SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Investigational Product	JNJ-54135419 (esketamine)

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Title of Study: A Placebo- and Active-Controlled Study to Evaluate the Effects of a Single-Dose and Repeat-Administration of Intranasal Esketamine on On-Road Driving in Subjects With Major Depressive Disorder (DriveSaFe2)

EudraCT Number: 2016-002424-86

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Publication (Reference): None

Study Period: 18 October 2016 to 01 March 2018 (data cut-off date), study is ongoing

Phase of Development: 1

Objectives:

Primary Objective

To evaluate the effect of a single 84-mg dose of intranasal esketamine compared to placebo, on next day driving performance and repeated administration of 84 mg intranasal esketamine on same-day driving performance as assessed by the mean difference of standard deviation of lateral position (SDLP) from an on-road driving test.

Secondary Objectives

The secondary objectives are:

To evaluate the effect of esketamine on:

- Subjective driving ability and mental effort scale
- Karolinska Sleepiness Scale (KSS)
- Efficacy measured by the Montgomery Asberg Depression Rating Scale (MADRS)
- Safety and tolerability with special attention to:
  a. Effects on suicidal ideation/behavior measured by the Columbia Suicide Severity Rating Scale (C-SSRS)
  b. Effects on dissociative symptoms using the clinician-administered dissociative states scale (CADSS)
- To evaluate the potential relationship between changes in driving performance and the plasma concentration of esketamine and noresketamine.

Methodology:

This was a placebo- and active-controlled study in men and women with major depressive disorder (MDD) consisting of 2 parts. Part A was a single-blind, double-dummy, placebo-controlled, randomized, 3-period, and crossover in design evaluating the effect of a single 84-mg dose of intranasal esketamine, compared to placebo, on next day driving performance. Oral ethanol was used in Part A as a positive control for assay sensitivity. Part B was open-label, placebo-controlled, fixed sequence, and consisted of a single period. assessing repeated administration of 84 mg intranasal esketamine on same-day driving performance.

Up to 30 subjects (22 to 60 years of age, inclusive) were to be enrolled. The minimum number of subjects that were to complete the study was 24, including at least 9 males and 9 females.

The total duration of the study was up to 98 days. This included a screening period of 21 days, a Part A consisting of three 2-day periods with 5 to 14 days of washout between each study drug administration, a Part B consisting of 25 days. Five to 14 days separated between the last dose of the study drug in Part A and the first dose of the study drug in Part B. End-of-study (EOS) procedures took place 7 to 10 days after the last dose in Part B.

Screening Phase (Day -21 to Day -1)

Subjects were screened within 21 days prior to Day 1 of Period 1 of Part A to ascertain their eligibility for the study according to the inclusion and exclusion criteria. During screening, subjects practiced driving in the same car used for the on-road driving tests in the Treatment Phase and intranasal administration using a placebo device. In the evening before the driving practice, subjects slept in the same facilities as during treatment conditions in Part A and B.

Treatment Phase

Eligible subjects were randomly assigned to 1 of the 6 treatment sequences and received all 3 treatments (1 treatment in each period, as described below). A 5- to 14-day washout period separate each treatment in Part A.

Treatment sequences in Part A

Sequence	Period 1	Period 2	Period 3
1	Treatment A	Treatment B	Treatment C
2	Treatment B	Treatment C	Treatment A
3	Treatment C	Treatment A	Treatment B
4	Treatment C	Treatment B	Treatment A
5	Treatment A	Treatment C	Treatment B
6	Treatment B	Treatment A	Treatment C

Intranasal study drug was administered on Day 1 of each period. A pharmacokinetic (PK) sample was collected 1 hour after dosing. The driving test was conducted on Day 2 at 18±2 hours after intranasal administration on Day 1. Oral ethanol or placebo was administered 45 minutes before the scheduled start of the driving test on Day 2. In the period during which oral alcohol was administered, the driving test started immediately after it was demonstrated, based on results of 2 or more assessments, the blood alcohol concentration (BAC) were either stable or in decline with the last assessment ≤235 µg/L in breath (which correlates to 0.05% weight/volume [w/v] in blood), approximately 45 minutes after ingestion of the oral dose began).

Description and Timing in Part A

Treatment A	• Day 1: Intranasal placebo in afternoon • Day 2: Oral placebo in morning
Treatment B	• Day 1: Intranasal placebo in afternoon • Day 2: Oral alcohol in morning
Treatment C	• Day 1: Intranasal esketamine in afternoon • Day 2: Oral placebo in morning

Note: For each treatment, on-road driving took place on Day 2 after administration of oral study drug

There was no randomization in Part B; all subjects received the same treatments in the same order. A 5- to 14-day washout period separated the last treatment in Part A and the first treatment in Part B. Subjects who had completed Part A of the study also participated in Part B.

Subjects were admitted to the clinical unit on Days 1, 4, 8, 11, 15, 18, 22, and 25 for a series of assessments according to the Time and Events Schedule of the protocol. Subjects received intranasal placebo in the morning of Day 1 and intranasal esketamine in the morning of Days 4, 8, 11, 15, 18, 22, and 25. On-road driving took place on Days 1, 11, 18, and 25. A time window of +/- 1 day for Days 4 through 25 was permitted.

End-of-Study or Early Withdrawal Phase

Safety and tolerability was assessed from the time of consent until the end of the study (EOS). Seven to 10 days after last dose administration or after early withdrawal, all subjects returned to the clinical unit for a follow-up visit. The procedures to be completed during the follow-up visit are listed in the Time and Events Schedule of the protocol.

Number of Subjects (planned and analyzed):

Planned: Thirty subjects were to be enrolled initially. The minimum number of subjects that were to complete the study was 24, including at least 9 males and 9 females.

Analyzed: A total of 23 subjects were enrolled in Part A of the study and received at least one dose of the study drug. Twenty subjects who were enrolled in Part A continued to participate in Part B of the study.

Overall, a total of 18 subjects completed the study participation, while 1 subject enrolled in study sequence ABC was ongoing during the cut-off date.

Diagnosis and Main Criteria for Inclusion:

Thirty male or female subjects with MDD between 22 and 60 years of age (inclusive) but without psychotic features, based upon clinical assessment and as confirmed by the Mini International Neuropsychiatric Interview (MINI), a MADRS score of ≥18 at screening, a body mass index (BMI) between 18 and 32 kg/m² (inclusive) and body weight not less than 50 kg, possessing a valid driving license in good standing for more than 60 months and has driven regularly in the past year, and by self-report able to consume an amount of alcohol that typically produces a BAC of 0.05% were eligible for enrollment into the study. Subjects suffering from primary sleep disorder, those who had consumed more than 21 alcoholic drinks per week in the month prior to the Screening visit, or were of Japanese origin were excluded from the study.

Test Product, Dose and Mode of Administration, Batch No.:

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

A placebo solution was used to practice intranasal administration during screening and during the treatment phase (Parts A and B). It was provided as a clear, colorless intranasal solution of 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 solution with active drug. Benzalkonium chloride was added as a preservative at a concentration of 0.3 mg/mL.

The study agent with batch lot numbers 502264, 502228, 160663, and 161330 were used during the study.

The dose of oral ethanol was prepared by mixing the appropriate volume of ethanol with sugar-free orange juice up to a final volume of 250 mL and was blinded by adding a taste masker (menthae piperitae aetheroleum, Ph. Eur.). The placebo beverage was also prepared with sugar-free orange juice up to a volume of 250 mL and was blinded by adding the same taste marker.

Duration of Treatment:

In Part A, intranasal esketamine or placebo (according to the sequence to which the subject was randomized) was administered on Day 1 of each period as follows: each 28-mg dose of esketamine was self-administered as 2 sprays (one 100-µL spray into each nostril in rapid succession) at Time 0, 5, and 10 minutes for a total of 84 mg. Oral ethanol or placebo were administered 45 minutes before the scheduled start of the driving test on Day 2.

The subjects consumed the chilled beverage (ethanol or placebo) within 15 minutes. Blood alcohol measurements were performed using a breathalyzer every 5 minutes beginning at 25 minutes after the start of oral administration.

Subjects received a dose of ethanol to achieve an initial targeted BAC of 0.055% [w/v] (which correlates to approximately 239 µg/L in breath). The driving test started immediately after it was demonstrated, based on results of 2 or more assessments, that the BAC was either stable or in decline with the last assessment ≤ 235 µg/L in breath, approximately 45 minutes after ingestion of the oral dose began. The BAC was also measured using a breathalyzer immediately after completion of the driving test.

The driving test started approximately 45-75 minutes after the start of oral dosing of the placebo beverage. A blood alcohol level measurement was performed using a breathalyzer at 25 minutes after the start of oral administration and every 5 minutes thereafter until 30-60 minutes after ingestion of the oral placebo was completed. The BAC was also measured using a breathalyzer immediately after completion of the driving test.

In Part B, intranasal placebo (1 spray of placebo solution in each nostril at Time 0, 5, and 10 minutes) was administered in the morning on Day 1. Intranasal esketamine was administered in the morning on Days 4, 8, 11, 15, 18, 22, and 25. The driving test started 6 hours after administration of intranasal placebo or esketamine on the scheduled study days.

In Parts A and B, study drug was administered at least 2 hours after any food intake. Fluid consumption was restricted for at least 30 minutes before the first nasal spray of study drug. Subjects were instructed to refrain from blowing their nose for at least 1 hour after the last intranasal spray. In general, subjects were only served standard institutional meals and breakfast during confinement and could resume their normal diet thereafter.

Criteria for Evaluation:

Pharmacokinetics:

Part A: A blood sample was collected 1 hour post dose for measurement of esketamine and noresketamine concentrations in plasma on Day 1 of each period. Blood alcohol levels were measured using a breathalyzer prior to the driving test and after performing the driving test on Day 2.

Part B: Blood samples were collected at 1 hour post dose on Days 11, 18, and 25 for measurement of esketamine and noresketamine concentrations in plasma.

Pharmacodynamics:

On-the-road driving test

Subjects participated in validated on-road car driving tests. SDLP was a primary outcome variable and standard deviation of speed (SDS, km/h) was a secondary variable. Mean lateral position (MLP, +/- cm), and mean speed (MS, km/h) were control variables.

In Part A, a single nasal spray was performed on Day 1 and the driving test was performed on the next day (Day 2, 18 ± 2 hours). In the period during which oral alcohol was administered, the driving test started immediately after it was demonstrated, based on results of 2 or more assessments, the BAC was either stable or in decline with the last assessment ≤ 235 µg/L in breath (which correlated to 0.05% [w/v] in blood), approximately 45 minutes after ingestion of the oral dose begins).

In Part B, driving on the primary highway circuit started 6 hours after intranasal administration of placebo on Day 1 and 6 hours after esketamine nasal spray administration on Days 11, 18, and 25.

Other Evaluations**:**

Karolinska Sleepiness Scale, subjective assessments of driving performance, and pharmacogenomics (blood sample for DNA analysis of *CYP2B6*).

Efficacy Evaluations:

Montgomery Asberg Depression Rating Scale (MADRS, 7-day recall and since last assessment -24 hours recall). The MADRS was performed according to the time points provided in the Time and Events Schedule of the study protocol.

Safety Evaluations:

Reported adverse events (AEs), clinical laboratory tests, 12-lead electrocardiograms (ECGs), vital signs, physical examinations including weight. Other safety evaluations included C-SSRS to assess suicidal ideation and behavior, and the CADSS to assess treatment-emergent dissociative symptoms.

Statistical Methods:

Sample size:

The sample size and power estimation was based upon the SDLP, the primary endpoint of the study. The estimate of within-subject standard deviation (SD) in a crossover for the SDLP of 1.72 cm was obtained from ESKETINTRD1006. However, a slightly higher SDLP of 2.1 cm was used for the present study based on literature.

A non-inferiority margin of 2.4 cm in SDLP (associated with a BAC of 0.05%) that is considered clinically relevant was used for the power calculation. The true difference in SDLP between the active (esketamine) and placebo was assumed to be 0.63 cm. The intra-subject SD for SDLP was assumed to be 2.1 cm. A conservative value for the SD of 2.97 cm for paired difference between active and placebo was used for the calculation of sample size in the study.

Part A: With two-sided significance level of 0.05 (one-sided level of 0.025) for each comparison and an SD of 2.97 cm for paired differences, a sample size of 24 subjects was sufficient to achieve an 80% power to detect non-inferiority of each treatment (esketamine or alcohol) to placebo when the non-inferiority margin is 2.4 cm and the true difference between each treatment and placebo is 0.63 cm.

Part B: With two-sided significance level of 0.05 (one-sided level of 0.025) for comparison of esketamine to placebo on each day of driving test and an SD of 2.97 cm for paired differences, a sample size of 24 subjects was sufficient to achieve an 80% power to detect non-inferiority of esketamine to placebo on each driving day when the non-inferiority margin is 2.4 cm and the true difference between the active (esketamine) and placebo is 0.63 cm.

Subjects who withdraw from the study were to be replaced in order to have the requisite 24 subjects who complete the study. Subjects were to be enrolled to participate in only Part B to ensure that 24 subjects complete this part of the study.

Pharmacokinetic

Blood alcohol levels measured by breathalyzer were listed by subjects and summarized using descriptive statistics. The concentration of esketamine and noresketamine in plasma samples collected in Part A and Part B were listed by study day and summarized using descriptive statistics.

Pharmacodynamic

All subjects who received at least 1 dose of study drug were included in the pharmacodynamic (PD) analyses. No adjustments were made for multiplicity testing in Parts A and B.

Part A: The statistical analysis of SDLP was conducted using a mixed effects model with treatment, sequence, and period as fixed effects, and subjects as a random effect. Pairwise comparisons between active treatments and placebo (esketamine vs. placebo, and alcohol vs. placebo) were conducted. The non-inferiority of esketamine compared to placebo was concluded if the upper limit of two-sided 95% confidence interval (CI) of the mean difference between the active (esketamine) and placebo was <2.4 cm. Assay sensitivity was established if lower limit of two-sided 95% CI of mean difference between alcohol and placebo was >0 cm.

Part B: The statistical analysis of SDLP was conducted using a mixed effects model with day of driving as fixed effect, and subject as a random effect. Pairwise comparisons between active treatments and placebo on each day of driving were conducted. For the SDLP, non-inferiority between treatments were concluded if the upper limit of two-sided 95% CI of the mean difference between the active (esketamine) and placebo was <2.4 cm.

In addition, summary of descriptive statistics and graphical representation of the SDLP, SDS, MLP, and MS, and subjective driving assessments, and KSS in Parts A and B were provided.

Pharmacogenomic

Allele and genotype frequencies were tabulated. No formal statistical tests were performed. Results of the pharmacogenomic analysis were to be listed and summarized with other clinical studies in a separate pharmacogenomics report.

Efficacy

Montgomery Asberg Depression Rating Scale (MADRS)

The MADRS total score and change from baseline were listed and summarized for each visit and timepoint. The MADRS at predose on Day 1 of Part A and Part B were the baseline for Part A and Part B respectively.

Safety

All subjects who received at least 1 dose of the study drug were included in the safety and tolerability analysis. Safety was evaluated by examining the incidence and type of AEs, changes in clinical laboratory test values, 12-lead ECGs, physical examination results, and vital signs measurements from the Screening Phase through study completion. Data from the safety assessments, including the CADSS and C-SSRS, were summarized descriptively.

RESULTS:

STUDY POPULATION:

A total of 23 subjects were randomized to 1 of the 6 study sequences in Part A and received at least one dose of the study drug. Twenty subjects who were enrolled in Part A continued to participate in Part B of the study. Of these,18 subjects completed Part B. Overall, a total of 18 subjects completed Part A and B of the study, while 1 subject enrolled in study sequence ABC was ongoing when the study reached the cut-off date. Part A of the study had more females (16 subjects, 69.6%) than males (7 subjects, 30.4%),

majority of subjects were white (21 subjects, 91.3%) and all (23 subjects, 100.0%) were of non-Hispanic or -Latino ethnicity, with mean (SD) age of 37.1 (10.61) years. Part B of the study also had more females (14 subjects, 70.0%) than males (6 subjects, 30.0%), majority of subjects were white (18 subjects, 90.0%) and all (20 subjects, 100.0%) were of non-Hispanic or -Latino ethnicity, with mean (SD) age of 36.8 (10.84) years. The mean (SD) MADRS scores for Part A at baseline (Period 1, Day 1, predose assessment) were 22.9 (5.75), 21.6 (6.67), and 24.1 (4.84) for Treatment A, Treatment B, and Treatment C, respectively. During Part B of the study, the mean (SD) MADRS as baseline (Day 1, predose assessment) was 21.2 (6.69).

PHARMACOKINETIC RESULTS:

The mean (SD) concentrations of esketamine and noresketamine in plasma collected at 1 hour post dose (Treatment C) were 109 (31.2) ng/mL and 93.9 (71.8) ng/mL, respectively. The mean (SD) concentrations of ethanol in blood in the morning of Day 2 (Treatment B) assessed by breath analyzer immediately before the beginning of the driving test and after completion of the driving test were 9.97 (0.578) mmol/L and 4.11 (0.996) mmol/L, respectively. The mean values expressed as g/dL (using a molecular weight for ethanol of 46.07 g/mol) were 0.046 and 0.019, respectively.

PHARMACODYNAMIC RESULTS

On-the-road driving test

Pharmacodynamic results (next day on-the-road driving test) for Part A (only) are summarized based on the data that was available by the cutoff date for interim analysis. The results from an interim analysis of driving performance (n=21 subjects for esketamine and placebo and n=22 subjects for ethanol) in Part A are provided below.

Standard Deviation of Lateral Position (SDLP): Ethanol significantly impaired driving performance when compared to placebo. The difference in mean SDLP (LS mean) between ethanol and placebo was +1.88 cm The lower limit of the two-sided 95% confidence interval of the mean difference between ethanol and placebo was 0.99 cm (>0 cm) ($p<0.001$), establishing assay sensitivity. There were no statistically significant differences between ethanol and placebo on the other measures of driving performance ie, SDS, MLP, or MS (p=0.077, 0.436, and 0.601, respectively).

The difference in mean SDLP (LS mean) between esketamine and placebo was -0.22 cm which was not statistically different as the upper limit of the two-sided 95% CI of the mean difference between the treatments was 0.70 cm (p=0.655). This upper limit is less than the pre-specified non-inferiority margin of 2.4 cm. There were no statistically significant differences between the treatment with esketamine and placebo on the other measures of driving performance ie, SDS, MLP, or MS (p=0.180, 0.854, and 0.183, respectively).

Secondary Endpoints: Driving performance was also assessed in subjects using the Perceived Driving Quality Scale and Perceived Efforts Scale (subject-reported assessment on a scale of 0 [‘I drove exceptionally poorly’] to 20 [‘I drove exceptionally well’] and around a midpoint of ‘I drove normally’). Secondary endpoints between the active treatments (ie, esketamine or ethanol) and placebo were not statistically significant.

Driving Test Results on the Day after Administration of 84 mg Esketamine Nasal Spray or Immediately after Ingestion of Oral Ethanol Solution Compared to Placebo

	Least Squares Mean (95% CI for the Difference in Least Squares Mean) Difference of LS Means; p-value		
	Esketamine vs Placebo	Ethanol vs Placebo	
	Esketamine	Ethanol	Placebo
On-the-Road Driving Test			
Standard deviation of lateral position	19.31 (-1.11; 0.70) -0.20; 0.655	21.39 (0.99; 2.77) 1.88; <0.001	19.51
Standard deviation of speed	2.57 (-0.08; 0.39) 0.16; 0.180	2.61 (-0.02; 0.44) 0.21; 0.077	2.41
Mean lateral position	6.67 (-2.27; 2.73) 0.23; 0.854	7.39 (-1.50; 3.41) 0.95; 0.436	6.44
Mean speed	97.30 (-0.18; 0.93) 0.37; 0.183	97.07 (-0.41; 0.69) 0.14; 0.601	96.93
Subjective Driving Assessment			
Perceived driving quality scale	9.86 (-1.56; 2.63) 0.54; 0.607	9.19 (-2.23; 1.96) -0.14; 0.895	9.32
Perceived effort scale	6.43 (-1.64; 0.96) -0.34; 0.598	6.60 (-1.54; 1.19) -0.17; 0.800	6.77

Note: P-values (2-sided with level of significance of 5%) and CIs (2-sided) were based on the mixed-effect model with treatment, period, gender, and sequence as fixed effects, and subject within sequence as a random effect.

Karolinska sleepiness scale

The KSS is a subject-reported assessment used to rate sleepiness on a scale of 1 to 9, ranging from 'extremely alert' (1) to 'very sleepy, great effort to keep awake, fighting sleep (9). Results of the KSS are summarized in the tables below. In Part A, mean sleepiness scores were higher prior to the start of driving for the alcohol and esketamine treatments, relative to placebo. Smaller differences in mean scores between the active treatments (Treatment B and Treatment C) and placebo (Treatment A) were observed at completion of the on-road driving test. Across all groups, an overall increase in sedation was reported following 1-hour of on-road driving.

During Part B of the study, subjects after esketamine treatment reported similar means over time at 6 and 7 hours compared to placebo.

Summary of Karolinska Sleepiness Scale (KSS) by Treatment for Part A

Parameter/ Part/ Treatment/ Time point	N	Mean	SD	Median	Range
Sleepiness					
Part A					
IN Placebo + Oral Placebo					
Day 1, 18h (Day 2)	21	3.9	1.55	3.0	(2; 7)
Day 1, 19h (Day 2)	21	6.0	2.07	7.0	(3; 9)
IN Placebo + Oral Alcohol					
Day 1, 18h (Day 2)	20	4.9	1.41	5.0	(3; 8)
Day 1, 19h (Day 2)	19	5.8	1.84	6.0	(3; 9)
IN Esketamine 84 mg + Oral Placebo					
Day 1, 18h (Day 2)	22	4.7	1.98	4.5	(2; 8)
Day 1, 19h (Day 2)	21	5.7	2.22	6.0	(3; 9)

Summary of Karolinska Sleepiness Scale (KSS) by Treatment for Part B

Parameter/ Treatment/ Time point	N	Mean	SD	Median	Range
IN Placebo					
Day 1, 6h	20	4.1	2.21	3.0	(1; 8)
Day 1, 7h	20	4.9	2.07	4.5	(2; 9)
IN Esketamine 84 mg					
Day 11, 6h	18	5.0	2.00	4.5	(3; 8)
Day 11, 7h	18	5.2	1.86	4.5	(3; 8)
Day 18, 6h	19	4.5	1.90	3.0	(2; 8)
Day 18, 7h	17	5.2	1.94	5.0	(2; 8)
Day 25, 6h	18	5.0	1.81	5.5	(2; 8)
Day 25, 7h	17	5.1	2.15	5.0	(2; 8)

PHARMACOGENOMIC RESULTS

The results for pharmacogenomics analysis for polymorphism and allele of *CYP2B6* genotype are listed and summarized in a separate pharmacogenomics report

EFFICACY EVALUATION

Montgomery Asberg Depression Rating Scale (MADRS)

The MADRS 24-hr recall was used to assess efficacy. Part A was a cross-over design with efficacy as a secondary objective in this study. The mean (SD) MADRS scores for Part A at baseline (Period 1, Day 1, predose assessment) were 22.9 (5.75), 21.6 (6.67), and 24.1 (4.84) for Treatment A, Treatment B, and Treatment C, respectively. During Part A of the study, the mean (SD) change from baseline in MADRS (24-hr recall) on Day 2 were:

- -11.0 (4.76) for 84 mg esketamine nasal spray+oral placebo
- -7.5 (5.29) for intranasal placebo +oral placebo
- -8.3 (6.19) for intranasal placebo +oral alcohol

During Part B of the study, the mean (SD) MADRS at baseline (Day 1, predose assessment) was 21.2 (6.69). The mean (SD) changes from baseline in MADRS 7-day recall were -2.6 (6.16), -3.7 (6.16), and -6.3 (8.24) on Day 11, Day 18, and Day 25, respectively.

SAFETY RESULTS

Adverse Events:

Part A

- All 23 subjects (100.0%) reported at least 1 or more treatment-emergent adverse events (TEAEs). The incidence of TEAEs in the esketamine nasal spray 84 mg+oral placebo, intranasal placebo+oral alcohol, and intranasal placebo+oral placebo treatment periods were reported in 22 subjects (100.0%), 18 subjects (81.8%), and 14 subjects (63.6%), respectively.
- The highest incidence of TEAE by system organ class (SOC) was nervous system disorders (23 subjects, 100%).
- The most frequently reported TEAEs (≥20% of subjects) in the esketamine nasal spray 84 mg+oral placebo treatment were dissociation (18 subjects, 81.8%), dizziness (16 subjects, 72.7%), paraesthesia (11 subjects, 50.0%), dysgeusia (10 subjects, 45.5%), paraesthesia oral (9 subjects, 40.9%), fatigue (6 subjects, 27.3%), feeling of relaxation and nausea (5 subjects each, 22.7%).

- The most frequently reported TEAEs (≥20% of subjects) in the intranasal placebo+oral alcohol treatment were dizziness (8 subjects, 36.4%), headache (7 subjects, 31.8%), and dysgeusia (5 subjects, 22.7%); while in the in the intranasal placebo+oral placebo treatment, the most frequently reported TEAE (≥20% of subjects) was fatigue (6 subjects, 27.3%).
- Overall, across all 3 treatment periods in Part A, the reported TEAEs (17 subjects, 73.9%) were assessed as mild or moderate in severity by the Investigator and the majority resolved within 24 hours. The TEAE's of moderate severity were reported in 4 subjects (18.2%) treated with esketamine nasal spray 84 mg+oral placebo (dissociation was reported in 3 subjects, and nausea and fatigue each was reported in 1 subject) and 2 subjects (9.1%) treated with intranasal placebo +oral placebo (influenza and anxiety each was reported in 1 subject).

Part B

- All 20 subjects (100%) reported at least 1 or more TEAEs.
- The highest incidence of TEAE by SOC were nervous system disorders and psychiatric disorders (each reported in 20 subjects, 100%)
- The most frequently reported TEAEs (≥20% of subjects) in subjects treated with esketamine nasal spray were dissociation (19 subjects, 95.0%), dizziness (18 subjects, 90.0%), dysgeusia (15 subjects, 75.0%), fatigue (13 subjects, 65.0%), headache (11 subjects, 55.0%), paraesthesia (10 subjects, 50.0%), paraesthesia oral (9 subjects, 45.0%), nausea, feeling abnormal, and nasal discomfort (8 subjects each, 40.0%), vision blurred, somnolence, and euphoric mood (7 subjects each, 35.0%), tinnitus, diplopia, blood pressure increased, feeling drunk, and dysarthria (5 subjects each, 25.0%), illusion, hypoaesthesia, and time perception altered (4 subjects each, 20.0%).
- In the intranasal placebo treatment, 2 subjects (10.0%) each reported TEAEs of fatigue and headache.
- The reported TEAEs in Part B (14 subjects, 70.0%) were assessed as mild or moderate in severity by the Investigator and resolved the same day. Six subjects (30.0%) reported moderate TEAE's following treatment with esketamine nasal spray (fatigue, feeling drunk, dizziness, headache, dissociation, emotional distress, and euphoric mood each was reported in 1 subject) and 1 subject (5.0%) with intranasal placebo (reported dissociation).

There were no deaths, SAEs, or discontinuation due to AEs, reported in this study.

Blood Pressure:

In Part A and Part B of the study, transient increases in the systolic and diastolic blood pressure (SBP and DBP) were observed at 40 minutes after intranasal esketamine administrations.

In Part A - following administration esketamine nasal spray 84 mg mean (SD) increase of SBP at 40 minutes was 22.3 (12.38) mm Hg (median SBP: 135.5 mm Hg, range: 112 to 153 mm Hg) and, the mean (SD) increase of DBP at 40 minutes was 14.6 (7.13) mm Hg (median DBP: 82.5 mm Hg, range: 65 to 97 mm Hg).

Part B - following administration of esketamine nasal spray 84 mg treatment on Day 4 (subjects second exposure), the increase in mean (SD) SBP at 40 minutes was 13.7 (13.46) mm Hg (median SBP: 126.5 mm Hg, range: 102 to 165 mm Hg). After repeated administrations of esketamine, the maximum mean (SD) SBP on Days 8, 11, 15, 18, 22, and 25 increased by 15.3 (11.68) mm Hg, 14.2 (10.80) mm Hg, 10.3 (8.91) mm Hg, 9.5 (9.54) mm Hg, 10.2 (9.10) mm Hg, and 11.1 (6.55) mm Hg, respectively.

The increase in mean (SD) DBP at 40 minutes on Day 4 was 13.0 (7.87) mm Hg (median DBP: 74 mm Hg, range: 63 to 97 mm Hg), and on average the increase in DBP declined slightly across multiple treatments, 13.8 (11.01) mm Hg, 12.9 (10.54) mm Hg, 11.8 (10.94) mm Hg, 8.4 (9.38) mm Hg, 9.6 (9.33) mm Hg, and 11.3 (9.06) mm Hg, on Days 8, 11, 15, 18, 22, and 25, respectively.

The SBP and DBP values were found to be at baseline or near baseline values when measured predose either during the subsequent treatment days or at EOS/EW.

Other Safety Measures:

No clinically meaningful treatment-related findings were noted in respiratory rate, pulse rate, ECG parameters or TEAEs related to ECG parameters were reported in this study.

There were no clinically meaningful mean changes in hematology, biochemistry and urinalysis parameters.

In Part A and B of the study, the mean (SD) change from baseline for the CADSS total scores and CADSS component scores for subjects administered intranasal esketamine increased at 1 hour postdose. The maximum mean (SD) increase across the study was 10.9 (7.35) and subsequently decreased to near baseline at 2 hours postdose.

There were no reports of suicidal ideations with intent or ideations with plan/intent (scores 1 to 5) at baseline or suicidal behavior (scores 6 to 10) as assessed using the C-SSRS throughout the study. These interim analysis result did not identify any increased suicidal ideation/behavior as measured by the C-SSRS.

STUDY LIMITATIONS:

No notable study limitations were identified by the Sponsor.

CONCLUSION(S):

The study results are for the period from 18 October 2016 to 01 March 2018 (cut-off date for interim analysis)

- The next-day driving performance after a single 84-mg dose of esketamine nasal spray was not inferior (ie, not different) to placebo based on SDLP. However, alcohol (0.05% BAC) significantly worsened driving performance in SDLP compared to the placebo control.
- There were no differences in subjective assessment of driving ability or perceived effort scale following next-day driving after a single 84-mg dose of esketamine nasal spray or after ingestion of the ethanol beverage as compared to the placebo.
- Levels of alertness varied across the treatment groups prior to the driving test; however, a similar level of alertness was reported after the 1-hour driving test.
- Safety assessments and TEAEs demonstrated no measurable impact on next day driving performance. These safety results are consistent with previous esketamine studies; no new safety concerns were identified.
- The MADRS scores indicated improvement in overall depression scores following esketamine nasal spray as compared to placebo in Part A of the study.
- This study supports the use of esketamine in the target patient population as safely tolerated and without impact on next-day driving performance.

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