



Clinical trial results:

A Randomized, Double-blind, Multicenter, Active-controlled Study of Intranasal Esketamine Plus an Oral Antidepressant for Relapse Prevention in Treatment-resistant Depression

Summary

| | |
|--------------------------|-------------------------|
| EudraCT number | 2014-004586-24 |
| Trial protocol | DE BE PL ES HU CZ SK IT |
| Global end of trial date | 15 February 2018 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 03 March 2019 |
| First version publication date | 03 March 2019 |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | ESKETINTRD3003 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02493868 |
| 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 | 15 February 2018 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 15 February 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main purpose of the study was to assess the efficacy of intranasal esketamine + oral antidepressant compared with an oral antidepressant + intranasal placebo in delaying relapse of depressive symptoms in subjects with treatment-resistant depression (TRD) who were in stable remission after an induction and optimization course of intranasal esketamine + oral antidepressant.

Protection of trial subjects:

The 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 clinical laboratory tests (hematology, serum chemistry, and urinalysis), vital sign measurements (temperature, pulse/heart rate, respiratory rate, and blood pressure), physical examinations, height, body weight, and neck circumference, electrocardiograms (ECGs), pulse oximetry, nasal examination.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 06 October 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: 14 |
| Country: Number of subjects enrolled | Brazil: 64 |
| Country: Number of subjects enrolled | Canada: 5 |
| Country: Number of subjects enrolled | Czech Republic: 99 |
| Country: Number of subjects enrolled | Germany: 7 |
| Country: Number of subjects enrolled | Spain: 16 |
| Country: Number of subjects enrolled | Estonia: 1 |
| Country: Number of subjects enrolled | France: 10 |
| Country: Number of subjects enrolled | Hungary: 35 |
| Country: Number of subjects enrolled | Italy: 21 |
| Country: Number of subjects enrolled | Mexico: 35 |
| Country: Number of subjects enrolled | Poland: 132 |
| Country: Number of subjects enrolled | Slovakia: 7 |
| Country: Number of subjects enrolled | Sweden: 16 |
| Country: Number of subjects enrolled | Turkey: 53 |
| Country: Number of subjects enrolled | United States: 190 |

| | |
|------------------------------------|-----|
| Worldwide total number of subjects | 705 |
| EEA total number of subjects | 358 |

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) | 705 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Total of 705 subjects were enrolled. Out of which 437 (direct entry [DE] subjects) entered in induction (IND) phase and 268 subjects (150 transferred-entry [TE] subjects from study ESKETINTRD3001 [NCT02417064] and 118 subjects from study ESKETINTRD3002 [NCT02418585]) entered in this study in optimization (OP) phase.

Period 1

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

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | No |
| Arm title | IND: Intranasal Esketamine + Oral AD (DE Subjects) |

Arm description:

Subjects in open-label induction (IND) phase received 56 or 84 milligram intranasal esketamine solution twice weekly with open-label oral antidepressant (AD) (one of: duloxetine/escitalopram/sertraline/venlafaxine extended release [XR]) once daily for 4 weeks. Subjects who completed IND phase and met predefined response criteria entered optimization (OP) phase.

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

Dosage and administration details:

Subjects received 56 or 84 mg intranasal esketamine solution twice weekly.

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

Dosage and administration details:

Subjects received one of duloxetine/escitalopram/sertraline/venlafaxine XR oral antidepressant once daily.

| | |
|------------------|--|
| Arm title | OP: Intranasal Esketamine + Oral AD (DE+TE Subjects) |
|------------------|--|

Arm description:

Subjects received intranasal esketamine (same dose) solution once per week for first 4 weeks, then once per week/once every other week based on severity of depressive symptoms, and continued same oral AD from IND phase for 12 weeks. Subjects who completed and met the predefined remission/response criteria entered maintenance (MA) phase.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|-----------------------|
| Investigational medicinal product name | Esketamine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Nasal spray, solution |
| Routes of administration | Nasal use |

Dosage and administration details:

Subjects received 56 or 84 mg intranasal esketamine solution once per week for first 4 weeks, then once per week/once every other week.

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

Dosage and administration details:

Subjects received one of duloxetine/escitalopram/sertraline/venlafaxine XR oral antidepressant once daily.

| | |
|------------------|--|
| Arm title | OP: Oral AD + Intranasal Placebo (TE Subjects) |
|------------------|--|

Arm description:

Optimization phase (transferred-entry subjects): Subjects received intranasal esketamine matching placebo solution once per week for the first 4 weeks, then once per week or once every other week depending on severity of depressive symptoms with open-label oral AD (one of: duloxetine/escitalopram/sertraline/venlafaxine XR), once daily for 12 weeks. Subjects who completed and met the predefined remission/response criteria entered MA phase.

| | |
|--|---------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Oral Antidepressant |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet, Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received one of duloxetine/escitalopram/sertraline/venlafaxine XR oral antidepressant once daily.

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

Dosage and administration details:

Subjects received intranasal esketamine matching placebo solution once per week for the first 4 weeks, then once per week or once every other week.

| | |
|------------------|--|
| Arm title | MA: Intranasal Esketamine + Oral AD (DE+TE Subjects) |
|------------------|--|

Arm description:

MA phase (DE+TE): subjects were randomized (at end of OP phase) to receive intranasal esketamine (same dose) once weekly/once every other week based on severity of depressive symptoms and continued same oral AD from IND phase.

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

Dosage and administration details:

Subjects received 56 or 84 mg intranasal esketamine solution once weekly or once every other week.

| | |
|---|---|
| Investigational medicinal product name | Oral Antidepressant |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet, Capsule |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Subjects received one of duloxetine/escitalopram/sertraline/venlafaxine XR oral antidepressant once daily | |
| Arm title | MA: Oral AD + Intranasal Placebo (DE+TE Subjects) |
| Arm description: | |
| Maintenance phase (DE+TE subjects): Subjects (including randomized subjects from intranasal esketamine arm after OP phase and TE subjects who continued from previous phase in this group) to receive intranasal esketamine placebo with oral AD. | |
| Arm type | Placebo |
| Investigational medicinal product name | Oral Antidepressant |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet, Capsule |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Subjects received one of duloxetine/escitalopram/sertraline/venlafaxine XR oral antidepressant once daily. | |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Nasal spray, solution |
| Routes of administration | Nasal use |
| Dosage and administration details: | |
| Subjects received intranasal esketamine placebo once weekly or once every other week. | |
| Arm title | FU: Intranasal Esketamine + Oral AD |
| Arm description: | |
| Follow-up (FU) phase: subjects received no intranasal esketamine but continued oral AD for 2 weeks unless determined to not be clinically appropriate. Subjects who were non-responders at the end of IND phase or who were early terminated at any phase proceeded directly to FU phase. | |
| Arm type | Experimental |
| Investigational medicinal product name | Oral Antidepressant |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet, Capsule |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Subjects received one of duloxetine/escitalopram/sertraline/venlafaxine XR oral antidepressant once daily. | |
| Arm title | FU: Oral AD + Intranasal Placebo |
| Arm description: | |
| FU Phase: subjects received oral AD for 2 weeks of the follow-up phase unless it was determined to not be clinically appropriate. Subjects who were non-responders in IND phase and who were in OP and MA phase at study termination proceeded directly to FU phase. | |
| Arm type | Placebo |

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

Dosage and administration details:

Subjects received one of duloxetine/escitalopram/sertraline/venlafaxine XR oral antidepressant once daily.

| Number of subjects in period 1 | IND: Intranasal Esketamine + Oral AD (DE Subjects) | OP: Intranasal Esketamine + Oral AD (DE+TE Subjects) | OP: Oral AD + Intranasal Placebo (TE Subjects) |
|--|--|--|--|
| | | | |
| Started | 437 | 455 | 86 |
| Completed | 273 | 297 | 54 |
| Not completed | 164 | 158 | 32 |
| Consent withdrawn by subject | 15 | 8 | 3 |
| Adverse Event | 22 | 5 | - |
| Non Compliance with Study Drug | - | - | - |
| Pregnancy | - | - | - |
| Subject did not meet crit for next phase | 114 | 107 | 20 |
| Unspecified | 8 | 10 | 2 |
| MADRS \geq 22 for 2 Consecutive Visit | - | 14 | 5 |
| Lost to follow-up | 1 | 2 | 1 |
| PI Decision | - | - | - |
| Protocol deviation | 2 | 4 | 1 |
| Lack of efficacy | 2 | 8 | - |

| Number of subjects in period 1 | MA: Intranasal Esketamine + Oral AD (DE+TE Subjects) | MA: Oral AD + Intranasal Placebo (DE+TE Subjects) | FU: Intranasal Esketamine + Oral AD |
|--|--|---|-------------------------------------|
| | | | |
| Started | 152 | 199 | 481 |
| Completed | 139 | 177 | 470 |
| Not completed | 13 | 22 | 11 |
| Consent withdrawn by subject | 5 | 7 | 3 |
| Adverse Event | 1 | 4 | - |
| Non Compliance with Study Drug | - | 1 | - |
| Pregnancy | 1 | - | - |
| Subject did not meet crit for next phase | - | - | - |
| Unspecified | 4 | 9 | 2 |
| MADRS \geq 22 for 2 Consecutive Visit | - | - | - |
| Lost to follow-up | 1 | - | 1 |

| | | | |
|--------------------|---|---|---|
| PI Decision | - | - | 5 |
| Protocol deviation | 1 | 1 | - |
| Lack of efficacy | - | - | - |

| Number of subjects in period 1 | FU: Oral AD + Intranasal Placebo |
|--|---|
| Started | 64 |
| Completed | 62 |
| Not completed | 2 |
| Consent withdrawn by subject | - |
| Adverse Event | - |
| Non Compliance with Study Drug | - |
| Pregnancy | - |
| Subject did not meet crit for next phase | - |
| Unspecified | 1 |
| MADRS ≥ 22 for 2 Consecutive Visit | - |
| Lost to follow-up | - |
| PI Decision | 1 |
| Protocol deviation | - |
| Lack of efficacy | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Overall Study |
|-----------------------|---------------|

Reporting group description: -

| Reporting group values | Overall Study | Total | |
|---|---------------|-------|--|
| Number of subjects | 705 | 705 | |
| Title for AgeCategorical Units: subjects | | | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 705 | 705 | |
| From 65 to 84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Title for AgeContinuous Units: years | | | |
| arithmetic mean | 46.1 | | |
| standard deviation | ± 11.10 | - | |
| Title for Gender Units: subjects | | | |
| Female | 457 | 457 | |
| Male | 248 | 248 | |

End points

End points reporting groups

| | |
|--|--|
| Reporting group title | IND: Intranasal Esketamine + Oral AD (DE Subjects) |
| Reporting group description: Subjects in open-label induction (IND) phase received 56 or 84 milligram intranasal esketamine solution twice weekly with open-label oral antidepressant (AD) (one of: duloxetine/escitalopram/sertraline/venlafaxine extended release [XR]) once daily for 4 weeks. Subjects who completed IND phase and met predefined response criteria entered optimization (OP) phase. | |
| Reporting group title | OP: Intranasal Esketamine + Oral AD (DE+TE Subjects) |
| Reporting group description: Subjects received intranasal esketamine (same dose) solution once per week for first 4 weeks, then once per week/once every other week based on severity of depressive symptoms, and continued same oral AD from IND phase for 12 weeks. Subjects who completed and met the predefined remission/response criteria entered maintenance (MA) phase. | |
| Reporting group title | OP: Oral AD + Intranasal Placebo (TE Subjects) |
| Reporting group description: Optimization phase (transferred-entry subjects): Subjects received intranasal esketamine matching placebo solution once per week for the first 4 weeks, then once per week or once every other week depending on severity of depressive symptoms with open-label oral AD (one of: duloxetine/escitalopram/sertraline/venlafaxine XR), once daily for 12 weeks. Subjects who completed and met the predefined remission/response criteria entered MA phase. | |
| Reporting group title | MA: Intranasal Esketamine + Oral AD (DE+TE Subjects) |
| Reporting group description: MA phase (DE+TE): subjects were randomized (at end of OP phase) to receive intranasal esketamine (same dose) once weekly/once every other week based on severity of depressive symptoms and continued same oral AD from IND phase. | |
| Reporting group title | MA: Oral AD + Intranasal Placebo (DE+TE Subjects) |
| Reporting group description: Maintenance phase (DE+TE subjects): Subjects (including randomized subjects from intranasal esketamine arm after OP phase and TE subjects who continued from previous phase in this group) to receive intranasal esketamine placebo with oral AD. | |
| Reporting group title | FU: Intranasal Esketamine + Oral AD |
| Reporting group description: Follow-up (FU) phase: subjects received no intranasal esketamine but continued oral AD for 2 weeks unless determined to not be clinically appropriate. Subjects who were non-responders at the end of IND phase or who were early terminated at any phase proceeded directly to FU phase. | |
| Reporting group title | FU: Oral AD + Intranasal Placebo |
| Reporting group description: FU Phase: subjects received oral AD for 2 weeks of the follow-up phase unless it was determined to not be clinically appropriate. Subjects who were non-responders in IND phase and who were in OP and MA phase at study termination proceeded directly to FU phase. | |
| Subject analysis set title | Stable Remitters :Intranasal Esketamine + Oral AD |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Subjects who were in stable remission at the end of the optimization phase and who received at least 1 dose of intranasal study drug and 1 dose of oral antidepressant during the maintenance phase. | |
| Subject analysis set title | Stable Remitters: Oral AD + Intranasal Placebo |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Subjects who were in stable remission at the end of the optimization phase and who received at least 1 dose of intranasal placebo and 1 dose of oral antidepressant during the maintenance phase. | |
| Subject analysis set title | Stable Responders: Intranasal Esketamine + Oral AD |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Subjects who were stable responders (but not stable remitters) at the end of the optimization phase and who received at least 1 dose of intranasal study drug and 1 dose of oral antidepressant during the | |

maintenance phase.

| | |
|----------------------------|---|
| Subject analysis set title | Stable Responders: Oral AD + Intranasal Placebo |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Subjects who were stable responders (but not stable remitters) at the end of the optimization phase and who received at least 1 dose of intranasal placebo and 1 dose of oral antidepressant during the maintenance phase.

Primary: Time to Relapse in Subjects with Stable Remission (Maintenance Phase)

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|-----------------|---|
| End point title | Time to Relapse in Subjects with Stable Remission (Maintenance Phase) |
|-----------------|---|

End point description:

Relapse (any of following): MADRS total score ≥ 22 for 2 consecutive assessments separated by 5-15 days and/or hospitalization for worsening depression/any clinical event suggestive of relapse of depressive illness such as suicide attempt/completed suicide/hospitalization to prevent suicide; If hospitalized, start date of hospitalization will be date of relapse, if not then date of event will be used. Stable remission: MADRS total score ≤ 12 for at least 3 of last 4 weeks of OP phase, with 1 excursion total score > 12 or 1 missing assessment at OP week 13/14. FAS (stable remitters) = all randomized subjects who were in stable remission at end of OP phase and received at least 1 dose of study drug and oral AD in MA phase. '99999' = for esketamine arm that median time to relapse (time point at which cumulative survival function equals 0.5 or 50%) was not estimable, as group never reached 50%; 99999 (placebo arm) = upper limit of CI could not be estimated due to insufficient data.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Time from randomization to the first relapse during the maintenance phase (up to 92 Weeks)

| End point values | Stable Remitters :Intranasal Esketamine + Oral AD | Stable Remitters: Oral AD + Intranasal Placebo | | |
|----------------------------------|---|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 90 | 86 | | |
| Units: Days | | | | |
| median (confidence interval 95%) | 99999 (99999 to 99999) | 273.0 (97.0 to 99999) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Stable Remitters :Intranasal Esketamine + Oral AD v Stable Remitters: Oral AD + Intranasal Placebo |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.003 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.49 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.29 |
| upper limit | 0.83 |

Secondary: Time to Relapse in Subjects with Stable Response (but not in Stable Remission) (Maintenance Phase)

| | |
|-----------------|--|
| End point title | Time to Relapse in Subjects with Stable Response (but not in Stable Remission) (Maintenance Phase) |
|-----------------|--|

End point description:

Relapse (any of following): MADRS total score ≥ 22 for 2 consecutive assessments separated by 5-15 days and/or hospitalization for worsening depression/any clinical event suggestive of relapse of depressive illness such as suicide attempt/completed suicide/hospitalization to prevent suicide; If hospitalized, start date of hospitalization will be date of relapse, if not then date of event will be used. MADRS: scale to measure depression severity and to detect changes due to AD treatment. It has 10 items, scored from 0-6 (not present/normal-severe/continuous symptoms), total score =60. Higher scores: more severe condition. Stable response: $\geq 50\%$ reduction in MADRS total score from baseline (Day 1: IND phase [before first dose]) in each of last 2 weeks of OP phase, but no stable remission. FAS Stable responders: all randomized subjects who were stable responders (not stable remitters) at end of OP phase and who received at least 1 dose of intranasal study drug and oral AD in MA phase.

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

End point timeframe:

Time from randomization to the first relapse during the maintenance phase (up to 92 Weeks)

| End point values | Stable Responders: Intranasal Esketamine + Oral AD | Stable Responders: Oral AD + Intranasal Placebo | | |
|----------------------------------|--|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 62 | 59 | | |
| Units: Days | | | | |
| median (confidence interval 95%) | 635.0 (264.0 to 635.0) | 88.0 (46.0 to 196.0) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Montgomery-asberg Depression Rating Scale (MADRS) Total Score at Endpoint in Subjects with Stable Remission (Maintenance Phase)

| | |
|-----------------|---|
| End point title | Change from Baseline in Montgomery-asberg Depression Rating Scale (MADRS) Total Score at Endpoint in Subjects with Stable Remission (Maintenance Phase) |
|-----------------|---|

End point description:

MADRS: scale to measure depression severity and to detect changes due to AD treatment. It has 10 items, scored from 0-6 (not present/normal-severe/continuous symptoms), total score = 60. Higher scores: more severe condition. The change from baseline in MADRS total score (last observation carried

forward [LOCF] data), at endpoint was reported. The last post baseline observation was carried forward as the endpoint. FAS Stable remitters included all randomized subjects who were in stable remission at end of OP phase and received at least 1 dose of study drug and oral AD in MA phase. Here 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Endpoint (Up to 92 Weeks) | |

| End point values | Stable Remitters :Intranasal Esketamine + Oral AD | Stable Remitters: Oral AD + Intranasal Placebo | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 89 | 86 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | 7.5 (± 11.59) | 12.5 (± 13.63) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in MADRS Total Score at Endpoint in Subjects with Stable Response (but not in Stable Remission) (Maintenance Phase)

| | |
|-----------------|--|
| End point title | Change from Baseline in MADRS Total Score at Endpoint in Subjects with Stable Response (but not in Stable Remission) (Maintenance Phase) |
|-----------------|--|

End point description:

MADRS: scale to measure depression severity and to detect changes due to AD treatment. It has 10 items, scored from 0-6 (not present/normal-severe/continuous symptoms), total score = 60. Higher scores: more severe condition. The change from baseline in MADRS total score (LOCF data), at endpoint was reported. The last post baseline observation was carried forward as the endpoint. FAS Stable responders included all randomized subjects who were stable responders (but not stable remitters) at end of OP phase and who received at least 1 dose of intranasal study drug and oral AD in MA phase.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Endpoint (Up to 92 Weeks) | |

| End point values | Stable Responders: Intranasal Esketamine + Oral AD | Stable Responders: Oral AD + Intranasal Placebo | | |
|--------------------------------------|--|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 62 | 59 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | 4.4 (± 11.38) | 11.4 (± 12.00) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Patient Health Questionnaire-9 (PHQ-9) Total Score at Endpoint in Subjects with Stable Remission (Maintenance Phase)

| | |
|-----------------|--|
| End point title | Change from Baseline in Patient Health Questionnaire-9 (PHQ-9) Total Score at Endpoint in Subjects with Stable Remission (Maintenance Phase) |
|-----------------|--|

End point description:

PHQ-9 is a 9-item, self-report scale assessing depressive symptoms. Each item is rated on a 4-point scale (0 = Not at all, 1 = Several Days, 2 = More than half the days, and 3 = Nearly every day). The subject's item responses are summed to provide a total score (range of 0 to 27) with higher scores indicating greater severity of depressive symptoms. The severity of the PHQ-9 is categorized as follows: None-minimal (0-4), mild (5-9), moderate (10-14), moderately severe (15-19) and severe (20-27). The change from baseline in PHQ-9 total score, (LOCF data) at endpoint was reported. The last post baseline observation was carried forward as the endpoint. FAS Stable remitters included all randomized subjects who were in stable remission at end of OP phase and received at least 1 dose of study drug and oral AD in MA phase. Here 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

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

End point timeframe:

Baseline and Endpoint (Up to 92 Weeks)

| End point values | Stable Remitters :Intranasal Esketamine + Oral AD | Stable Remitters: Oral AD + Intranasal Placebo | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 89 | 86 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | 3.3 (± 5.58) | 5.9 (± 7.09) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in PHQ-9 Total Score at Endpoint in Subjects with Stable Response (but not in Stable Remission) (Maintenance Phase)

| | |
|-----------------|--|
| End point title | Change from Baseline in PHQ-9 Total Score at Endpoint in Subjects with Stable Response (but not in Stable Remission) (Maintenance Phase) |
|-----------------|--|

End point description:

PHQ-9 is a 9-item, self-report scale assessing depressive symptoms. Each item is rated on a 4-point

scale (0 = Not at all, 1 = Several Days, 2 = More than half the days, and 3 = Nearly every day). The subject's item responses are summed to provide a total score (range of 0 to 27) with higher scores indicating greater severity of depressive symptoms. The severity of the PHQ-9 is categorized as follows: None-minimal (0-4), mild (5-9), moderate (10-14), moderately severe (15-19) and severe (20-27). The change from baseline in PHQ-9 total score, (LOCF data) at endpoint was reported. The last post baseline observation was carried forward as the endpoint. FAS (Stable responders) included all randomized subjects who were stable responders (but not stable remitters) at end of OP phase and who received at least 1 dose of intranasal study drug and oral AD in MA phase. Here 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

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

End point timeframe:

Baseline and Endpoint (Up to 92 Weeks)

| End point values | Stable Responders: Intranasal Esketamine + Oral AD | Stable Responders: Oral AD + Intranasal Placebo | | |
|--------------------------------------|--|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 61 | 58 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | 1.7 (± 5.02) | 4.7 (± 5.48) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Clinical Global Impression-Severity (CGI-S) Score at Endpoint in Subjects with Stable Remission (Maintenance Phase)

| | |
|-----------------|---|
| End point title | Change from Baseline in Clinical Global Impression-Severity (CGI-S) Score at Endpoint in Subjects with Stable Remission (Maintenance Phase) |
|-----------------|---|

End point description:

CGI-S: clinician-determined summary measure of severity of subject's illness that considers all available information, including knowledge of subject's history, psychosocial circumstances, symptoms, behavior, impact of symptoms on ability to function. CGI-S evaluates severity of psychopathology on a scale of 0-7. Subject is assessed on severity of mental illness at time of rating as: 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. Change from baseline in CGI-S score, (LOCF data) at endpoint was reported. Last post baseline observation was carried forward as endpoint. FAS (Stable remitters) included all randomized subjects who were in stable remission at end of OP phase and received at least 1 dose of study drug and oral AD in MA phase. Here 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

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

End point timeframe:

Baseline and Endpoint (Up to 92 Weeks)

| End point values | Stable Remitters :Intranasal Esketamine + Oral AD | Stable Remitters: Oral AD + Intranasal Placebo | | |
|-------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 89 | 86 | | |
| Units: Units on a scale | | | | |
| median (full range (min-max)) | 0.0 (-3 to 4) | 1.0 (-2 to 5) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Clinical Global Impression-Severity Score at Endpoint in Subjects with Stable Response (but not in Stable Remission) (Maintenance Phase)

| | |
|-----------------|--|
| End point title | Change from Baseline in Clinical Global Impression-Severity Score at Endpoint in Subjects with Stable Response (but not in Stable Remission) (Maintenance Phase) |
|-----------------|--|

End point description:

CGI-S: clinician-determined summary measure of severity of subject's illness that considers information, including knowledge of subject's history, psychosocial circumstances, symptoms, behavior, impact of symptoms on ability to function. CGI-S evaluates severity of psychopathology on a scale of 0-7. Subject is assessed on severity of mental illness at time of rating as: 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. Change from baseline in CGI-S score, (LOCF data) at endpoint was reported. Last post baseline observation was carried forward as endpoint. FAS (Stable responders): all randomized subjects who were stable responders (but not stable remitters) at end of OP phase and who received at least 1 dose of intranasal study drug and oral AD in MA phase. 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

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

End point timeframe:

Baseline and Endpoint (Up to 92 Weeks)

| End point values | Stable Responders: Intranasal Esketamine + Oral AD | Stable Responders: Oral AD + Intranasal Placebo | | |
|-------------------------------|---|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 62 | 58 | | |
| Units: Units on a scale | | | | |
| median (full range (min-max)) | 0.0 (-2 to 4) | 1.0 (-3 to 5) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Generalized Anxiety Disorder-7 Items (GAD-7) Total Score at Endpoint in Subjects with Stable Remission (Maintenance Phase)

| | |
|-----------------|--|
| End point title | Change from Baseline in Generalized Anxiety Disorder-7 Items (GAD-7) Total Score at Endpoint in Subjects with Stable Remission (Maintenance Phase) |
|-----------------|--|

End point description:

GAD-7 is brief and validated 7-item self-report assessment of overall anxiety. Subjects respond to each item using a 4-point scale with response categories: 0=not at all, 1=several days, 2=more than half the days, 3=nearly every day. Item responses are summed to yield total score with range of 0-21, higher scores indicate more anxiety. Severity of GAD-7 is categorized as: None (0-4), Mild (5-9), Moderate (10-14) and Severe (15 -21). Item responses are summed for total score (range of 0-21), higher scores indicating more anxiety. Change from baseline in GAD-7 total score, (LOCF data), at endpoint was reported. Last post baseline observation was carried forward as endpoint. FAS (Stable remitters) included all randomized subjects who were in stable remission at end of OP phase and received at least 1 dose of study drug and oral AD in MA phase. Here 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

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

End point timeframe:

Baseline and Endpoint (Up to 92 Weeks)

| End point values | Stable Remitters :Intranasal Esketamine + Oral AD | Stable Remitters: Oral AD + Intranasal Placebo | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 89 | 86 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | 2.2 (± 4.45) | 4.0 (± 5.93) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Generalized Anxiety Disorder-7 Items Total Score at Endpoint in Subjects with Stable Response (but not in Stable Remission) (Maintenance Phase)

| | |
|-----------------|---|
| End point title | Change from Baseline in Generalized Anxiety Disorder-7 Items Total Score at Endpoint in Subjects with Stable Response (but not in Stable Remission) (Maintenance Phase) |
|-----------------|---|

End point description:

GAD-7 is brief and validated 7-item self-report assessment of overall anxiety. Subjects respond to each item using a 4-point scale with response categories: 0=not at all, 1=several days, 2=more than half the days, 3=nearly every day. Item responses are summed to yield total score with range of 0-21, higher score means more anxiety. Severity of GAD-7 is categorized as: None (0-4), Mild (5-9), Moderate (10-14), Severe (15 -21). Item responses are summed for total score (range of 0-21), higher scores indicating more anxiety. Change from baseline in GAD-7 total score, (LOCF data), at endpoint was reported. Last post baseline observation was carried forward as endpoint. FAS (Stable responders) included all randomized subjects who were stable responders (but not stable remitters) at end of OP phase and who received at least 1 dose of intranasal study drug and oral AD in MA phase. Here 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

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

End point timeframe:

Baseline and Endpoint (Up to 92 Weeks)

| End point values | Stable Responders: Intranasal Esketamine + Oral AD | Stable Responders: Oral AD + Intranasal Placebo | | |
|--------------------------------------|--|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 61 | 58 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | 1.4 (± 3.76) | 2.6 (± 4.26) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in EuroQol-5 Dimension-5 Level (EQ-5D-5L) Sum Score at Endpoint in Subjects with Stable Remission (Maintenance Phase)

| | |
|-----------------|--|
| End point title | Change from Baseline in EuroQol-5 Dimension-5 Level (EQ-5D-5L) Sum Score at Endpoint in Subjects with Stable Remission (Maintenance Phase) |
|-----------------|--|

End point description:

EQ-5D-5L consists of EQ-5D-5L descriptive system and EQ VAS. EQ-5D-5L descriptive system has 5 dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. Each has 5 levels of perceived problems (1-no problem; 2-slight; 3-moderate; 4-severe; 5-extreme problems). Responses from all 5 dimensions answered by subject as per his/her health "today" were used to generate HIS, range=0-1.00 (dead-full health). EQ VAS self-rating records respondent's own assessment of his/her overall health status at time of completion, scale range=0-100 (worst health-best health). Sum score range=0-100. sum score= (sum of the scores from the 5 dimensions minus 5) *5. Higher score indicates worst health state. FAS (Stable remitters) included all randomized subjects in stable remission at end of OP phase and received at least 1 dose of study drug and oral AD in MA phase. 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

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

End point timeframe:

Baseline and Endpoint (Up to 92 Weeks)

| End point values | Stable Remitters :Intranasal Esketamine + Oral AD | Stable Remitters: Oral AD + Intranasal Placebo | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 88 | 86 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | 7.5 (± 11.87) | 10.9 (± 14.74) | | |

Statistical analyses

Secondary: Change from Baseline in EQ Visual Analogue Scale (EQ VAS) Score at Endpoint in Subjects with Stable Remission (Maintenance Phase)

| | |
|-----------------|---|
| End point title | Change from Baseline in EQ Visual Analogue Scale (EQ VAS) Score at Endpoint in Subjects with Stable Remission (Maintenance Phase) |
|-----------------|---|

End point description:

EQ VAS self-rating records respondent's own assessment of his/her overall health status at time of completion, scale range = 0-100 (worst health-best health). FAS (Stable remitters) included all randomized subjects who were in stable remission at end of OP phase and received at least 1 dose of study drug and oral AD in MA phase. Here 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

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

End point timeframe:

Baseline and Endpoint (Up to 92 Weeks)

| End point values | Stable Remitters :Intranasal Esketamine + Oral AD | Stable Remitters: Oral AD + Intranasal Placebo | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 88 | 86 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | -10.4 (± 20.29) | -16.1 (± 21.80) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in EQ-5D-5L Health Status Index (HSI) at Endpoint in Subjects with Stable Remission (Maintenance Phase)

| | |
|-----------------|--|
| End point title | Change from Baseline in EQ-5D-5L Health Status Index (HSI) at Endpoint in Subjects with Stable Remission (Maintenance Phase) |
|-----------------|--|

End point description:

EQ-5D-5L consists of EQ-5D-5L descriptive system and EQ VAS. EQ-5D-5L descriptive system has 5 dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. Each has 5 levels of perceived problems (1-no problem; 2-slight; 3-moderate; 4-severe; 5-extreme problems). Responses from all 5 dimensions answered by subject as per his/her health "today" were used to generate HSI. HSI range: 0-1.00 (dead-full health). FAS (Stable remitters) included all randomized subjects in stable remission at end of OP phase and received at least 1 dose of study drug and oral AD in MA phase. Here 'N' (number of subjects analyzed) included number of subjects who were evaluable for this endpoint.

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

End point timeframe:

Baseline and Endpoint (Up to 92 Weeks)

| End point values | Stable Remitters :Intranasal Esketamine + Oral AD | Stable Remitters: Oral AD + Intranasal Placebo | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 88 | 86 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | -0.067 (± 0.1180) | -0.096 (± 0.1484) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in EuroQol-5 Dimension-5 Level Sum Score at Endpoint in Subjects with Stable Response (but not in Stable Remission) (Maintenance Phase)

| | |
|-----------------|--|
| End point title | Change from Baseline in EuroQol-5 Dimension-5 Level Sum Score at Endpoint in Subjects with Stable Response (but not in Stable Remission) (Maintenance Phase) |
|-----------------|--|

End point description:

EQ-5D-5L consists of EQ-5D-5L descriptive system and EQ VAS. Descriptive system has 5 dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. Each has 5 levels of perceived problems (1-no problem; 2-slight; 3-moderate; 4-severe; 5-extreme problems). Responses from all 5 dimensions answered by subject as per his/her health "today" were used to generate HIS, range: 0-1.00 (dead-full health). EQ VAS self-rating records respondent's own assessment of his/her overall health status at time of completion, scale range=0-100 (worst health-best health). Sum score range=0-100. sum score= (sum score of 5 dimensions minus 5) *5. Higher score: worst health state. FAS (Stable responders): all randomized subjects who were stable responders (but not stable remitters) at end of OP phase and who received at least 1 dose of intranasal study drug and oral AD in MA phase. 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

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

End point timeframe:

Baseline and Endpoint (Up to 92 Weeks)

| End point values | Stable Responders: Intranasal Esketamine + Oral AD | Stable Responders: Oral AD + Intranasal Placebo | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 61 | 58 | | |
| Units: Units on scale | | | | |
| arithmetic mean (standard deviation) | 3.0 (± 8.13) | 8.4 (± 13.55) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in EQ-5D-5L EQ Visual Analogue Scale Score at Endpoint in Subjects with Stable Response (but not in Stable Remission) (Maintenance Phase)

| | |
|-----------------|--|
| End point title | Change from Baseline in EQ-5D-5L EQ Visual Analogue Scale Score at Endpoint in Subjects with Stable Response (but not in Stable Remission) (Maintenance Phase) |
|-----------------|--|

End point description:

EQ VAS self-rating records respondent's own assessment of his/her overall health status at time of completion, scale range=0-100 (worst health-best health). FAS (Stable responders) included all randomized subjects who were stable responders (but not stable remitters) at end of OP phase and who received at least 1 dose of intranasal study drug and oral AD in MA phase. Here 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

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

End point timeframe:

Baseline and Endpoint (Up to 92 Weeks)

| End point values | Stable Responders: Intranasal Esketamine + Oral AD | Stable Responders: Oral AD + Intranasal Placebo | | |
|--------------------------------------|--|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 61 | 58 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | -1.3 (± 15.55) | -13.8 (± 19.81) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in EQ-5D-5L Health Status Index at Endpoint in Subjects with Stable Response (but not in Stable Remission) (Maintenance Phase)

| | |
|-----------------|---|
| End point title | Change from Baseline in EQ-5D-5L Health Status Index at Endpoint in Subjects with Stable Response (but not in Stable Remission) (Maintenance Phase) |
|-----------------|---|

End point description:

EQ-5D-5L consists of EQ-5D-5L descriptive system and EQ VAS. EQ-5D-5L descriptive system has 5 dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. Each has 5 levels of perceived problems (1-no problem; 2-slight; 3-moderate; 4-severe; 5-extreme problems). Responses from all 5 dimensions answered by subject as per his/her health "today" were used to generate HSI. HSI range: 0-1.00 (dead-full health). FAS (Stable responders) included all randomized subjects who were stable responders (but not stable remitters) at end of OP phase and who received at least 1 dose of intranasal study drug and oral AD in MA phase. Here 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

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

End point timeframe:

Baseline and Endpoint (Up to 92 Weeks)

| End point values | Stable Responders: Intranasal Esketamine + Oral AD | Stable Responders: Oral AD + Intranasal Placebo | | |
|--------------------------------------|--|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 61 | 58 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | -0.023 (\pm 0.0753) | -0.073 (\pm 0.1383) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Sheehan Disability Scale (SDS) Total Score at Endpoint in Subjects with Stable Remission (Maintenance Phase)

| | |
|-----------------|--|
| End point title | Change from Baseline in Sheehan Disability Scale (SDS) Total Score at Endpoint in Subjects with Stable Remission (Maintenance Phase) |
|-----------------|--|

End point description:

SDS: 5-item questionnaire used for assessment of functional impairment and associated disability. First 3 items assess disruption of 1: work/school 2: social life 3: family life/home responsibilities on a 0-10 rating scale. It has 1 item for each day lost from school/work and when underproductive. First 3 items scores are summed to make total score of 0-30, higher score: greater impairment. Recall period is 7 days. Response: scores ≤ 4 for each item, ≤ 12 for total score. Remission: scores ≤ 2 for each item, ≤ 6 for total score. Change from baseline in SDS total Score, (LOCF data), at endpoint was reported. Last post baseline observation was carried forward as endpoint. FAS (Stable remitters) included all randomized subjects in stable remission at end of OP phase and received at least 1 dose of study drug and oral AD in MA phase. 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

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

End point timeframe:

Baseline and Endpoint (Up to 92 Weeks)

| End point values | Stable Remitters: Intranasal Esketamine + Oral AD | Stable Remitters: Oral AD + Intranasal Placebo | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 82 | 77 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | 4.7 (\pm 7.34) | 7.2 (\pm 10.44) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Sheehan Disability Total Score at Endpoint in

Subjects with Stable Response (but not in Stable Remission) (Maintenance Phase)

| | |
|-----------------|---|
| End point title | Change from Baseline in Sheehan Disability Total Score at Endpoint in Subjects with Stable Response (but not in Stable Remission) (Maintenance Phase) |
|-----------------|---|

End point description:

SDS: 5-item questionnaire for assessment of functional impairment and associated disability. First 3 items assess disruption of 1: work/school 2: social life 3: family life/home responsibilities on a 0-10 rating scale. It has 1 item for each day lost from school/work and when underproductive. First 3 items sum score gives total score of 0-30, higher score: greater impairment. Recall period is 7 days. Response: scores ≤ 4 for each item, ≤ 12 for total score. Remission: scores ≤ 2 for each item, ≤ 6 for total score. Change from baseline in SDS total Score, (LOCF data) at endpoint was reported. Last post baseline observation was carried forward as endpoint. FAS (Stable responders) included all randomized subjects who were stable responders (but not stable remitters) at end of OP phase and who received at least 1 dose of intranasal study drug and oral AD in MA phase. 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

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

End point timeframe:

Baseline and Endpoint (Up to 92 Weeks)

| End point values | Stable Responders: Intranasal Esketamine + Oral AD | Stable Responders: Oral AD + Intranasal Placebo | | |
|--------------------------------------|--|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 58 | 53 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | 2.2 (\pm 6.63) | 6.8 (\pm 7.64) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Approximately 2.4 years

Adverse event reporting additional description:

Safety analysis set included all subjects who received at least 1 dose of intranasal study medication or 1 dose of oral antidepressant in respective phase (Induction, Optimization, Maintenance). Follow-up analysis set included all subjects who entered the follow-up phase.

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

Dictionary used

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

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

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | IND: DE Subjects: Intranasal Esketamine + Oral AD |
|-----------------------|---|

Reporting group description:

Subjects in open-label induction (IND) phase received 56 or 84 milligram intranasal esketamine solution twice weekly with open-label oral AD (one of: duloxetine/escitalopram/sertraline/venlafaxine extended release [XR]) once daily for 4 weeks.

| | |
|-----------------------|--|
| Reporting group title | MA: Intranasal Esketamine + Oral AD (DE+TE Subjects) |
|-----------------------|--|

Reporting group description:

Maintenance (MA) phase (both direct-entry and transferred-entry subjects): received 56 mg or 84 mg intranasal esketamine solution once per week for the first 4 weeks, then once per week or once every other week depending on severity of depressive symptoms with open-label oral AD (one of: duloxetine/escitalopram/sertraline/venlafaxine XR), once daily until relapse or study termination.

| | |
|-----------------------|--|
| Reporting group title | OP: Intranasal Esketamine + Oral AD (DE+TE Subjects) |
|-----------------------|--|

Reporting group description:

Subjects received intranasal esketamine (same dose) solution once per week for first 4 weeks, then once per week/once every other week based on severity of depressive symptoms, and continued same oral AD from IND phase for 12 weeks.

| | |
|-----------------------|---|
| Reporting group title | MA: Oral AD + Intranasal Placebo (DE+TE Subjects) |
|-----------------------|---|

Reporting group description:

Maintenance phase (both direct-entry and transferred-entry subjects): received intranasal esketamine matching placebo solution once per week for the first 4 weeks, then once per week or once every other week depending on severity of depressive symptoms with open-label oral AD (one of: duloxetine/escitalopram/sertraline/venlafaxine XR), until relapse or study termination.

| | |
|-----------------------|-------------------------------------|
| Reporting group title | FU: Intranasal Esketamine + Oral AD |
|-----------------------|-------------------------------------|

Reporting group description:

Subjects (who were non-responders in IND phase and who were in OP and MA phase at study termination) who received at least 1 dose of 56 mg or 84 mg intranasal esketamine participated in the follow-up (FU) phase. No intranasal esketamine was administered during FU phase. Subjects received oral AD for 2 weeks of the follow-up phase unless it was determined to not be clinically appropriate.

| | |
|-----------------------|----------------------------------|
| Reporting group title | FU: Oral AD + Intranasal Placebo |
|-----------------------|----------------------------------|

Reporting group description:

Subjects (who were non-responders in IND phase and who were in OP and MA phase at study termination) who received intranasal esketamine matching placebo with oral AD participated in the FU phase. Subjects received oral AD for 2 weeks of the follow-up phase unless it was determined to not be clinically appropriate.

| | |
|-----------------------|--------------------------------------|
| Reporting group title | OP_TES: Oral AD + Intranasal Placebo |
|-----------------------|--------------------------------------|

Reporting group description:

OP phase (transferred-entry subjects [TES]): received intranasal esketamine matching placebo solution once per week for the first 4 weeks, then once per week or once every other week depending on severity of depressive symptoms with open-label oral AD (one of: duloxetine/escitalopram/sertraline/venlafaxine XR), once daily for 12 weeks.

| | |
|-----------------------|--------------------------------------|
| Reporting group title | MA_TES: Oral AD + Intranasal Placebo |
|-----------------------|--------------------------------------|

Reporting group description:

Maintenance phase (transferred-entry subjects): Subjects were randomized (at the end of optimization phase) to intranasal esketamine matching placebo solution once per week for the first 4 weeks, then once per week or once every other week depending on severity of depressive symptoms with open-label oral AD (one of: duloxetine/escitalopram/sertraline/venlafaxine XR).

| Serious adverse events | IND: DE Subjects: Intranasal Esketamine + Oral AD | MA: Intranasal Esketamine + Oral AD (DE+TE Subjects) | OP: Intranasal Esketamine + Oral AD (DE+TE Subjects) |
|---|--|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 13 / 437 (2.97%) | 4 / 152 (2.63%) | 11 / 455 (2.42%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Injury, poisoning and procedural complications | | | |
| Procedural Pain | | | |
| subjects affected / exposed | 1 / 437 (0.23%) | 0 / 152 (0.00%) | 0 / 455 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clavicle Fracture | | | |
| subjects affected / exposed | 0 / 437 (0.00%) | 0 / 152 (0.00%) | 0 / 455 (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 |
| Vascular disorders | | | |
| Hypertensive Crisis | | | |
| subjects affected / exposed | 0 / 437 (0.00%) | 0 / 152 (0.00%) | 1 / 455 (0.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Orthostatic Hypotension | | | |
| subjects affected / exposed | 1 / 437 (0.23%) | 0 / 152 (0.00%) | 0 / 455 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Sinus Tachycardia | | | |
| subjects affected / exposed | 0 / 437 (0.00%) | 0 / 152 (0.00%) | 1 / 455 (0.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Autonomic Nervous System Imbalance | | | |
| subjects affected / exposed | 1 / 437 (0.23%) | 0 / 152 (0.00%) | 0 / 455 (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 |
| Headache | | | |
| subjects affected / exposed | 0 / 437 (0.00%) | 0 / 152 (0.00%) | 1 / 455 (0.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lacunar Stroke | | | |
| subjects affected / exposed | 1 / 437 (0.23%) | 0 / 152 (0.00%) | 0 / 455 (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 |
| Migraine | | | |
| subjects affected / exposed | 0 / 437 (0.00%) | 0 / 152 (0.00%) | 1 / 455 (0.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 437 (0.00%) | 0 / 152 (0.00%) | 1 / 455 (0.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sedation | | | |
| subjects affected / exposed | 1 / 437 (0.23%) | 0 / 152 (0.00%) | 0 / 455 (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 |
| Simple Partial Seizures | | | |
| subjects affected / exposed | 1 / 437 (0.23%) | 0 / 152 (0.00%) | 0 / 455 (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 |
| Pregnancy, puerperium and perinatal conditions | | | |
| Ectopic Pregnancy | | | |
| subjects affected / exposed | 0 / 437 (0.00%) | 1 / 152 (0.66%) | 0 / 455 (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 |

| | | | |
|--|-----------------|-----------------|-----------------|
| General disorders and administration site conditions | | | |
| Chest Pain | | | |
| subjects affected / exposed | 0 / 437 (0.00%) | 0 / 152 (0.00%) | 1 / 455 (0.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypothermia | | | |
| subjects affected / exposed | 1 / 437 (0.23%) | 0 / 152 (0.00%) | 0 / 455 (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 |
| Gastrointestinal disorders | | | |
| Anal Fissure | | | |
| subjects affected / exposed | 0 / 437 (0.00%) | 0 / 152 (0.00%) | 1 / 455 (0.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis Acute | | | |
| subjects affected / exposed | 0 / 437 (0.00%) | 0 / 152 (0.00%) | 1 / 455 (0.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 2 / 437 (0.46%) | 0 / 152 (0.00%) | 0 / 455 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Depression | | | |
| subjects affected / exposed | 3 / 437 (0.69%) | 2 / 152 (1.32%) | 1 / 455 (0.22%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Disorientation | | | |
| subjects affected / exposed | 1 / 437 (0.23%) | 0 / 152 (0.00%) | 0 / 455 (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 |
| Major Depression | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 437 (0.00%) | 1 / 152 (0.66%) | 0 / 455 (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 |
| Mania | | | |
| subjects affected / exposed | 0 / 437 (0.00%) | 0 / 152 (0.00%) | 0 / 455 (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 |
| Panic Attack | | | |
| subjects affected / exposed | 0 / 437 (0.00%) | 0 / 152 (0.00%) | 1 / 455 (0.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Suicidal Ideation | | | |
| subjects affected / exposed | 1 / 437 (0.23%) | 0 / 152 (0.00%) | 0 / 455 (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 |
| Renal and urinary disorders | | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 437 (0.23%) | 0 / 152 (0.00%) | 0 / 455 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Intervertebral Disc Protrusion | | | |
| subjects affected / exposed | 0 / 437 (0.00%) | 0 / 152 (0.00%) | 0 / 455 (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 |
| Pain in Extremity | | | |
| subjects affected / exposed | 0 / 437 (0.00%) | 0 / 152 (0.00%) | 1 / 455 (0.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 437 (0.00%) | 0 / 152 (0.00%) | 1 / 455 (0.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Sepsis | | | |
| subjects affected / exposed | 0 / 437 (0.00%) | 0 / 152 (0.00%) | 1 / 455 (0.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | MA: Oral AD + Intranasal Placebo (DE+TE Subjects) | FU: Intranasal Esketamine + Oral AD | FU: Oral AD + Intranasal Placebo |
|---|---|---|-------------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 145 (0.69%) | 3 / 481 (0.62%) | 0 / 64 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Injury, poisoning and procedural complications | | | |
| Procedural Pain | | | |
| subjects affected / exposed | 0 / 145 (0.00%) | 0 / 481 (0.00%) | 0 / 64 (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 |
| Clavicle Fracture | | | |
| subjects affected / exposed | 0 / 145 (0.00%) | 0 / 481 (0.00%) | 0 / 64 (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 |
| Vascular disorders | | | |
| Hypertensive Crisis | | | |
| subjects affected / exposed | 0 / 145 (0.00%) | 0 / 481 (0.00%) | 0 / 64 (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 |
| Orthostatic Hypotension | | | |
| subjects affected / exposed | 0 / 145 (0.00%) | 0 / 481 (0.00%) | 0 / 64 (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 |
| Cardiac disorders | | | |
| Sinus Tachycardia | | | |
| subjects affected / exposed | 0 / 145 (0.00%) | 0 / 481 (0.00%) | 0 / 64 (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 |
| Nervous system disorders | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| Autonomic Nervous System Imbalance | | | |
| subjects affected / exposed | 0 / 145 (0.00%) | 0 / 481 (0.00%) | 0 / 64 (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 |
| Headache | | | |
| subjects affected / exposed | 0 / 145 (0.00%) | 0 / 481 (0.00%) | 0 / 64 (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 |
| Lacunar Stroke | | | |
| subjects affected / exposed | 0 / 145 (0.00%) | 0 / 481 (0.00%) | 0 / 64 (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 |
| Migraine | | | |
| subjects affected / exposed | 0 / 145 (0.00%) | 0 / 481 (0.00%) | 0 / 64 (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 |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 145 (0.00%) | 0 / 481 (0.00%) | 0 / 64 (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 |
| Sedation | | | |
| subjects affected / exposed | 0 / 145 (0.00%) | 0 / 481 (0.00%) | 0 / 64 (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 |
| Simple Partial Seizures | | | |
| subjects affected / exposed | 0 / 145 (0.00%) | 0 / 481 (0.00%) | 0 / 64 (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 |
| Pregnancy, puerperium and perinatal conditions | | | |
| Ectopic Pregnancy | | | |
| subjects affected / exposed | 0 / 145 (0.00%) | 0 / 481 (0.00%) | 0 / 64 (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 |

| | | | |
|--|-----------------|-----------------|----------------|
| General disorders and administration site conditions | | | |
| Chest Pain | | | |
| subjects affected / exposed | 0 / 145 (0.00%) | 1 / 481 (0.21%) | 0 / 64 (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 |
| Hypothermia | | | |
| subjects affected / exposed | 0 / 145 (0.00%) | 0 / 481 (0.00%) | 0 / 64 (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 |
| Gastrointestinal disorders | | | |
| Anal Fissure | | | |
| subjects affected / exposed | 0 / 145 (0.00%) | 0 / 481 (0.00%) | 0 / 64 (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 |
| Hepatobiliary disorders | | | |
| Cholecystitis Acute | | | |
| subjects affected / exposed | 0 / 145 (0.00%) | 0 / 481 (0.00%) | 0 / 64 (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 | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 145 (0.00%) | 0 / 481 (0.00%) | 0 / 64 (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 |
| Depression | | | |
| subjects affected / exposed | 1 / 145 (0.69%) | 1 / 481 (0.21%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Disorientation | | | |
| subjects affected / exposed | 0 / 145 (0.00%) | 0 / 481 (0.00%) | 0 / 64 (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 |
| Major Depression | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 145 (0.00%) | 0 / 481 (0.00%) | 0 / 64 (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 |
| Mania | | | |
| subjects affected / exposed | 0 / 145 (0.00%) | 1 / 481 (0.21%) | 0 / 64 (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 |
| Panic Attack | | | |
| subjects affected / exposed | 0 / 145 (0.00%) | 0 / 481 (0.00%) | 0 / 64 (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 / 145 (0.00%) | 0 / 481 (0.00%) | 0 / 64 (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 |
| Renal and urinary disorders | | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 145 (0.00%) | 0 / 481 (0.00%) | 0 / 64 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Intervertebral Disc Protrusion | | | |
| subjects affected / exposed | 0 / 145 (0.00%) | 1 / 481 (0.21%) | 0 / 64 (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 |
| Pain in Extremity | | | |
| subjects affected / exposed | 0 / 145 (0.00%) | 0 / 481 (0.00%) | 0 / 64 (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 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 145 (0.00%) | 0 / 481 (0.00%) | 0 / 64 (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 |

| | | | |
|---|-----------------|-----------------|----------------|
| Sepsis | | | |
| subjects affected / exposed | 0 / 145 (0.00%) | 0 / 481 (0.00%) | 0 / 64 (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 | OP_TES: Oral AD + Intranasal Placebo | MA_TES: Oral AD + Intranasal Placebo | |
|---|---|---|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 86 (0.00%) | 1 / 54 (1.85%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Injury, poisoning and procedural complications | | | |
| Procedural Pain | | | |
| subjects affected / exposed | 0 / 86 (0.00%) | 0 / 54 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clavicle Fracture | | | |
| subjects affected / exposed | 0 / 86 (0.00%) | 1 / 54 (1.85%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Hypertensive Crisis | | | |
| subjects affected / exposed | 0 / 86 (0.00%) | 0 / 54 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Orthostatic Hypotension | | | |
| subjects affected / exposed | 0 / 86 (0.00%) | 0 / 54 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Sinus Tachycardia | | | |
| subjects affected / exposed | 0 / 86 (0.00%) | 0 / 54 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Autonomic Nervous System Imbalance | | | |

| | | | |
|--|----------------|----------------|--|
| subjects affected / exposed | 0 / 86 (0.00%) | 0 / 54 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 0 / 86 (0.00%) | 0 / 54 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lacunar Stroke | | | |
| subjects affected / exposed | 0 / 86 (0.00%) | 0 / 54 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Migraine | | | |
| subjects affected / exposed | 0 / 86 (0.00%) | 0 / 54 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 86 (0.00%) | 0 / 54 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sedation | | | |
| subjects affected / exposed | 0 / 86 (0.00%) | 0 / 54 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Simple Partial Seizures | | | |
| subjects affected / exposed | 0 / 86 (0.00%) | 0 / 54 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Ectopic Pregnancy | | | |
| subjects affected / exposed | 0 / 86 (0.00%) | 0 / 54 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |

| | | | |
|---|----------------|----------------|--|
| Chest Pain | | | |
| subjects affected / exposed | 0 / 86 (0.00%) | 0 / 54 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypothermia | | | |
| subjects affected / exposed | 0 / 86 (0.00%) | 0 / 54 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Anal Fissure | | | |
| subjects affected / exposed | 0 / 86 (0.00%) | 0 / 54 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis Acute | | | |
| subjects affected / exposed | 0 / 86 (0.00%) | 0 / 54 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 86 (0.00%) | 0 / 54 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depression | | | |
| subjects affected / exposed | 0 / 86 (0.00%) | 0 / 54 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Disorientation | | | |
| subjects affected / exposed | 0 / 86 (0.00%) | 0 / 54 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Major Depression | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 86 (0.00%) | 0 / 54 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mania | | | |
| subjects affected / exposed | 0 / 86 (0.00%) | 0 / 54 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Panic Attack | | | |
| subjects affected / exposed | 0 / 86 (0.00%) | 0 / 54 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Suicidal Ideation | | | |
| subjects affected / exposed | 0 / 86 (0.00%) | 0 / 54 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 86 (0.00%) | 0 / 54 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Intervertebral Disc Protrusion | | | |
| subjects affected / exposed | 0 / 86 (0.00%) | 0 / 54 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain in Extremity | | | |
| subjects affected / exposed | 0 / 86 (0.00%) | 0 / 54 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 86 (0.00%) | 0 / 54 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Sepsis | | | |
| subjects affected / exposed | 0 / 86 (0.00%) | 0 / 54 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 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 | IND: DE Subjects: Intranasal Esketamine + Oral AD | MA: Intranasal Esketamine + Oral AD (DE+TE Subjects) | OP: Intranasal Esketamine + Oral AD (DE+TE Subjects) |
|---|--|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 306 / 437 (70.02%) | 114 / 152 (75.00%) | 279 / 455 (61.32%) |
| Investigations | | | |
| Blood Pressure Increased | | | |
| subjects affected / exposed | 34 / 437 (7.78%) | 10 / 152 (6.58%) | 26 / 455 (5.71%) |
| occurrences (all) | 99 | 40 | 97 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 97 / 437 (22.20%) | 31 / 152 (20.39%) | 61 / 455 (13.41%) |
| occurrences (all) | 347 | 170 | 241 |
| Dizziness Postural | | | |
| subjects affected / exposed | 33 / 437 (7.55%) | 10 / 152 (6.58%) | 26 / 455 (5.71%) |
| occurrences (all) | 188 | 98 | 168 |
| Dysgeusia | | | |
| subjects affected / exposed | 90 / 437 (20.59%) | 41 / 152 (26.97%) | 79 / 455 (17.36%) |
| occurrences (all) | 429 | 494 | 529 |
| Headache | | | |
| subjects affected / exposed | 60 / 437 (13.73%) | 27 / 152 (17.76%) | 57 / 455 (12.53%) |
| occurrences (all) | 86 | 77 | 91 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 30 / 437 (6.86%) | 9 / 152 (5.92%) | 24 / 455 (5.27%) |
| occurrences (all) | 102 | 179 | 115 |
| Paraesthesia | | | |
| subjects affected / exposed | 48 / 437 (10.98%) | 11 / 152 (7.24%) | 23 / 455 (5.05%) |
| occurrences (all) | 161 | 82 | 85 |
| Sedation | | | |

| | | | |
|---|--------------------------|--------------------------|--------------------------|
| subjects affected / exposed occurrences (all) | 43 / 437 (9.84%) 223 | 10 / 152 (6.58%) 77 | 19 / 455 (4.18%) 86 |
| Somnolence subjects affected / exposed occurrences (all) | 65 / 437 (14.87%) 183 | 32 / 152 (21.05%) 154 | 63 / 455 (13.85%) 240 |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 99 / 437 (22.65%) 385 | 38 / 152 (25.00%) 260 | 91 / 455 (20.00%) 406 |
| Eye disorders Diplopia subjects affected / exposed occurrences (all) | 16 / 437 (3.66%) 39 | 9 / 152 (5.92%) 31 | 10 / 455 (2.20%) 34 |
| Vision Blurred subjects affected / exposed occurrences (all) | 45 / 437 (10.30%) 148 | 24 / 152 (15.79%) 217 | 30 / 455 (6.59%) 170 |
| Gastrointestinal disorders Hypoaesthesia Oral subjects affected / exposed occurrences (all) | 32 / 437 (7.32%) 87 | 20 / 152 (13.16%) 144 | 34 / 455 (7.47%) 156 |
| Nausea subjects affected / exposed occurrences (all) | 94 / 437 (21.51%) 158 | 25 / 152 (16.45%) 60 | 48 / 455 (10.55%) 83 |
| Paraesthesia Oral subjects affected / exposed occurrences (all) | 16 / 437 (3.66%) 61 | 8 / 152 (5.26%) 15 | 13 / 455 (2.86%) 35 |
| Vomiting subjects affected / exposed occurrences (all) | 29 / 437 (6.64%) 39 | 10 / 152 (6.58%) 15 | 17 / 455 (3.74%) 26 |
| Diarrhoea subjects affected / exposed occurrences (all) | 0 / 437 (0.00%) 0 | 0 / 152 (0.00%) 0 | 0 / 455 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Nasal Discomfort subjects affected / exposed occurrences (all) | 29 / 437 (6.64%) 95 | 11 / 152 (7.24%) 94 | 26 / 455 (5.71%) 98 |

| | | | |
|---|--------------------------|--------------------------|--------------------------|
| Throat Irritation subjects affected / exposed occurrences (all) | 26 / 437 (5.95%) 100 | 8 / 152 (5.26%) 75 | 16 / 455 (3.52%) 97 |
| Psychiatric disorders | | | |
| Anxiety subjects affected / exposed occurrences (all) | 31 / 437 (7.09%) 38 | 12 / 152 (7.89%) 17 | 11 / 455 (2.42%) 19 |
| Confusional State subjects affected / exposed occurrences (all) | 13 / 437 (2.97%) 36 | 9 / 152 (5.92%) 53 | 9 / 455 (1.98%) 24 |
| Dissociation subjects affected / exposed occurrences (all) | 82 / 437 (18.76%) 333 | 35 / 152 (23.03%) 181 | 73 / 455 (16.04%) 321 |
| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal Pain subjects affected / exposed occurrences (all) | 0 / 437 (0.00%) 0 | 0 / 152 (0.00%) 0 | 0 / 455 (0.00%) 0 |
| Spinal Pain subjects affected / exposed occurrences (all) | 0 / 437 (0.00%) 0 | 0 / 152 (0.00%) 0 | 0 / 455 (0.00%) 0 |
| Infections and infestations | | | |
| Viral Upper Respiratory Tract Infection subjects affected / exposed occurrences (all) | 5 / 437 (1.14%) 6 | 11 / 152 (7.24%) 16 | 22 / 455 (4.84%) 23 |
| Urinary Tract Infection subjects affected / exposed occurrences (all) | 0 / 437 (0.00%) 0 | 0 / 152 (0.00%) 0 | 0 / 455 (0.00%) 0 |

| Non-serious adverse events | MA: Oral AD + Intranasal Placebo (DE+TE Subjects) | FU: Intranasal Esketamine + Oral AD | FU: Oral AD + Intranasal Placebo |
|--|---|---|-------------------------------------|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 45 / 145 (31.03%) | 14 / 481 (2.91%) | 1 / 64 (1.56%) |
| Investigations | | | |
| Blood Pressure Increased subjects affected / exposed occurrences (all) | 5 / 145 (3.45%) 11 | 0 / 481 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Nervous system disorders | | | |

| | | | |
|-----------------------------|------------------|-----------------|----------------|
| Dizziness | | | |
| subjects affected / exposed | 7 / 145 (4.83%) | 0 / 481 (0.00%) | 1 / 64 (1.56%) |
| occurrences (all) | 13 | 0 | 1 |
| Dizziness Postural | | | |
| subjects affected / exposed | 3 / 145 (2.07%) | 0 / 481 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 6 | 0 | 0 |
| Dysgeusia | | | |
| subjects affected / exposed | 10 / 145 (6.90%) | 0 / 481 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 125 | 0 | 0 |
| Headache | | | |
| subjects affected / exposed | 14 / 145 (9.66%) | 8 / 481 (1.66%) | 0 / 64 (0.00%) |
| occurrences (all) | 23 | 11 | 0 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 145 (0.00%) | 0 / 481 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 145 (0.00%) | 0 / 481 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sedation | | | |
| subjects affected / exposed | 1 / 145 (0.69%) | 0 / 481 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Somnolence | | | |
| subjects affected / exposed | 3 / 145 (2.07%) | 0 / 481 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 7 | 0 | 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 8 / 145 (5.52%) | 2 / 481 (0.42%) | 0 / 64 (0.00%) |
| occurrences (all) | 26 | 3 | 0 |
| Eye disorders | | | |
| Diplopia | | | |
| subjects affected / exposed | 0 / 145 (0.00%) | 0 / 481 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vision Blurred | | | |
| subjects affected / exposed | 1 / 145 (0.69%) | 0 / 481 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Gastrointestinal disorders | | | |

| | | | |
|---|-----------------------|----------------------|---------------------|
| Hypoaesthesia Oral subjects affected / exposed occurrences (all) | 0 / 145 (0.00%) 0 | 0 / 481 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Nausea subjects affected / exposed occurrences (all) | 1 / 145 (0.69%) 2 | 2 / 481 (0.42%) 3 | 1 / 64 (1.56%) 1 |
| Paraesthesia Oral subjects affected / exposed occurrences (all) | 1 / 145 (0.69%) 1 | 0 / 481 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Vomiting subjects affected / exposed occurrences (all) | 1 / 145 (0.69%) 1 | 0 / 481 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Diarrhoea subjects affected / exposed occurrences (all) | 0 / 145 (0.00%) 0 | 0 / 481 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Nasal Discomfort subjects affected / exposed occurrences (all) | 4 / 145 (2.76%) 19 | 0 / 481 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Throat Irritation subjects affected / exposed occurrences (all) | 1 / 145 (0.69%) 7 | 0 / 481 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 5 / 145 (3.45%) 6 | 2 / 481 (0.42%) 2 | 0 / 64 (0.00%) 0 |
| Confusional State subjects affected / exposed occurrences (all) | 0 / 145 (0.00%) 0 | 0 / 481 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Dissociation subjects affected / exposed occurrences (all) | 0 / 145 (0.00%) 0 | 0 / 481 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Musculoskeletal Pain subjects affected / exposed occurrences (all) | 0 / 145 (0.00%) 0 | 0 / 481 (0.00%) 0 | 0 / 64 (0.00%) 0 |

| | | | |
|--|------------------------|----------------------|---------------------|
| Spinal Pain subjects affected / exposed occurrences (all) | 0 / 145 (0.00%) 0 | 0 / 481 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Infections and infestations Viral Upper Respiratory Tract Infection subjects affected / exposed occurrences (all) | 12 / 145 (8.28%) 18 | 1 / 481 (0.21%) 1 | 0 / 64 (0.00%) 0 |
| Urinary Tract Infection subjects affected / exposed occurrences (all) | 0 / 145 (0.00%) 0 | 0 / 481 (0.00%) 0 | 0 / 64 (0.00%) 0 |

| Non-serious adverse events | OP_TES: Oral AD + Intranasal Placebo | MA_TES: Oral AD + Intranasal Placebo | |
|--|---|---|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 40 / 86 (46.51%) | 37 / 54 (68.52%) | |
| Investigations Blood Pressure Increased subjects affected / exposed occurrences (all) | 0 / 86 (0.00%) 0 | 0 / 54 (0.00%) 0 | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 6 / 86 (6.98%) 0 | 0 / 54 (0.00%) 0 | |
| Dizziness Postural subjects affected / exposed occurrences (all) | 0 / 86 (0.00%) 0 | 0 / 54 (0.00%) 0 | |
| Dysgeusia subjects affected / exposed occurrences (all) | 8 / 86 (9.30%) 67 | 8 / 54 (14.81%) 144 | |
| Headache subjects affected / exposed occurrences (all) | 16 / 86 (18.60%) 40 | 12 / 54 (22.22%) 24 | |
| Hypoaesthesia subjects affected / exposed occurrences (all) | 0 / 86 (0.00%) 0 | 0 / 54 (0.00%) 0 | |
| Paraesthesia | | | |

| | | | |
|--|----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 86 (0.00%) 0 | 0 / 54 (0.00%) 0 | |
| Sedation subjects affected / exposed occurrences (all) | 0 / 86 (0.00%) 0 | 0 / 54 (0.00%) 0 | |
| Somnolence subjects affected / exposed occurrences (all) | 5 / 86 (5.81%) 13 | 4 / 54 (7.41%) 12 | |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 0 / 86 (0.00%) 0 | 0 / 54 (0.00%) 0 | |
| Eye disorders Diplopia subjects affected / exposed occurrences (all) | 0 / 86 (0.00%) 0 | 0 / 54 (0.00%) 0 | |
| Vision Blurred subjects affected / exposed occurrences (all) | 0 / 86 (0.00%) 0 | 0 / 54 (0.00%) 0 | |
| Gastrointestinal disorders Hypoaesthesia Oral subjects affected / exposed occurrences (all) | 0 / 86 (0.00%) 0 | 0 / 54 (0.00%) 0 | |
| Nausea subjects affected / exposed occurrences (all) | 0 / 86 (0.00%) 0 | 3 / 54 (5.56%) 5 | |
| Paraesthesia Oral subjects affected / exposed occurrences (all) | 0 / 86 (0.00%) 0 | 0 / 54 (0.00%) 0 | |
| Vomiting subjects affected / exposed occurrences (all) | 0 / 86 (0.00%) 0 | 0 / 54 (0.00%) 0 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 0 / 86 (0.00%) 0 | 4 / 54 (7.41%) 4 | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|---------------------|------------------------|--|
| Nasal Discomfort subjects affected / exposed occurrences (all) | 0 / 86 (0.00%) 0 | 0 / 54 (0.00%) 0 | |
| Throat Irritation subjects affected / exposed occurrences (all) | 0 / 86 (0.00%) 0 | 0 / 54 (0.00%) 0 | |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 5 / 86 (5.81%) 9 | 0 / 54 (0.00%) 0 | |
| Confusional State subjects affected / exposed occurrences (all) | 0 / 86 (0.00%) 0 | 0 / 54 (0.00%) 0 | |
| Dissociation subjects affected / exposed occurrences (all) | 0 / 86 (0.00%) 0 | 0 / 54 (0.00%) 0 | |
| Musculoskeletal and connective tissue disorders Musculoskeletal Pain subjects affected / exposed occurrences (all) | 0 / 86 (0.00%) 0 | 3 / 54 (5.56%) 3 | |
| Spinal Pain subjects affected / exposed occurrences (all) | 0 / 86 (0.00%) 0 | 3 / 54 (5.56%) 14 | |
| Infections and infestations Viral Upper Respiratory Tract Infection subjects affected / exposed occurrences (all) | 0 / 86 (0.00%) 0 | 13 / 54 (24.07%) 14 | |
| Urinary Tract Infection subjects affected / exposed occurrences (all) | 0 / 86 (0.00%) 0 | 3 / 54 (5.56%) 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|--|
| 13 January 2016 | The overall reason for the amendment was to update and clarify the protocol based on ongoing feedback received during study initiation activities. |
| 09 June 2016 | The overall reason for the amendment was based on feedback received from investigators involved in the study, the subject entry criteria had been revised to improve recruitment. |
| 04 April 2017 | The overall reason for the amendment was to enhance the number of clinically valid subjects proceeding to the maintenance phase as stable remitters, the stable remission criteria had been revised. |

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.

Esketamine's known transient dissociative, sedative effect difficult to blind, potential for treatment - emergent symptoms to have biased site staff who observed dosing was mitigated by independent, remote, blinded MADRS raters who assessed response.

Notes: