild depression for both esketamine 0.20 and 0.40 mg/kg groups.

Montgomery-Asberg Depression Rating Scale (MADRS) Total Score and Change From Day 1 to Day 2
(Study ESKETIVTRD2001: Intent-to-Treat Analysis Set)

	Placebo	Esketamine 0.20 mg/kg	Esketamine 0.40 mg/kg	Total
Day 1 Baseline (Predose)				
N	10	9	11	30
Mean (SD)	33.9 (4.15)	33.1 (3.55)	33.7 (5.82)	33.6 (4.54)
Median	32	33	32	32
Range	(30,42)	(28,41)	(23,43)	(23,43)
Day 2				
N	10	9	11	30
Mean (SD)	29.0 (3.97)	16.3 (8.87)	15.9 (9.12)	20.4 (9.67)
Median	29.5	20	15	22
Range	(22,36)	(0,27)	(4,33)	(0,36)
Change From Baseline				
N	10	9	11	30
Mean (SD)	-4.9 (4.72)	-16.8 (10.12)	-17.8 (9.45)	-13.2 (10.09)
Median	-5.5	-12	-19	-10
LS Mean (SE)	-3.8 (2.97)	-16.8 (3.00)	-16.9 (2.61)	
P-value (minus placebo)[a]		0.001	0.001	
Difference of LS means (SE)		-12.9 (3.76)	-13.1 (3.64)	
80% Confidence interval[a]		(-17.93,-7.94)	(-17.93,-8.25)	

LS = least-squares; SD = standard deviation; SE = standard error.
[a] P-values (1-sided with level of significance of 10%) and confidence intervals (2-sided) are based on the mixed-effect model using repeated measures (MMRM) with baseline score as a covariate, and day, treatment, center and day-by-treatment interaction as fixed effects, and a random subject effect.
Cross-reference: Attachment TEFMAD01 (20AUG2013, 13:36).

Secondary Efficacy

After the first infusion, the following proportions were MADRS responders (defined as a reduction in MADRS total score of >50% from baseline to Day 2, 3, or 4 [prior to dosing]): 0 of 10 subjects in the placebo group, 6 (66.7%) of 9 subjects in the esketamine 0.20 mg/kg group, and 7 (63.6%) of 11 subjects in the esketamine 0.40 mg/kg group. The response rates were statistically significantly greater in both esketamine dose groups ($p \leq 0.0143$ for both odds ratios) when compared with the placebo group.

Since none of the 10 placebo subjects responded on Day 1, they were re-randomized for the next dose (on Day 4): 3 subjects were assigned to esketamine 0.20 mg/kg and 7 subjects were assigned to esketamine 0.40 mg/kg. Since 3 of the 6 subjects in the esketamine 0.20 mg/kg group did not respond on Day 1, they were assigned to esketamine 0.40 mg/kg on Day 4.

For all of the following measures of change in MDD symptoms, posttreatment time points showed strong mean or median esketamine efficacy outcomes (versus placebo where relevant) but no clear dose dependence:

- MADRS outcomes from Day 1 to Day 4 and from Day 4 to Day 7 indicated durable efficacy of esketamine (lasting for days) and showed that nonresponders to lower doses or placebo on Day 1 improved after receiving higher doses or initial active doses (respectively) on Day 4.
- MADRS outcomes from Day 1 to Day 35 indicated durable efficacy of esketamine (lasting for weeks).
- QIDS-SR_{14} outcomes from Day 1 to Day 4 and from Day 4 to Day 7 indicated durable efficacy of esketamine (lasting for days).

- QIDS-SR_{16} outcomes from Day 1 to Day 14 indicated durable efficacy of esketamine (lasting for days), though results were complicated by baseline differences among treatment sequences.
- CGI-S, CGI-I, PGI-S, and PGI-C outcomes from Day 1 to Day 7 indicated durable efficacy of esketamine (lasting for days) from the perspectives of both clinicians and subjects.

Exploratory Efficacy

- Change from predose to 2 and 4 hours postdose on Day 1 and 4 in MDD symptoms using the MADRS and the QIDS-SR_{10} indicated rapid onset of efficacy (ie, within hours).
- Remission, defined as a MADRS score of 10 or less, was recorded for 17 (60.7%) of 28 subjects on Day 28 (ie, 1 week after the last optional open-label dose) and 14 (51.9%) of 27 subjects on Day 35 (ie, 2 weeks after the last optional open-label dose), indicating strong and durable efficacy of esketamine.
- In exploration of subjects' experience with esketamine on Day 7, using the STEP interview, many positive health changes were reported (eg, improved mood, increase in activities, improved thinking/cognition, increased energy), and most subjects indicated they would have interest in continuing to take the study medication.

SAFETY RESULTS:

Treatment-emergent Adverse Events

Summaries of TEAEs and other safety data are based on the 30 subjects who received at least 1 dose of study medication and who contributed any safety data after the start of study treatment (ie, the safety analysis set). Safety analysis sets by phase represented 30 double-blind subjects, 26 open-label subjects, 30 subjects in the combined double-blind and open-label phases, and 28 subjects in the follow-up phase.

During the overall double-blind phase (Day 1 to Day 7, during which period all subjects received at least 1 dose of esketamine), no deaths occurred, no SAEs occurred, 1 subject discontinued (after a TEAE of substance-induced psychotic disorder), and TEAEs were reported for 25 (83.3%) of 30 subjects. From Day 1 to predose on Day 4 (the only study period with placebo subjects),

- The overall frequency of all TEAEs considered together showed some evidence of dose dependence, as follows: 5 (50.0%) of 10 placebo subjects, 6 (66.7%) of 9 subjects in the esketamine 0.20 mg/kg group, and 9 (81.8%) of 11 subjects in the esketamine 0.40 mg/kg group.
- The only TEAEs reported for more than 1 placebo subject were nausea and headache; these did not show clear evidence of dose dependence in the esketamine groups. Other than headache and nausea, the only TEAEs reported for more than 1 subject who received esketamine were dry mouth, dissociation, and dizziness; low frequency of these individual TEAEs limited assessment of dose dependence.
  - Nausea was reported in 2 (20.0%) of 10 placebo subjects, 3 (33.3%) of 9 subjects in the esketamine 0.20 mg/kg group, and 1 (9.1%) of 11 subjects in the esketamine 0.40 mg/kg group.
  - Headache was reported in 2 (20.0%) of 10 placebo subjects, 2 (22.2%) of 9 subjects in the esketamine 0.20 mg/kg group, and 3 (27.3%) of 11 subjects in the esketamine 0.40 mg/kg group.
  - Dry mouth, dizziness, and dissociation did not occur in any of the 10 placebo subjects, but was reported in esketamine groups as follows:
    - Dry mouth in 1 (11.1%) of 9 subjects in the esketamine 0.20 mg/kg group and 1 (9.1%) of 11 subjects in the esketamine 0.40 mg/kg group.

- Dizziness in 1 (11.1%) of 9 subjects in the esketamine 0.20 mg/kg group and 1 (9.1%) of 11 subjects in the esketamine 0.40 mg/kg group.
- Dissociation in 1 (11.1%) of 9 subjects in the esketamine 0.20 mg/kg group and 2 (18.2%) of 11 subjects in the esketamine 0.40 mg/kg group.

During the open-label phase, no deaths, SAEs, or discontinuations due to TEAEs were reported. Treatment-emergent AEs were reported for 13 (50.0%) of 26 subjects and most commonly were headache (in 4 [15.4%] of 26 subjects) and dissociation (in 3 [11.5%] of 26 open-label subjects).

During the follow-up phase, the only TEAEs reported in more than 1 subject were headache (3 [10.7%] of 28 subjects), nausea (2 [7.1%] of 28 subjects), and constipation (2 [7.1%] of 28 subjects). One subject had 2 SAEs, both in the system organ class of neoplasms benign, malignant and unspecified (including cysts and polyps); these were assessed by the investigator as not related to study medication.

All TEAEs during the study had mild or moderate intensity, with 3 exceptions; the aforementioned 1 subject with substance-induced psychotic disorder that led to discontinuation, the aforementioned 1 subject with SAEs (neoplasms), and 1 subject with 1 hour and 45 minutes of dissociation associated with esketamine 0.40 mg/kg treatment.

Clinical Laboratory Tests (Hematology, Serum Chemistry, and Urinalysis)

No clinically significant changes in laboratory tests were observed.

Physical Examinations, Vital Signs, Electrocardiograms, and Pulse Oximetry

From screening to Day 7, mean changes for weight, BMI, ECGs, and all vital signs had standard deviations that overlapped with zero change, with no clear evidence of dose dependence for any parameter. Heart rate was normal in all but 3 subjects (representing elevations versus baseline of ≥15 bpm to 103, 104, and 105 bpm). Treatment-emergent ECGs that met prespecified abnormality criteria were observed in 3 subjects but were interpreted by the study sites as normal or as abnormal but not clinically significant.

For vital signs, ECGs, and pulse oximetry monitored continuously starting 5 minutes before an infusion through 1 hour after the start of the infusion, the only treatment-emergent abnormalities described as clinically significant were a case of irregular breathing and a case of transient high blood pressure, both of which were reported with esketamine 0.40 mg/kg. No respiratory depression was reported.

Columbia Suicide Severity Rating Scale (C-SSRS)

During the combined double-blind and open-label phases, C-SSRS results indicated that no subjects had suicidal behavior or self-injurious behavior without suicidal intent. Suicidal ideation scores either improved or were maintained from screening through the open-label phase for all but 1 subject, whose C-SSRS scores fluctuated between improvement and worsening at various time points, but ultimately returned to be similar to baseline at the last measurement point.

Clinician Administered Dissociative States Scale (CADSS)

For the 10 placebo subjects, mean CADSS scores were less than 1 (range, 0 to 3) of 92 possible at all relevant time points. In esketamine groups, maximum mean CADSS scores were observed at 40 minutes after the start of the infusion and showed some evidence of dose dependence on each dosing day and of habituation over the course of the 2 double-blind dosing days. On Day 1, maximum mean (SD) values were 15.56 (24.653) for the 9 subjects in the esketamine 0.20 mg/kg group and 22.00 (9.192) for the 9 subjects in the esketamine 0.40 mg/kg group. On Day 4, maximum mean (SD) values were 6.38 (7.963) for the 8 subjects assigned to esketamine 0.20 mg/kg and 15.67 (13.932) for the 15 subjects assigned to esketamine 0.40 mg/kg. For both days considered together, the majority of subjects (≥50%) experienced

dissociative symptoms that were "medium" severity with esketamine 0.20 mg/kg and were "high" or "medium" severity with esketamine 0.40 mg/kg.

Overall, CADSS score increases generally subsided and resolved at 4 hours after the start of the infusion.

Brief Psychiatric Rating Scale (BPRS)

For the 10 placebo subjects, BPRS scores were ≤2 of 24 possible at all relevant time points. In esketamine groups, maximum mean and median BPRS scores were observed at 30 to 40 minutes after the start of the infusion and showed some evidence of dose response. On Day 1, the median BPRS scores indicated minimal psychosis-like symptoms, with medians of 0 (range, 0 to 8) at all time points for the 9 subjects in the esketamine 0.20 mg/kg group and a maximum median of 3 (range, 0 to 10) for 9 subjects in the esketamine 0.40 mg/kg group. Overall, BPRS score increases generally subsided and resolved at 2 to 4 hours after the start of the infusion.

Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (MGH-CPFQ)

On Day 1 baseline, mean MGH-CPFQ scores in all treatment sequences ranged from 28.6 to 31.6, where 42 was the worst possible score. On Days 2 and 4 versus Day 1 baseline, subjects in placebo sequences and subjects classified as nonresponders by MADRS criteria to esketamine 0.20 mg/kg had the smallest changes in mean MGH-CPFQ scores and had standard deviations that overlapped with zero change. The 6 subjects classified as responders to esketamine 0.20 mg/kg and the 11 subjects assigned to esketamine 0.40 mg/kg exhibited mean improvements in MGH-CPFQ scores ranging from -8.1 to -10.5 units.

On Day 5 versus Day 4 baseline, the largest MGH-CPFQ improvements were observed in subjects who were switched from placebo to active treatment (means of -5.0 to -5.7 units); changes in MGH-CPFQ were smaller and had standard deviations that overlapped with zero change for subjects in all other treatment sequences.

Overall, cognitive function appeared to improve during the study.

STUDY LIMITATIONS:

The small number of subjects limited assessment of safety and efficacy in the study. It was a proof-of-concept study that did not provide the full dose-response range (ie, doses of esketamine even lower than 0.20 mg/kg might be efficacious).

CONCLUSION(S):

In these 30 subjects with TRD, doses of esketamine 0.20 mg/kg and 0.40 mg/kg administered intravenously over 40 minutes were similarly efficacious by various measures, including the primary efficacy measure versus placebo at 1 day after the first dose. Some evidence from 3 of the safety and tolerability measures (CADSS scores, BPRS scores, and overall frequency of TEAEs) suggested slightly better outcomes with the 0.20 mg/kg dose than the 0.40 mg/kg dose. One subject had interrupted therapy during an infusion of esketamine 0.40 mg/kg and then discontinued participation in the trial due to onset of psychosis. While efficacy had rapid onset (within hours) and was durable (for days or weeks), questionnaire measures of dissociation and psychosis indicated only transient effects (for hours). Esketamine at 0.20 and 0.40 mg/kg was generally well tolerated compared with placebo.

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