Clinical trial results:
A Randomized, Double-blind, Multicenter, Active-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Flexible Doses of Intranasal Esketamine Plus an Oral Antidepressant in Adult Subjects with Treatment-resistant Depression

Summary

EudraCT number	2014-004585-22
Trial protocol	DE PL ES CZ
Global end of trial date	06 November 2017

Results information

Result version number	v1 (current)
This version publication date	09 November 2018
First version publication date	09 November 2018

Trial information

Trial identification

Sponsor protocol code	ESKETINTRD3002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02418585
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	06 November 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the efficacy of switching adult subjects with treatment-resistant depression (TRD) from a prior antidepressant treatment (to which they have not responded) to flexibly dosed intranasal esketamine (56 milligram [mg] or 84 mg) plus a newly initiated oral antidepressant compared with switching to a newly initiated oral antidepressant (active comparator) plus intranasal placebo, in improving depressive symptoms, as assessed by the change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) total score from Day 1 (pre-randomization) to the end of the 4-week double-blind induction phase.

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.The safety assessments included adverse events, clinical laboratory, Vital sign measurements, Physical examinations, height, body weight, and neck circumference, Electrocardiogram (ECG), Pulse oximetry, Nasal examinations and nasal symptom questionnaire, Columbia-Suicide Severity Rating Scale (C-SSRS), Clinician-Administered Dissociative States Scale (CADSS), Brief Psychiatric Rating Scale (BPRS+), Modified Observer's Assessment of Alertness/Sedation (MOAA/S), Clinical Global Assessment of Discharge Readiness (CGADR), Physician Withdrawal Checklist; 20-Item (PWC-20), Bladder Pain / Interstitial Cystitis Symptom Score (BPIC-SS), Cognition testing, University of Pennsylvania Smell Identification Test (UPSIT) and Smell Threshold Test

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 August 2015
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	Czech Republic: 59
Country: Number of subjects enrolled	Germany: 20
Country: Number of subjects enrolled	Spain: 18
Country: Number of subjects enrolled	Poland: 39
Country: Number of subjects enrolled	United States: 91
Worldwide total number of subjects	227
EEA total number of subjects	136

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)	227
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 227 subjects with a Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnosis of major depressive disorder (MDD) were randomly assigned to treatment in which 116 subjects in Arm A and 111 subjects in Arm B, out of which 98 subjects from arm A and 99 subjects from arm B completed the study.

Period 1

Period 1 title	Overall Study
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	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)

Arm description:

Subjects self-administered esketamine either 56 milligram (mg) or 84 mg intranasally twice weekly for 4 weeks (on Day 1, 4, 8, 11, 15, 18, 22 and 25) as determined by investigator based on efficacy and tolerability in Double-Blind(DB) Induction Phase. Subjects simultaneously initiated titration schedule for open-label Oral antidepressant (AD) with one of the following four oral AD that was not used in current depression episode: [Duloxetine (60 mg/day during Weeks 1-4 with minimum dose for tolerability at 30 mg/day); Escitalopram (10 mg/day during Week 1 and 20 mg/day during Weeks 2-4 with minimum dose for tolerability at 10 mg/day); Sertraline (50 mg/day during Week 1, 100 mg/day during Week 2, 150 mg/day during Week 3 and 200 mg/day during Week 4 with minimum dose for tolerability of 50 mg/Day) or Venlafaxine XR (75 mg/day during Week 1, 150 mg/day during Week 2, and 225 mg/day during Weeks 3 and 4 with minimum dose for tolerability of 75 mg/day) during DB Induction Phase.

Arm type	Experimental
Investigational medicinal product name	Esketamine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray
Routes of administration	Intranasal use

Dosage and administration details:

Subjects self-administered esketamine 56 mg or 84 mg twice weekly for 4 weeks (on Day 1, 4, 8, 11, 15, 18, 22 and 25) during Double-Blind Induction Phase.

Investigational medicinal product name	Sertraline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received an open-label antidepressant (AD) Sertraline (50 mg/day during Week 1, 100 mg/day during Week 2, 150 mg/day during Week 3 and 200 mg/day during Week 4 with minimum dose for tolerability of 50 mg/Day) during Double-Blind Induction Phase.

Investigational medicinal product name	Venlafaxine XR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received an open-label AD Venlafaxine XR 75 mg/day during Week 1, 150 mg/day during Week 2, and 225 mg/day during Weeks 3 and 4 with minimum dose for tolerability of 75 mg/day) during Double-Blind Induction Phase.

Investigational medicinal product name	Escitalopram
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received an open-label AD escitalopram 10 mg/day during Week 1 and 20 mg/day during Weeks 2-4 with minimum dose for tolerability at 10 mg/day during Double-Blind Induction Phase.

Investigational medicinal product name	Duloxetine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received an open-label AD Duloxetine (60 mg/day during Weeks 1-4 with minimum dose for tolerability at 30 mg/day).

Arm title	Oral AD Plus Intranasal Placebo

Arm description:

Subjects self-administered esketamine matched placebo intranasally twice weekly for 4 weeks (on Day 1, 4, 8, 11, 15, 18, 22 and 25) as determined by investigator based on efficacy and tolerability in the Double-Blind Induction Phase. Subjects simultaneously initiated titration schedule for open-label Oral antidepressant (AD) with one of the following four oral AD that was not used in current depression episode: [Duloxetine (60 mg/day during Weeks 1-4 with minimum dose for tolerability at 30 mg/day); Escitalopram (10 mg/day during Week 1 and 20 mg/day during Weeks 2-4 with minimum dose for tolerability at 10 mg/day); Sertraline (50 mg/day during Week 1, 100 mg/day during Week 2, 150 mg/day during Week 3 and 200 mg/day during Week 4 with minimum dose for tolerability of 50 mg/Day) or Venlafaxine XR (75 mg/day during Week 1, 150 mg/day during Week 2, and 225 mg/day during Weeks 3 and 4 with minimum dose for tolerability of 75 mg/day) during DB Induction Phase.

Arm type	Active comparator
Investigational medicinal product name	Sertraline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Sertraline (50 mg/day during Week 1, 100 mg/day during Week 2, 150 mg/day during Week 3 and 200 mg/day during Week 4 with minimum dose for tolerability of 50 mg/Day).

Investigational medicinal product name	Venlafaxine XR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Venlafaxine XR (75 mg/day during Week 1, 150 mg/day during Week 2, and 225 mg/day during Weeks 3 and 4 with minimum dose for tolerability of 75 mg/day).

Investigational medicinal product name	Escitalopram
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received escitalopram (10 mg/day during Week 1 and 20 mg/day during Weeks 2-4 with

minimum dose for tolerability at 10 mg/day).

Investigational medicinal product name	Duloxetine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Duloxetine (60 mg/day during Weeks 1-4 with minimum dose for tolerability at 30 mg/day).

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

Dosage and administration details:

Subjects self-administered esketamine matched placebo intranasally twice weekly for 4 weeks (on Day 1, 4, 8, 11, 15, 18, 22 and 25) in the Double-Blind Induction Phase.

Number of subjects in period 1	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)	Oral AD Plus Intranasal Placebo
Started	116	111
Completed	98	99
Not completed	18	12
Consent withdrawn by subject	4	7
Adverse Event	9	1
Other	-	1
Lost to follow-up	1	1
Protocol deviation	2	2
Lack of efficacy	2	-

Period 2

Period 2 title	Follow-up Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes

Arm title	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD

Arm description:

Participants who were not eligible or who chose to not participate in the maintenance of effect study (ESKETINTRD3003) and had received at least 1 dose of intranasal study medication (Esketamine (Esk) Plus Oral Antidepressant (AD) in the double-blind induction phase were followed in posttreatment follow-up phase for up to 24 weeks in duration, to assess safety and tolerability of intranasal study medication, including potential withdrawal symptoms.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Oral AD Plus Intranasal Placebo

Arm description:

Participants who were not eligible or who chose to not participate in the maintenance of effect study (ESKETINTRD3003) and had received at least 1 dose of intranasal study medication (Oral AD Plus Intranasal Placebo) in the double-blind induction phase were followed in posttreatment follow-up phase for up to 24 weeks in duration, to assess safety and tolerability of intranasal study medication, including potential withdrawal symptoms.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2[1]	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD	Oral AD Plus Intranasal Placebo
Started	34	52
Completed	16	27
Not completed	18	25
Withdrawn	6	3
Unspecified	3	2
PI to discontinue FU, proceed to 54135419TRD3008	6	17
Lost to follow-up	3	3

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Subjects in follow up phase included subjects who were not eligible or who chose to not participate in the maintenance of effect study (ESKETINTRD3003) and therefore number of subjects starting the period is not consistent with the number completing the preceding period.

Baseline characteristics

Reporting groups

Reporting group title	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)

Reporting group description:

Subjects self-administered esketamine either 56 milligram (mg) or 84 mg intranasally twice weekly for 4 weeks (on Day 1, 4, 8, 11, 15, 18, 22 and 25) as determined by investigator based on efficacy and tolerability in Double-Blind(DB) Induction Phase. Subjects simultaneously initiated titration schedule for open-label Oral antidepressant (AD) with one of the following four oral AD that was not used in current depression episode: [Duloxetine (60 mg/day during Weeks 1-4 with minimum dose for tolerability at 30 mg/day); Escitalopram (10 mg/day during Week 1 and 20 mg/day during Weeks 2-4 with minimum dose for tolerability at 10 mg/day); Sertraline (50 mg/day during Week 1, 100 mg/day during Week 2, 150 mg/day during Week 3 and 200 mg/day during Week 4 with minimum dose for tolerability of 50 mg/Day) or Venlafaxine XR (75 mg/day during Week 1, 150 mg/day during Week 2, and 225 mg/day during Weeks 3 and 4 with minimum dose for tolerability of 75 mg/day) during DB Induction Phase.

Reporting group title	Oral AD Plus Intranasal Placebo

Reporting group description:

Subjects self-administered esketamine matched placebo intranasally twice weekly for 4 weeks (on Day 1, 4, 8, 11, 15, 18, 22 and 25) as determined by investigator based on efficacy and tolerability in the Double-Blind Induction Phase. Subjects simultaneously initiated titration schedule for open-label Oral antidepressant (AD) with one of the following four oral AD that was not used in current depression episode: [Duloxetine (60 mg/day during Weeks 1-4 with minimum dose for tolerability at 30 mg/day); Escitalopram (10 mg/day during Week 1 and 20 mg/day during Weeks 2-4 with minimum dose for tolerability at 10 mg/day); Sertraline (50 mg/day during Week 1, 100 mg/day during Week 2, 150 mg/day during Week 3 and 200 mg/day during Week 4 with minimum dose for tolerability of 50 mg/Day) or Venlafaxine XR (75 mg/day during Week 1, 150 mg/day during Week 2, and 225 mg/day during Weeks 3 and 4 with minimum dose for tolerability of 75 mg/day) during DB Induction Phase.

Reporting group values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)	Oral AD Plus Intranasal Placebo	Total
Number of subjects	116	111	227
Title for AgeCategorical Units: subjects			
Adults (18-64 years)	116	111	227
Title for AgeContinuous Units: years			
arithmetic mean	45.2	46.7	
standard deviation	± 12.57	± 11.23	-
Title for Gender Units: subjects			
Female	77	65	142
Male	39	46	85

End points

End points reporting groups

Reporting group title	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)

Reporting group description:

Subjects self-administered esketamine either 56 milligram (mg) or 84 mg intranasally twice weekly for 4 weeks (on Day 1, 4, 8, 11, 15, 18, 22 and 25) as determined by investigator based on efficacy and tolerability in Double-Blind(DB) Induction Phase. Subjects simultaneously initiated titration schedule for open-label Oral antidepressant (AD) with one of the following four oral AD that was not used in current depression episode: [Duloxetine (60 mg/day during Weeks 1-4 with minimum dose for tolerability at 30 mg/day); Escitalopram (10 mg/day during Week 1 and 20 mg/day during Weeks 2-4 with minimum dose for tolerability at 10 mg/day); Sertraline (50 mg/day during Week 1, 100 mg/day during Week 2, 150 mg/day during Week 3 and 200 mg/day during Week 4 with minimum dose for tolerability of 50 mg/Day) or Venlafaxine XR (75 mg/day during Week 1, 150 mg/day during Week 2, and 225 mg/day during Weeks 3 and 4 with minimum dose for tolerability of 75 mg/day) during DB Induction Phase.

Reporting group title	Oral AD Plus Intranasal Placebo

Reporting group description:

Subjects self-administered esketamine matched placebo intranasally twice weekly for 4 weeks (on Day 1, 4, 8, 11, 15, 18, 22 and 25) as determined by investigator based on efficacy and tolerability in the Double-Blind Induction Phase. Subjects simultaneously initiated titration schedule for open-label Oral antidepressant (AD) with one of the following four oral AD that was not used in current depression episode: [Duloxetine (60 mg/day during Weeks 1-4 with minimum dose for tolerability at 30 mg/day); Escitalopram (10 mg/day during Week 1 and 20 mg/day during Weeks 2-4 with minimum dose for tolerability at 10 mg/day); Sertraline (50 mg/day during Week 1, 100 mg/day during Week 2, 150 mg/day during Week 3 and 200 mg/day during Week 4 with minimum dose for tolerability of 50 mg/Day) or Venlafaxine XR (75 mg/day during Week 1, 150 mg/day during Week 2, and 225 mg/day during Weeks 3 and 4 with minimum dose for tolerability of 75 mg/day) during DB Induction Phase.

Reporting group title	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD

Reporting group description:

Participants who were not eligible or who chose to not participate in the maintenance of effect study (ESKETINTRD3003) and had received at least 1 dose of intranasal study medication (Esketamine (Esk) Plus Oral Antidepressant (AD) in the double-blind induction phase were followed in posttreatment follow-up phase for up to 24 weeks in duration, to assess safety and tolerability of intranasal study medication, including potential withdrawal symptoms.

Reporting group title	Oral AD Plus Intranasal Placebo

Reporting group description:

Participants who were not eligible or who chose to not participate in the maintenance of effect study (ESKETINTRD3003) and had received at least 1 dose of intranasal study medication (Oral AD Plus Intranasal Placebo) in the double-blind induction phase were followed in posttreatment follow-up phase for up to 24 weeks in duration, to assess safety and tolerability of intranasal study medication, including potential withdrawal symptoms.

Primary: Change from Baseline in Montgomery-Asberg Depression Rating Scale (MADRS) Total Score up to End of 4-Week (Day 28) Double-blind Induction Phase

End point title	Change from Baseline in Montgomery-Asberg Depression Rating Scale (MADRS) Total Score up to End of 4-Week (Day 28) Double-blind Induction Phase

End point description:

MADRS is clinician-rated scale designed to measure depression severity, to detect changes due to antidepressant treatment. Scale consists of 10 items (evaluates apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, inability to feel [interest level], pessimistic thoughts and suicidal thoughts), each is scored from 0 (item is not present or is normal) to 6 (severe or continuous presence of symptoms), for total possible score range of 0-60. FAS defined as all randomized subjects who received at least 1 dose of intranasal study medication, 1 dose of oral antidepressant medication during double-blind induction phase (D-BIP). Here 'N' signifies number of subjects who were evaluable for this endpoint. Last post-baseline observation during the D-BIP was carried forward as endpoint for that phase. Missing data was imputed using LOCF method and the last post baseline observation during the phase was carried forward as “End Point” for that phase.

End point type	Primary

End point timeframe:

Baseline up to the End-point (last post-baseline assessment value during 4 weeks of IND period)

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)	Oral AD Plus Intranasal Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	109		
Units: Units on a scale				
arithmetic mean (standard deviation)	-19.6 (± 13.58)	-16.3 (± 14.24)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD) v Oral AD Plus Intranasal Placebo
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.034
Method	ANCOVA
Parameter estimate	Difference of Least Square (LS) Means
Point estimate	-3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.67
upper limit	-0.26

Secondary: Percentage of Subjects with Onset of Clinical Response on Day 2 and Day 8

End point title	Percentage of Subjects with Onset of Clinical Response on Day 2 and Day 8

End point description:

A subject is defined as having a clinical response if there is at least 50% improvement from baseline in the MADRS total score with onset by Day 2 and Day 8 that was maintained to Day 28. Subjects are allowed one excursion (non-response) on Days 8, 15 or 22, however the score must show at least 25% improvement. Subjects who do not meet such criterion or discontinue during the study before Day 28 for any reason were considered as non-responders. FAS is defined as all randomized subjects who received at least 1 dose of intranasal study medication and 1 dose of oral antidepressant medication during the double-blind induction phase.

End point type	Secondary

End point timeframe:

Day 2 and 8

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)	Oral AD Plus Intranasal Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	109		
Units: Percentage of subjects				
number (not applicable)				
With clinical response on Day 2	7.9	4.6		
With clinical response on Day 8	10.5	6.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Sheehan Disability Scale (SDS) Total Score up to End of 4-Week (Day 28) Double-blind Induction Phase

End point title	Change From Baseline in Sheehan Disability Scale (SDS) Total Score up to End of 4-Week (Day 28) Double-blind Induction Phase

End point description:

SDS: Subject-reported outcome measure and 5 item questionnaire used for assessment of functional impairment and associated disability. First three items assess disruption of 1 work/school, 2 social life, 3 family life/home responsibilities using a 0(no impairment)-10 (most severe impairment). Score for first 3 items are summed to create total score of 0-30 where higher score indicates greater impairment and a negative change in score indicates improvement. FAS set is defined as all randomized subjects who received at least 1 dose of intranasal study medication and 1 dose of oral AD medication during double-blind induction phase. Here 'N' signifies number of subjects who were evaluable for this endpoint. Missing data was imputed using LOCF method and the last post baseline observation during the phase was carried forward as “End Point” for that phase.

End point type	Secondary

End point timeframe:

Baseline up to the End-point (last post-baseline assessment value during 4 weeks of IND period)

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)	Oral AD Plus Intranasal Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	89		
Units: Units on a scale				
arithmetic mean (standard deviation)	-12.5 (± 8.85)	-9.3 (± 8.39)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Patient Health Questionnaire – 9-Item Depression Module (PHQ-9) Total Score up to End of 4-Week (Day 28) Double-blind Induction Phase

End point title	Change From Baseline in Patient Health Questionnaire – 9-Item Depression Module (PHQ-9) Total Score up to End of 4-Week (Day 28) Double-blind Induction Phase

End point description:

PHQ-9 is 9-item, self-report scale assessing depressive symptoms. Each item is rated on 4-point scale (0=Not at all, 1=Several Days, 2=More than half days, 3=Nearly every day), total score range of 0-27. Higher score indicates greater severity of depression. Scale scores each of 9 symptom domains of Diagnostic and Statistical Manual of Mental Disorders, Major Depressive Disorder criteria and it has been used both as screening tool and measure of response to treatment for depression. Severity of PHQ-9 categorized as follows: None-minimal (0-4), Mild (5 9), Moderate (10-14), Moderately Severe (15-19), Severe (20-27). FAS: all randomized subjects who received at least 1 dose of intranasal study medication and 1 dose of oral AD medication during D-BIP.'N' signifies number of subjects who were evaluable for this endpoint. Missing data was imputed using LOCF method, last post baseline observation during the phase was carried forward as "End Point" for that phase.

End point type	Secondary

End point timeframe:

Baseline up to the End-point (last post-baseline assessment value during 4 Weeks of IND period)

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)	Oral AD Plus Intranasal Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111	105		
Units: Units on a scale				
arithmetic mean (standard deviation)	-12.2 (± 6.87)	-10.1 (± 7.87)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Achieved >=50% Reduction from Baseline in MADRS Total Score at the End of 4-week Double-Blind Induction Phase

End point title	Percentage of Subjects Who Achieved >=50% Reduction from Baseline in MADRS Total Score at the End of 4-week Double-Blind Induction Phase

End point description:

A subject is defined as a responder at a given time point if the percent improvement from baseline in MADRS total score is at least 50%. The percent of subjects with greater than or equal to (>=50) % improvement from baseline is reported. FAS: all randomized subjects who received at least 1 dose of intranasal study medication and 1 dose of oral antidepressant medication during the double-blind induction phase. Here 'N' signifies number of subjects who were evaluable for this endpoint. Missing data was imputed using last observed carried forward (LOCF) method and the last post baseline observation during the phase was carried forward as "End Point" for that phase.

End point type	Secondary

End point timeframe:

At Day 28 [end of Double-Blind Induction Phase (Week 4)]

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)	Oral AD Plus Intranasal Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	109		
Units: Percentage of subjects				
number (not applicable)	63.4	49.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects in Remission (MADRS<=12) at the End of 4-week (Day 28) Double-Blind Induction Phase

End point title	Percentage of Subjects in Remission (MADRS<=12) at the End of 4-week (Day 28) Double-Blind Induction Phase

End point description:

Subjects called as remitters who have a MADRS total score of less than or equal to (=<) 12. FAS defined as all randomized subjects who received at least 1 dose of intranasal study medication and 1 dose of oral antidepressant medication during the double-blind induction phase. Here 'N' signifies number of subjects who were evaluable for this endpoint. Missing data was imputed using last observed carried forward (LOCF) method and the last post baseline observation during the phase was carried forward as "End Point" for that phase.

End point type	Secondary

End point timeframe:

At Day 28 [end of Double-Blind Induction Phase (Week 4)]

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)	Oral AD Plus Intranasal Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	109		
Units: Percentage of subjects				
number (not applicable)	48.2	30.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects in Response (SDS<=12) at the End of 4-week Double-Blind Induction Phase

End point title	Percentage of Subjects in Response (SDS<=12) at the End of 4-week Double-Blind Induction Phase

End point description:

Response defined as SDS total score =< 12 and individual item scores each =< 4. SDS is a subject-reported outcome measure and is a 5 item questionnaire used and accepted for assessment of functional impairment and associated disability. First three items assess disruption of (1) work/school, (2) social life and (3) family life/home responsibilities using a 0 (no impairment)-10 (greater impairment) rating scale. It also has one item on days lost from school or work and one item on days when under productive. Score for first three items are summed to create a total score of 0-30 where higher score indicates greater impairment. FAS defined as all randomized subjects who received at least 1 dose of intranasal study medication and 1 dose of oral antidepressant medication during the double-blind induction phase. Here 'N'(number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

At Day 28 [end of Double-Blind Induction Phase (Week 4)]

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)	Oral AD Plus Intranasal Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	86		
Units: Percentage of subjects				
number (not applicable)	57.0	39.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects in Remission (SDS<=12) at the End of 4-week Double-Blind Induction Phase

End point title	Percentage of Subjects in Remission (SDS<=12) at the End of 4-week Double-Blind Induction Phase

End point description:

Remission defined as SDS total score =< 6 and individual item scores each =< 2. SDS is a subject-reported outcome measure and is a 5 item questionnaire which has been widely used and accepted for assessment of functional impairment and associated disability. The first three items assess disruption of (1) work/school, (2) social life, and (3) family life/home responsibilities using a 0-10 rating scale. The score for the first three items are summed to create a total score of 0-30 where a higher score indicates greater impairment. It also has one item on days lost from school or work and one item on days when underproductive. Here 'N'(number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint. FAS defined as all randomized subjects who received at least 1 dose of intranasal study medication and 1 dose of oral antidepressant medication during the double-blind induction phase.

End point type	Secondary

End point timeframe:

At Day 28 [end of Double-Blind Induction Phase (Week 4)]

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)	Oral AD Plus Intranasal Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	86		
Units: Percentage of Subjects				
number (not applicable)	39.5	20.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Clinical Global Impression-Severity (CGI-S) Total Score up to End of 4-Week (Day 28) Double-blind Induction Phase

End point title	Change From Baseline in Clinical Global Impression-Severity (CGI-S) Total Score up to End of 4-Week (Day 28) Double-blind Induction Phase

End point description:

CGI-S provides measure of severity of subject's illness including subject's history, psychosocial circumstances, symptoms, behavior and impact of symptoms on ability to function. CGI-S evaluates severity of psychopathology on scale of 0 to 7. Considering total clinical experience, subject is assessed on severity of mental illness according to: 0=not assessed; 1=normal (not at all ill); 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=among most extremely ill patients. CGI-S permits global evaluation of subject's condition at given time. FAS: all randomized subjects who received atleast 1 dose of intranasal study medication, 1 dose of oral antidepressant medication during double-blind induction phase. 'N':number of subjects who were evaluable for this endpoint. Missing data was imputed using LOCF method and last post baseline observation during the phase was carried forward as "End Point" for that phase.

End point type	Secondary

End point timeframe:

Baseline up to the End-point (last post-baseline assessment value during 4 Weeks of IND period)

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)	Oral AD Plus Intranasal Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111	109		
Units: Units on a scale				
median (full range (min-max))	-2.0 (-5 to 1)	-2.0 (-5 to 1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Generalized Anxiety Disorder (GAD-7) Total Score up to End of 4-Week (Day 28) Double-blind Induction Phase

End point title	Change From Baseline in Generalized Anxiety Disorder (GAD-7) Total Score up to End of 4-Week (Day 28) Double-blind Induction Phase

End point description:

GAD-7 is a brief and validated 7-item self-report assessment of overall anxiety. Subjects respond to each item using a 4-point scale with response categories of 0=not at all, 1=several days, 2=more than half the days, and 3=nearly every day. Item responses are summed to yield a total score with a range of 0 to 21, where higher scores indicate more anxiety. The recall period is 2 weeks. The severity of the GAD-7 is categorized as follows: None (0-4), Mild (5-9), Moderate (10-14) and Severe (15 -21). FAS defined as all randomized subjects who received at least 1 dose of intranasal study medication and 1 dose of oral antidepressant medication during the double-blind induction phase. Here 'N'(number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint. Missing data was imputed using last observed carried forward (LOCF) method and the last post baseline observation during the phase was carried forward as "End Point" for that phase.

End point type	Secondary

End point timeframe:

Baseline up to the End-point (last post-baseline assessment value during 4 Weeks of IND period)

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)	Oral AD Plus Intranasal Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	102		
Units: Units on a scale				
arithmetic mean (standard deviation)	-7.9 (± 6.12)	-6.8 (± 5.75)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Endpoint in Health-Related Quality of Life and Health Status as European Quality of Life (EuroQol) Group, 5-Dimension, 5-Level (EQ 5D-5L) During Double-blind Induction Phase

End point title	Change From Baseline to Endpoint in Health-Related Quality of Life and Health Status as European Quality of Life (EuroQol) Group, 5-Dimension, 5-Level (EQ 5D-5L) During Double-blind Induction Phase

End point description:

EQ-5D-5L measures health outcome self-completed by respondents. It consists of EQ visual analogue scale (EQ VAS), EQ-5D-5L descriptive system. It comprises of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. Each has 5 levels (1-no problem, 2-slight problems, 3-moderate problems, 4-severe problems, 5-extreme problems). Health Status Index range is -0.148 - 0.949, is anchored at 0 (dead) and 1 (full health), EQ-VAS score from 0 (worst health you can imagine) to 100 (best health you can imagine), Sum score from 0 - 100, Sum score=(sum of scores from 5 dimensions - 5) by 5". SD in EQ-5D health status index score from baseline (IND) to endpoint (4 weeks) was evaluated. FAS defined as all randomized subjects who received at least 1 dose of intranasal study

medication and 1 dose of oral antidepressant medication during the double-blind induction phase. 'N' signifies number of subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to the End-point (last post-baseline assessment value during 4 Weeks of IND period)

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)	Oral AD Plus Intranasal Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111	105		
Units: Units on a Scale				
arithmetic mean (standard deviation)				
Health Status Index	0.288 (± 0.2317)	0.231 (± 0.2506)		
EQ VAS Score	29.1 (± 26.32)	20.9 (± 26.60)		
Sum Score	-23.2 (± 16.64)	-17.1 (± 19.66)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Approximately up to 2.2 Years

Adverse event reporting additional description:

The safety analysis set included all randomized subjects who received at least 1 dose of intranasal study medication or 1 dose of oral antidepressant medication during the double-blind induction phase.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Oral AD Plus Intranasal Placebo

Reporting group description:

Subjects self-administered esketamine matched placebo intranasally twice weekly for 4 weeks (on Day 1, 4, 8, 11, 15, 18, 22 and 25) as determined by investigator based on efficacy and tolerability in the Double-Blind Induction Phase. Subjects simultaneously initiated titration schedule for open-label Oral antidepressant (AD) with one of the following four oral AD that was not used in current depression episode: [Duloxetine (60 mg/day during Weeks 1-4 with minimum dose for tolerability at 30 mg/day); Escitalopram (10 mg/day during Week 1 and 20 mg/day during Weeks 2-4 with minimum dose for tolerability at 10 mg/day); Sertraline (50 mg/day during Week 1, 100 mg/day during Week 2, 150 mg/day during Week 3 and 200 mg/day during Week 4 with minimum dose for tolerability of 50 mg/Day) or Venlafaxine XR (75 mg/day during Week 1, 150 mg/day during Week 2, and 225 mg/day during Weeks 3 and 4 with minimum dose for tolerability of 75 mg/day) during DB Induction Phase.

Reporting group title	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)

Reporting group description:

Subjects self-administered esketamine either 56 milligram (mg) or 84 mg intranasally twice weekly for 4 weeks (on Day 1, 4, 8, 11, 15, 18, 22 and 25) as determined by investigator based on efficacy and tolerability in Double-Blind(DB) Induction Phase. Subjects simultaneously initiated titration schedule for open-label Oral antidepressant (AD) with one of the following four oral AD that was not used in current depression episode: [Duloxetine (60 mg/day during Weeks 1-4 with minimum dose for tolerability at 30 mg/day); Escitalopram (10 mg/day during Week 1 and 20 mg/day during Weeks 2-4 with minimum dose for tolerability at 10 mg/day); Sertraline (50 mg/day during Week 1, 100 mg/day during Week 2, 150 mg/day during Week 3 and 200 mg/day during Week 4 with minimum dose for tolerability of 50 mg/Day) or Venlafaxine XR (75 mg/day during Week 1, 150 mg/day during Week 2, and 225 mg/day during Weeks 3 and 4 with minimum dose for tolerability of 75 mg/day) during DB Induction Phase.

Serious adverse events	Oral AD Plus Intranasal Placebo	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 109 (0.92%)	1 / 115 (0.87%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Multiple Injuries			

subjects affected / exposed	0 / 109 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Road Traffic Accident			
subjects affected / exposed	0 / 109 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ear and labyrinth disorders			
Vertigo Positional			
subjects affected / exposed	1 / 109 (0.92%)	0 / 115 (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	Oral AD Plus Intranasal Placebo	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	52 / 109 (47.71%)	90 / 115 (78.26%)	
Investigations			
Blood Pressure Increased			
subjects affected / exposed	0 / 109 (0.00%)	11 / 115 (9.57%)	
occurrences (all)	0	22	
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 109 (4.59%)	24 / 115 (20.87%)	
occurrences (all)	5	59	
Dizziness Postural			
subjects affected / exposed	1 / 109 (0.92%)	8 / 115 (6.96%)	
occurrences (all)	1	43	
Dysgeusia			
subjects affected / exposed	13 / 109 (11.93%)	28 / 115 (24.35%)	
occurrences (all)	61	151	
Headache			

subjects affected / exposed	19 / 109 (17.43%)	23 / 115 (20.00%)	
occurrences (all)	29	33	
Hypoaesthesia			
subjects affected / exposed	1 / 109 (0.92%)	8 / 115 (6.96%)	
occurrences (all)	1	26	
Paraesthesia			
subjects affected / exposed	1 / 109 (0.92%)	13 / 115 (11.30%)	
occurrences (all)	1	44	
Somnolence			
subjects affected / exposed	7 / 109 (6.42%)	15 / 115 (13.04%)	
occurrences (all)	11	65	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	6 / 109 (5.50%)	5 / 115 (4.35%)	
occurrences (all)	6	6	
Feeling Drunk			
subjects affected / exposed	1 / 109 (0.92%)	9 / 115 (7.83%)	
occurrences (all)	7	50	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	3 / 109 (2.75%)	30 / 115 (26.09%)	
occurrences (all)	6	157	
Eye disorders			
Vision Blurred			
subjects affected / exposed	3 / 109 (2.75%)	14 / 115 (12.17%)	
occurrences (all)	14	69	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	10 / 109 (9.17%)	10 / 115 (8.70%)	
occurrences (all)	15	13	
Dry Mouth			
subjects affected / exposed	3 / 109 (2.75%)	9 / 115 (7.83%)	
occurrences (all)	5	23	
Hypoaesthesia Oral			
subjects affected / exposed	1 / 109 (0.92%)	9 / 115 (7.83%)	
occurrences (all)	1	34	

Nausea			
subjects affected / exposed	7 / 109 (6.42%)	30 / 115 (26.09%)	
occurrences (all)	8	73	
Paraesthesia Oral			
subjects affected / exposed	1 / 109 (0.92%)	9 / 115 (7.83%)	
occurrences (all)	1	28	
Vomiting			
subjects affected / exposed	2 / 109 (1.83%)	11 / 115 (9.57%)	
occurrences (all)	2	16	
Respiratory, thoracic and mediastinal disorders			
Nasal Discomfort			
subjects affected / exposed	2 / 109 (1.83%)	8 / 115 (6.96%)	
occurrences (all)	2	33	
Throat Irritation			
subjects affected / exposed	5 / 109 (4.59%)	9 / 115 (7.83%)	
occurrences (all)	14	23	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	5 / 109 (4.59%)	12 / 115 (10.43%)	
occurrences (all)	5	18	
Dissociation			
subjects affected / exposed	4 / 109 (3.67%)	30 / 115 (26.09%)	
occurrences (all)	14	173	
Insomnia			
subjects affected / exposed	5 / 109 (4.59%)	11 / 115 (9.57%)	
occurrences (all)	5	11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 January 2016	Revised inclusion criteria to 1. specify that the criteria for non-response to oral antidepressant treatments in current episode of depression was less than or equal to (=<)25% improvement; specify that at the start of the screening/prospective observational phase, non-response to oral antidepressant treatment was to be documented on the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH-ATRQ) (oral antidepressant must have been taken for at least 6 weeks at the minimum therapeutic dose with a lack of clinically meaningful improvement), 2. indicate that the severity of a subject's depressive symptoms in the current major depressive episode was to be confirmed using a Site Independent Qualification Assessment to ensure enrollment of subjects who have symptoms that reflect the current state of illness, 3. include a lab test which measures levels of free thyroxine if thyroid-stimulating hormone values are out of range, 4. clarify the criteria for assessing pregnancy in women of childbearing potential, and 5. update criteria for methods of birth control. Revised exclusion criteria to 1. exclude subjects with at least 7 bilateral electroconvulsive therapy treatments, 2. exclude subjects who received vagal nerve stimulation in the current depressive episode, 3. exclude subjects with autism spectrum disorder 4. clarify that subjects with major depressive disorder (MDD) with psychotic features are excluded 5. update the list of cardiovascular conditions for exclusion of subjects with coronary artery disease, 6. clarify the definition of clinically significant ECG abnormalities, 7. permit use of concomitant medications that prolong the QT interval/corrected QT interval, 8. include a repeat screening test for abnormal alanine aminotransferase and aspartate aminotransferase values, 9. clarify a positive test for cannabinoids at screening is not exclusionary 10. clarify that uncontrolled diabetes is exclusionary.
03 June 2016	Revised inclusion criteria to update minimum antidepressant treatment requirements at study entry to non-response to greater than equal to (=>)1 oral antidepressant treatments (from non-response to ≥2 oral antidepressant treatments) and to update the minimum amount of time the current oral antidepressant treatment must have been taken to at least 2 weeks (from at least 6 weeks); these changes allowed subjects to document non-response to a second oral antidepressant treatment for a minimum of 6 weeks and meet the criteria for Treatment-Resistant Depression (TRD) during the 4-week screening/prospective observational phase. The inclusion criteria were also revised to update the definition of non-response at the end of the screening/prospective observational phase to ≤25% improvement in the MADRS total score from Week 1 to Week 4 and a MADRS total score of ≥28 on Week 2 and Week 4 (from ≤25% improvement in the MADRS total score for 2 consecutive visits and a MADRS total score of ≥28 for 2 consecutive visits), to specify the same requirements for contraception for female partners of male subjects as specified for female subjects, and to clarify inclusion of subjects who have thyroid-stimulating hormone outside the normal ranges was permitted. Revised exclusion criteria to delete the exclusion for first degree atrioventricular (AV) block, allow prescription use of psychostimulants with dosing restrictions on intranasal treatment session days, and clarified exclusion of subjects based on obstructive sleep apnea. Reordered the list of key secondary objectives, evaluations, and endpoints to correspond to the revised order of the planned analysis. Deleted the interim analysis for sample size re-estimation. Revised the analysis of onset of clinical response to indicate that subjects were allowed one excursion.

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.

As this was a flexible-dose study, dose-response relationships could not be evaluated because direct comparisons between dose groups could not be made.

Notes: