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

Summary

EudraCT number	2014-004584-20
Trial protocol	BE SK HU PL
Global end of trial date	20 February 2018

Results information

Result version number	v1 (current)
This version publication date	06 March 2019
First version publication date	06 March 2019

Trial information

Trial identification

Sponsor protocol code	ESKETINTRD3001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02417064
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen-Cilag International NV
Sponsor organisation address	Turnhoutseweg 30, Beerse, Belgium, 2340
Public contact	Clinical Registry Group, Janssen-Cilag International NV, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen-Cilag International NV, 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	20 February 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 February 2018
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 had not responded) to 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. Safety evaluations included monitoring of adverse events (AEs), clinical laboratory tests (hematology, serum chemistry, and urinalysis), vital sign’s (temperature, pulse/heart rate, respiratory rate, blood pressure [BP]), physical examinations (height, body weight, and neck circumference), electrocardiograms (ECG's), pulse oximetry, nasal examinations and nasal symptom questionnaire, columbia-suicide severity rating scale (C-SSRS), clinician administered dissociative states scale (CADSS), four-item positive symptom subscale of the 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), computerized cognitive battery, hopkins verbal learning testrevised (HVLT-R), university of pennsylvania smell identification test (UPSIT), and smell threshold test.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 September 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	Belgium: 30
Country: Number of subjects enrolled	Brazil: 57
Country: Number of subjects enrolled	Canada: 20
Country: Number of subjects enrolled	Estonia: 10
Country: Number of subjects enrolled	France: 31
Country: Number of subjects enrolled	Hungary: 6
Country: Number of subjects enrolled	Mexico: 45
Country: Number of subjects enrolled	Slovakia: 10
Country: Number of subjects enrolled	United States: 137

Worldwide total number of subjects	346
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)	346
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 346 subjects with treatment-resistant depression (TRD) were randomly assigned to receive treatment- intranasal esketamine (Esk) 56 mg+oral AD (117 subjects), intranasal Esk 84 mg+oral AD (116 subjects), or oral AD+intranasal placebo (113 subjects), out of which 111, 97 and 107 subjects completed the double-blind phase respectively.

Period 1

Period 1 title	Double-blind Induction Phase
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 56 mg Plus Oral Antidepressant

Arm description:

Subjects self-administered 56 mg of intranasal esketamine (Esk) twice per week for 4 weeks in double-blind (DB) induction phase. Also, subjects simultaneously initiated new oral antidepressant (AD) with one of following: duloxetine (60 milligram [mg]/day- Weeks 1, 2, 3 and 4), escitalopram (10 mg/day- Week 1 and 20 mg/day- Weeks 2 to 4 with minimum therapeutic dose [MTD] of 10 mg/day), sertraline (50 mg/day- Week 1, 100 mg/day- Week 2, 150 mg/day- Week 3 and 200 mg/day- Week 4 with MTD of 50 mg/day) or venlafaxine XR (75 mg/day- Week 1, 150 mg/day- Week 2, 225 mg/day- Weeks 3 and 4 with MTD of 150 mg/day) on Day 1 taken daily in DB induction phase. Subjects who were not eligible or chose to not participate in maintenance of effect study (ESKETINTRD3003) and had received at least 1 dose of intranasal Esk 56 mg+ Oral AD in DB induction phase were followed in posttreatment follow-up phase for up to 24 weeks to assess safety and tolerability including withdrawal symptoms of study drug.

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 56 mg of esketamine, twice per week for 4 Weeks in double-blind induction phase.

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

Dosage and administration details:

Subjects received duloxetine 60 mg/day daily during Weeks 1 to 4 in double-blind induction phase. Subjects that have in the past shown increased sensitivity towards SSRIs/SNRIs could be started on a 30 mg dose and uptitrated into the therapeutic range of 60 mg by the start of Week 2.

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 to 4 daily in 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 venlafaxine extended release (XR) 75 mg/day during Week 1, 150 mg/day during Week 2, 225 mg/day during Weeks 3 and 4 daily in double-blind induction phase.

Investigational medicinal product name	Sertraline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
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 daily in double-blind induction phase.

Arm title	Intranasal Esketamine 84 mg Plus Oral AD

Arm description:

Subjects self-administered 56 mg of intranasal esketamine on Day 1 and then 84 mg from Day 4 onwards twice per week for 4 Weeks in DB induction phase. Also, subjects simultaneously initiated new oral AD with one of following: duloxetine (60 mg/day- Weeks 1, 2, 3 and 4), escitalopram (10 mg/day- Week 1 and 20 mg/day- Weeks 2 to 4 with minimum therapeutic dose [MTD] of 10 mg/day), sertraline (50 mg/day- Week 1, 100 mg/day- Week 2, 150 mg/day- Week 3 and 200 mg/day- Week 4 with MTD of 50 mg/day) or venlafaxine XR (75 mg/day- Week 1, 150 mg/day- Week 2, 225 mg/day- Weeks 3 and 4 with MTD of 150 mg/day) on Day 1 taken daily in DB induction phase. Subjects who were not eligible or chose to not participate in maintenance of effect study (ESKETINTRD3003) and had received at least 1 dose of intranasal Esk 84 mg+ Oral AD in DB induction phase were followed in posttreatment follow-up phase for up to 24 weeks to assess safety and tolerability including withdrawal symptoms of study drug.

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 56 mg of esketamine on Day 1 and then 84 mg of esketamine from Day 4 onwards, twice per week for 4 Weeks in double-blind induction phase.

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

Dosage and administration details:

Subjects received duloxetine 60 mg/day daily during Weeks 1 to 4 in double-blind induction phase. Subjects that have in the past shown increased sensitivity towards selective serotonin reuptake inhibitors (SSRI)/serotonin and norepinephrine reuptake inhibitors (SNRI) could be started on a 30 mg dose and uptitrated into the therapeutic range of 60 mg by the start of Week 2.

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 to 4 daily in double-blind induction phase.

Investigational medicinal product name	Sertraline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
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 daily in 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 venlafaxine XR 75 mg/day during Week 1, 150 mg/day during Week 2, 225 mg/day during Weeks 3 and 4 daily in double-blind induction phase.

Arm title	Oral AD Plus Intranasal Placebo

Arm description:

Subjects self-administered intranasal matching placebo, twice per week for 4 weeks in DB induction phase. Also, subjects simultaneously initiated new oral AD with one of following: duloxetine (60 mg/day- Weeks 1, 2, 3 and 4), escitalopram (10 mg/day- Week 1 and 20 mg/day- Weeks 2 to 4 with minimum therapeutic dose [MTD] of 10 mg/day), sertraline (50 mg/day- Week 1, 100 mg/day- Week 2, 150 mg/day- Week 3 and 200 mg/day- Week 4 with MTD of 50 mg/day) or venlafaxine XR (75 mg/day- Week 1, 150 mg/day- Week 2, 225 mg/day- Weeks 3 and 4 with MTD of 150 mg/day) on Day 1 taken daily in DB induction phase. Subjects who were not eligible or chose to not participate in maintenance of effect study (ESKETINTRD3003) and had received at least 1 dose of intranasal placebo+ Oral AD in DB induction phase were followed in posttreatment follow-up phase for up to 24 weeks to assess safety and tolerability including withdrawal symptoms of study drug.

Arm type	Active comparator
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 matching placebo twice per week for 4 Weeks in double-blind Induction Phase.

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

Dosage and administration details:

Subjects received duloxetine 60 mg/day daily during Weeks 1 to 4 in double-blind induction phase. Subjects that have in the past shown increased sensitivity towards SSRIs/SNRIs could be started on a 30 mg dose and uptitrated into the therapeutic range of 60 mg by the start of Week 2.

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 to 4 daily in double-blind induction phase.

Investigational medicinal product name	Sertraline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
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 daily in 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 venlafaxine XR 75 mg/day during Week 1, 150 mg/day during Week 2, 225 mg/day during Weeks 3 and 4 daily in double-blind induction phase.

Number of subjects in period 1	Intranasal Esketamine 56 mg Plus Oral Antidepressant	Intranasal Esketamine 84 mg Plus Oral AD	Oral AD Plus Intranasal Placebo
Started	117	116	113
Full Analysis Set	115	114	113
Safety Analysis Set	115	116	113
Completed	111	97	107
Not completed	6	19	6
Consent withdrawn by subject	1	5	1
Adverse event, non-fatal	1	7	2
Unspecified	1	4	2
Lost to follow-up	-	1	-
Protocol deviation	2	1	1
Lack of efficacy	1	1	-

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 56 mg Plus Oral AD

Arm description:

Subjects self-administered 56 mg of intranasal esketamine (Esk) twice per week for 4 weeks in double-blind (DB) induction phase. Also, subjects simultaneously initiated new oral antidepressant (AD) with one of following: duloxetine (60 milligram [mg]/day- Weeks 1, 2, 3 and 4), escitalopram (10 mg/day- Week 1 and 20 mg/day- Weeks 2 to 4 with minimum therapeutic dose [MTD] of 10 mg/day), sertraline (50 mg/day- Week 1, 100 mg/day- Week 2, 150 mg/day- Week 3 and 200 mg/day- Week 4 with MTD of 50 mg/day) or venlafaxine XR (75 mg/day- Week 1, 150 mg/day- Week 2, 225 mg/day- Weeks 3 and 4 with MTD of 150 mg/day) on Day 1 taken daily in DB induction phase. Subjects who were not eligible or chose to not participate in maintenance of effect study (ESKETINTRD3003) and had received at least 1 dose of intranasal Esk 56 mg+ Oral AD in DB induction phase were followed in posttreatment follow-up phase for up to 24 weeks to assess safety and tolerability including withdrawal symptoms of study drug.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Intranasal Esketamine 84 mg Plus Oral AD

Arm description:

Subjects self-administered 56 mg of intranasal esketamine on Day 1 and then 84 mg from Day 4 onwards twice per week for 4 Weeks in DB induction phase. Also, subjects simultaneously initiated new oral AD with one of following: duloxetine (60 mg/day- Weeks 1, 2, 3 and 4), escitalopram (10 mg/day- Week 1 and 20 mg/day- Weeks 2 to 4 with minimum therapeutic dose [MTD] of 10 mg/day), sertraline (50 mg/day- Week 1, 100 mg/day- Week 2, 150 mg/day- Week 3 and 200 mg/day- Week 4 with MTD of 50 mg/day) or venlafaxine XR (75 mg/day- Week 1, 150 mg/day- Week 2, 225 mg/day- Weeks 3 and 4 with MTD of 150 mg/day) on Day 1 taken daily in DB induction phase. Subjects who were not eligible or chose to not participate in maintenance of effect study (ESKETINTRD3003) and had received at least 1 dose of intranasal Esk 84 mg+ Oral AD in DB induction phase were followed in posttreatment follow-up phase for up to 24 weeks to assess safety and tolerability including withdrawal symptoms of study drug.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Oral AD Plus Intranasal Placebo

Arm description:

Subjects self-administered intranasal matching placebo, twice per week for 4 weeks in DB induction phase. Also, subjects simultaneously initiated new oral AD with one of following: duloxetine (60 mg/day- Weeks 1, 2, 3 and 4), escitalopram (10 mg/day- Week 1 and 20 mg/day- Weeks 2 to 4 with minimum therapeutic dose [MTD] of 10 mg/day), sertraline (50 mg/day- Week 1, 100 mg/day- Week 2, 150 mg/day- Week 3 and 200 mg/day- Week 4 with MTD of 50 mg/day) or venlafaxine XR (75 mg/day- Week 1, 150 mg/day- Week 2, 225 mg/day- Weeks 3 and 4 with MTD of 150 mg/day) on Day 1 taken daily in DB induction phase. Subjects who were not eligible or chose to not participate in maintenance of effect study (ESKETINTRD3003) and had received at least 1 dose of intranasal placebo+ Oral AD in DB induction phase were followed in posttreatment follow-up phase for up to 24 weeks to assess safety and tolerability including withdrawal symptoms of study drug.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2[1]	Intranasal Esketamine 56 mg Plus Oral AD	Intranasal Esketamine 84 mg Plus Oral AD	Oral AD Plus Intranasal Placebo
Started	47	52	69
Completed	8	10	18
Not completed	39	42	51
Consent withdrawn by subject	3	9	2
PI decision	34	29	44
Unspecified	2	2	3
Lost to follow-up	-	2	1
Protocol deviation	-	-	1

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 56 mg Plus Oral Antidepressant

Reporting group description:

Subjects self-administered 56 mg of intranasal esketamine (Esk) twice per week for 4 weeks in double-blind (DB) induction phase. Also, subjects simultaneously initiated new oral antidepressant (AD) with one of following: duloxetine (60 milligram [mg]/day- Weeks 1, 2, 3 and 4), escitalopram (10 mg/day- Week 1 and 20 mg/day- Weeks 2 to 4 with minimum therapeutic dose [MTD] of 10 mg/day), sertraline (50 mg/day- Week 1, 100 mg/day- Week 2, 150 mg/day- Week 3 and 200 mg/day- Week 4 with MTD of 50 mg/day) or venlafaxine XR (75 mg/day- Week 1, 150 mg/day- Week 2, 225 mg/day- Weeks 3 and 4 with MTD of 150 mg/day) on Day 1 taken daily in DB induction phase. Subjects who were not eligible or chose to not participate in maintenance of effect study (ESKETINTRD3003) and had received at least 1 dose of intranasal Esk 56 mg+ Oral AD in DB induction phase were followed in posttreatment follow-up phase for up to 24 weeks to assess safety and tolerability including withdrawal symptoms of study drug.

Reporting group title	Intranasal Esketamine 84 mg Plus Oral AD

Reporting group description:

Subjects self-administered 56 mg of intranasal esketamine on Day 1 and then 84 mg from Day 4 onwards twice per week for 4 Weeks in DB induction phase. Also, subjects simultaneously initiated new oral AD with one of following: duloxetine (60 mg/day- Weeks 1, 2, 3 and 4), escitalopram (10 mg/day- Week 1 and 20 mg/day- Weeks 2 to 4 with minimum therapeutic dose [MTD] of 10 mg/day), sertraline (50 mg/day- Week 1, 100 mg/day- Week 2, 150 mg/day- Week 3 and 200 mg/day- Week 4 with MTD of 50 mg/day) or venlafaxine XR (75 mg/day- Week 1, 150 mg/day- Week 2, 225 mg/day- Weeks 3 and 4 with MTD of 150 mg/day) on Day 1 taken daily in DB induction phase. Subjects who were not eligible or chose to not participate in maintenance of effect study (ESKETINTRD3003) and had received at least 1 dose of intranasal Esk 84 mg+ Oral AD in DB induction phase were followed in posttreatment follow-up phase for up to 24 weeks to assess safety and tolerability including withdrawal symptoms of study drug.

Reporting group title	Oral AD Plus Intranasal Placebo

Reporting group description:

Subjects self-administered intranasal matching placebo, twice per week for 4 weeks in DB induction phase. Also, subjects simultaneously initiated new oral AD with one of following: duloxetine (60 mg/day- Weeks 1, 2, 3 and 4), escitalopram (10 mg/day- Week 1 and 20 mg/day- Weeks 2 to 4 with minimum therapeutic dose [MTD] of 10 mg/day), sertraline (50 mg/day- Week 1, 100 mg/day- Week 2, 150 mg/day- Week 3 and 200 mg/day- Week 4 with MTD of 50 mg/day) or venlafaxine XR (75 mg/day- Week 1, 150 mg/day- Week 2, 225 mg/day- Weeks 3 and 4 with MTD of 150 mg/day) on Day 1 taken daily in DB induction phase. Subjects who were not eligible or chose to not participate in maintenance of effect study (ESKETINTRD3003) and had received at least 1 dose of intranasal placebo+ Oral AD in DB induction phase were followed in posttreatment follow-up phase for up to 24 weeks to assess safety and tolerability including withdrawal symptoms of study drug.

Reporting group values	Intranasal Esketamine 56 mg Plus Oral Antidepressant	Intranasal Esketamine 84 mg Plus Oral AD	Oral AD Plus Intranasal Placebo
Number of subjects	117	116	113
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	117	116	113
From 65 to 84 years	0	0	0
85 years and over	0	0	0
Title for AgeContinuous Units: years			
arithmetic mean	46.5	45.7	46.8
standard deviation	± 11.12	± 11.02	± 11.36

Title for Gender Units: subjects			
Female	82	80	81
Male	35	36	32

Reporting group values	Total		
Number of subjects	346		
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	346		
From 65 to 84 years	0		
85 years and over	0		
Title for AgeContinuous Units: years			
arithmetic mean			
standard deviation	-		
Title for Gender Units: subjects			
Female	243		
Male	103		

End points

End points reporting groups

Reporting group title	Intranasal Esketamine 56 mg Plus Oral Antidepressant

Reporting group description:

Subjects self-administered 56 mg of intranasal esketamine (Esk) twice per week for 4 weeks in double-blind (DB) induction phase. Also, subjects simultaneously initiated new oral antidepressant (AD) with one of following: duloxetine (60 milligram [mg]/day- Weeks 1, 2, 3 and 4), escitalopram (10 mg/day- Week 1 and 20 mg/day- Weeks 2 to 4 with minimum therapeutic dose [MTD] of 10 mg/day), sertraline (50 mg/day- Week 1, 100 mg/day- Week 2, 150 mg/day- Week 3 and 200 mg/day- Week 4 with MTD of 50 mg/day) or venlafaxine XR (75 mg/day- Week 1, 150 mg/day- Week 2, 225 mg/day- Weeks 3 and 4 with MTD of 150 mg/day) on Day 1 taken daily in DB induction phase. Subjects who were not eligible or chose to not participate in maintenance of effect study (ESKETINTRD3003) and had received at least 1 dose of intranasal Esk 56 mg+ Oral AD in DB induction phase were followed in posttreatment follow-up phase for up to 24 weeks to assess safety and tolerability including withdrawal symptoms of study drug.

Reporting group title	Intranasal Esketamine 84 mg Plus Oral AD

Reporting group description:

Subjects self-administered 56 mg of intranasal esketamine on Day 1 and then 84 mg from Day 4 onwards twice per week for 4 Weeks in DB induction phase. Also, subjects simultaneously initiated new oral AD with one of following: duloxetine (60 mg/day- Weeks 1, 2, 3 and 4), escitalopram (10 mg/day- Week 1 and 20 mg/day- Weeks 2 to 4 with minimum therapeutic dose [MTD] of 10 mg/day), sertraline (50 mg/day- Week 1, 100 mg/day- Week 2, 150 mg/day- Week 3 and 200 mg/day- Week 4 with MTD of 50 mg/day) or venlafaxine XR (75 mg/day- Week 1, 150 mg/day- Week 2, 225 mg/day- Weeks 3 and 4 with MTD of 150 mg/day) on Day 1 taken daily in DB induction phase. Subjects who were not eligible or chose to not participate in maintenance of effect study (ESKETINTRD3003) and had received at least 1 dose of intranasal Esk 84 mg+ Oral AD in DB induction phase were followed in posttreatment follow-up phase for up to 24 weeks to assess safety and tolerability including withdrawal symptoms of study drug.

Reporting group title	Oral AD Plus Intranasal Placebo

Reporting group description:

Subjects self-administered intranasal matching placebo, twice per week for 4 weeks in DB induction phase. Also, subjects simultaneously initiated new oral AD with one of following: duloxetine (60 mg/day- Weeks 1, 2, 3 and 4), escitalopram (10 mg/day- Week 1 and 20 mg/day- Weeks 2 to 4 with minimum therapeutic dose [MTD] of 10 mg/day), sertraline (50 mg/day- Week 1, 100 mg/day- Week 2, 150 mg/day- Week 3 and 200 mg/day- Week 4 with MTD of 50 mg/day) or venlafaxine XR (75 mg/day- Week 1, 150 mg/day- Week 2, 225 mg/day- Weeks 3 and 4 with MTD of 150 mg/day) on Day 1 taken daily in DB induction phase. Subjects who were not eligible or chose to not participate in maintenance of effect study (ESKETINTRD3003) and had received at least 1 dose of intranasal placebo+ Oral AD in DB induction phase were followed in posttreatment follow-up phase for up to 24 weeks to assess safety and tolerability including withdrawal symptoms of study drug.

Reporting group title	Intranasal Esketamine 56 mg Plus Oral AD

Reporting group description:

Subjects self-administered 56 mg of intranasal esketamine (Esk) twice per week for 4 weeks in double-blind (DB) induction phase. Also, subjects simultaneously initiated new oral antidepressant (AD) with one of following: duloxetine (60 milligram [mg]/day- Weeks 1, 2, 3 and 4), escitalopram (10 mg/day- Week 1 and 20 mg/day- Weeks 2 to 4 with minimum therapeutic dose [MTD] of 10 mg/day), sertraline (50 mg/day- Week 1, 100 mg/day- Week 2, 150 mg/day- Week 3 and 200 mg/day- Week 4 with MTD of 50 mg/day) or venlafaxine XR (75 mg/day- Week 1, 150 mg/day- Week 2, 225 mg/day- Weeks 3 and 4 with MTD of 150 mg/day) on Day 1 taken daily in DB induction phase. Subjects who were not eligible or chose to not participate in maintenance of effect study (ESKETINTRD3003) and had received at least 1 dose of intranasal Esk 56 mg+ Oral AD in DB induction phase were followed in posttreatment follow-up phase for up to 24 weeks to assess safety and tolerability including withdrawal symptoms of study drug.

Reporting group title	Intranasal Esketamine 84 mg Plus Oral AD

Reporting group description:

Subjects self-administered 56 mg of intranasal esketamine on Day 1 and then 84 mg from Day 4 onwards twice per week for 4 Weeks in DB induction phase. Also, subjects simultaneously initiated new oral AD with one of following: duloxetine (60 mg/day- Weeks 1, 2, 3 and 4), escitalopram (10 mg/day- Week 1 and 20 mg/day- Weeks 2 to 4 with minimum therapeutic dose [MTD] of 10 mg/day), sertraline (50 mg/day- Week 1, 100 mg/day- Week 2, 150 mg/day- Week 3 and 200 mg/day- Week 4 with MTD of 50 mg/day) or venlafaxine XR (75 mg/day- Week 1, 150 mg/day- Week 2, 225 mg/day- Weeks 3 and 4 with MTD of 150 mg/day) on Day 1 taken daily in DB induction phase. Subjects who were not eligible or chose to not participate in maintenance of effect study (ESKETINTRD3003) and had received at least 1 dose of intranasal Esk 84 mg+ Oral AD in DB induction phase were followed in posttreatment follow-up phase for up to 24 weeks to assess safety and tolerability including withdrawal symptoms of study drug.

Reporting group title	Oral AD Plus Intranasal Placebo

Reporting group description:

Subjects self-administered intranasal matching placebo, twice per week for 4 weeks in DB induction phase. Also, subjects simultaneously initiated new oral AD with one of following: duloxetine (60 mg/day- Weeks 1, 2, 3 and 4), escitalopram (10 mg/day- Week 1 and 20 mg/day- Weeks 2 to 4 with minimum therapeutic dose [MTD] of 10 mg/day), sertraline (50 mg/day- Week 1, 100 mg/day- Week 2, 150 mg/day- Week 3 and 200 mg/day- Week 4 with MTD of 50 mg/day) or venlafaxine XR (75 mg/day- Week 1, 150 mg/day- Week 2, 225 mg/day- Weeks 3 and 4 with MTD of 150 mg/day) on Day 1 taken daily in DB induction phase. Subjects who were not eligible or chose to not participate in maintenance of effect study (ESKETINTRD3003) and had received at least 1 dose of intranasal placebo+ Oral AD in DB induction phase were followed in posttreatment follow-up phase for up to 24 weeks to assess safety and tolerability including withdrawal symptoms of study drug.

Primary: Change From Baseline in Montgomery-Asberg Depression Rating Scale (MADRS) Total Score up to Endpoint Double-blind Induction Phase (Day 28)

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

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), for total possible score of 0 to 60. Higher scores represent more severe condition. Full analysis set (FAS): all randomized subjects who received at least 1 dose of intranasal study medication and 1 dose of oral antidepressant medication during double-blind induction phase. Here 'N' (number of subjects analysed) signifies number of subjects who were evaluable for this endpoint. Missing data was imputed using Last Observation Carried Forward (LOCF) method and last post baseline observation during phase was carried forward as “End Point (Day 28 LOCF)” for that phase.

End point type	Primary

End point timeframe:

Baseline up to Double-blind Endpoint (Day 28)

End point values	Intranasal Esketamine 56 mg Plus Oral Antidepressant	Intranasal Esketamine 84 mg Plus Oral AD	Oral AD Plus Intranasal Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	115	113	113	
Units: Units on a scale				
arithmetic mean (standard deviation)	-18.3 (± 14.21)	-17.4 (± 14.25)	-14.3 (± 15.00)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Intranasal Esketamine 84 mg Plus Oral AD v Oral AD Plus Intranasal Placebo

Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.25
Method	ANCOVA
Parameter estimate	Difference of Least Square (LS) Means
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.52
upper limit	1.42

Statistical analysis title	Statistical Analysis 2
Comparison groups	Intranasal Esketamine 56 mg Plus Oral Antidepressant v Oral AD Plus Intranasal Placebo
Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference of Least Square (LS) Means
Point estimate	-4.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.53
upper limit	-0.6

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

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

End point description:

A subject was defined as having a clinical response if there was at least 50% improvement (decrease) from baseline in the MADRS total score with onset by Day 2 and Day 8 that was maintained to Day 28. Subjects were allowed one excursion (non-response) on Days 8, 15 or 22, however the score must show at least 25% improvement. Subjects who did not meet these criteria, or discontinued during the study before Day 28 were considered as non-responders and were assigned the value of 0 (that is no). 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.

End point type	Secondary

End point timeframe:

Day 2 and Day 8

End point values	Intranasal Esketamine 56 mg Plus Oral Antidepressant	Intranasal Esketamine 84 mg Plus Oral AD	Oral AD Plus Intranasal Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	115	114	113	
Units: Percentage of subjects				
number (not applicable)				
Day 2	10.4	8.8	1.8	
Day 8	13.0	11.4	3.5	

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

The SDS is a subject-reported outcome measure and 5 item questionnaire used for assessment of functional impairment and associated disability. The first 3 items assess disruption of 1) work/school, 2) social life, and 3) family life/home responsibilities using 0-10 rating scale. Score for first 3 items are summed to create total score of 0-30 where higher score indicates greater impairment. 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' (number of subjects analysed) 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 (Day 28 LOCF)" for that phase.

End point type	Secondary

End point timeframe:

Baseline up to Double-blind Endpoint (Day 28)

End point values	Intranasal Esketamine 56 mg Plus Oral Antidepressant	Intranasal Esketamine 84 mg Plus Oral AD	Oral AD Plus Intranasal Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	91	99	95	
Units: Units on a scale				
arithmetic mean (standard deviation)	-10.7 (± 9.39)	-10.2 (± 10.00)	-8.1 (± 9.57)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Patient Health Questionnaire-9 (PHQ-9) Item Total Score up to Endpoint Double-blind Induction Phase (Day 28)

End point title	Change From Baseline in Patient Health Questionnaire-9 (PHQ-9) Item Total Score up to Endpoint Double-blind Induction Phase (Day 28)

End point description:

PHQ-9 is 9-item, self-reported scale assessing 9 symptom domains of Diagnostic and Statistical Manual of Mental Disorders, Major Depressive Disorder criteria. Each item is rated on 4-point scale (0 = Not at all, 1 = Several Days, 2 = More than half days, 3 = Nearly every day). The scores are summed for a total score ranging from 0-27. Higher score indicates greater severity of 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). The recall period is 2 weeks. FAS: all randomized subjects who received at least 1 dose of intranasal study medication and 1 dose of oral AD medication during the double-blind induction phase. Here 'N' (number of subjects analysed) 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 (Day 28 LOCF)" for that phase.

End point type	Secondary

End point timeframe:

Baseline up to Double-blind Endpoint (Day 28)

End point values	Intranasal Esketamine 56 mg Plus Oral Antidepressant	Intranasal Esketamine 84 mg Plus Oral AD	Oral AD Plus Intranasal Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	113	112	113	
Units: Units on a scale				
arithmetic mean (standard deviation)	-10.9 (± 8.26)	-10.9 (± 7.81)	-8.9 (± 8.37)	

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 Endpoint Double-blind Induction Phase (Day 28)

End point title	Percentage of Subjects who Achieved >=50% Reduction from Baseline in MADRS Total Score at the Endpoint Double-blind Induction Phase (Day 28)

End point description:

A subject is defined as a responder (yes=1 and no=0) at a given time point if the percent improvement from baseline in MADRS total score is at >= 50 percentage(%). The percentage 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' (number of subjects analysed) 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 (Day 28 LOCF)" for that phase.

End point type	Secondary

End point timeframe:

At Day 28 (Double-blind Endpoint)

End point values	Intranasal Esketamine 56 mg Plus Oral Antidepressant	Intranasal Esketamine 84 mg Plus Oral AD	Oral AD Plus Intranasal Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	115	113	113	
Units: Percentage of subjects				
number (not applicable)	53.0	47.8	37.2	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects in Remission (MADRS<=12) at the Endpoint Double-blind Induction Phase (Day 28)

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

End point description:

Subjects who had a MADRS total score of less than or equal to (=<) 12 were considered as remitters. 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' (number of subjects analysed) 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 (Day 28 LOCF)" for that phase.

End point type	Secondary

End point timeframe:

At Day 28 (Double-blind Endpoint)

End point values	Intranasal Esketamine 56 mg Plus Oral Antidepressant	Intranasal Esketamine 84 mg Plus Oral AD	Oral AD Plus Intranasal Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	115	113	113	
Units: Percentage of subjects				
number (not applicable)	34.8	35.4	29.2	

Statistical analyses

No statistical analyses for this end point

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

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

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 (a decrease in score indicates improvement). FAS: all randomized subjects who received at least 1 dose of intranasal study medication and 1 dose of oral antidepressant medication during double-blind induction phase. Here 'N' (number of subjects analysed) signifies 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 (Day 28 LOCF)" for that phase.

End point type	Secondary

End point timeframe:

Baseline up to Double-blind Endpoint (Day 28)

End point values	Intranasal Esketamine 56 mg Plus Oral Antidepressant	Intranasal Esketamine 84 mg Plus Oral AD	Oral AD Plus Intranasal Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	115	113	113	
Units: Units on a scale				
median (full range (min-max))	-2.0 (-5 to 1)	-2.0 (-5 to 1)	-1.0 (-6 to 3)	

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

GAD-7 is a brief and validated 7-item self-reported assessment of overall anxiety. Subjects responded 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: 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 analysed) 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 (Day 28 LOCF)" for that phase.

End point type	Secondary

End point timeframe:

Baseline up to Double-blind Endpoint (Day 28)

End point values	Intranasal Esketamine 56 mg Plus Oral Antidepressant	Intranasal Esketamine 84 mg Plus Oral AD	Oral AD Plus Intranasal Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	111	109	111	
Units: Units on a scale				
arithmetic mean (standard deviation)	-7.4 (± 5.94)	-7.7 (± 5.72)	-6.0 (± 6.01)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Health-related Quality of Life and Health Status as Assessed by EuroQol-5 Dimension-5 Level (EQ-5D-5L) up to End of Double-blind Induction Phase (Day 28)

End point title	Change From Baseline in Health-related Quality of Life and Health Status as Assessed by EuroQol-5 Dimension-5 Level (EQ-5D-5L) up to End of Double-blind Induction Phase (Day 28)

End point description:

EQ-5D-5L measures health outcome self-completed by respondents. It consists of EQ visual analogue scale (EQ-VAS), and 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). The responses are used to generate Health Status Index (HSI). HSI range is -0.148 to 0.949, is anchored at 0 (dead) and 1 (full health). EQ-VAS self-rating records the respondent's own assessment of his/her overall health status at time of completion, on scale of 0 (the worst health you can imagine) to 100 (the best health you can imagine). FAS: all randomized subjects who received at least 1 dose of intranasal study medication and 1 dose of oral antidepressant medication during double-blind induction phase. Here 'N' (number of subjects analysed) signifies number of subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to Double-blind Endpoint (Day 28)

End point values	Intranasal Esketamine 56 mg Plus Oral Antidepressant	Intranasal Esketamine 84 mg Plus Oral AD	Oral AD Plus Intranasal Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	113	112	112	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Health Status Index	0.224 (± 0.2481)	0.243 (± 0.2395)	0.181 (± 0.2495)	
EQ VAS Score	20.9 (± 25.04)	19.1 (± 26.86)	14.9 (± 27.15)	

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

Screening up to follow up phase (up to 35 weeks)

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	DB Phase: Intranasal Esketamine 56 mg Plus Oral Antidepressant

Reporting group description:

Subjects self-administered 56 mg of intranasal esketamine (Esk) twice per week for 4 weeks in double-blind (DB) induction phase. Also, subjects simultaneously initiated new oral antidepressant (AD) with one of following: duloxetine (60 milligram [mg]/day- Weeks 1, 2, 3 and 4), escitalopram (10 mg/day- Week 1 and 20 mg/day- Weeks 2 to 4 with minimum therapeutic dose [MTD] of 10 mg/day), sertraline (50 mg/day- Week 1, 100 mg/day- Week 2, 150 mg/day- Week 3 and 200 mg/day- Week 4 with MTD of 50 mg/day) or venlafaxine XR (75 mg/day- Week 1, 150 mg/day- Week 2, 225 mg/day- Weeks 3 and 4 with MTD of 150 mg/day) on Day 1 taken daily in DB induction phase.

Reporting group title	DB Phase: Intranasal Esketamine 84 mg Plus Oral AD

Reporting group description:

Subjects self-administered 56 mg of intranasal esketamine on Day 1 and then 84 mg from Day 4 onwards twice per week for 4 Weeks in DB induction phase. Also, subjects simultaneously initiated new oral AD with one of following: duloxetine (60 mg/day- Weeks 1, 2, 3 and 4), escitalopram (10 mg/day- Week 1 and 20 mg/day- Weeks 2 to 4 with minimum therapeutic dose [MTD] of 10 mg/day), sertraline (50 mg/day- Week 1, 100 mg/day- Week 2, 150 mg/day- Week 3 and 200 mg/day- Week 4 with MTD of 50 mg/day) or venlafaxine XR (75 mg/day- Week 1, 150 mg/day- Week 2, 225 mg/day- Weeks 3 and 4 with MTD of 150 mg/day) on Day 1 taken daily in DB induction phase.

Reporting group title	DB Phase: Oral AD Plus Intranasal Placebo

Reporting group description:

Subjects self-administered intranasal matching placebo, twice per week for 4 weeks in DB induction phase. Also, subjects simultaneously initiated new oral AD with one of following: duloxetine (60 mg/day- Weeks 1, 2, 3 and 4), escitalopram (10 mg/day- Week 1 and 20 mg/day- Weeks 2 to 4 with minimum therapeutic dose [MTD] of 10 mg/day), sertraline (50 mg/day- Week 1, 100 mg/day- Week 2, 150 mg/day- Week 3 and 200 mg/day- Week 4 with MTD of 50 mg/day) or venlafaxine XR (75 mg/day- Week 1, 150 mg/day- Week 2, 225 mg/day- Weeks 3 and 4 with MTD of 150 mg/day) on Day 1 taken daily in DB induction phase.

Reporting group title	FU Phase: Intranasal Esketamine 56 mg Plus Oral AD

Reporting group description:

Subjects who were not eligible or chose to not participate in maintenance of effect study (ESKETINTRD3003) and had received at least 1 dose of intranasal Esk 56 mg+ Oral AD in DB induction phase were followed in posttreatment follow-up (FU) phase for up to 24 weeks to assess safety and tolerability including withdrawal symptoms of study drug and for collection of additional informative data to assess the course of the subject’s major depressive episode over a 24-week period.

Reporting group title	FU Phase: Intranasal Esketamine 84 mg Plus Oral AD

Reporting group description:

Subjects who were not eligible or chose to not participate in maintenance of effect study (ESKETINTRD3003) and had received at least 1 dose of intranasal Esk 84 mg+ Oral AD in DB induction phase were followed in posttreatment follow-up phase for up to 24 weeks to assess safety and tolerability including withdrawal symptoms of study drug and for collection of additional informative data to assess the course of the subject’s major depressive episode over a 24-week period.

Reporting group title	FU Phase: Oral AD Plus Intranasal Placebo

Reporting group description:

Subjects who were not eligible or chose to not participate in maintenance of effect study (ESKETINTRD3003) and had received at least 1 dose of intranasal placebo+ Oral AD in DB induction phase were followed in posttreatment follow-up phase for up to 24 weeks to assess safety and tolerability including withdrawal symptoms of study drug and for collection of additional informative data to assess the course of the subject’s major depressive episode over a 24-week period.

Serious adverse events	DB Phase: Intranasal Esketamine 56 mg Plus Oral Antidepressant	DB Phase: Intranasal Esketamine 84 mg Plus Oral AD	DB Phase: Oral AD Plus Intranasal Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 115 (1.74%)	0 / 116 (0.00%)	0 / 113 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 115 (0.87%)	0 / 116 (0.00%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 115 (0.87%)	0 / 116 (0.00%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	0 / 115 (0.00%)	0 / 116 (0.00%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Insomnia			
subjects affected / exposed	0 / 115 (0.00%)	0 / 116 (0.00%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal Ideation			
subjects affected / exposed	0 / 115 (0.00%)	0 / 116 (0.00%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	FU Phase: Intranasal Esketamine 56 mg Plus Oral AD	FU Phase: Intranasal Esketamine 84 mg Plus Oral AD	FU Phase: Oral AD Plus Intranasal Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 47 (4.26%)	2 / 52 (3.85%)	1 / 69 (1.45%)

number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 47 (0.00%)	0 / 52 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	2 / 47 (4.26%)	1 / 52 (1.92%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	0 / 47 (0.00%)	1 / 52 (1.92%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Insomnia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 52 (1.92%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal Ideation			
subjects affected / exposed	0 / 47 (0.00%)	0 / 52 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	DB Phase: Intranasal Esketamine 56 mg Plus Oral Antidepressant	DB Phase: Intranasal Esketamine 84 mg Plus Oral AD	DB Phase: Oral AD Plus Intranasal Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	93 / 115 (80.87%)	92 / 116 (79.31%)	64 / 113 (56.64%)
Investigations			
Blood Pressure Increased			
subjects affected / exposed	8 / 115 (6.96%)	11 / 116 (9.48%)	5 / 113 (4.42%)
occurrences (all)	24	36	5

Nervous system disorders			
Dizziness			
subjects affected / exposed	32 / 115 (27.83%)	26 / 116 (22.41%)	10 / 113 (8.85%)
occurrences (all)	111	86	12
Dizziness Postural			
subjects affected / exposed	7 / 115 (6.09%)	7 / 116 (6.03%)	0 / 113 (0.00%)
occurrences (all)	28	28	0
Dysgeusia			
subjects affected / exposed	17 / 115 (14.78%)	20 / 116 (17.24%)	17 / 113 (15.04%)
occurrences (all)	63	56	81
Headache			
subjects affected / exposed	23 / 115 (20.00%)	24 / 116 (20.69%)	19 / 113 (16.81%)
occurrences (all)	42	38	34
Hypoaesthesia			
subjects affected / exposed	14 / 115 (12.17%)	16 / 116 (13.79%)	2 / 113 (1.77%)
occurrences (all)	33	48	2
Lethargy			
subjects affected / exposed	7 / 115 (6.09%)	5 / 116 (4.31%)	1 / 113 (0.88%)
occurrences (all)	18	13	3
Mental Impairment			
subjects affected / exposed	6 / 115 (5.22%)	3 / 116 (2.59%)	1 / 113 (0.88%)
occurrences (all)	13	9	1
Paraesthesia			
subjects affected / exposed	19 / 115 (16.52%)	11 / 116 (9.48%)	3 / 113 (2.65%)
occurrences (all)	48	31	9
Sedation			
subjects affected / exposed	6 / 115 (5.22%)	8 / 116 (6.90%)	1 / 113 (0.88%)
occurrences (all)	31	22	1
Somnolence			
subjects affected / exposed	24 / 115 (20.87%)	21 / 116 (18.10%)	13 / 113 (11.50%)
occurrences (all)	55	87	23
Tremor			
subjects affected / exposed	4 / 115 (3.48%)	6 / 116 (5.17%)	2 / 113 (1.77%)
occurrences (all)	5	8	4
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	12 / 115 (10.43%)	8 / 116 (6.90%)	5 / 113 (4.42%)
occurrences (all)	20	13	5
Feeling Drunk			
subjects affected / exposed	7 / 115 (6.09%)	3 / 116 (2.59%)	0 / 113 (0.00%)
occurrences (all)	19	10	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	24 / 115 (20.87%)	24 / 116 (20.69%)	2 / 113 (1.77%)
occurrences (all)	86	102	5
Eye disorders			
Vision Blurred			
subjects affected / exposed	8 / 115 (6.96%)	9 / 116 (7.76%)	0 / 113 (0.00%)
occurrences (all)	18	11	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	8 / 115 (6.96%)	5 / 116 (4.31%)	3 / 113 (2.65%)
occurrences (all)	8	5	3
Hypoaesthesia Oral			
subjects affected / exposed	16 / 115 (13.91%)	12 / 116 (10.34%)	2 / 113 (1.77%)
occurrences (all)	61	56	7
Nausea			
subjects affected / exposed	31 / 115 (26.96%)	37 / 116 (31.90%)	12 / 113 (10.62%)
occurrences (all)	73	72	12
Paraesthesia Oral			
subjects affected / exposed	9 / 115 (7.83%)	1 / 116 (0.86%)	2 / 113 (1.77%)
occurrences (all)	17	1	9
Vomiting			
subjects affected / exposed	7 / 115 (6.09%)	14 / 116 (12.07%)	2 / 113 (1.77%)
occurrences (all)	11	20	3
Respiratory, thoracic and mediastinal disorders			
Nasal Discomfort			
subjects affected / exposed	4 / 115 (3.48%)	5 / 116 (4.31%)	7 / 113 (6.19%)
occurrences (all)	10	8	19
Throat Irritation			

subjects affected / exposed	5 / 115 (4.35%)	9 / 116 (7.76%)	4 / 113 (3.54%)
occurrences (all)	21	32	5
Psychiatric disorders			
Anxiety			
subjects affected / exposed	10 / 115 (8.70%)	9 / 116 (7.76%)	7 / 113 (6.19%)
occurrences (all)	14	20	10
Dissociation			
subjects affected / exposed	30 / 115 (26.09%)	32 / 116 (27.59%)	4 / 113 (3.54%)
occurrences (all)	127	153	21
Euphoric Mood			
subjects affected / exposed	8 / 115 (6.96%)	2 / 116 (1.72%)	2 / 113 (1.77%)
occurrences (all)	15	9	3
Insomnia			
subjects affected / exposed	10 / 115 (8.70%)	8 / 116 (6.90%)	11 / 113 (9.73%)
occurrences (all)	10	8	11
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	6 / 115 (5.22%)	2 / 116 (1.72%)	1 / 113 (0.88%)
occurrences (all)	8	3	1

Non-serious adverse events	FU Phase: Intranasal Esketamine 56 mg Plus Oral AD	FU Phase: Intranasal Esketamine 84 mg Plus Oral AD	FU Phase: Oral AD Plus Intranasal Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 47 (14.89%)	4 / 52 (7.69%)	7 / 69 (10.14%)
Investigations			
Blood Pressure Increased			
subjects affected / exposed	0 / 47 (0.00%)	0 / 52 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 47 (0.00%)	1 / 52 (1.92%)	1 / 69 (1.45%)
occurrences (all)	0	1	1
Dizziness Postural			
subjects affected / exposed	0 / 47 (0.00%)	0 / 52 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
Dysgeusia			

subjects affected / exposed	0 / 47 (0.00%)	0 / 52 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	4 / 47 (8.51%)	2 / 52 (3.85%)	3 / 69 (4.35%)
occurrences (all)	4	2	3
Hypoaesthesia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 52 (1.92%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Lethargy			
subjects affected / exposed	0 / 47 (0.00%)	0 / 52 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
Mental Impairment			
subjects affected / exposed	0 / 47 (0.00%)	0 / 52 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	0 / 47 (0.00%)	0 / 52 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
Sedation			
subjects affected / exposed	0 / 47 (0.00%)	0 / 52 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	0 / 47 (0.00%)	0 / 52 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	1 / 47 (2.13%)	0 / 52 (0.00%)	1 / 69 (1.45%)
occurrences (all)	1	0	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 47 (0.00%)	0 / 52 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Feeling Drunk			
subjects affected / exposed	0 / 47 (0.00%)	0 / 52 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	0 / 47 (0.00%)	0 / 52 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Vision Blurred			
subjects affected / exposed	0 / 47 (0.00%)	0 / 52 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 47 (0.00%)	1 / 52 (1.92%)	2 / 69 (2.90%)
occurrences (all)	0	1	2
Hypoaesthesia Oral			
subjects affected / exposed	0 / 47 (0.00%)	0 / 52 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	2 / 47 (4.26%)	1 / 52 (1.92%)	1 / 69 (1.45%)
occurrences (all)	3	2	1
Paraesthesia Oral			
subjects affected / exposed	0 / 47 (0.00%)	0 / 52 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	1 / 47 (2.13%)	0 / 52 (0.00%)	0 / 69 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Nasal Discomfort			
subjects affected / exposed	0 / 47 (0.00%)	0 / 52 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
Throat Irritation			
subjects affected / exposed	0 / 47 (0.00%)	0 / 52 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 47 (2.13%)	0 / 52 (0.00%)	2 / 69 (2.90%)
occurrences (all)	3	0	3
Dissociation			

subjects affected / exposed	0 / 47 (0.00%)	0 / 52 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
Euphoric Mood			
subjects affected / exposed	0 / 47 (0.00%)	0 / 52 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 52 (1.92%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 47 (0.00%)	0 / 52 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 January 2016	Amendment INT-1 included following changes: Revised exclusion criteria; revised inclusion criteria; removal of prohibition of concomitant medications that prolonged the QT interval/corrected QT (QTc); indicated that the severity of a subject's depressive symptoms was also being confirmed using a Site Independent Qualification Assessment (SIQA), and the required Week 1 Montgomery-Asberg depression rating scale (MADRS) total score was added; allowed option to start at a 30 milligram (mg) dose of duloxetine in the oral antidepressant titration schedule for subjects who had increased sensitivity towards selective serotonin reuptake inhibitors (SSRI)/serotonin and norepinephrine reuptake inhibitors (SNRI); addition of an additional sheehan disability scale (SDS) assessment on Day 15 (Week 2) of the double-blind induction phase; addition of discontinuation criteria related to electrocardiogram (ECG) readings; provided the criterion for non-response at the end of the screening/prospective observational phase; clarification on the (1) mandatory use of oral antidepressant dosing titration schedule, (2) guidance on BP monitoring on intranasal treatment session days, (3) use of prestudy and concomitant therapies, (3) language regarding mandatory discontinuation of subjects who developed treatment emergent ulcerative cystitis, (4) medication(s) that were used for depression had to be discontinued after completion of the 4-week screening/ prospective observational phase, (5) statement that there were no changes to the current oral antidepressant treatment regimen for the duration of the screening/prospective observational phase, (6) definition of clinically significant ECG abnormalities as defined by QT interval corrected according to Fridericia's formula (QTcF).
31 May 2016	Amendment INT-2 included following changes: Revised inclusion; deleted the exclusion for first degree atrioventricular (AV) block; revision was made to the analysis of onset of clinical response (defined as >=50% reduction in the MADRS total score by the day after taking the first dose of double-blind medication [Day 2, 24 hours] that continued through the end of the 4-week double-blind induction phase) to indicate that subjects were allowed 1 excursion; permitted use of prescribed psychostimulants for indications other than major depressive disorder (MDD) with dosing restrictions on intranasal treatment session days; addition of (1) MADRS assessment during the follow-up phase, (2) information about 54135419TRD3008, an open-label safety extension study; maximum dose of sertraline in oral antidepressant titration schedule increased from 150 mg/day to 200 mg/day; clarification of procedure to be followed if subjects withdrew from the study.

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.

Transient, dissociative effects of esketamine are difficult to blind, site staff who observed treatment sessions could have been biased. To ensure unbiased efficacy evaluations, independent, remote, blinded MADRS raters assessed treatment response.

Notes: