Clinical trial results:
A Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy and Safety of Intranasal Esketamine in Addition to Comprehensive Standard of Care for the Rapid Reduction of the Symptoms of Major Depressive Disorder, Including Suicidal Ideation, in Adult Subjects Assessed to be at Imminent Risk for Suicide

Summary

EudraCT number	2016-003992-23
Trial protocol	BE PL CZ AT LT FR ES
Global end of trial date	11 April 2019

Results information

Result version number	v1
This version publication date	19 April 2020
First version publication date	19 April 2020

Trial information

Trial identification

Sponsor protocol code	54135419SUI3002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03097133
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Research & Development, LLC
Sponsor organisation address	920 Route 202, Raritan, United States, NJ 08869
Public contact	Clinical Registry group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 April 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to evaluate the efficacy of intranasal esketamine 84 milligram (mg) compared with intranasal placebo in addition to comprehensive standard of care in reducing the symptoms of major depressive disorder (MDD), including suicidal ideation, in subjects who were assessed to be at imminent risk for suicide, as measured by the change from baseline on the montgomery-asberg depression rating scale (MADRS) total score at 24 hours post first dose.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and applicable regulatory requirements. Safety evaluation included adverse events, clinical laboratory tests (hematology, serum chemistry, and urinalysis), vital sign measurements (temperature, pulse/heart rate, respiratory rate, blood pressure [BP]), physical examinations, height, body weight, electrocardiograms (ECGs), pulse oximetry, and nasal examinations. Other safety evaluations included: Modified observer's assessment of alertness/sedation (MOAA/S) to measure treatment-emergent sedation, clinician-administered dissociative states scale (CADSS) to assess dissociative symptoms, and the columbia classification algorithm for suicide assessment (C-CASA) to classify potentially suicide-related events based on responses to the suicide ideation and behavior assessment tool (SIBAT).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 June 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 17
Country: Number of subjects enrolled	Austria: 9
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Brazil: 36
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Czech Republic: 3
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	France: 25
Country: Number of subjects enrolled	Lithuania: 4
Country: Number of subjects enrolled	Poland: 33
Country: Number of subjects enrolled	Turkey: 23
Country: Number of subjects enrolled	United States: 66

Worldwide total number of subjects	230
EEA total number of subjects	87

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	230
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Total 230 subjects were randomly assigned to 1 of 2 treatment groups (esketamine and placebo) in a 1:1 ratio. Out of which 114 and 113 subjects received treatment in esketamine and placebo group respectively. Total 166 subjects completed the study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo + Standard of Care (SOC)

Arm description:

Subjects self-administered intranasal placebo (1 spray in each nostril at 0, 5 and 10 minutes using 3 devices on a single day) twice per week for 4 weeks on days 1, 4, 8, 11, 15, 18, 22, and 25 along with SOC antidepressant treatment (determined by the physician based on clinical judgment and practice guidelines) on Day 1 and continued for the duration of the double-blind (DB) treatment phase.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray, solution
Routes of administration	Intranasal use

Dosage and administration details:

Subjects self-administered intranasal placebo (1 spray in each nostril at 0, 5 and 10 minutes using 3 devices on a single day) twice per week for 4 weeks on days 1, 4, 8, 11, 15, 18, 22, and 25 in the double-blind treatment phase.

Arm title	Esketamine 84 mg + SOC

Arm description:

Subjects self-administered esketamine 84 milligram (mg) (1 spray containing esketamine 14 mg in each nostril at 0, 5 and 10 minutes using 3 devices on a single day) twice per week for 4 weeks on Days 1, 4, 8, 11, 15, 18, 22, and Day 25 along with SOC antidepressant treatment (determined by physician based on clinical judgment and practice guidelines) on Day 1 and continued for duration of DB treatment phase. After Day 1, a single dose reduction from esketamine 84 mg to esketamine 56 mg was permitted if a subject was unable to tolerate intranasal esketamine 84 mg dose. Subjects for whom dose was reduced continued to receive reduced dose for duration of DB treatment phase.

Arm type	Experimental
Investigational medicinal product name	Esketamine
Investigational medicinal product code	
Other name	JNJ-54135419
Pharmaceutical forms	Nasal spray, solution
Routes of administration	Intranasal use

Dosage and administration details:

Subjects self-administered esketamine 84 mg (1 spray containing esketamine 14 mg in each nostril at 0, 5 and 10 minutes using 3 devices on a single day) twice per week for 4 weeks on Days 1, 4, 8, 11, 15, 18, 22, and Day 25 in the double-blind treatment phase.

Number of subjects in period 1	Placebo + Standard of Care (SOC)	Esketamine 84 mg + SOC
Started	115	115
Treated	113	114
Completed	85	81
Not completed	30	34
Consent withdrawn by subject	2	5
Adverse event, non-fatal	1	-
Unspecified	3	2
Lost to follow-up	3	2
Discontinued from DB phase, not entered FU Phase	21	25

Baseline characteristics

Reporting groups	
Reporting group title	Placebo + Standard of Care (SOC)
Reporting group description:	
Subjects self-administered intranasal placebo (1 spray in each nostril at 0, 5 and 10 minutes using 3 devices on a single day) twice per week for 4 weeks on days 1, 4, 8, 11, 15, 18, 22, and 25 along with SOC antidepressant treatment (determined by the physician based on clinical judgment and practice guidelines) on Day 1 and continued for the duration of the double-blind (DB) treatment phase.	
Reporting group title	Esketamine 84 mg + SOC
Reporting group description:	
Subjects self-administered esketamine 84 milligram (mg) (1 spray containing esketamine 14 mg in each nostril at 0, 5 and 10 minutes using 3 devices on a single day) twice per week for 4 weeks on Days 1, 4, 8, 11, 15, 18, 22, and Day 25 along with SOC antidepressant treatment (determined by physician based on clinical judgment and practice guidelines) on Day 1 and continued for duration of DB treatment phase. After Day 1, a single dose reduction from esketamine 84 mg to esketamine 56 mg was permitted if a subject was unable to tolerate intranasal esketamine 84 mg dose. Subjects for whom dose was reduced continued to receive reduced dose for duration of DB treatment phase.	

Reporting group values	Placebo + Standard of Care (SOC)	Esketamine 84 mg + SOC	Total
Number of subjects	115	115	230
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	115	115	230
From 65 to 84 years	0	0	0
85 years and over	0	0	0
Title for AgeContinuous Units: years			
arithmetic mean	41.3	40.4	
standard deviation	± 13.38	± 12.75	-
Title for Gender Units: subjects			
Female	68	70	138
Male	47	45	92

End points

End points reporting groups

Reporting group title	Placebo + Standard of Care (SOC)

Reporting group description:

Subjects self-administered intranasal placebo (1 spray in each nostril at 0, 5 and 10 minutes using 3 devices on a single day) twice per week for 4 weeks on days 1, 4, 8, 11, 15, 18, 22, and 25 along with SOC antidepressant treatment (determined by the physician based on clinical judgment and practice guidelines) on Day 1 and continued for the duration of the double-blind (DB) treatment phase.

Reporting group title	Esketamine 84 mg + SOC

Reporting group description:

Subjects self-administered esketamine 84 milligram (mg) (1 spray containing esketamine 14 mg in each nostril at 0, 5 and 10 minutes using 3 devices on a single day) twice per week for 4 weeks on Days 1, 4, 8, 11, 15, 18, 22, and Day 25 along with SOC antidepressant treatment (determined by physician based on clinical judgment and practice guidelines) on Day 1 and continued for duration of DB treatment phase. After Day 1, a single dose reduction from esketamine 84 mg to esketamine 56 mg was permitted if a subject was unable to tolerate intranasal esketamine 84 mg dose. Subjects for whom dose was reduced continued to receive reduced dose for duration of DB treatment phase.

Primary: Change From Baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) Total Score at 24 Hours Post First Dose (Last Observation Carried Forward [LOCF] Data): Double-blind (DB) Treatment Phase

End point title	Change From Baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) Total Score at 24 Hours Post First Dose (Last Observation Carried Forward [LOCF] Data): Double-blind (DB) Treatment Phase

End point description:

MADRS is clinician-rated scale designed to used in subjects with Major Depressive Disorder (MDD) to measure depression severity and detect changes due to antidepressant treatment. It evaluates apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, interest level, pessimistic and suicidal thoughts. Instrument consists of 10 items, each of which is scored from 0 (item not present or normal) to 6 (severe or continuous presence of symptoms), for total possible score of 0 to 60. Higher scores represent more severe condition. Negative change in score indicates improvement. Full efficacy analysis set included all randomized subjects who received at least 1 dose of intranasal study agent during DB treatment phase and had both baseline and post baseline evaluation for MADRS total score or clinical global impression–severity of suicidality–revised (CGI-SS-R). Here 'N' (number of subjects analyzed) signifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline (Day 1, predose) and 24 hours first post dose (Day 2)

End point values	Placebo + Standard of Care (SOC)	Esketamine 84 mg + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	113		
Units: Units on a scale				
arithmetic mean (standard deviation)	-12.4 (± 10.43)	-15.7 (± 11.56)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo + Standard of Care (SOC) v Esketamine 84 mg + SOC
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	ANCOVA
Parameter estimate	Difference (Diff.) of Least Square Means
Point estimate	-3.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.6
upper limit	-1.11
Variability estimate	Standard error of the mean
Dispersion value	1.39

Secondary: Change From Baseline in Clinical Global Impression-Severity of Suicidality - revised Scale at 24 Hours Post First Dose (LOCF Data): DB Treatment Phase

End point title	Change From Baseline in Clinical Global Impression-Severity of Suicidality - revised Scale at 24 Hours Post First Dose (LOCF Data): DB Treatment Phase

End point description:

CGI-SS-R is revised version of the clinical global impression severity scale (CGI-S). The CGI-SS-R summarizes the clinician's overall impression of severity of suicidality on a 7-point scale from 0 (normal, not at all suicidal) to 6 (among the most extremely suicidal subjects), based on the totality of information available to the clinician. Analysis was performed on full efficacy analysis set. Negative change in score indicates improvement. Here 'N' (number of subjects analyzed) signifies number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (Day 1, predose) and 24 hours first post dose (Day 2)

End point values	Placebo + Standard of Care (SOC)	Esketamine 84 mg + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	113		
Units: Units on a scale				
median (full range (min-max))	-1.0 (-5 to 2)	-1.0 (-6 to 2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Remission of Major Depressive Disorder (MADRS Less Than or Equal to [<=] 12): DB Treatment Phase

End point title	Number of Subjects With Remission of Major Depressive Disorder (MADRS Less Than or Equal to [<=] 12): DB Treatment Phase

End point description:

MADRS is a clinician-rated scale designed to be used in subjects with MDD to measure depression severity and detect changes due to antidepressant treatment. MADRS evaluates apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, interest level, pessimistic thoughts, and suicidal thoughts. The instrument consists of 10 items, each of which is scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms), for a total possible score of 0 to 60. Higher scores represent a more severe condition. A subject was considered to achieve remission of MDD at a given time point if the MADRS total score was <= 12. Subjects who did not met such criterion or discontinued prior to the time point for any reason were not considered to be in remission. Analysis was performed on full efficacy analysis set.

End point type	Secondary

End point timeframe:

Days 1 (4 hours [h] postdose), 2, 4, 8, 11, 15, 18, 22 and 25 (predose and 4h postdose)

End point values	Placebo + Standard of Care (SOC)	Esketamine 84 mg + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	114		
Units: Subjects				
Day 1: 4 hours post dose	4	12		
Day 2	12	25		
Day 4	20	26		
Day 8	23	28		
Day 11	26	32		
Day 15	29	36		
Day 18	32	29		
Day 22	37	42		
Day 25: Predose	31	49		
Day 25: 4 hours postdose	42	54		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in MADRS Total Score at 4 Hours Post First Dose on Day 1 and Up to the end of the DB Treatment Phase (LOCF Data): DB Treatment Phase

End point title	Change From Baseline in MADRS Total Score at 4 Hours Post First Dose on Day 1 and Up to the end of the DB Treatment Phase (LOCF Data): DB Treatment Phase

End point description:

MADRS is a clinician-rated scale designed to be used in subjects with MDD to measure depression severity and detect changes due to antidepressant treatment. MADRS evaluates apparent sadness,

reported sadness, inner tension, sleep, appetite, concentration, lassitude, interest level, pessimistic thoughts, and suicidal thoughts. The instrument consists of 10 items, each of which is scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms), for a total possible score of 0 to 60. Higher scores represent a more severe condition. Negative change in score indicates improvement. Analysis was performed on full efficacy analysis set. Here 'n' (number analyzed) signifies number of subjects evaluable for each specified time point.

End point type	Secondary

End point timeframe:

Baseline (Day 1, predose), Days 1 (4h postdose), 2, 4, 8, 11, 15, 18, 22 and 25 (predose and 4h postdose)

End point values	Placebo + Standard of Care (SOC)	Esketamine 84 mg + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	114		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Change at Day 1: 4 hours postdose (n= 112, 112)	-8.2 (± 7.62)	-12.2 (± 9.87)		
Change at Day 2 (n= 113, 113)	-12.4 (± 10.43)	-15.7 (± 11.56)		
Change at Day 4 (n= 113, 114)	-15.7 (± 11.51)	-17.3 (± 11.84)		
Change at Day 8 (n= 113, 114)	-17.2 (± 11.46)	-19.4 (± 11.63)		
Change at Day 11 (n= 113, 114)	-19.1 (± 11.87)	-20.7 (± 11.79)		
Change at Day 15 (n= 113, 114)	-19.6 (± 12.69)	-21.9 (± 11.14)		
Change at Day 18 (n= 113, 114)	-20.6 (± 12.99)	-21.6 (± 11.78)		
Change at Day 22 (n= 113, 114)	-20.7 (± 13.00)	-22.6 (± 12.23)		
Change at Day 25: Predose (n= 113, 114)	-20.8 (± 13.24)	-23.9 (± 11.91)		
Change at Day 25: 4 hours postdose (n= 113, 114)	-23.7 (± 12.85)	-25.9 (± 12.21)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CGI-SS-R Score at 4 Hours Post First Dose on Day 1 and up to the End of the DB Treatment Phase (LOCF Data)

End point title	Change From Baseline in CGI-SS-R Score at 4 Hours Post First Dose on Day 1 and up to the End of the DB Treatment Phase (LOCF Data)

End point description:

CGI-SS-R is revised version of the CGI-S. The CGI-SS-R summarizes the clinician's overall impression of severity of suicidality on a 7-point scale from 0 (normal, not at all suicidal) to 6 (among the most extremely suicidal subjects), based on the totality of information available to the clinician. Full efficacy analysis set included all randomized subjects who received at least 1 dose of intranasal study agent during the DB treatment phase and had both a baseline and a post baseline evaluation for the MADRS

total score or CGI-SS-R. Full efficacy analysis set included all randomized subjects who received at least 1 dose of intranasal study agent during the DB treatment phase and had both a baseline and a post baseline evaluation for MADRS total score or CGI-SS-R. Here 'n' (number analyzed) signifies number of subjects evaluable for each specified time point.

End point type	Secondary

End point timeframe:

Baseline (Day 1, predose), Days 1 (4h postdose), 2, 4, 8, 11, 15, 18, 22 and 25

End point values	Placebo + Standard of Care (SOC)	Esketamine 84 mg + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	114		
Units: Units on a scale				
median (full range (min-max))				
Change at Day 1: 4 hours postdose (n= 112, 112)	-1.0 (-4 to 1)	-1.0 (-6 to 1)		
Change at Day 2 (n= 113, 113)	-1.0 (-5 to 2)	-1.0 (-6 to 2)		
Change at Day 4 (n= 113, 114)	-2.0 (-5 to 2)	-2.0 (-6 to 1)		
Change at Day 8 (n= 113, 114)	-2.0 (-5 to 2)	-2.0 (-5 to 2)		
Change at Day 11 (n= 113, 114)	-2.0 (-6 to 2)	-2.0 (-6 to 2)		
Change at Day 15 (n= 113, 114)	-3.0 (-5 to 2)	-3.0 (-6 to 2)		
Change at Day 18 (n= 113, 114)	-3.0 (-6 to 2)	-3.0 (-5 to 2)		
Change at Day 22 (n= 113, 114)	-3.0 (-5 to 3)	-3.0 (-5 to 2)		
Change at Day 25 (n= 113, 114)	-3.0 (-6 to 4)	-3.0 (-6 to 2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Who Achieved Resolution of Suicidality (CGI-SS-R Score of 0 or 1): DB Treatment Phase

End point title	Number of Subjects Who Achieved Resolution of Suicidality (CGI-SS-R Score of 0 or 1): DB Treatment Phase

End point description:

CGI-SS-R is revised version of the CGI-S. The CGI-SS-R summarizes the clinician's overall impression of severity of suicidality on a 7-point scale from 0 (normal, not at all suicidal) to 6 (among the most extremely suicidal subjects), based on the totality of information available to the clinician. A subject was considered to have achieved resolution of suicidality at a given time point if the CGI-SS-R score was 0 (normal, not at all suicidal) or 1 (questionably suicidal). Subjects who did not met such criterion or discontinued prior to the time point for any reason were not considered to have resolution of suicidality. Analysis was performed on full efficacy analysis set.

End point type	Secondary

End point timeframe:

Days 1 (4h postdose), 2, 4, 8, 11, 15, 18, 22 and 25

End point values	Placebo + Standard of Care (SOC)	Esketamine 84 mg + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	114		
Units: Subjects				
Day 1: 4 hours postdose	20	38		
Day 2	35	36		
Day 4	51	52		
Day 8	54	53		
Day 11	58	62		
Day 15	58	65		
Day 18	59	62		
Day 22	65	68		
Day 25	66	69		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Clinical Global Impression of Imminent Suicide Risk (CGI-SR-I) at 4 Hours Post First Dose and up to the end of the DB Treatment Phase (LOCF Data)

End point title	Change From Baseline in Clinical Global Impression of Imminent Suicide Risk (CGI-SR-I) at 4 Hours Post First Dose and up to the end of the DB Treatment Phase (LOCF Data)

End point description:

The CGI-SR-I is a scale summarizing the clinician's best assessment of the likelihood that the subject will attempt suicide in the next 7 days. The CGI-SR-I rating is scored on a 7-point scale: where' 0 (no imminent suicide risk); 1 (minimal imminent suicide risk), 2 (mild imminent suicide risk), 3 (moderate imminent suicide risk), 4 (marked imminent suicide risk), 5 (severely imminent suicide risk), 6 (extreme imminent suicide risk). Negative change in score indicates improvement. Analysis was performed on full efficacy analysis set. Here 'n' (number analyzed) signifies number of subjects evaluable for each specified time point.

End point type	Secondary

End point timeframe:

Baseline (Day 1, predose), Days 1 (4h postdose), 2, 4, 8, 11, 15, 18, 22 and 25

End point values	Placebo + Standard of Care (SOC)	Esketamine 84 mg + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	114		
Units: Units on a scale				
median (full range (min-max))				
Change at Day 1: 4 hours postdose (n= 112, 112)	0.0 (-4 to 2)	-1.0 (-6 to 3)		
Change at Day 2 (n= 113, 113)	-1.0 (-4 to 2)	-1.0 (-6 to 2)		
Change at Day 4 (n= 113, 114)	-2.0 (-5 to 2)	-1.0 (-6 to 1)		
Change at Day 8 (n= 113, 114)	-2.0 (-5 to 2)	-2.0 (-5 to 2)		

Change at Day 11 (n= 113, 114)	-2.0 (-5 to 1)	-2.0 (-6 to 2)		
Change at Day 15 (n= 113, 114)	-2.0 (-5 to 2)	-2.0 (-6 to 2)		
Change at Day 18 (n= 113, 114)	-3.0 (-5 to 2)	-3.0 (-6 to 2)		
Change at Day 22 (n= 113, 114)	-3.0 (-5 to 2)	-3.0 (-6 to 2)		
Change at Day 25 (n= 113, 114)	-3.0 (-5 to 2)	-3.0 (-6 to 2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Beck Hopelessness Scale (BHS) Total Score at Day 8 and 25 in DB Treatment Phase

End point title	Change From Baseline in Beck Hopelessness Scale (BHS) Total Score at Day 8 and 25 in DB Treatment Phase

End point description:

BHS is a self-reported measure to assess one's level of negative expectations or pessimism regarding future. It consists of 20 true-false items that examine respondent's attitude over past week by either endorsing a pessimistic statement or denying an optimistic statement; 9 are keyed false and 11 are keyed true. For every statement, each response was assigned score of 0 or 1. Total BHS score is sum of item responses, ranged from 0-20, where higher score represented higher level of hopelessness. Analysis was performed on full efficacy analysis set. Here 'N' (number of subjects analyzed) signifies number of subjects evaluable for this endpoint and 'n' (number analyzed) signifies number of subjects evaluable for each specified time point.

End point type	Secondary

End point timeframe:

Baseline, Day 8 and 25

End point values	Placebo + Standard of Care (SOC)	Esketamine 84 mg + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	112		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Change at Day 8 (n= 108, 104)	-6.3 (± 6.31)	-6.1 (± 6.17)		
Change at Day 25 (n= 96, 91)	-7.0 (± 6.47)	-8.0 (± 6.31)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Quality of Life Group, 5-Dimension, 5-Level (EQ-5D-5L) Sum Score up to the end of the DB Treatment Phase

End point title	Change From Baseline in European Quality of Life Group, 5-Dimension, 5-Level (EQ-5D-5L) Sum Score up to the end of the DB Treatment Phase

End point description:

EQ-5D-5L consists of EQ-5D-5L descriptive system and EQ visual analogue scale (EQ-VAS). EQ-5D-5L

descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each has 5 levels of perceived problems (no problem, slight, moderate, severe and extreme problems). Subject selects answer for each of 5 dimensions considering response that best matches his/her health "today". Responses were used to generate Health Status Index (HSI). HSI ranges from 0-1.00 (dead-full health). EQ-VAS self-rating records respondent's own assessment of his/her overall health status at time of completion, on a scale of 0 (worst imaginable health)-100 (best imaginable health). Sum score ranges from 0 -100. Higher score indicates worse health state. Analysis was performed on full efficacy analysis set. Here 'N' (number of subjects analyzed) = subjects evaluable for this endpoint and 'n' (number analyzed) = subjects evaluable for each specified time point.

End point type	Secondary

End point timeframe:

Baseline, Days 2, 11 and 25

End point values	Placebo + Standard of Care (SOC)	Esketamine 84 mg + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	113		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Change at Day 2 (n= 111, 107)	-9.0 (± 12.30)	-11.8 (± 14.45)		
Change at Day 11 (n= 103, 103)	-15.1 (± 16.32)	-15.0 (± 15.51)		
Change at Day 25 (n = 95, 92)	-15.3 (± 15.78)	-18.8 (± 16.96)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EQ Visual Analogue Scale Score up to the end of the DB Treatment Phase

End point title	Change From Baseline in EQ Visual Analogue Scale Score up to the end of the DB Treatment Phase

End point description:

EQ-5D-5L is a 2-part instrument for use as a measure of health outcome, designed for self-completion by respondents. It consists of EQ-5D-5L descriptive system and EQ VAS. The EQ VAS self-rating records the respondent's own assessment of his or her overall health status at the time of completion, on a scale of 0 (the worst health you can imagine) to 100 (the best health you can imagine). Analysis was performed on full efficacy analysis set. Here 'N' (number of subjects analyzed) signifies number of subjects evaluable for this endpoint and 'n' (number analyzed) signifies number of subjects evaluable for each specified time point.

End point type	Secondary

End point timeframe:

Baseline, Days 2, 11 and 25

End point values	Placebo + Standard of Care (SOC)	Esketamine 84 mg + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	113		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Change at Day 2 (n = 111, 107)	9.7 (± 15.57)	13.4 (± 22.58)		
Change at Day 11 (n = 103, 103)	17.6 (± 24.87)	21.4 (± 26.95)		
Change at Day 25 (n = 95, 92)	18.6 (± 25.39)	27.0 (± 27.54)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EQ-5D-5L Health Status Index up to the end of the DB Treatment Phase

End point title	Change From Baseline in EQ-5D-5L Health Status Index up to the end of the DB Treatment Phase

End point description:

EQ-5D-5L is a 2-part instrument for use as a measure of health outcome, designed for self-completion by respondents. It consists of EQ-5D-5L descriptive system and EQ VAS. EQ-5D-5L descriptive system comprises of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each has 5 levels of perceived problems (1-no problem, 2-slight problems, 3-moderate problems, 4-severe problems, 5-extreme problems). Subject selects answer for each of 5 dimensions considering response that best matches his/her health "today". Responses were used to generate a HSI. HSI ranges from 0 (dead) to 1.00 (full health). Analysis was performed on full efficacy analysis set. Here ‘N’ (number of subjects analyzed) signifies number of subjects evaluable for this endpoint and ‘n’ (number analyzed) signifies number of subjects evaluable for each specified time point.

End point type	Secondary

End point timeframe:

Baseline, Days 2, 11 and 25

End point values	Placebo + Standard of Care (SOC)	Esketamine 84 mg + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	113		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Change at Day 2 (n = 111, 107)	0.129 (± 0.1732)	0.160 (± 0.1872)		
Change at Day 11 (n = 103, 103)	0.194 (± 0.2173)	0.202 (± 0.2051)		
Change at Day 25 (n = 95, 92)	0.194 (± 0.2149)	0.235 (± 0.2228)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Quality of Life in Depression Scale (QLDS) Score up to the end of the DB Treatment Phase

End point title	Change From Baseline in Quality of Life in Depression Scale (QLDS) Score up to the end of the DB Treatment Phase

End point description:

The QLDS is a disease-specific patient-reported outcome designed to assess health-related quality of life in patients with MDD, it captures the impact of depression and its treatment from the subject's perspective. The instrument has a recall period of "at the moment" and contains 34 items with "true"/"not true" response options. The score range is from 0 (good quality of life) to 34 (very poor quality of life). Analysis was performed on full efficacy analysis set. Here 'N' (number of subjects analyzed) signifies number of subjects evaluable for this endpoint and 'n' (number analyzed) signifies number of subjects evaluable for each specified time point.

End point type	Secondary

End point timeframe:

Baseline, Days 2, 11 and 25

End point values	Placebo + Standard of Care (SOC)	Esketamine 84 mg + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	113		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Change at Day 2 (n = 111, 107)	-2.5 (± 3.93)	-3.5 (± 4.93)		
Change at Day 11 (n = 103, 103)	-5.2 (± 5.55)	-5.1 (± 6.16)		
Change at Day 25 (n = 95, 92)	-5.5 (± 6.03)	-6.3 (± 6.26)		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment Satisfaction Questionnaire for Medication (TSQM-9) Domain Score: DB Treatment Phase

End point title	Treatment Satisfaction Questionnaire for Medication (TSQM-9) Domain Score: DB Treatment Phase

End point description:

The TSQM-9 is a 9-item generic patient-reported outcome instrument to assess subjects' satisfaction with medication. It covers domains of effectiveness, convenience, and global satisfaction. The TSQM-9 domain scores were calculated as recommended by the instrument authors. (i) Effectiveness = [(item 1 + item 2 + item 3) - 3]/18*100, (ii) Convenience = [(item 4 + item 5 + item 6) - 3]/18*100 and (iii) Global satisfaction = [(item 7 + item 8 + item 9) - 3]/14*100. Each domain score can be calculated only if all the three items considered in the calculation of that score are not missing. The TSQM-9 domain scores range from 0 to 100, with higher scores representing higher satisfaction. Analysis was performed on full efficacy analysis. Here 'N' (number of subjects analyzed) signifies number of subjects evaluable for this endpoint and 'n' (number analyzed) signifies number of subjects evaluable for each specified time point for each specified category.

End point type	Secondary

End point timeframe:

Days 11 and 25

End point values	Placebo + Standard of Care (SOC)	Esketamine 84 mg + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	103		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Effectiveness: Day 11 (n= 97, 101)	55.3 (± 27.93)	63.5 (± 26.05)		
Effectiveness: Day 25 (n= 97, 90)	54.8 (± 28.84)	68.8 (± 25.41)		
Convenience: Day 11 (n= 97, 101)	77.2 (± 16.73)	71.3 (± 18.38)		
Convenience: Day 25 (n= 97, 90)	76.9 (± 17.92)	77.0 (± 18.66)		
Global Satisfaction: Day 11 (n= 97, 101)	59.7 (± 27.12)	63.6 (± 27.69)		
Global Satisfaction: Day 25 (n= 97, 90)	56.8 (± 28.31)	71.5 (± 24.85)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Suicide Ideation and Behavior Assessment Tool (SIBAT) Module 5 (My Risk) Question 3 (Subject-Reported Frequency of Suicidal Thinking) Score: DB Treatment Phase

End point title	Change From Baseline in Suicide Ideation and Behavior Assessment Tool (SIBAT) Module 5 (My Risk) Question 3 (Subject-Reported Frequency of Suicidal Thinking) Score: DB Treatment Phase

End point description:

SIBAT is an assessment tool that captures suicidal ideation, behavior, and risk. It permits assessment of change in suicidal ideation and behavior and documents clinician assessment of severity of suicidality and suicide risk. SIBAT is organized into 8 modules divided into 2 major divisions: patient-reported section (Modules 1-5) and clinician-rated section (Modules 6-8). Patient-reported section has modules of demographics and suicide history, risk/protective factors, suicidal thinking, suicide behavior, and suicide risk. Question 3 from Module 5 asks subjects to describe their thinking about suicide right now from 5 response options ranging from 0 (I have no suicidal thoughts) to 4 (I have suicidal thoughts all of time). Analysis was performed on full efficacy analysis set. Here 'N' (number of subjects analyzed) signifies number of subjects evaluable for this endpoint and 'n' (number analyzed) signifies number of subjects evaluable for each specified time point.

End point type	Secondary

End point timeframe:

Baseline, Days 1 (4h postdose), 2, 4, 8, 11, 15, 18, 22 and 25

End point values	Placebo + Standard of Care (SOC)	Esketamine 84 mg + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	114		
Units: Units on a scale				
median (full range (min-max))				
Change at Day 1: 4 hours (n= 111, 109)	-1.0 (-3 to 1)	-1.0 (-4 to 2)		
Change at Day 2 (n= 110, 106)	-1.0 (-4 to 1)	-1.0 (-4 to 2)		
Change at Day 4 (n= 109, 107)	-1.0 (-4 to 1)	-1.0 (-4 to 4)		
Change at Day 8 (n= 105, 98)	-2.0 (-4 to 1)	-2.0 (-4 to 4)		
Change at Day 11 (n= 97, 96)	-2.0 (-4 to 1)	-2.0 (-4 to 4)		
Change at Day 15 (n= 96, 87)	-2.0 (-4 to 0)	-2.0 (-4 to 1)		
Change at Day 18 (n= 89, 92)	-2.0 (-4 to 1)	-2.0 (-4 to 3)		
Change at Day 22 (n= 96, 83)	-2.0 (-4 to 1)	-2.0 (-4 to 3)		
Change at Day 25 (n= 88, 90)	-2.0 (-4 to 1)	-2.0 (-4 to 4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Suicide Ideation and Behavior Assessment Tool (SIBAT) Module 7 (Clinician-rated Frequency of Suicidal Thinking [FoST]) Score: DB Treatment Phase

End point title	Change From Baseline in Suicide Ideation and Behavior Assessment Tool (SIBAT) Module 7 (Clinician-rated Frequency of Suicidal Thinking [FoST]) Score: DB Treatment Phase

End point description:

SIBAT is assessment tool that captures suicidal ideation, behavior, and risk. It permits assessment of change in suicidal ideation and behavior and documents clinician assessment of severity of suicidality and suicide risk. SIBAT has 8 modules divided into 2 major divisions: patient-reported section (Modules 1-5) and clinician-rated section (Modules 6-8). Clinician-rated section has modules for semi-structured interview, clinical global impressions of current severity of suicidality and imminent suicide risk, clinical global impression of long-term suicide risk, and clinical judgment of optimal suicide management. Module 7-FoST score ranges from 0-5; higher score indicates more severe condition. Negative change in score indicates improvement. Analysis was performed on full efficacy analysis set. Here 'N' (number of subjects analyzed) signifies number of subjects evaluable for this endpoint and 'n' (number analyzed) signifies number of subjects evaluable for each specified time point.

End point type	Secondary

End point timeframe:

Baseline, Days 1 (4h postdose), 2, 4, 8, 11, 15, 18, 22 and 25

End point values	Placebo + Standard of Care (SOC)	Esketamine 84 mg + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	114		
Units: Units on a scale				
median (full range (min-max))				
Change at Day 1: 4 hours (n= 112, 112)	-1.0 (-4 to 2)	-1.0 (-5 to 1)		

Change at Day 2 (n= 111, 108)	-1.0 (-5 to 1)	-1.0 (-5 to 1)		
Change at Day 4 (n= 111, 107)	-2.0 (-5 to 1)	-2.0 (-5 to 1)		
Change at Day 8 (n= 105, 99)	-2.0 (-4 to 1)	-2.0 (-5 to 1)		
Change at Day 11 (n= 99, 95)	-2.0 (-5 to 2)	-2.0 (-5 to 1)		
Change at Day 15 (n= 99, 91)	-2.0 (-5 to 2)	-3.0 (-5 to 0)		
Change at Day 18 (n= 90, 84)	-2.0 (-5 to 1)	-3.0 (-5 to 1)		
Change at Day 22 (n= 95, 90)	-2.0 (-5 to 2)	-3.0 (-5 to 2)		
Change at Day 25 (n= 88, 85)	-2.0 (-5 to 4)	-3.0 (-5 to 2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Treatment Emergent Adverse events (TEAEs): DB Treatment Phase

End point title	Number of Subjects with Treatment Emergent Adverse events (TEAEs): DB Treatment Phase

End point description:

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. A TEAE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent. Safety analysis set included all randomized subjects who received at least 1 dose of study drug in the DB treatment phase.

End point type	Secondary

End point timeframe:

Up to Day 25

End point values	Placebo + Standard of Care (SOC)	Esketamine 84 mg + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	114		
Units: Subjects	87	104		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinical Laboratory Abnormal Findings: DB Treatment Phase

End point title	Number of Subjects With Clinical Laboratory Abnormal Findings: DB Treatment Phase

End point description:

Number of subjects with clinical laboratory abnormal findings (serum chemistry, hematology and urinalysis) were reported. Safety analysis set included all randomized subjects who received at least 1

dose of study drug in the DB treatment phase. Here 'N' (number of subjects analyzed) signifies number of subjects evaluable for this endpoint and 'n' (number analyzed) signifies number of subjects evaluable for each specified category. Abbreviations: ALT= alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; GGT = gamma glutamyl transferase; ULN = upper limit of normal.

End point type	Secondary

End point timeframe:

Up to Day 25

End point values	Placebo + Standard of Care (SOC)	Esketamine 84 mg + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	101		
Units: Subjects				
ALT: ALT>3*ULN (n= 92, 97)	2	2		
ALT: Abnormal High (n= 92, 97)	0	0		
Albumin: Abnormal High (n= 101, 101)	0	0		
Albumin: Abnormal Low (n= 101, 101)	0	0		
ALP: Abnormal High (n= 99, 99)	0	0		
AST: AST>3*ULN (90, 97)	0	0		
AST: Abnormal High (90, 97)	0	0		
Bicarbonate: Abnormal High (n= 91, 96)	0	0		
Bicarbonate: Abnormal Low (n= 91, 96)	0	0		
Bilirubin: Abnormal High (n= 92, 97)	0	0		
Calcium: Abnormal High (n= 99, 99)	0	0		
Calcium: Abnormal Low (n= 99, 99)	0	0		
Chloride: Abnormal High (n= 99, 99)	0	0		
Chloride: Abnormal Low (n= 99, 99)	0	0		
Creatine Kinase: Abnormal High (n= 92, 97)	0	0		
Creatinine: Abnormal High (n= 99, 99)	0	0		
GGT: Abnormal High (n= 99, 99)	3	1		
Glucose: Abnormal High (n= 92, 97)	0	1		
Glucose: Abnormal Low (n= 92, 97)	0	0		
ALT>3*ULN or AST>3*ULN and BILI>2*ULN (n= 92, 97)	0	0		
Lactate Dehydrogenase: Abnormal High (n= 86, 89)	0	0		
Phosphate: Abnormal High (n= 101, 101)	0	0		
Phosphate: Abnormal Low (n= 101, 101)	0	1		
Potassium: Abnormal High (n= 99, 99)	1	0		
Potassium: Abnormal Low (n= 99, 99)	0	0		
Protein: Abnormal Low (n= 99, 99)	0	0		
Sodium: Abnormal High (n= 99, 99)	0	0		
Sodium: Abnormal Low (n= 99, 99)	0	0		
Urate: Abnormal High (n= 99, 99)	0	0		
Urate: Abnormal Low (n= 99, 99)	0	0		
Basophils: Abnormal High (n= 87, 94)	0	0		
Eosinophils: Abnormal High (n= 87, 94)	0	0		

Erythrocytes: Abnormal High (n= 87, 94)	0	1		
Erythrocytes: Abnormal Low (n= 87, 94)	0	0		
Hematocrit: Abnormal High (n= 86, 92)	0	2		
Hematocrit: Abnormal Low (n= 86, 92)	0	0		
Hemoglobin: Abnormal High (n= 87, 94)	0	1		
Hemoglobin: Abnormal Low (n= 87, 94)	0	0		
Leukocytes: Abnormal High (n= 87, 94)	1	0		
Leukocytes: Abnormal Low (n= 87, 94)	0	0		
Lymphocytes: Abnormal High (n= 87, 94)	0	0		
Lymphocytes: Abnormal Low (n= 87, 94	2	1		
Monocytes: Abnormal High (n= 87, 94)	0	0		
Neutrophils: Abnormal High (n= 87, 94)	0	0		
Neutrophils: Abnormal Low (n= 87, 94)	0	1		
Platelets: Abnormal High (n= 87, 94)	0	0		
Platelets: Abnormal Low (n= 87, 94)	0	1		
Urine pH: Abnormal High (n= 96, 97)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Abnormal Nasal Examinations at Day 25: DB Treatment Phase

End point title	Number of Subjects With Abnormal Nasal Examinations at Day 25: DB Treatment Phase

End point description:

Number of subjects with abnormal nasal examination were reported. Nasal examination of visual inspection of the nostrils, nasal mucosa, and throat for nasal erythema, rhinorrhea, rhinitis, capillary/blood vessel disruption and epistaxis was performed.

End point type	Secondary

End point timeframe:

at Day 25

End point values	Placebo + Standard of Care (SOC)	Esketamine 84 mg + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	104		
Units: Subjects				
Epistaxis: Mild	1	1		
Epistaxis: Moderate	0	0		
Epistaxis: Severe	0	0		
Nasal Crusts: Mild	0	1		
Nasal Crusts: Moderate	0	0		
Nasal Crusts: Severe	0	0		
Nasal Discharge: Mild	0	1		

Nasal Discharge: Moderate	0	0		
Nasal Discharge: Severe	0	0		
Nasal Erythema: Mild	1	4		
Nasal Erythema: Moderate	1	0		
Nasal Erythema: Severe	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-emergent Abnormal Electrocardiogram (ECG) Values at Any Time: DB Treatment Phase

End point title	Number of Subjects With Treatment-emergent Abnormal Electrocardiogram (ECG) Values at Any Time: DB Treatment Phase

End point description:

Number of subjects with treatment emergent abnormal ECG values for variables including heart rate (abnormally low refers to less than or equal to [<=] 50 beats per minute [bpm] , abnormally high refers greater than or equal to [>=] 100 bpm) , pulse rate interval (abnormally high refers to >= 210 milliseconds [msec]), QRS interval (abnormally Low refers to <= 50, abnormally high refers to >= 120 msec) and QT interval (abnormally low refers to <= 200, abnormally high >= 500 msec) were reported. Safety analysis set included all randomized subjects who received at least 1 dose of study drug in the DB treatment phase. Here 'N' (number of subjects analyzed) signifies number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Up to Day 25

End point values	Placebo + Standard of Care (SOC)	Esketamine 84 mg + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	112		
Units: Subjects				
Heart Rate <= 50 bpm	9	2		
Heart Rate >= 100 bpm	3	2		
PR Duration >= 210 msec	2	2		
QRS Duration <= 50 msec	0	0		
QRS Duration >= 120 msec	1	0		
QT Duration <= 200 msec	0	0		
QT Duration >= 500 msec	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Abnormal Arterial Oxygen Saturation (SpO2)

Levels (less than [<] 93%) as Assessed by Pulse Oximetry at Any Time: DB Treatment Phase

End point title	Number of Subjects with Abnormal Arterial Oxygen Saturation (SpO2) Levels (less than [<] 93%) as Assessed by Pulse Oximetry at Any Time: DB Treatment Phase

End point description:

Pulse oximetry was used to measure arterial SpO2 levels. On each dosing day, the device was attached to the finger, toe, or ear, and SpO2 was monitored and documented. If oxygen saturation levels were less than (<) 93% at any time during the 1.5 hour postdose interval, pulse oximetry was recorded every 5 minutes until levels return to >= 93% or until the subject is referred for appropriate medical care, if clinically indicated. Safety analysis set included all randomized subjects who received at least 1 dose of study drug in the DB treatment phase.

End point type	Secondary

End point timeframe:

Up to Day 25

End point values	Placebo + Standard of Care (SOC)	Esketamine 84 mg + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	114		
Units: Subjects	4	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-emergent Vital Signs Abnormalities: DB Treatment Phase

End point title	Number of Subjects With Treatment-emergent Vital Signs Abnormalities: DB Treatment Phase

End point description:

Number of subjects with treatment-emergent vital signs abnormalities (pulse rate [abnormally low = a decrease from baseline of >= 15 to a value <= 50; abnormally high = an increase from baseline of >=15 to a value >=100] , systolic blood pressure [SBP] [abnormally low = a decrease from baseline of >= 20 to a value <= 90; abnormally high = an increase from baseline of >= 20 to a value >= 180], and diastolic blood pressure [DBP] [abnormally low= a decrease from baseline of >=15 to a value <= 50; abnormally high = an increase from baseline of >= 15 to a value >= 105) were reported. Safety analysis set included all randomized subjects who received at least 1 dose of study drug in the DB treatment phase.

End point type	Secondary

End point timeframe:

Up to Day 25

End point values	Placebo + Standard of Care (SOC)	Esketamine 84 mg + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	114		
Units: Subjects				
Pulse rate: Decrease of >=15 to <=50	2	1		
Pulse rate: Increase of >=15 to >=100	11	12		
SBP: decrease of >=20 to <=90	5	2		
SBP: increase of >=20 to >=180	2	3		
DBP: Decrease of >=15 to <=50	4	4		
DBP: Increase of >=15 to >=105	3	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Sedated Subjects as Assessed by Modified Observer's Assessment of Alertness/Sedation (MOAA/S) Score at any Time: DB Treatment Phase

End point title	Number of Sedated Subjects as Assessed by Modified Observer's Assessment of Alertness/Sedation (MOAA/S) Score at any Time: DB Treatment Phase

End point description:

MOAA/S was used to measure treatment-emergent sedation with correlation to levels of sedation defined by the american society of anesthesiologists (ASA) continuum. The MOAA/S scores range from 0 to 5 where,0 = no response to painful stimulus; ASA continuum = general anesthesia, 1 = responds to trapezius squeeze; ASA continuum = deep sedation, 2 = purposeful response to mild prodding or mild shaking; ASA continuum = moderate sedation, 3 = responds after name called loudly or repeatedly; ASA continuum = moderate sedation, 4 = lethargic response to name spoken in normal tone; ASA continuum = moderate sedation and 5 = readily responds to name spoken in normal tone (awake); ASA continuum = minimal sedation. Safety analysis set included all randomized subjects who received at least 1 dose of study drug in the DB treatment phase.

End point type	Secondary

End point timeframe:

Up to Day 25

End point values	Placebo + Standard of Care (SOC)	Esketamine 84 mg + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	114		
Units: Subjects				
Score <=2: Yes	0	4		
Score <=3: Yes	3	21		
Score <=4: Yes	20	65		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With an Increase in Clinician-administered Dissociative States Scale (CADSS) Total Score: DB Treatment Phase

End point title	Number of Subjects With an Increase in Clinician-administered Dissociative States Scale (CADSS) Total Score: DB Treatment Phase

End point description:

The CADSS is an instrument for the measurement of present-state dissociative symptoms and was administered to assess treatment-emergent dissociative symptoms. The CADSS consists of 23 subjective items, divided into 3 components: depersonalization, derealization, and amnesia. Subject's responses were coded on a 5-point scale (0 = not at all to 4 = extremely). Number of subjects with an increase in CADSS total score (increase based on maximum CADSS total score change from predose of > 0) was reported. Safety analysis set included all randomized subjects who received at least 1 dose of study drug in the DB treatment phase. Here 'N' (number of subjects analyzed) signifies number of subjects evaluable for this endpoint and 'n' (number analyzed) signifies number of subjects evaluable for each specified time point.

End point type	Secondary

End point timeframe:

Days 1, 4, 8, 11, 15, 18, 22 and 25

End point values	Placebo + Standard of Care (SOC)	Esketamine 84 mg + SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111	113		
Units: Subjects				
Day 1 (n= 111, 113)	28	106		
Day 4 (n= 105, 104)	21	86		
Day 8 (n= 106, 98)	16	75		
Day 11 (n= 96, 90)	8	68		
Day 15 (n= 96, 91)	11	68		
Day 18 (n= 88, 80)	8	53		
Day 22 (n= 93, 89)	7	58		
Day 25 (n= 88, 85)	4	56		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From screening up to Day 25

Adverse event reporting additional description:

Safety analysis set included all randomized subjects who received at least 1 dose of study drug in the double-blind treatment phase.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Esketamine 84 mg + SOC

Reporting group description:

Subjects self-administered esketamine 84 milligram (mg) (1 spray containing esketamine 14 mg in each nostril at 0, 5 and 10 minutes using 3 devices on a single day) twice per week for 4 weeks on Days 1, 4, 8, 11, 15, 18, 22, and Day 25 along with SOC antidepressant treatment (determined by physician based on clinical judgment and practice guidelines) on Day 1 and continued for duration of DB treatment phase. After Day 1, a single dose reduction from esketamine 84 mg to esketamine 56 mg was permitted if a subject was unable to tolerate intranasal esketamine 84 mg dose. Subjects for whom dose was reduced continued to receive reduced dose for duration of DB treatment phase.

Reporting group title	Placebo + Standard of Care (SOC)

Reporting group description:

Subjects self-administered intranasal placebo (1 spray in each nostril at 0, 5 and 10 minutes using 3 devices on a single day) twice per week for 4 weeks on days 1, 4, 8, 11, 15, 18, 22, and 25 along with SOC antidepressant treatment (determined by the physician based on clinical judgment and practice guidelines) on Day 1 and continued for the duration of the double-blind (DB) treatment phase.

Serious adverse events	Esketamine 84 mg + SOC	Placebo + Standard of Care (SOC)	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 114 (4.39%)	6 / 113 (5.31%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 114 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial Effusion			
subjects affected / exposed	0 / 114 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal			

disorders			
Pneumothorax			
subjects affected / exposed	0 / 114 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depersonalisation/Derealisation Disorder			
subjects affected / exposed	1 / 114 (0.88%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 114 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal Ideation			
subjects affected / exposed	1 / 114 (0.88%)	2 / 113 (1.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide Attempt			
subjects affected / exposed	3 / 114 (2.63%)	3 / 113 (2.65%)	
occurrences causally related to treatment / all	1 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Esketamine 84 mg + SOC	Placebo + Standard of Care (SOC)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	98 / 114 (85.96%)	73 / 113 (64.60%)	
Investigations			
Blood Pressure Increased			
subjects affected / exposed	7 / 114 (6.14%)	3 / 113 (2.65%)	
occurrences (all)	18	3	
Nervous system disorders			
Dizziness			

subjects affected / exposed	47 / 114 (41.23%)	21 / 113 (18.58%)	
occurrences (all)	177	41	
Dizziness Postural			
subjects affected / exposed	9 / 114 (7.89%)	1 / 113 (0.88%)	
occurrences (all)	20	1	
Dysgeusia			
subjects affected / exposed	29 / 114 (25.44%)	18 / 113 (15.93%)	
occurrences (all)	123	58	
Headache			
subjects affected / exposed	25 / 114 (21.93%)	26 / 113 (23.01%)	
occurrences (all)	32	56	
Hypoaesthesia			
subjects affected / exposed	12 / 114 (10.53%)	1 / 113 (0.88%)	
occurrences (all)	27	5	
Paraesthesia			
subjects affected / exposed	23 / 114 (20.18%)	7 / 113 (6.19%)	
occurrences (all)	53	11	
Sedation			
subjects affected / exposed	16 / 114 (14.04%)	3 / 113 (2.65%)	
occurrences (all)	47	11	
Somnolence			
subjects affected / exposed	26 / 114 (22.81%)	12 / 113 (10.62%)	
occurrences (all)	69	19	
General disorders and administration site conditions			
Feeling Drunk			
subjects affected / exposed	6 / 114 (5.26%)	1 / 113 (0.88%)	
occurrences (all)	17	1	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	7 / 114 (6.14%)	0 / 113 (0.00%)	
occurrences (all)	18	0	
Eye disorders			
Diplopia			
subjects affected / exposed	6 / 114 (5.26%)	0 / 113 (0.00%)	
occurrences (all)	9	0	
Vision Blurred			

subjects affected / exposed	17 / 114 (14.91%)	6 / 113 (5.31%)	
occurrences (all)	26	9	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	7 / 114 (6.14%)	9 / 113 (7.96%)	
occurrences (all)	7	11	
Dry Mouth			
subjects affected / exposed	8 / 114 (7.02%)	5 / 113 (4.42%)	
occurrences (all)	14	9	
Hypoaesthesia Oral			
subjects affected / exposed	7 / 114 (6.14%)	2 / 113 (1.77%)	
occurrences (all)	13	10	
Nausea			
subjects affected / exposed	38 / 114 (33.33%)	16 / 113 (14.16%)	
occurrences (all)	63	31	
Paraesthesia Oral			
subjects affected / exposed	14 / 114 (12.28%)	3 / 113 (2.65%)	
occurrences (all)	32	5	
Vomiting			
subjects affected / exposed	18 / 114 (15.79%)	5 / 113 (4.42%)	
occurrences (all)	21	5	
Respiratory, thoracic and mediastinal disorders			
Nasal Discomfort			
subjects affected / exposed	10 / 114 (8.77%)	9 / 113 (7.96%)	
occurrences (all)	22	28	
Oropharyngeal Pain			
subjects affected / exposed	6 / 114 (5.26%)	3 / 113 (2.65%)	
occurrences (all)	6	3	
Throat Irritation			
subjects affected / exposed	6 / 114 (5.26%)	4 / 113 (3.54%)	
occurrences (all)	14	9	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	6 / 114 (5.26%)	3 / 113 (2.65%)	
occurrences (all)	8	3	
Psychiatric disorders			

Anxiety			
subjects affected / exposed	17 / 114 (14.91%)	7 / 113 (6.19%)	
occurrences (all)	28	7	
Depersonalisation/Derealisation Disorder			
subjects affected / exposed	9 / 114 (7.89%)	0 / 113 (0.00%)	
occurrences (all)	23	0	
Dissociation			
subjects affected / exposed	44 / 114 (38.60%)	9 / 113 (7.96%)	
occurrences (all)	202	28	
Euphoric Mood			
subjects affected / exposed	13 / 114 (11.40%)	1 / 113 (0.88%)	
occurrences (all)	26	1	
Insomnia			
subjects affected / exposed	9 / 114 (7.89%)	11 / 113 (9.73%)	
occurrences (all)	11	12	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 April 2017	The overall reason for the amendment was to update and/or clarify protocol content based on feedback received during study initiation activities.
31 January 2018	The overall reason for the amendment was to remove the interim analysis from the protocol; to clarify that Module 3 suicide ideation and behavior assessment tool (SIBAT) is an exploratory objective; to modify the timing of screening procedures to be consistent with the time and events schedule; to clarify which potential subjects were not excluded from participation in the study due to having a positive screening test for prescribed psychostimulants that are permitted during the study; and updated text regarding the presentation of nasal examination data.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Esketamine’s known characteristic effects such as dissociative symptoms, sedation, and elevation of blood pressure may have impact on blinding, to minimize this bias, protocol specified that different raters perform efficacy and safety assessments.

Notes: