# 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 |

**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 (HVLT-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 | Investigator, Subject |

### 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) |
|---|---|

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 |
|---|---|

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<br>Units: subjects | | | |
| From 65 to 84 years | 71 | 66 | 137 |
| 85 years and over | 1 | 0 | 1 |
| Title for AgeContinuous<br>Units: years | | | |
| arithmetic mean | 70.6 | 69.6 | |
| standard deviation | ± 4.79 | ± 4.44 | - |
| Title for Gender<br>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) |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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) |
|---|---|

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 |
|---|---|

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) |
|---|---|

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 |
|---|---|

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 |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 20.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Oral antidepressant (AD) + Intranasal Placebo |

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) |

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

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 65 (1.54%) | 5 / 72 (6.94%) | |
| occurrences (all) | 1 | 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: