SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Investigational Product	JNJ-54135419 (Esketamine, S-(+)-ketamine)

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Prepared by: Janssen Research & Development, LLC

Protocol No.: 54135419TRD1014

Title of Study: An Open-Label, Single-Dose, Parallel-Group Study to Assess the Effects of Renal Impairment on the Pharmacokinetics, Safety, and Tolerability of Intranasally Administered Esketamine

NCT No.: NCT02606084

Clinical Registry No.: CR108058

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Study Center(s): New Orleans Center for Clinical Research, USA; Advanced Pharma CR, LLC; USA

Publication (Reference): None

Study Period: 22 December 2015 to 02 February 2018

Phase of Development: Phase 1

Objectives: The primary objective of this study was to evaluate the pharmacokinetics (PK) of a single dose of intranasally administered esketamine in subjects with impaired renal function when compared to subjects with normal renal function.

The secondary objectives were to evaluate safety and tolerability of a single dose of intranasally administered esketamine in subjects with impaired renal function when compared to subjects with normal renal function.

Methodology: This was an open-label, single-dose, parallel-group study to characterize the PK and safety of a single 28 mg dose of esketamine in both subjects with varying stages of renal impairment and healthy subjects.

A total of approximately 32 medically stable men and women of non-Asian origin with varying degrees of renal impairment and healthy subjects were enrolled in total of 4 cohorts (up to 8 subject per cohort). The subjects were assigned to 1 of 4 groups based on creatinine clearance ($CL_{CR,m}$) which was measured using urine and serum creatinine concentration during Screening and within 2 weeks of dosing.

- Cohort 1: 8 subjects with mild renal impairment ($CL_{CR,m}$≥50 to 79 mL/min)
- Cohort 2: 8 subjects with moderate renal impairment ($CL_{CR,m}$≥30 to 49 mL/min)
- Cohort 3: 6 to 8 subjects with severe renal impairment ($CL_{CR,m}$<30 mL/min), not on dialysis

- Cohort 4: 8 subjects with normal renal function and no evidence of kidney damage ($CL_{CR,m}$≥80 mL/min)

Healthy subjects in the control group (Cohort 4) were to be enrolled after enrollment of subjects with renal impairment, including 8 subjects in Cohort 1 and 8 subjects in Cohort 2, and at least 6 subjects in Cohort 3 had completed the study related procedures including the 60 hour PK sample. The 8 healthy subjects in Cohort 4 were matched to the mean age (±7 years) and mean body weight (±20%) of subjects with impaired renal function, and were enrolled in this study to avoid large differences in age and weight between healthy subjects and renal impaired subjects (Cohort 1, 2 and 3). For the control group (Cohort 4), at least 3 subjects with an individual value above and at least 3 subjects with an individual value below the combined mean age/body mass index (BMI) values were to be enrolled. In addition, a similar number of men and women (at least 3 of each sex) were to be enrolled into Cohorts 1, 2, and 4. An interim analysis of the PK and safety/tolerability data was not performed and 8 subjects were enrolled into each cohort.

The subjects in all cohorts self-administered, under supervision, an intranasal dose of esketamine on Day 1. The subjects were advised to remain seated or remain in bed in a semi-reclined position, for approximately 2 hours after esketamine administration or until any postdose nervous system or psychiatric adverse event (AE) had resolved, whichever was longer. Subjects were dosed in a staggered fashion to provide sufficient time to record any AEs and ensure adequate safety monitoring.

A subject was to be replaced in each cohort if the number of completers was less than 8 subjects in Cohorts 1, 2, and 4, or less than 6 subjects in Cohort 3, and a new identification number was given to those subjects who replaced subjects that had been originally enrolled during the active treatment phase.

For all subjects, serial PK venous blood samples and urine samples for analysis of levels of esketamine and noresketamine were collected for up to 60 hours after dosing on Day 1.

Safety and tolerability were assessed from the time of consent until the end of the study. The subjects returned to the study center 11(±2) days after the last dose of study medication for End-of-Study (EOS) assessments. Alternatively, the EOS assessments were to be conducted at the time of early withdrawal (EW) visit. The EOS was the date of the last visit for the last subject participating in the study.

Number of Subjects (planned and analyzed):

Planned: Approximately 32 medically stable men and women (18 to 70 years of age [inclusive]) were planned to be enrolled in 1 of 4 cohorts to complete up to 8 subjects in each cohort.

Analyzed: A total of 32 subjects (8 subjects each in Cohort 1 to Cohort 4) with varying degrees of renal function impairment or no renal impairment were enrolled and dosed in the study.

Diagnosis and Main Criteria for Inclusion: The study population included men and women of non-Asian origin, 18 to 70 years of age (inclusive), who had a BMI between 18 to 36 kg/m^2 (inclusive), and a body weight of not less than 50 kg, and were characterized as having either mild ($CL_{CR,m}$ ≥50 to 79 mL/min), moderate ($CL_{CR,m}$ ≥30 to 49 mL/min), or severe renal impairment ($CL_{CR,m}$ <30 mL/min) or were healthy matched control subjects ($CL_{CR,m}$ ≥80 mL/min).

Subjects enrolled in the study had a stable renal function.

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

The reference numbers, batch numbers, and expiry dates of the supplied study agents are provided below:

Study Agent	Description, dose and mode of administration	Reference No.	Batch No.	Expiration date
Esketamine	aqueous solution consisting of 161.4 mg/mL esketamine hydrochloride (equivalent to 140 mg of esketamine base) in water for injection, nasal spray	FCTK011	500491	22 March 2018
Placebo*	clear, colorless intranasal solution of water for injection with a bittering agent (denatonium benzoate [Bitrex®]) at a final concentration of 0.001 mg/mL and benzalkonium chloride as a preservative at a concentration of 0.3 mg/mL	FCTK012	500472	21 March 2018

* The placebo solution was used by all subjects on Day -1 to practice using the intranasal spray device prior to administration of study drug

Duration of Treatment: The total study duration, from the Screening Phase through Follow-up Phase, was approximately 34 to 38 days for all cohorts.

Criteria for Evaluation: Serial blood samples (6 mL each) were collected for esketamine and noresketamine plasma concentrations. Samples were collected predose and at various intervals postdose with the last sample taken on Day 4 (60 hours postdose). An additional 9 mL blood sample was collected predose to the assess the degree to which esketamine and noresketamine gets bound to plasma proteins.

The following key noncomparmental PK parameters were to be determined for each cohort from plasma: maximum observed plasma concentration (C_{max}); time to reach the maximum observed plasma concentration (t_{max}); area under the plasma concentration-time curve from time 0 to the time of the last observed quantifiable concentration (AUC_{last}); area under the plasma concentration-time curve from time 0 to infinite time (AUC_{∞}); elimination half-life ($t_{1/2}$); area under the plasma concentration-time curve over the time interval 0 to 12 hours ($AUC_{0\text{-}12h}$); individual estimate of the terminal elimination rate constant (λ_z); fraction unbound (f_u); metabolite to parents ratio of C_{max}, AUC_{last}, AUC_{∞}.

Urine was collected for determination of esketamine and noresketamine concentrations (predose and over timed intervals till last sample collected 60 hour postdose). A 24-hour urine collection test, and a serum sample taken at midpoint of the 24-hour urine collection interval (12 hours) during the Screening was used to measure the $CL_{CR,m}$.

The following key noncompartmental PK parameters were to be determined from urine in each cohort: total amount of analyte excreted into urine (Ae); percentage of the administered dose excreted in urine (Ae%dose); CLR; CLCR,m; estimated creatinine clearance (CLCR,e); estimated glomerular filtration rate (eGFR); and metabolite-to-parent ratio of Ae.

A pharmacogenomic blood sample (10 mL) was collected to allow for pharmacogenomic research.

Safety and tolerability was assessed from the time of consent until the end of the study. Safety and tolerability assessments included: treatment-emergent adverse events (TEAEs), singular 12-lead electrocardiograms (ECGs), vital signs, pulse oximetry, clinical laboratory results, physical examinations, and targeted nasal examinations. The potential effects of intranasal esketamine on sedation were also evaluated by the use of the Modified Observer's Assessment of Alertness/Sedation [MOAA/S] rating scale that was completed by the investigator or a designated representative of the investigator. These assessments were completed predose and at multiple time-points. The Columbia-Suicide Severity Rating Scale (C-SSRS) was performed to assess suicidal ideation and behavior. The subjects returned to the study center 11 (±2) days after the last dose of study medication for EOS assessments. In case of early withdrawal, the EOS assessments were to be conducted at the time of early withdrawal visit. The end of the study was the date of the last visit for the last subject participating in the study.

Statistical Methods:

Sample Size

Based on the previous study (ESKETINTRD1003), the estimated inter-subject coefficients of variations for PK parameters (C_{max} and AUCs) were ≤31% for healthy subjects. Using a conservative estimate of 35% as inter-subject coefficients of variation for healthy and renal impaired subjects, a sample size of 8 subjects in each cohort was sufficient for the point estimates of the ratios (ie, Cohort 1/Cohort 4, Cohort 2/Cohort 4, Cohort 3/Cohort 4) of mean PK parameters to fall within 73% to 136% of its true values with 90% confidence.

Analysis

Initial subject characteristics

For all subjects who received at least one dose of study drug, descriptive statistics (mean, standard deviation [SD], median, minimum, and maximum) were performed for age, BMI, weight, and height. Sex and race were listed and tabulated.

Pharmacokinetics

Individual and mean plasma esketamine and noresketamine concentration-time profiles were plotted for each group of subjects. Plasma concentration data at each time point was summarized for each cohort with mean, median, minimum, maximum, SD, and percent coefficient of variation for all subjects who received study drug. In addition, plots of plasma esketamine and noresketamine (and other metabolites if analyzed) PK parameters as a function of CL_{CR} were prepared.

All estimated PK parameters of esketamine and noresketamine were summarized for each subject group with mean, median, minimum, maximum, SD, percent coefficient of variation, and geometric mean.

For comparison of renal impairment groups (Cohort 1, 2 and 3) to normal renal function (Cohort 4), an analysis of variance (ANOVA) model was fitted to log-transformed esketamine and noresketamine AUCs (AUC_{∞} and AUC_{last}) and C_{max} with renal impairment group as a factor. Ninety percent confidence intervals (CIs) for the ratio of mean PK parameters AUCs and C_{max} for subjects with renal impairment (Cohorts 1, 2, or 3) compared to subjects with a normal renal function (Cohort 4) were constructed using the estimated least squares means and inter-subject variance from analysis of variance models.

Descriptive statistics were used to summarize the results of esketamine and noresketamine protein binding.

The total urine volume excreted during each collection interval and the concentration of esketamine and of noresketamine in each of the aliquots obtained from each collection interval were summarized for each cohort. In addition, the amount of esketamine and noresketamine excreted in urine during each collection interval and the entire 60 hour period was summarized. Additional analyses, was performed if considered necessary.

Pharmacogenomic

A composite genotype and predicted phenotype was derived from the raw genotyping data for *CYP2B6*. Allele and genotype frequencies were tabulated. No formal statistical tests were performed.

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, and changes in clinical laboratory test values, physical examination results (including targeted nasal examinations), singular 12-lead ECGs, arterial oxygen saturation (SpO_2) by pulse oximetry, and vital signs measurements from

the Screening Phase through study completion, including the washout interval. Data from the safety assessments, including the MOAA/S and C-SSRS, was summarized descriptively.

RESULTS:

STUDY POPULATION:

A total of 32 subjects (8 subjects each in Cohort 1 to Cohort 4) were enrolled and dosed in the study and all 32 subjects completed the study. Overall, there were equal number of male and female subjects, majority of them were White (93.8%) and of non-Hispanic or -Latino ethnicity, with mean (SD) age of 57.3 (6.83) years and mean (SD) baseline BMI of 27.99 (4.12) kg/m^2. Two subjects in Cohort 1 received esketamine that was dispensed from the clinical supply of different protocol utilizing the exact dosage, formulation, and route of administration. Two subjects from Cohort 3 entered the study but did not satisfy criteria. One of the subjects had systolic blood pressure (SBP) >140 mm Hg during the Screening period, and in the other subject the Day -1 ALT value was >2-times the upper laboratory normal value. No inclusion/exclusion deviations were reported during the study.

The measured creatinine clearance (CL_{CRm}) values at Screening for the subjects with mild renal impairment, moderate renal impairment, severe renal impairment (not on dialysis), and normal renal function were 58 to 77 mL/min, 30 to 47 mL/min, 5 to 28 mL/min, and 88 to 140 mL/min, respectively.

PHARMACOKINETIC RESULTS:

Esketamine

After administration of a single intranasal dose of 28 mg esketamine, mean esketamine plasma concentrations increased rapidly after dosing for all 4 cohorts, after which plasma concentrations decreased. The concentrations of esketamine appeared to decline at a similar rate in all 4 renal function groups. Overall, mean esketamine plasma concentrations appeared to be slightly higher in subjects with renal impairment compared to subjects with normal renal function.

The median esketamine t_{max} was observed at similar times for subjects in all cohorts (median values between 0.33 and 0.42 hours, range 0.17 to 2.00 hours). The apparent $t_{1/2term}$ of esketamine was similar for the 4 renal function groups with mean values ranging between 11.0 and 16.3 hours. Based on geometric mean ratios (ie, impaired/healthy), the C_{max}, AUC_{last}, and AUC_{∞} were 20.32%, 13.52%, and 13.46% higher, respectively, in subjects with mild renal impairment, compared to subjects with normal renal function. Esketamine C_{max}, AUC_{last}, and AUC_{∞} values in subjects with moderate renal impairment were 24.66%, 32.38%, and 36.30% higher, respectively, compared to subjects with normal renal function. In subjects with severe renal impairment, esketamine C_{max}, AUC_{last}, and AUC_{∞} were 26.00%, 19.63%, and 17.30% higher, respectively, compared to subjects with normal renal function. Most of the corresponding 90% CIs for the ratios (ie., mild, moderate or severe renal impairment versus normal renal function) included 100%. However, all 90% CIs exceeded the conventional criteria to demonstrate bioequivalence (ie., 80% to 125%). The mean f_u of esketamine was similar in all cohorts. Mean values ranged from 57.4 % to 60.0% in subjects with renal impairment and was 54.7% in subjects with normal renal function.

The inter-subject variability (obtained from the statistical model) in the esketamine PK parameters was moderate for C_{max}, AUC_{last}, and AUC_{∞}, with inter-subject CV ranging from 31.7% to 44.0%.

In general, there was a low correlation between plasma PK of esketamine and individual calculations of the renal function ($CL_{CR,m}$, $CL_{CR,e}$, and eGFR).

Pharmacokinetics of total esketamine (mean [SD], t_{max}: median [range])	**Mild Renal Impairment (test 1)**	**Moderate Renal Impairment (test 2)**	**Severe Renal Impairment (test 3)**	**Normal Renal Function (reference)**
N	8[a]	8	8[b]	8[b]
C_{max} (ng/mL)	79.3 (33.1)	78.3 (25.5)	77.0 (19.9)	64.4 (21.4)
t_{max} (h)	0.33 (0.17-2.00)	0.33 (0.17-0.50)	0.42 (0.17-0.75)	0.33 (0.17-0.75)
AUC_{last} (ng.h/mL)	197 (53.4)	222 (29.6)	213 (88.5)	172 (44.7)
AUC_{∞} (ng.h/mL)	208 (62.9)	238 (26.8)	221 (100)	179 (45.4)
λ_z (1/h)	0.0711 (0.0274)	0.0488 (0.0176)	0.0802 (0.0488)	0.0715 (0.0286)
$t_{1/2}$ (h)	12.0 (7.6)	16.3 (7.1)	11.0 (4.6)	11.1 (4.4)
f_u (%)	57.5 (4.98)	60.0 (4.86)	57.4 (2.12)	54.7 (5.01)
Alpha-1 acid glycoprotein (mg/dL)	88.4 (28.6)	86.1 (30.4)	100 (25.9)	86.8 (21.9)
Albumin (g/dL)	4.00 (0.299)	3.72 (0.243)	4.02 (0.454)	4.29 (0.298)
Protein (g/dL)	6.16 (0.473)	5.83 (0.561)	6.64 (0.316)	6.75 (0.591)

a: n=6 for AUC_{∞}, λ_z and $t_{1/2}$.
b: n=7 for AUC_{∞}, λ_z and $t_{1/2}$.

Urinary excretion of esketamine was low in all cohorts. The mean amount of esketamine excreted unchanged expressed as percentage of the administered dose ranged between 0.598% to 1.34% across the renal function groups. Mean renal clearance ranged between 0.985 and 1.97 L/h.

Pharmacokinetics of urinary esketamine (mean [SD])	**Mild Renal Impairment (test 1)**	**Moderate Renal Impairment (test 2)**	**Severe Renal Impairment (test 3)**	**Normal Renal Function (reference)**
N	8[a]	8	8[b]	8[b]
Ae_{total} (mg)	0.376 (0.452)	0.247 (0.0950)	0.285 (0.228)	0.167 (0.0881)
$Ae,\%Dose_{total}$ (%)	1.34 (1.61)	0.881 (0.339)	1.02 (0.815)	0.598 (0.315)
CL_R (L/h)	1.97 (1.73)	1.03 (0.385)	1.89 (1.88)	0.985 (0.376)

a: n=6 for CL_R.
b: n=7 for CL_R.

Noresketamine

After administration of a single intranasal dose of 28 mg esketamine, mean noresketamine plasma concentrations increased rapidly after dosing for all 4 cohorts, after which plasma concentrations decreased. The concentrations of noresketamine appeared to decline at a similar rate in all 4 renal function groups. Overall, mean noresketamine plasma concentrations were higher in subjects with moderate and severe renal impairment compared to subjects with mild renal impairment and normal renal function.

After treatment with a single intranasal dose of 28 mg esketamine, median noresketamine t_{max} was observed at similar times for subjects in all cohorts (median values between 1.25 and 1.50 hours, range 0.50 to 3.00 hours). The apparent $t_{1/2term}$ of noresketamine was overall similar for all 4 renal function groups with mean values ranging between 12.5 and 17.8 hours. Based on geometric mean ratios, noresketamine C_{max}, AUC_{last}, and AUC_{∞} were 6.57%, 6.45%, and 6.13% lower, respectively, in subjects with mild renal impairment. In subjects with moderate renal impairment, noresketamine C_{max}, AUC_{last}, and AUC_{∞} were 14.66%, 48.37%, and 55.36% higher, respectively, compared to subjects with normal

renal function. In subjects with severe renal impairment, noresketamine C_{max}, AUC_{last}, and AUC_{∞} were 22.55%, 35.81%, and 38.83% higher, respectively, compared to subjects with normal renal function. All corresponding 90% CIs for the ratios (ie., mild, moderate or severe impairment versus normal renal function) included 100%. However, they exceeded the conventional criteria to demonstrate bioequivalence (ie., 80 to 125%). Mean MPR C_{max}, AUC_{last}, and AUC_{∞} values were generally similar for the 4 renal function groups with mean values ranging between 1.22 and 1.36, between 2.75 and 3.63, and between 2.82 and 3.68 for C_{max}, AUC_{last}, and AUC_{∞}, respectively. The mean f_u of noresketamine was similar in all cohorts. Mean values ranged from 62.0% to 63.3% in subjects with renal impairment and was 57.4% in subjects with normal renal function.

The inter-subject variability (obtained from the statistical model) in the noresketamine PK parameters was moderate for C_{max}, AUC_{last}, and AUC_{∞}, with inter-subject CV ranging from 48.4% to 56.1%.

In general, there was a low correlation between plasma noresketamine concentration and individual calculations of the renal function ($CL_{CR,m}$, $CL_{CR,e}$, and eGFR).

Pharmacokinetics of total noresketamine (mean [SD], t_{max}: median [range])	**Mild Renal Impairment (test 1)**	**Moderate Renal Impairment (test 2)**	**Severe Renal Impairment (test 3)**	**Normal Renal Function (reference)**
n	8[a]	8	8[b]	8[b]
C_{max} (ng/mL)	77.2 (35.2)	90.6 (34.4)	96.5 (37.9)	80.5 (35.5)
t_{max} (h)	1.50 (0.75-3.00)	1.50 (0.75-1.50)	1.25 (0.50-1.50)	1.25 (0.75-3.00)
AUC_{last} (ng.h/mL)	520 (247)	808 (300)	705 (281)	492 (107)
AUC_{∞} (ng.h/mL)	539 (256)	883 (334)	758 (332)	509 (101)
λ_z (1/h)	0.0530 (0.00970)	0.0432 (0.0158)	0.0581 (0.0289)	0.0628 (0.0216)
$t_{1/2}$ (h)	13.5 (2.4)	17.8 (5.7)	14.4 (6.1)	12.5 (5.3)
f_u (%)	63.2 (3.25)	63.3 (5.22)	62.0 (2.78)	57.4 (4.38)
MPR C_{max}	1.22 (0.911)	1.27 (0.526)	1.32 (0.628)	1.36 (0.610)
MPR AUC_{last}	2.75 (1.28)	3.63 (1.29)	3.38 (0.821)	3.05 (0.937)
MPR AUC_{∞}	2.82 (0.991)	3.68 (1.34)	3.49 (0.789)	3.05 (0.794)

a: n=6 for MPR AUC_{∞}.
b: n=7 for MPR AUC_{∞}.

Urinary excretion of noresketamine was low in all cohorts. The mean amount of noresketamine excreted unchanged expressed as percentage of the administered dose ranged between 1.58% to 1.75% and was similar across the renal function groups. Mean renal clearance ranged between 0.532 and 0.875 L/h.

Pharmacokinetics of urinary noresketamine (mean [SD])	**Mild Renal Impairment (test 1)**	**Moderate Renal Impairment (test 2)**	**Severe Renal Impairment (test 3)**	**Normal Renal Function (reference)**
n	8	8	8	8
Ae_{total} (mg)	0.461 (0.212)	0.460 (0.200)	0.445 (0.276)	0.417 (0.181)
$Ae,\%Dose_{total}$ (%)	1.75 (0.804)	1.74 (0.757)	1.69 (1.05)	1.58 (0.688)
CL_R (L/h)	0.875 (0.417)	0.532 (0.144)	0.822 (0.856)	0.809 (0.256)

PHARMACOGENOMICS RESULTS:

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

SAFETY RESULTS:

Overall, 17 subjects (53.1%) reported at least 1 or more TEAE. The incidence of TEAEs was greater in Cohort 1 and Cohort 2 (7 subjects [87.5%] each) as compared to Cohort 3 (2 subjects [25.0%]) and Cohort 4 (1 subject [12.5%]).

In Cohort 1, the most commonly reported TEAEs by SOC (≥20% of subjects) were nervous system disorders (5 [62.5%]); and respiratory, thoracic and mediastinal disorders, and general disorders and administration site conditions (each reported in 2 subjects [25.0%]). In Cohort 2, the most commonly reported TEAEs by SOC (≥20% of subjects) were nervous system disorders (5 [62.5%]), gastrointestinal disorders (3 [37.5%]), and psychiatric disorders (2 [25.0%]). In Cohort 3 and Cohort 4, no TEAEs were reported in ≥20% of subjects. Nervous system disorders was reported in 1 subject (12.5%) in both Cohort 3 and Cohort 4, among the other TEAEs by SOC. The most frequently reported TEAE was dizziness in Cohort 1 (4 subjects) and Cohort 2 (3 subjects). In Cohort 3, one subject each reported TEAE of dizziness, hypoaesthesia oral, pharyngeal hypoaesthesia, and diplopia; while in Cohort 4, one subject each reported TEAE of headache and depression.

All of the TEAEs were assessed as mild in severity. The majority of the TEAEs in all the Cohorts were assessed as possibly related to esketamine by the Investigator. There were no deaths, serious AEs, discontinuations due to AEs, or persistent AEs reported in this study

There were no clinically meaningful, treatment-related mean changes observed in the hematology and serum chemistry. No clinically relevant individual subject changes in laboratory analytes from Screening to EOS were observed. None of the abnormalities in laboratory analytes were reported as TEAEs.

Mean increases in the SBP and diastolic blood pressure (DBP) were observed in each cohort after intranasal esketamine administration. The SBP increased during the first 2 hours postdose. The maximal increase in the mean SBP was similar for Cohort 1 (14.3 mm Hg at 50 min) and Cohort 4 (13.3 mm Hg at 32 min) followed by Cohort 2 (10.6 mm Hg at 32 min) and Cohort 3 (6.8 mm Hg at 50 min). The maximal mean increase in the DBP was similar across most cohorts [Cohort 1 (6.6 mm Hg at 32 min and 50 min), Cohort 2 (7.9 mm Hg at 32 min), Cohort 3 (4.6 mm Hg at 32 min), and Cohort 4 (5.4 mm Hg at 32 min)]. This increase in the SBP and DBP returned to near baseline values at 5 hours and 2 hours postdose, respectively, on the same day.

No clinically meaningful treatment-related findings were noted in the respiratory rate and pulse oximetry.

No clinically significant changes in ECG parameters were observed in this study. No clinically meaningful effects in ECG parameters (PR, RR, QRS, QT, QTcB, and QTcF intervals) were observed in this study.

None of the subjects had a MOAA/S score of ≤3 (a score of 3 corresponds to moderate sedation). None of the subjects experienced deep sedation and majority of subjects remained alert after dosing with esketamine. One subject in Cohort 2 reported suicidal ideation (wished to be dead) at Screening. None of the subjects in the study had a postbaseline occurrence of suicidal ideation and/or suicidal behavior. Two subjects subject in Cohort 4 exhibited slight septal deviation at Screening. These findings did not

have any effect on nasal spray or nasal absorption. One subject in Cohort 1 exhibited mild nasal erythema on Day 1, +60 hours, postdose. None of the subjects experienced any moderate or severe nasal tolerability symptoms on Day 1, +60 hours, postdose. None of these abnormalities were clinically significant

STUDY LIMITATIONS:

No notable study limitations were identified by the sponsor.

CONCLUSION(S):

Relative to subjects with normal renal function (CL_{CRm}: 88 to 140 mL/min), the C_{max} of esketamine was on average 20 to 26% higher in subjects with mild (CL_{CRm}: 58 to 77 mL/min), moderate (CL_{CRm}: 30 to 47 mL/min), or severe (CL_{CRm}: 5 to 28 mL/min, not on dialysis) renal impairment. Esketamine AUC values were 14 to 36% higher in subjects with mild to severe impairment.

Relative to subjects with normal renal function, noresketamine C_{max} and AUC values were slightly lower in subjects with mild renal impairment. The C_{max} was on average 15% and 23% higher in subjects with moderate and severe impairment, respectively. Noresketamine AUC values were 36 to 55% higher.

The extent to which esketamine and noresketamine are bound to plasma proteins was similar across the range of renal function.

Overall, a single dose of intranasally administered esketamine was generally safe and well tolerated in subjects with impaired renal function and in subjects with normal renal function.

Results of safety assessments were consistent with previous esketamine studies, and no new safety concerns were identified.

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