



Clinical trial results:

Randomized, Double-blind, Multicenter, Active-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Intranasal Esketamine Plus an Oral Antidepressant in Elderly Subjects with Treatment-resistant Depression.

Summary

EudraCT number	2014-004588-19
Trial protocol	SE BE ES GB LT FI BG IT
Global end of trial date	10 August 2017

Results information

Result version number	v1 (current)
This version publication date	22 August 2018
First version publication date	22 August 2018

Trial information

Trial identification

Sponsor protocol code	ESKETINTRD3005
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02422186
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	10 August 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	10 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose of the study was to evaluate the efficacy of switching elderly subjects with Treatment-Resistant Depression (TRD) from a prior antidepressant treatment (to which they have not responded) to flexibly-dosed intranasal esketamine (28 milligram (mg), 56 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 Physical Examinations, Electrocardiograms (ECG's), Nasal Examinations, Nasal Symptom Questionnaire, Cognition Testing, Clinical Laboratory Tests (hematology, serum chemistry, and urinalysis), Pulse Oximetry, 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 [Computerized Cognitive Battery and Hopkins Verbal Learning Test-Revised (HVLIT-R)], University of Pennsylvania Smell Identification Test (UPSIT).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 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	Belgium: 6
Country: Number of subjects enrolled	Bulgaria: 3
Country: Number of subjects enrolled	Brazil: 2
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	Finland: 2
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Lithuania: 2
Country: Number of subjects enrolled	Poland: 7
Country: Number of subjects enrolled	Sweden: 14

Country: Number of subjects enrolled	United States: 70
Country: Number of subjects enrolled	South Africa: 7
Worldwide total number of subjects	138
EEA total number of subjects	59

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)	0
From 65 to 84 years	137
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 148 subjects were planned and 138 subjects with Major Depressive Disorder (MDD) were enrolled and randomly assigned to treatments with either intranasal esketamine plus oral antidepressant (72 subjects) or oral antidepressant plus intranasal placebo (66 subjects) following results from a planned interim analysis in this study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Intranasal Esketamine (Esk) Plus Oral antidepressant (AD)

Arm description:

Subjects self-administered esketamine 28 milligram (mg) or 56 mg or 84 mg intranasally twice weekly for 4 weeks (on Day 1, 4, 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 (30 mg/day during Week 1 and 60 mg/day during Weeks 2, 3 and 4 with minimum dose for tolerability at 30 mg/day); Escitalopram (10 mg/day during Weeks 1-4 with minimum dose for tolerability at 5 mg/day); Sertraline (25 mg/day during Week 1, 50 mg/day during Week 2, 100 mg/day during Week 3 and 150 mg/day during Week 4 with minimum dose for tolerability of 25 mg/Day) or Venlafaxine XR (37.5 mg/day during Week 1, 75 mg/day during Week 2, and 150 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 28 milligram (mg) or 56 mg or 84 mg twice weekly for 4 weeks (on Day 1, 4, 11, 15, 18, 22 and 25) 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 antidepressant (AD) Duloxetine (30 mg/day during Week 1 and 60 mg/day during Weeks 2, 3, and 4 with minimum dose allowed for tolerability of 30 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 antidepressant (AD) Escitalopram (10 mg/day) during Weeks 1-4 with minimum dose allowed for tolerability of 5 mg/Day 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 (25 mg/day during Week 1, 50 mg/day during Week 2, 100 mg/day during Weeks 3 and 150 mg/Day during Week 4, with minimum dose allowed for tolerability of 25 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 antidepressant (AD) Venlafaxine XR (37.5 mg/day during Week 1, 75 mg/day during Week 2 and 150 mg/day during weeks 3 and 4 with minimum dose allowed for tolerability of 75 mg/Day during Double- Blind Induction Phase.	
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, 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 (30 mg/day during Week 1 and 60 mg/day during Weeks 2, 3 and 4 with minimum dose for tolerability at 30 mg/day); Escitalopram (10 mg/day during Weeks 1-4 with minimum dose for tolerability at 5 mg/day); Sertraline (25 mg/day during Week 1, 50 mg/day during Week 2, 100 mg/day during Week 3 and 150 mg/day during Week 4 with minimum dose for tolerability of 25 mg/Day) or Venlafaxine XR (37.5 mg/day during Week 1, 75 mg/day during Week 2, and 150 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	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, 11, 15, 18, 22 and 25) 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 antidepressant (AD) Duloxetine (30 mg/day during Week 1 and 60 mg/day during Weeks 2, 3, and 4 with minimum dose allowed for tolerability of 30 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 antidepressant (AD) Escitalopram (10 mg/day) during Weeks 1-4 with minimum dose allowed for tolerability of 5 mg/Day 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 (25 mg/day during Week 1, 50 mg/day during Week 2, 100 mg/day during Weeks 3 and 150 mg/Day during Week 4, with minimum dose allowed for tolerability of 25 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 antidepressant (AD) Venlafaxine XR (37.5 mg/day during Week 1, 75 mg/day during Week 2 and 150 mg/day during weeks 3 and 4 with minimum dose allowed for tolerability of 75 mg/Day during Double- Blind Induction Phase.

Number of subjects in period 1	Intranasal Esketamine (Esk) Plus Oral antidepressant (AD)	Oral AD Plus Intranasal Placebo
Started	72	66
Safety Analysis	72	65
Completed	62	60
Not completed	10	6
Consent withdrawn by subject	1	2
Adverse event, non-fatal	4	2
Other	1	-
Lost to follow-up	1	-
Lack of efficacy	3	1
Protocol deviation	-	1

Baseline characteristics

Reporting groups

Reporting group title	Intranasal Esketamine (Esk) Plus Oral antidepressant (AD)
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Reporting group description:

Subjects self-administered esketamine 28 milligram (mg) or 56 mg or 84 mg intranasally twice weekly for 4 weeks (on Day 1, 4, 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 (30 mg/day during Week 1 and 60 mg/day during Weeks 2, 3 and 4 with minimum dose for tolerability at 30 mg/day); Escitalopram (10 mg/day during Weeks 1-4 with minimum dose for tolerability at 5 mg/day); Sertraline (25 mg/day during Week 1, 50 mg/day during Week 2, 100 mg/day during Week 3 and 150 mg/day during Week 4 with minimum dose for tolerability of 25 mg/Day) or Venlafaxine XR (37.5 mg/day during Week 1, 75 mg/day during Week 2, and 150 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
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Reporting group description:

Subjects self-administered esketamine matched placebo intranasally twice weekly for 4 weeks (on Day 1, 4, 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 (30 mg/day during Week 1 and 60 mg/day during Weeks 2, 3 and 4 with minimum dose for tolerability at 30 mg/day); Escitalopram (10 mg/day during Weeks 1-4 with minimum dose for tolerability at 5 mg/day); Sertraline (25 mg/day during Week 1, 50 mg/day during Week 2, 100 mg/day during Week 3 and 150 mg/day during Week 4 with minimum dose for tolerability of 25 mg/Day) or Venlafaxine XR (37.5 mg/day during Week 1, 75 mg/day during Week 2, and 150 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	72	66	138
Title for AgeCategorical Units: subjects			
From 65 to 84 years	71	66	137
85 years and over	1	0	1
Title for AgeContinuous Units: years			
arithmetic mean	70.6	69.6	
standard deviation	± 4.79	± 4.44	-
Title for Gender Units: subjects			
Female	45	41	86
Male	27	25	52

End points

End points reporting groups

Reporting group title	Intranasal Esketamine (Esk) Plus Oral antidepressant (AD)
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Reporting group description:

Subjects self-administered esketamine 28 milligram (mg) or 56 mg or 84 mg intranasally twice weekly for 4 weeks (on Day 1, 4, 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 (30 mg/day during Week 1 and 60 mg/day during Weeks 2, 3 and 4 with minimum dose for tolerability at 30 mg/day); Escitalopram (10 mg/day during Weeks 1-4 with minimum dose for tolerability at 5 mg/day); Sertraline (25 mg/day during Week 1, 50 mg/day during Week 2, 100 mg/day during Week 3 and 150 mg/day during Week 4 with minimum dose for tolerability of 25 mg/Day) or Venlafaxine XR (37.5 mg/day during Week 1, 75 mg/day during Week 2, and 150 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
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Reporting group description:

Subjects self-administered esketamine matched placebo intranasally twice weekly for 4 weeks (on Day 1, 4, 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 (30 mg/day during Week 1 and 60 mg/day during Weeks 2, 3 and 4 with minimum dose for tolerability at 30 mg/day); Escitalopram (10 mg/day during Weeks 1-4 with minimum dose for tolerability at 5 mg/day); Sertraline (25 mg/day during Week 1, 50 mg/day during Week 2, 100 mg/day during Week 3 and 150 mg/day during Week 4 with minimum dose for tolerability of 25 mg/Day) or Venlafaxine XR (37.5 mg/day during Week 1, 75 mg/day during Week 2, and 150 mg/day during Weeks 3 and 4 with minimum dose for tolerability of 75 mg/day) during DB Induction Phase.

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
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End point description:

The MADRS is a clinician-rated scale designed to measure depression severity and detects changes due to antidepressant treatment. The scale consists of 10 items (to evaluates apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, inability to feel [interest level], pessimistic thoughts, and suicidal thoughts), each of which is scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms), for a total possible score range of 0-60. Higher scores represent a more severe condition. The full analysis set was 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 Observation Carried Forward (LOCF) method.

End point type	Primary
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End point timeframe:

Baseline up to 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	71	64		
Units: Units on a scale				
arithmetic mean (standard deviation)	-9.3 (± 12.28)	-5.6 (± 9.11)		

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	135
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.026
Method	Weighted Combination Test Statistics
Parameter estimate	Least Square (LS) Mean Difference
Point estimate	-3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.16
upper limit	-0.03

Secondary: Percentage of Subjects Who Achieved ≥50% Reduction from Baseline in MADRS Total Score

End point title	Percentage of Subjects Who Achieved ≥50% Reduction from Baseline in MADRS Total Score
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 participants with greater than or equal to (≥50) percent (%) improvement from baseline is reported. The full analysis set was 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 LOCF method.	
End point type	Secondary
End point timeframe:	
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	71	64		
Units: Percentage of Subjects				
number (not applicable)	23.9	12.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects in Remission (MADRS≤12) at the End of Double-Blind Induction Phase

End point title	Percentage of Subjects in Remission (MADRS≤12) at the End of Double-Blind Induction Phase
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End point description:

Remission is defined as subjects who have a MADRS total score ≤12. 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. The full analysis set was 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 LOCF method.

End point type	Secondary
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End point timeframe:

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	71	64		
Units: Percentage of Subjects				
number (not applicable)	15.5	6.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Clinical Global Impression-Severity (CGI-S) Score at End of Double-Blind Induction Phase (Week 4)

End point title	Change From Baseline in Clinical Global Impression-Severity (CGI-S) Score at End of Double-Blind Induction Phase (Week 4)
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End point description:

The CGI-S provides an overall clinician-determined summary measure of the severity of the subject's illness including subject's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the subject's ability to function. The CGI-S evaluates the severity of psychopathology on a scale of 0 to 7. Considering total clinical experience, a subject is assessed on severity of mental illness at the time of rating 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 the most extremely ill patients. The full analysis set was 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 LOCF method.

End point type	Secondary
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End point timeframe:

Baseline and 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	71	65		
Units: Units on a scale				
median (full range (min-max))	-1.0 (-4 to 1)	0.0 (-4 to 3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With a Response to The EuroQoL Group 5 Dimension 5-Level Self-Report Questionnaire (EQ-5D-5L)

End point title	Percentage of Subjects With a Response to The EuroQoL Group 5 Dimension 5-Level Self-Report Questionnaire (EQ-5D-5L)
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End point description:

The EQ-5D-5L questionnaire is a brief, generic health related quality of life assessment (HRQOL) that can also be used to incorporate subject preferences into health economic evaluations. The EQ-5D-5L descriptive system comprises the following 5 dimensions with 5 levels (level 1 indicates no problem to level 5 indicates extreme problem): mobility, self-care, usual activities, pain/discomfort and anxiety/depression and as overall health using a "thermometer" visual analog scale with response options ranging from 0 (worst imaginable health) to 100 (best imaginable health). The full analysis set was 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
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End point timeframe:

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	70	64		
Units: Percentage of Subjects				
number (not applicable)				
Mobility: Level 1	68.6	60.9		
Mobility: Level 2	20.0	23.4		
Mobility: Level 3	8.6	14.1		
Mobility: Level 4	2.9	1.6		
Mobility: Level 5	0	0		
Self-care: Level 1	67.1	71.9		
Self-care: Level 2	18.6	14.1		
Self-care: Level 3	8.6	12.5		
Self-care: Level 4	5.7	1.6		
Self-care: Level 5	0	0		
Usual activities: Level 1	31.4	20.3		
Usual activities: Level 2	15.7	17.2		
Usual activities: Level 3	27.1	29.7		
Usual activities: Level 4	21.4	29.7		
Usual activities: Level 5	4.3	3.1		
Pain/discomfort: Level 1	31.4	39.1		
Pain/discomfort: Level 2	34.3	23.4		
Pain/discomfort: Level 3	21.4	31.3		
Pain/discomfort: Level 4	5.7	4.7		
Pain/discomfort: Level 5	7.1	1.6		
Anxiety/depression: Level 1	12.9	7.8		
Anxiety/depression: Level 2	20.0	12.5		
Anxiety/depression: Level 3	27.1	45.3		
Anxiety/depression: Level 4	31.4	25.0		
Anxiety/depression: Level 5	8.6	9.4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Approximately up to 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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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Reporting groups

Reporting group title	Oral antidepressant (AD) + Intranasal Placebo
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Reporting group description:

Subjects self-administered esketamine matched placebo intranasally twice weekly for 4 weeks (on Day 1, 4, 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 (30 mg/day during Week 1 and 60 mg/day during Weeks 2, 3 and 4 with minimum dose for tolerability at 30 mg/day); Escitalopram (10 mg/day during Weeks 1-4 with minimum dose for tolerability at 5 mg/day); Sertraline (25 mg/day during Week 1, 50 mg/day during Week 2, 100 mg/day during Week 3 and 150 mg/day during Week 4 with minimum dose for tolerability of 25 mg/Day) or Venlafaxine XR (37.5 mg/day during Week 1, 75 mg/day during Week 2, and 150 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) + Oral antidepressant (AD)
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Reporting group description:

Subjects self-administered esketamine 28 milligram (mg) or 56 mg or 84 mg intranasally twice weekly for 4 weeks (on Day 1, 4, 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 (30 mg/day during Week 1 and 60 mg/day during Weeks 2, 3 and 4 with minimum dose for tolerability at 30 mg/day); Escitalopram (10 mg/day during Weeks 1-4 with minimum dose for tolerability at 5 mg/day); Sertraline (25 mg/day during Week 1, 50 mg/day during Week 2, 100 mg/day during Week 3 and 150 mg/day during Week 4 with minimum dose for tolerability of 25 mg/Day) or Venlafaxine XR (37.5 mg/day during Week 1, 75 mg/day during Week 2, and 150 mg/day during Weeks 3 and 4 with minimum dose for tolerability of 75 mg/day) during DB Induction Phase.

Serious adverse events	Oral antidepressant (AD) + Intranasal Placebo	Intranasal Esketamine (Esk) + Oral antidepressant (AD)	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 65 (3.08%)	3 / 72 (4.17%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
Blood Pressure Increased			

subjects affected / exposed	0 / 65 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Hip Fracture			
subjects affected / exposed	0 / 65 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 65 (1.54%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Gait Disturbance			
subjects affected / exposed	1 / 65 (1.54%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety Disorder			
subjects affected / exposed	0 / 65 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Feeling of Despair			
subjects affected / exposed	1 / 65 (1.54%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	1 / 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 antidepressant (AD) + Intranasal Placebo	Intranasal Esketamine (Esk) + Oral antidepressant (AD)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 65 (32.31%)	44 / 72 (61.11%)	

Investigations Blood Pressure Increased subjects affected / exposed occurrences (all)	3 / 65 (4.62%) 6	9 / 72 (12.50%) 19	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	4 / 65 (6.15%) 6	15 / 72 (20.83%) 43	
Dysgeusia subjects affected / exposed occurrences (all)	3 / 65 (4.62%) 9	4 / 72 (5.56%) 12	
Headache subjects affected / exposed occurrences (all)	2 / 65 (3.08%) 2	9 / 72 (12.50%) 15	
Hypoaesthesia subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 1	4 / 72 (5.56%) 5	
Paraesthesia subjects affected / exposed occurrences (all)	2 / 65 (3.08%) 2	4 / 72 (5.56%) 12	
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	5 / 65 (7.69%) 6	9 / 72 (12.50%) 15	
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	2 / 65 (3.08%) 10	8 / 72 (11.11%) 24	
Gastrointestinal disorders Hypoaesthesia Oral subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0	5 / 72 (6.94%) 11	
Nausea subjects affected / exposed occurrences (all)	3 / 65 (4.62%) 4	13 / 72 (18.06%) 18	
Vomiting			

subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 1	5 / 72 (6.94%) 5	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	5 / 65 (7.69%)	2 / 72 (2.78%)	
occurrences (all)	9	2	
Dissociation			
subjects affected / exposed	1 / 65 (1.54%)	9 / 72 (12.50%)	
occurrences (all)	1	40	
Dysphoria			
subjects affected / exposed	0 / 65 (0.00%)	4 / 72 (5.56%)	
occurrences (all)	0	4	
Insomnia			
subjects affected / exposed	3 / 65 (4.62%)	4 / 72 (5.56%)	
occurrences (all)	6	4	
Infections and infestations			
Urinary Tract Infection			
subjects affected / exposed	1 / 65 (1.54%)	6 / 72 (8.33%)	
occurrences (all)	1	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 June 2015	The overall reason for the amendment is to allow for a 28 mg dose throughout the study, based on pharmacokinetic data from study ESKETINTRD1012 in elderly subjects.
10 January 2016	The overall reason for the amendment is to update and/or clarify protocol content based on ongoing feedback received during study initiation activities.
18 July 2016	The overall reason for the amendment is to improve recruitment while maintaining the integrity of the study. Changes are made that relate to the elderly population specifically (which differ in some aspects from younger patients) not included in the original protocol.

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.

The use of remote raters to administer the MADRS assessment may have reduced the sensitivity of detecting early change. There was limited numbers of subjects 75 years of age and older limiting the generalizability of the results in this population.

Notes: