



Clinical trial results:

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

Summary

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

Results information

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

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | ESKETINTRD3002 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02418585 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Janssen Research & Development, LLC |
| Sponsor organisation address | 920 Route 202, Raritan, United States, NJ 08869 |
| Public contact | Clinical Registry group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com |
| Scientific contact | Clinical Registry group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 06 November 2017 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 06 November 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. The safety assessments included adverse events, clinical laboratory, Vital sign measurements, Physical examinations, height, body weight, and neck circumference, Electrocardiogram (ECG), Pulse oximetry, Nasal examinations and nasal symptom questionnaire, Columbia-Suicide Severity Rating Scale (C-SSRS), Clinician-Administered Dissociative States Scale (CADSS), Brief Psychiatric Rating Scale (BPRS+), Modified Observer's Assessment of Alertness/Sedation (MOAA/S), Clinical Global Assessment of Discharge Readiness (CGADR), Physician Withdrawal Checklist; 20-Item (PWC-20), Bladder Pain / Interstitial Cystitis Symptom Score (BPIC-SS), Cognition testing, University of Pennsylvania Smell Identification Test (UPSIT) and Smell Threshold Test

Background therapy: -

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 07 August 2015 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Czech Republic: 59 |
| Country: Number of subjects enrolled | Germany: 20 |
| Country: Number of subjects enrolled | Spain: 18 |
| Country: Number of subjects enrolled | Poland: 39 |
| Country: Number of subjects enrolled | United States: 91 |
| Worldwide total number of subjects | 227 |
| EEA total number of subjects | 136 |

Notes:

| Subjects enrolled per age group | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 227 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

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

Period 1

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

Arms

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

Arm description:

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

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

Dosage and administration details:

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

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

Dosage and administration details:

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

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

Dosage and administration details:

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

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

Dosage and administration details:

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

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

Dosage and administration details:

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

| | |
|------------------|---------------------------------|
| Arm title | Oral AD Plus Intranasal Placebo |
|------------------|---------------------------------|

Arm description:

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

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

Dosage and administration details:

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

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

Dosage and administration details:

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

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

Dosage and administration details:

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

minimum dose for tolerability at 10 mg/day).

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

Dosage and administration details:

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

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

Dosage and administration details:

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

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

Period 2

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

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|--|---|
| Arm title | Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD) |
| Arm description: | |
| Participants who were not eligible or who chose to not participate in the maintenance of effect study (ESKETINTRD3003) and had received at least 1 dose of intranasal study medication (Esketamine (Esk) Plus Oral Antidepressant (AD) in the double-blind induction phase were followed in posttreatment follow-up phase for up to 24 weeks in duration, to assess safety and tolerability of intranasal study medication, including potential withdrawal symptoms. | |
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |
| Arm title | Oral AD Plus Intranasal Placebo |
| Arm description: | |
| Participants who were not eligible or who chose to not participate in the maintenance of effect study (ESKETINTRD3003) and had received at least 1 dose of intranasal study medication (Oral AD Plus Intranasal Placebo) in the double-blind induction phase were followed in posttreatment follow-up phase for up to 24 weeks in duration, to assess safety and tolerability of intranasal study medication, including potential withdrawal symptoms. | |
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |

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

Notes:

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

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

Baseline characteristics

Reporting groups

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

Reporting group description:

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

| | |
|-----------------------|---------------------------------|
| Reporting group title | Oral AD Plus Intranasal Placebo |
|-----------------------|---------------------------------|

Reporting group description:

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

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

End points

End points reporting groups

| | |
|---|---|
| Reporting group title | Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD) |
| Reporting group description: Subjects self-administered esketamine either 56 milligram (mg) or 84 mg intranasally twice weekly for 4 weeks (on Day 1, 4, 8, 11, 15, 18, 22 and 25) as determined by investigator based on efficacy and tolerability in Double-Blind(DB) Induction Phase. Subjects simultaneously initiated titration schedule for open-label Oral antidepressant (AD) with one of the following four oral AD that was not used in current depression episode: [Duloxetine (60 mg/day during Weeks 1-4 with minimum dose for tolerability at 30 mg/day); Escitalopram (10 mg/day during Week 1 and 20 mg/day during Weeks 2-4 with minimum dose for tolerability at 10 mg/day); Sertraline (50 mg/day during Week 1, 100 mg/day during Week 2, 150 mg/day during Week 3 and 200 mg/day during Week 4 with minimum dose for tolerability of 50 mg/Day) or Venlafaxine XR (75 mg/day during Week 1, 150 mg/day during Week 2, and 225 mg/day during Weeks 3 and 4 with minimum dose for tolerability of 75 mg/day) during DB Induction Phase. | |
| Reporting group title | Oral AD Plus Intranasal Placebo |
| Reporting group description: Subjects self-administered esketamine matched placebo intranasally twice weekly for 4 weeks (on Day 1, 4, 8, 11, 15, 18, 22 and 25) as determined by investigator based on efficacy and tolerability in the Double-Blind Induction Phase. Subjects simultaneously initiated titration schedule for open-label Oral antidepressant (AD) with one of the following four oral AD that was not used in current depression episode: [Duloxetine (60 mg/day during Weeks 1-4 with minimum dose for tolerability at 30 mg/day); Escitalopram (10 mg/day during Week 1 and 20 mg/day during Weeks 2-4 with minimum dose for tolerability at 10 mg/day); Sertraline (50 mg/day during Week 1, 100 mg/day during Week 2, 150 mg/day during Week 3 and 200 mg/day during Week 4 with minimum dose for tolerability of 50 mg/Day) or Venlafaxine XR (75 mg/day during Week 1, 150 mg/day during Week 2, and 225 mg/day during Weeks 3 and 4 with minimum dose for tolerability of 75 mg/day) during DB Induction Phase. | |
| Reporting group title | Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD) |
| Reporting group description: Participants who were not eligible or who chose to not participate in the maintenance of effect study (ESKETINTRD3003) and had received at least 1 dose of intranasal study medication (Esketamine (Esk) Plus Oral Antidepressant (AD) in the double-blind induction phase were followed in posttreatment follow-up phase for up to 24 weeks in duration, to assess safety and tolerability of intranasal study medication, including potential withdrawal symptoms. | |
| Reporting group title | Oral AD Plus Intranasal Placebo |
| Reporting group description: Participants who were not eligible or who chose to not participate in the maintenance of effect study (ESKETINTRD3003) and had received at least 1 dose of intranasal study medication (Oral AD Plus Intranasal Placebo) in the double-blind induction phase were followed in posttreatment follow-up phase for up to 24 weeks in duration, to assess safety and tolerability of intranasal study medication, including potential withdrawal symptoms. | |

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

| | |
|--|---|
| End point title | Change from Baseline in Montgomery-Asberg Depression Rating Scale (MADRS) Total Score up to End of 4-Week (Day 28) Double-blind Induction Phase |
| End point description: MADRS is clinician-rated scale designed to measure depression severity, to detect changes due to antidepressant treatment. Scale consists of 10 items (evaluates apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, inability to feel [interest level], pessimistic thoughts and suicidal thoughts), each is scored from 0 (item is not present or is normal) to 6 (severe or continuous presence of symptoms), for total possible score range of 0-60. FAS defined as all randomized subjects who received at least 1 dose of intranasal study medication, 1 dose of oral antidepressant medication during double-blind induction phase (D-BIP). Here 'N' signifies number of subjects who were evaluable for this endpoint. Last post-baseline observation during the D-BIP was carried forward as endpoint for that phase. Missing data was imputed using LOCF method and the last post baseline observation during the phase was carried forward as "End Point" for that phase. | |
| End point type | Primary |

End point timeframe:

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

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

Statistical analyses

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

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 2 and 8

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

A subject is defined as a responder at a given time point if the percent improvement from baseline in MADRS total score is at least 50%. The percent of subjects with greater than or equal to ($\geq 50\%$) % 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' signifies number of subjects who were evaluable for this endpoint. Missing data was imputed using last observed carried forward (LOCF) method and the last post baseline observation during the phase was carried forward as "End Point" for that phase.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Statistical analyses

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Approximately up to 2.2 Years

Adverse event reporting additional description:

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

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 20.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------------------|
| Reporting group title | Oral AD Plus Intranasal Placebo |
|-----------------------|---------------------------------|

Reporting group description:

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

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

Reporting group description:

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

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

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 115 (0.87%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Road Traffic Accident | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 115 (0.87%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Ear and labyrinth disorders | | | |
| Vertigo Positional | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 115 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Oral AD Plus Intranasal Placebo | Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD) | |
|---|------------------------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 52 / 109 (47.71%) | 90 / 115 (78.26%) | |
| Investigations | | | |
| Blood Pressure Increased | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 11 / 115 (9.57%) | |
| occurrences (all) | 0 | 22 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 5 / 109 (4.59%) | 24 / 115 (20.87%) | |
| occurrences (all) | 5 | 59 | |
| Dizziness Postural | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 8 / 115 (6.96%) | |
| occurrences (all) | 1 | 43 | |
| Dysgeusia | | | |
| subjects affected / exposed | 13 / 109 (11.93%) | 28 / 115 (24.35%) | |
| occurrences (all) | 61 | 151 | |
| Headache | | | |

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

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

Notes: