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	2016-003990-17
Trial protocol	SK DE HU ES BG
Global end of trial date	18 December 2018

Results information

Result version number	v1
This version publication date	03 January 2020
First version publication date	03 January 2020

Trial information

Trial identification

Sponsor protocol code	54135419SUI3001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03039192
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Research & Development, LLC
Sponsor organisation address	920 US Route 202, Raritan,, United States, NJ 08869-0602
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	18 December 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this 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 are 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 was evaluated based on the following variables: Adverse events, Clinical laboratory tests (hematology, serum chemistry, and urinalysis), Vital sign measurements, Physical examinations, electrocardiogram (ECG), Nasal examinations, Suicide Ideation and Behavior Assessment Tool (SIBAT), Dosing day assessments (pulse oximetry, MOAA/S, CADSS).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 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	Bulgaria: 19
Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	Spain: 45
Country: Number of subjects enrolled	Estonia: 4
Country: Number of subjects enrolled	Hungary: 15
Country: Number of subjects enrolled	Korea, Republic of: 20
Country: Number of subjects enrolled	Malaysia: 16
Country: Number of subjects enrolled	Taiwan: 17
Country: Number of subjects enrolled	United States: 57
Country: Number of subjects enrolled	South Africa: 15
Worldwide total number of subjects	226
EEA total number of subjects	101

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)	226
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 226 subjects were enrolled and treated. Of the 226 subjects, 114 enrolled in the esketamine nasal spray 84 mg + standard of care (SOC) antidepressant treatment group and 112 enrolled in the placebo nasal spray + SOC antidepressant treatment group.

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 Plus SOC Antidepressant treatment

Arm description:

Subjects self-administered placebo matched to esketamine intranasally (1 spray of placebo to each nostril at 0, 5 and 10 minutes) twice per week for 4 weeks (Days 1, 4, 8, 11, 15, 18, 22, and 25) plus received standard of care (SOC) antidepressant treatment which was initiated or optimized on Day 1.

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

Dosage and administration details:

Subjects self-administered placebo intranasally (1 spray of placebo to each nostril at 0, 5 and 10 minutes) twice per week for 4 weeks (Days 1, 4, 8, 11, 15, 18, 22, and 25).

Arm title	Esketamine 84 mg Plus SOC Antidepressant Treatment

Arm description:

Subjects self-administered esketamine 84 milligram (mg) intranasally (1 spray of esketamine 14 mg to each nostril at 0, 5 and 10 minutes) twice per week for 4 weeks (Days 1, 4, 8, 11, 15, 18, 22, and 25) plus received SOC antidepressant treatment which was initiated or optimized on Day 1.

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

Dosage and administration details:

Subjects self-administered esketamine 84 milligram (mg) intranasally (1 spray of esketamine 14 mg to each nostril at 0, 5 and 10 minutes) twice per week for 4 weeks (Days 1, 4, 8, 11, 15, 18, 22, and 25)

Number of subjects in period 1	Placebo Plus SOC Antidepressant treatment	Esketamine 84 mg Plus SOC Antidepressant Treatment
Started	112	114
Treated	112	113
Completed	80	84
Not completed	32	30
Subject discontinued from treatment phase	19	11
Adverse event, serious fatal	-	1
Adverse event, non-fatal	-	2
Other	3	2
Lost to follow-up	4	4
Randomized, not treated	-	1
Withdrawal by subject	6	9

Baseline characteristics

Reporting groups	
Reporting group title	Placebo Plus SOC Antidepressant treatment
Reporting group description:	
Subjects self-administered placebo matched to esketamine intranasally (1 spray of placebo to each nostril at 0, 5 and 10 minutes) twice per week for 4 weeks (Days 1, 4, 8, 11, 15, 18, 22, and 25) plus received standard of care (SOC) antidepressant treatment which was initiated or optimized on Day 1.	
Reporting group title	Esketamine 84 mg Plus SOC Antidepressant Treatment
Reporting group description:	
Subjects self-administered esketamine 84 milligram (mg) intranasally (1 spray of esketamine 14 mg to each nostril at 0, 5 and 10 minutes) twice per week for 4 weeks (Days 1, 4, 8, 11, 15, 18, 22, and 25) plus received SOC antidepressant treatment which was initiated or optimized on Day 1.	

Reporting group values	Placebo Plus SOC Antidepressant treatment	Esketamine 84 mg Plus SOC Antidepressant Treatment	Total
Number of subjects	112	114	226
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	112	114	226
From 65 to 84 years	0	0	0
85 years and over	0	0	0
Title for AgeContinuous Units: years			
arithmetic mean	37.9	40.8	
standard deviation	± 12.54	± 13.11	-
Title for Gender Units: subjects			
Female	73	66	139
Male	39	48	87

	mg Plus SOC Antidepressant Treatment
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.006
Method	ANCOVA
Parameter estimate	Difference of Least Square Means
Point estimate	-3.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.56
upper limit	-1.09
Variability estimate	Standard error of the mean
Dispersion value	1.39

Secondary: Change From Baseline in Clinical Global Impression of Severity of Suicidality- Revised (CGI-SS-R) Score at 24 hours after the first dose (Day 2) During Double-blind Phase

End point title	Change From Baseline in Clinical Global Impression of Severity of Suicidality- Revised (CGI-SS-R) Score at 24 hours after the first dose (Day 2) During Double-blind Phase

End point description:

CGI-SS-R was derived from the Clinical Global Impression Severity Scale (CGI-S), a global rating scale that gives an overall measure of the severity of a subjects illness. The CGI-SS-R rating is scored on a 7-point scale from 0 (normal, not at all suicidal) to 6 (among the most extremely suicidal subjects) a higher score indicates a more severe condition and a reduction in score indicates improvement (that is, lower severity of suicidality). Full efficacy analysis set included all randomized subjects who received at least 1 dose of intranasal study agent during the double-blind phase and have had both a baseline and a postbaseline evaluation for the MADRS total score or CGI-SS-R. 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 Plus SOC Antidepressant treatment	Esketamine 84 mg Plus SOC Antidepressant Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	111		
Units: Unit on a scale				
median (full range (min-max))	-1.0 (-5 to 1)	-1.0 (-6 to 2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Who Achieved Remission (MADRS Total Score Less Than or Equal to [<=] 12) Through the Double-blind Phase

End point title	Number of Subjects Who Achieved Remission (MADRS Total Score Less Than or Equal to [<=] 12) Through the Double-blind Phase

End point description:

Subjects who had a MADRS total score of <=12 were considered remitters. MADRS is clinician-rated scale designed to measure depression severity, and to detect changes due to antidepressant treatment. Scale consists of 10 items (apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, interest level, pessimistic thoughts, and suicidal thoughts), each of which is scored from 0 (item is not present or is normal) to 6 (severe or continuous presence of symptoms), summed for a total possible score of 0 to 60. Higher scores represent more severe condition and a 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 the double-blind phase and have had both a baseline and a post-baseline evaluation for the MADRS total score or CGI-SS-R.

End point type	Secondary

End point timeframe:

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

End point values	Placebo Plus SOC Antidepressant treatment	Esketamine 84 mg Plus SOC Antidepressant Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	112		
Units: Subjects				
Day 1:(4 Hours)	9	12		
Day 2:	10	21		
Day 4	13	28		
Day 8	23	30		
Day 11	26	33		
Day 15	29	38		
Day 18	30	42		
Day 22	25	41		
Day 25 (Predose)	38	46		
Day 25 (4 hours postdose)	42	60		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Montgomery Asberg Depression Rating Scale Total Score During Double-blind Phase

End point title	Change From Baseline in Montgomery Asberg Depression Rating Scale Total Score During Double-blind Phase

End point description:

MADRS is clinician-rated scale designed to measure depression severity, and to detect changes due to antidepressant treatment. Scale consists of 10 items (apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, interest level, pessimistic thoughts, and suicidal thoughts), each of which is scored from 0 (item is not present or is normal) to 6 (severe or continuous presence of symptoms), summed for a total possible score of 0 to 60. Higher scores represent more severe condition and a 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 the double-blind phase and have had both a baseline and a post-baseline evaluation for the MADRS total score or CGI-SS-R. Here, 'n' (number analyzed) signifies number of subjects who were evaluable at specified time points.

End point type	Secondary

End point timeframe:

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

End point values	Placebo Plus SOC Antidepressant treatment	Esketamine 84 mg Plus SOC Antidepressant Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	112		
Units: Unit on a Scale				
arithmetic mean (standard deviation)				
Day 1 (n=112,110)	-10.9 (± 9.69)	-13.5 (± 10.89)		
Day 2 (n=111, 111)	-12.9 (± 10.72)	-16.4 (± 11.95)		
Day 4 (n=110, 109)	-14.5 (± 11.39)	-19.1 (± 12.29)		
Day 8 (n=108, 104)	-17.4 (± 12.59)	-19.7 (± 12.91)		
Day 11(n=103, 100)	-19.0 (± 12.08)	-21.8 (± 12.20)		
Day 15 (n=99, 104)	-20.4 (± 12.19)	-22.3 (± 11.70)		
Day 18 (n=94, 102)	-21.4 (± 12.00)	-23.9 (± 11.77)		
Day 22 (n=92, 103)	-21.6 (± 12.32)	-24.0 (± 12.38)		
Day 25: predose (n=92, 94)	-23.0 (± 12.41)	-24.8 (± 13.63)		
Day 25: 4 hours postdose (n=88, 94)	-25.8 (± 10.94)	-29.5 (± 10.89)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Clinical Global Impression- Severity of Suicidality-Revised (CGI-SS-R) Through the Double-blind Phase

End point title	Change From Baseline in Clinical Global Impression- Severity of Suicidality-Revised (CGI-SS-R) Through the Double-blind Phase

End point description:

CGI-SS-R was derived from the Clinical Global Impression Severity Scale (CGI-S), a global rating scale that gives an overall measure of the severity of a subjects illness. The CGI-SS-R rating is scored on a 7-point scale from 0 (normal, not at all suicidal) to 6 (among the most extremely suicidal subjects). A higher score indicates a 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 the double-blind phase and have had both a baseline and a post-baseline evaluation for the MADRS total score or CGI-SS-R. Here, 'n' (number analyzed) signifies number of subjects who were evaluable at specified time points.

End point type	Secondary

End point timeframe:

Baseline and Days 1, 2, 4, 8, 11, 15, 18, 22 and 25

End point values	Placebo Plus SOC Antidepressant treatment	Esketamine 84 mg Plus SOC Antidepressant Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	112		
Units: Unit on a scale				
median (full range (min-max))				
Day 1 (n=112,110)	0.0 (-5 to 1)	-1.0 (-6 to 1)		
Day 2 (n=112, 112)	-1.0 (-5 to 1)	-1.0 (-6 to 2)		
Day 4 (n=110, 110)	-1.0 (-5 to 1)	-2.0 (-6 to 2)		
Day 8 (n=108, 105)	-2.0 (-5 to 0)	-2.0 (-6 to 1)		
Day 11 (n=102,101)	-2.0 (-5 to 1)	-3.0 (-6 to 1)		
Day 15 (n=99, 105)	-2.0 (-5 to 0)	-3.0 (-5 to 0)		
Day 18 (n=94, 103)	-2.5 (-5 to 0)	-3.0 (-6 to 1)		
Day 22 (n=91, 105)	-3.0 (-5 to 1)	-3.0 (-6 to 1)		
Day 25 (n=93, 96)	-3.0 (-5 to 1)	-3.0 (-6 to 1)		

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) Total score Through Double-blind Phase

End point title	Number of Subjects Who Achieved Resolution of Suicidality (CGI-SS-R Score of 0 or 1) Total score Through Double-blind Phase

End point description:

CGI-SS-R was derived from the Clinical Global Impression Severity Scale (CGI-S), a global rating scale that gives an overall measure of the severity of a subjects illness. The CGI-SS-R rating is scored on a 7-point scale from 0 (normal, not at all suicidal) to 6 (among the most extremely suicidal subjects). A higher score indicates a more severe condition. Negative change in score indicates improvement. A subject was considered to achieve 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). Full efficacy analysis set included all randomized subjects who received at least 1 dose of intranasal study agent during the double-blind phase and have had both a baseline and a post-baseline evaluation for the MADRS total score or CGI-SS-R.

End point type	Secondary

End point timeframe:

Days 1, 2, 4, 8, 11, 15, 18, 22 and 25

End point values	Placebo Plus SOC Antidepressant treatment	Esketamine 84 mg Plus SOC Antidepressant Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	112		
Units: Subjects				
Day 1	25	37		
Day 2	39	42		
Day 4	45	49		
Day 8	48	53		
Day 11	46	60		
Day 15	52	68		
Day 18	55	68		
Day 22	62	70		
Day 25	57	71		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Clinical Global Impression of Imminent Suicide Risk (CGI-SR-I) Scale Total Score Through Double-blind Phase

End point title	Change From Baseline in Clinical Global Impression of Imminent Suicide Risk (CGI-SR-I) Scale Total Score Through Double-blind Phase

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 from 0 (no imminent suicide risk) to 6 (extreme imminent suicide risk). Score ranges from 0-6. A higher score indicates a more severe condition. Full efficacy analysis set included all randomized subjects who received at least 1 dose of intranasal study agent during the double-blind phase and have had both a baseline and a post-baseline evaluation for the MADRS total score or CGI-SS-R. Here, 'n' (number analyzed) signifies number of subjects who were evaluable at specified time points.

End point type	Secondary

End point timeframe:

Baseline and Days 1, 2, 4, 8, 11, 15, 18, 22 and 25

End point values	Placebo Plus SOC Antidepressant treatment	Esketamine 84 mg Plus SOC Antidepressant Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	112		
Units: Units on a scale				
median (full range (min-max))				
Day 1 (n=112,110)	0.0 (-4 to 2)	-1.0 (-5 to 3)		
Day 2 (n= 112, 112)	-1.0 (-5 to 2)	-1.0 (-5 to 2)		
Day 4 (n=110, 110)	-1.0 (-5 to 2)	-2.0 (-5 to 2)		
Day 8 (n=108, 105)	-2.0 (-5 to 2)	-2.0 (-6 to 1)		

Day 11 (n=102,101)	-2.0 (-5 to 1)	-2.0 (-6 to 1)		
Day 15 (n=99, 105)	-2.0 (-5 to 2)	-3.0 (-5 to 2)		
Day 18 (n=94, 103)	-3.0 (-5 to 1)	-3.0 (-5 to 2)		
Day 22 (n=91,105)	-3.0 (-5 to 1)	-3.0 (-6 to 1)		
Day 25 (n=93, 96)	-3.0 (-5 to 2)	-3.0 (-6 to 1)		

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 During Double-blind Phase

End point title	Change From Baseline in Beck Hopelessness Scale (BHS) Total Score at Day 8 and 25 During Double-blind Phase

End point description:

BHS is a self-reported measure consists of 20 true-false items. 9 are keyed false and 11 are keyed true. These items fall within 3 domains: feelings about the future; loss of motivation; future expectations. For every statement, each response was assigned a score of 0 or 1. Total score is a sum of item responses. Ranges from 0-20. Total scores 0-3 are normal range, 4-8 identify mild hopelessness, 9-14 identify moderate hopelessness, greater than 14 identify severe hopelessness. Full efficacy analysis set included all randomized subjects who received at least 1 dose of intranasal study agent during double-blind phase and have 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 who were evaluable at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Day 8 and 25

End point values	Placebo Plus SOC Antidepressant treatment	Esketamine 84 mg Plus SOC Antidepressant Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	112		
Units: Unit on a scale				
arithmetic mean (standard deviation)				
Day 8 (n=108, 111)	-4.4 (± 6.03)	-5.3 (± 6.06)		
Day 25 (n=98, 105)	-6.6 (± 6.63)	-6.9 (± 6.92)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EuroQol-5 Dimension-5 Level (EQ-5D-5L) Through Double-blind Phase: Health Status Index

End point title	Change From Baseline in EuroQol-5 Dimension-5 Level (EQ-5D-5L) Through Double-blind Phase: Health Status Index

End point description:

EQ-5D-5L measures health outcome. It consists of EQ-5D-5L descriptive system and EQ visual analogue

scale (EQ-VAS). EQ-5D-5L system comprises following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each of 5 dimensions is divided into 5 levels of perceived problems (Level 1-no problem, Level 2-slight problems, Level 3-moderate problems, Level 4-severe problems, Level 5-extreme problems). Health Status Index ranges from 0.148 - 0.949, anchored at 0 (dead) and 1 (full health), a lower score indicates worse health. Full efficacy analysis set included all randomized subjects who received at least 1 dose of intranasal study agent during double-blind phase, have 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 who were evaluable at specified time points.

End point type	Secondary

End point timeframe:

Baseline and Days 2, 11 and 25

End point values	Placebo Plus SOC Antidepressant treatment	Esketamine 84 mg Plus SOC Antidepressant Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	112		
Units: Unit on a scale				
arithmetic mean (standard deviation)				
Day 2 (n=110, 111)	0.096 (± 0.1785)	0.156 (± 0.1944)		
Day 11 (n=107, 106)	0.169 (± 0.2139)	0.206 (± 0.2043)		
Day 25 (n=97, 104)	0.189 (± 0.2336)	0.227 (± 0.2078)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EuroQol-5 Dimension-5 Level (EQ-5D-5L) Through Double-blind Phase: EQ-VAS

End point title	Change From Baseline in EuroQol-5 Dimension-5 Level (EQ-5D-5L) Through Double-blind Phase: EQ-VAS

End point description:

EQ-5D-5L measures health outcome. It consists of EQ-5D-5L descriptive system and the EQ visual analogue scale (EQ-VAS). EQ-5D-5L system comprises following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each of 5 dimensions is divided into 5 levels of perceived problems (Level 1-no problem, Level 2-slight problems, Level 3-moderate problems, Level 4-severe problems, and Level 5-extreme problems). EQ-VAS score from 0 (worst health) to 100 (best health), positive change in score indicates improvement. Full efficacy analysis set included all randomized subjects who received at least 1 dose of intranasal study agent during double-blind phase, have 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 who were evaluable at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Days 2, 11 and 25

End point values	Placebo Plus SOC Antidepressant treatment	Esketamine 84 mg Plus SOC Antidepressant Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	112		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Day 2 (n=110, 111)	7.8 (± 17.32)	13.5 (± 20.78)		
Day 11 (n=107, 106)	16.3 (± 22.27)	17.9 (± 24.55)		
Day 25 (n=97, 104)	20.0 (± 23.49)	21.4 (± 26.71)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EuroQol-5 Dimension-5 Level (EQ-5D-5L) Through Double-blind Phase: Sum Score

End point title	Change From Baseline in EuroQol-5 Dimension-5 Level (EQ-5D-5L) Through Double-blind Phase: Sum Score

End point description:

EQ-5D-5L measures health outcome. It consists of EQ-5D-5L system and EQ-VAS. EQ-5D-5L system comprises following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each of 5 dimensions is divided into 5 levels of perceived problems (Level 1-no problem, Level 2-slight problems, Level 3-moderate problems, Level 4-severe problems, and Level 5-extreme problems). Sum score=(sum of the scores from the 5 dimensions minus 5)*5”. Higher score indicates a more severe problem. 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 double-blind phase, have 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 who were evaluable at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Days 2, 11 and 25

End point values	Placebo Plus SOC Antidepressant treatment	Esketamine 84 mg Plus SOC Antidepressant Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	112		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Day 2 (n= 110, 111)	-6.1 (± 12.28)	-11.2 (± 14.87)		
Day 11 (n= 107, 106)	-12.3 (± 16.23)	-15.2 (± 15.75)		
Day 25 (n= 97, 104)	-13.4 (± 18.05)	-16.8 (± 16.30)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Quality of Life in Depression Scale (QLDS) Total Score Through Double-blind Phase

End point title	Change From Baseline in Quality of Life in Depression Scale (QLDS) Total Score Through Double-blind Phase

End point description:

The QLDS is a disease specific patient-reported outcome designed to assess health related quality of life in subjects with major depressive disorder (MDD). The instrument has a recall period of "at the moment", contains 34-items with "yes"/"no" or "true"/"not true" response options and takes approximately 5-10 minutes to complete. The score range is from 0 (good quality of life) to 34 (very poor quality of life). A higher score indicates a more severe condition. Negative change indicates improvement. Full efficacy analysis set included all randomized subjects who received at least 1 dose of intranasal study agent during the double-blind phase and have had both a baseline and a post-baseline evaluation for the MADRS total score or CGI-SS-R. Here, 'n' (number analyzed) signifies number of subjects who were evaluable at specified time points.

End point type	Secondary

End point timeframe:

Baseline and Days 2, 11 and 25

End point values	Placebo Plus SOC Antidepressant treatment	Esketamine 84 mg Plus SOC Antidepressant Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	112		
Units: Unit on a scale				
arithmetic mean (standard deviation)				
Day 2 (n=110, 112)	-2.5 (± 4.55)	-3.1 (± 5.14)		
Day 11 (n=107, 106)	-4.4 (± 5.93)	-5.6 (± 5.92)		
Day 25 (n= 97, 104)	-5.6 (± 5.99)	-6.8 (± 5.97)		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment Satisfaction Questionnaire for Medication (TSQM-9) Total Score Through Double-blind Phase

End point title	Treatment Satisfaction Questionnaire for Medication (TSQM-9) Total Score Through Double-blind Phase

End point description:

The TSQM-9 is a 9-item generic patient-reported outcome instrument to assess subject's satisfaction

with medication. It covers three domains (effectiveness, convenience, and global satisfaction) were each scored from 0 to 100 with a higher score indicating higher satisfaction and a lower score indicates lower satisfaction. Full efficacy analysis set included all randomized subjects who received at least 1 dose of intranasal study agent during the double-blind phase and have had both a baseline and a post-baseline evaluation for the MADRS total score or CGI-SS-R. Here, 'n' (number analyzed) signifies number of subjects who were evaluable at specified time points.

End point type	Secondary

End point timeframe:

Days 15 and 25

End point values	Placebo Plus SOC Antidepressant treatment	Esketamine 84 mg Plus SOC Antidepressant Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	112		
Units: Units on a scale				

End point values	Placebo Plus SOC Antidepressant treatment	Esketamine 84 mg Plus SOC Antidepressant Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	112		
Units: Units on a scale				
median (full range (min-max))				
Day 1 (n=111, 110)	0.0 (-4 to 2)	0.0 (-3 to 1)		
Day 2 (n=111, 110)	-1.0 (-4 to 1)	-1.0 (-4 to 2)		
Day 4 (n=110, 108)	-1.0 (-4 to 2)	-1.0 (-4 to 1)		
Day 8 (n=108, 104)	-1.0 (-4 to 1)	-1.0 (-4 to 1)		
Day 11 (n=103, 100)	-1.0 (-4 to 1)	-1.5 (-4 to 1)		
Day 15 (n=100, 104)	-1.0 (-4 to 1)	-2.0 (-4 to 1)		
Day 18 (n=94, 101)	-2.0 (-4 to 1)	-2.0 (-4 to 1)		
Day 22 (n= 92, 104)	-2.0 (-4 to 2)	-2.0 (-4 to 1)		
Day 25 (n=93, 96)	-2.0 (-4 to 1)	-2.0 (-4 to 1)		

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 FoST Total Score During Double-blind Phase

End point title	Change From Baseline in Suicide Ideation and Behavior Assessment Tool (SIBAT) Module 7 – Clinician-rated FoST Total Score During Double-blind Phase

End point description:

SIBAT Module 7 Assessment of frequency of suicidal thinking (FoST) is a clinician-reported global impression with response options of “Never”, “Rarely”, “Sometimes”, “Often”, “Most of the time”, and “All of the time.” The score ranges from 0 to 5. A higher score indicates a 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 the double-blind phase and have had both a baseline and a post-baseline evaluation for the MADRS total score or CGI-SS-R. Here, 'n' (number analyzed) signifies number of subjects who were evaluable at specified time points.

End point type	Secondary

End point timeframe:

Baseline and Days 1, 2, 4, 8, 11, 15, 18, 22 and 25

End point values	Placebo Plus SOC Antidepressant treatment	Esketamine 84 mg Plus SOC Antidepressant Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	112		
Units: Units on a scale				
median (full range (min-max))				

Day 1 (n=112, 109)	-1.0 (-5 to 2)	-1.0 (-5 to 1)		
Day 2 (n=112, 111)	-1.0 (-5 to 1)	-1.0 (-5 to 1)		
Day 4 (n=110, 109)	-1.0 (-5 to 1)	-2.0 (-5 to 2)		
Day 8 (n=108, 104)	-2.0 (-5 to 2)	-2.0 (-5 to 1)		
Day 11 (n=102, 100)	-2.0 (-5 to 2)	-2.0 (-5 to 2)		
Day 15 (n=99, 104)	-2.0 (-5 to 0)	-2.0 (-5 to 1)		
Day 18 (n=94, 102)	-2.0 (-5 to 1)	-2.0 (-5 to 1)		
Day 22 (n=91, 104	-2.0 (-5 to 1)	-2.0 (-5 to 1)		
Day 25 (n=93, 95)	-2.0 (-5 to 1)	-3.0 (-5 to 1)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 13 Weeks	
Adverse event reporting additional description:	
Safety analysis set included all randomized subjects who received at least 1 dose of study agent 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 Plus SOC Antidepressant Treatment
Reporting group description:	
Subjects self-administered esketamine 84 milligram (mg) intranasally (1 spray of esketamine 14 mg to each nostril at 0, 5 and 10 minutes) twice per week for 4 weeks (Days 1, 4, 8, 11, 15, 18, 22, and 25) plus SOC antidepressant treatment which was initiated on Day 1.	
Reporting group title	Placebo Plus SOC Antidepressant treatment (Placebo)
Reporting group description:	
Subjects self-administered placebo intranasally (1 spray of placebo to each nostril at 0, 5 and 10 minutes) twice per week for 4 weeks (Days 1, 4, 8, 11, 15, 18, 22, and 25) plus standard of care (SOC) antidepressant treatment which was initiated on Day 1.	

Serious adverse events	Esketamine 84 mg Plus SOC Antidepressant Treatment	Placebo Plus SOC Antidepressant treatment (Placebo)	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 113 (3.54%)	6 / 112 (5.36%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	0 / 113 (0.00%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 113 (0.00%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			

subjects affected / exposed	1 / 113 (0.88%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression Suicidal			
subjects affected / exposed	2 / 113 (1.77%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal Ideation			
subjects affected / exposed	0 / 113 (0.00%)	2 / 112 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide Attempt			
subjects affected / exposed	1 / 113 (0.88%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic Ketoacidosis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
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 Plus SOC Antidepressant Treatment	Placebo Plus SOC Antidepressant treatment (Placebo)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	91 / 113 (80.53%)	66 / 112 (58.93%)	
Investigations			
Blood Pressure Increased			
subjects affected / exposed	19 / 113 (16.81%)	6 / 112 (5.36%)	
occurrences (all)	47	8	
Nervous system disorders			
Dizziness			
subjects affected / exposed	40 / 113 (35.40%)	10 / 112 (8.93%)	
occurrences (all)	187	19	

Dizziness Postural			
subjects affected / exposed	6 / 113 (5.31%)	2 / 112 (1.79%)	
occurrences (all)	24	2	
Dysgeusia			
subjects affected / exposed	16 / 113 (14.16%)	11 / 112 (9.82%)	
occurrences (all)	89	46	
Headache			
subjects affected / exposed	21 / 113 (18.58%)	20 / 112 (17.86%)	
occurrences (all)	29	33	
Hypoaesthesia			
subjects affected / exposed	8 / 113 (7.08%)	2 / 112 (1.79%)	
occurrences (all)	42	3	
Sedation			
subjects affected / exposed	7 / 113 (6.19%)	2 / 112 (1.79%)	
occurrences (all)	16	2	
Somnolence			
subjects affected / exposed	21 / 113 (18.58%)	11 / 112 (9.82%)	
occurrences (all)	79	32	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	7 / 113 (6.19%)	1 / 112 (0.89%)	
occurrences (all)	18	1	
Eye disorders			
Vision Blurred			
subjects affected / exposed	10 / 113 (8.85%)	5 / 112 (4.46%)	
occurrences (all)	18	12	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	15 / 113 (13.27%)	5 / 112 (4.46%)	
occurrences (all)	15	5	
Nausea			
subjects affected / exposed	23 / 113 (20.35%)	15 / 112 (13.39%)	
occurrences (all)	38	16	
Vomiting			
subjects affected / exposed	8 / 113 (7.08%)	7 / 112 (6.25%)	
occurrences (all)	9	9	
Psychiatric disorders			

Anxiety			
subjects affected / exposed	6 / 113 (5.31%)	10 / 112 (8.93%)	
occurrences (all)	6	13	
Dissociation			
subjects affected / exposed	33 / 113 (29.20%)	4 / 112 (3.57%)	
occurrences (all)	166	9	
Insomnia			
subjects affected / exposed	7 / 113 (6.19%)	7 / 112 (6.25%)	
occurrences (all)	9	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 April 2017	The overall reason for the amendment was to revise based on comments received during an initial Voluntary Harmonisation Procedure (VHP) assessment; the following changes are included: Duration of hospitalization without the need for discussion with the Sponsor updated, A remote contact at Day 35 was added to the Time and Events Schedule, Exclusion criteria were revised to explicitly specify a detailed list of important medical conditions which are exclusionary, Text was added to emphasize that subjects may participate in the study only if they have adequate capacity to give consent and after fully understanding the potential risks, benefits, and potential adverse events of the study.
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. Exclusion criterion was revised to clarify which potential subjects are excluded from participation in the study due to substance or alcohol use disorder, a positive urine test result; to clarify that subjects who were previously enrolled in this study or the Sponsor's other studies in this population (54135419SUI3002 and ESKETINSUI2001) are excluded from participation in this study.
08 February 2018	The overall reason for the amendment was to remove the interim analysis from the 54135419SUI3001 protocol; to clarify that Module 3 Suicide Ideation and Behavior Assessment Tool (SIBAT) was 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 54135419SUI3001 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 has known effects that may impact blinding, these treatment-emergent events potentially could have biased research staff. To minimize this bias, protocol specified that different raters perform efficacy, safety assessments.

Notes: