



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 signs (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 test revised (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 $\geq 50\%$ Reduction from Baseline in MADRS Total Score at the Endpoint Double-blind Induction Phase (Day 28)

| | |
|---|--|
| End point title | Percentage of Subjects who Achieved $\geq 50\%$ 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 (\geq) 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 (\leq) 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

Adverse events

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

| | | | |
|--|-----------------------|-----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 5 / 115 (4.35%) 21 | 9 / 116 (7.76%) 32 | 4 / 113 (3.54%) 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 occurrences (all) | 0 / 47 (0.00%) 0 | 0 / 52 (0.00%) 0 | 0 / 69 (0.00%) 0 |
| Eye disorders Vision Blurred subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 0 / 52 (0.00%) 0 | 0 / 69 (0.00%) 0 |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 1 / 52 (1.92%) 1 | 2 / 69 (2.90%) 2 |
| Hypoaesthesia Oral subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 0 / 52 (0.00%) 0 | 0 / 69 (0.00%) 0 |
| Nausea subjects affected / exposed occurrences (all) | 2 / 47 (4.26%) 3 | 1 / 52 (1.92%) 2 | 1 / 69 (1.45%) 1 |
| Paraesthesia Oral subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 0 / 52 (0.00%) 0 | 0 / 69 (0.00%) 0 |
| Vomiting subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | 0 / 52 (0.00%) 0 | 0 / 69 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Nasal Discomfort subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 0 / 52 (0.00%) 0 | 0 / 69 (0.00%) 0 |
| Throat Irritation subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 0 / 52 (0.00%) 0 | 0 / 69 (0.00%) 0 |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 3 | 0 / 52 (0.00%) 0 | 2 / 69 (2.90%) 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 $\geq 50\%$ 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: