



Clinical trial results:

A Randomized, Open-label, Rater-Blinded, Active-Controlled, International, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Flexibly Dosed Esketamine Nasal Spray Compared With Quetiapine Extended-Release in Adult and Elderly Subjects With Treatment-Resistant Major Depressive Disorder Who are Continuing a Selective Serotonin Reuptake Inhibitor/Serotonin-Norepinephrine Reuptake Inhibitor

Summary

| | |
|--------------------------|---|
| EudraCT number | 2019-002992-33 |
| Trial protocol | NL CZ PL DE HU FR BE PT BG DK AT NO FI GR |
| Global end of trial date | 15 July 2022 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 28 July 2023 |
| First version publication date | 28 July 2023 |

Trial information

Trial identification

| | |
|-----------------------|-----------------|
| Sponsor protocol code | 54135419TRD3013 |
|-----------------------|-----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT04338321 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Janssen-Cilag International NV |
| Sponsor organisation address | Turnhoutseweg 30, Beerse, Belgium, B-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 July 2022 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 15 July 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the efficacy of flexibly dosed esketamine nasal spray compared with quetiapine extended-release (XR), both in combination with a continuing selective serotonin reuptake inhibitor (SSRI)/serotonin-norepinephrine reuptake inhibitor (SNRI), in achieving remission in subjects who have treatment-resistant major depressive disorder (TRD) with a current moderate to severe depressive episode.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices (GCP) and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 21 August 2020 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--|
| Country: Number of subjects enrolled | United Arab Emirates: 1 |
| Country: Number of subjects enrolled | Argentina: 64 |
| Country: Number of subjects enrolled | Austria: 9 |
| Country: Number of subjects enrolled | Belgium: 14 |
| Country: Number of subjects enrolled | Bulgaria: 32 |
| Country: Number of subjects enrolled | Brazil: 80 |
| Country: Number of subjects enrolled | Czechia: 69 |
| Country: Number of subjects enrolled | Denmark: 2 |
| Country: Number of subjects enrolled | Finland: 1 |
| Country: Number of subjects enrolled | Germany: 78 |
| Country: Number of subjects enrolled | Greece: 11 |
| Country: Number of subjects enrolled | Hungary: 19 |
| Country: Number of subjects enrolled | Israel: 3 |
| Country: Number of subjects enrolled | Kazakhstan: 5 |
| Country: Number of subjects enrolled | Korea, Democratic People's Republic of: 16 |
| Country: Number of subjects enrolled | Malaysia: 15 |
| Country: Number of subjects enrolled | Netherlands: 1 |
| Country: Number of subjects enrolled | Norway: 1 |

| | |
|--------------------------------------|------------------|
| Country: Number of subjects enrolled | Poland: 145 |
| Country: Number of subjects enrolled | Portugal: 7 |
| Country: Number of subjects enrolled | Sweden: 34 |
| Country: Number of subjects enrolled | Turkey: 30 |
| Country: Number of subjects enrolled | Taiwan: 24 |
| Country: Number of subjects enrolled | South Africa: 15 |
| Worldwide total number of subjects | 676 |
| EEA total number of subjects | 423 |

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) | 639 |
| From 65 to 84 years | 37 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total 676 subjects were enrolled in this study out of which 670 subjects were treated. Only 506 subjects completed the study.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Single blind |
| Roles blinded | Assessor ^[1] |

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | Yes |
| Arm title | Esketamine Nasal Spray + Oral Antidepressant (AD) |

Arm description:

Subjects received treatment with esketamine nasal spray (28 milligrams [mg] [initial dose for elderly subjects aged 65 to 74 years and adults of Japanese ancestry], 56 mg [initial dose for adult subjects aged 18 to 64 years], or 84 mg [maximum dose esketamine nasal spray]) twice-weekly with a flexible dose regimen from Day 1 until Week 4, once weekly from Week 5 to Week 8 and once-weekly or once every 2 weeks from Week 9 to Week 32 in combination with continuing serotonin-norepinephrine reuptake inhibitor/selective serotonin reuptake inhibitor (SSRI/SNRI).

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Esketamine |
| Investigational medicinal product code | |
| Other name | JNJ-54135419 |
| Pharmaceutical forms | Nasal spray |
| Routes of administration | Nasal use |

Dosage and administration details:

Esketamine nasal spray (28 mg [initial dose for elderly subjects 65 to 74 years of age and adults of Japanese ancestry; may be used throughout the study in these populations; may be uptitrated in 28 mg increments], 56 mg [initial dose for adult subjects aged 18 to 64 years and may be used for all age groups throughout the study], or 84 mg [maximum dose esketamine nasal spray may be uptitrated to]) twice-weekly with a flexible dose regimen from Day 1 until Week 4, once weekly from Week 5 to Week 8 and once-weekly or once every 2 weeks from Week 9 to Week 32.

| | |
|------------------|--|
| Arm title | Quetiapine Extended Release (XR) + Oral AD |
|------------------|--|

Arm description:

Subjects continued to take their current SSRI/SNRI augmented with quetiapine XR as per the Summary of Product Characteristics (SmPC) (or local equivalent, if applicable) at an initial dose of 50 mg/day on Days 1-2, 150 mg/day on Days 3-4 (lowest effective dose) in adult subjects aged 18 to 64 years; a further dose increase to 300 mg/day on Day 5 and onward were based on individual subject evaluation. In elderly subjects aged 65 to 74 years, the initial dose was 50 mg/day on Days 1-3, 100 mg/day on Days 4-7, and 150 mg/day on Day 8; a further dose increase to 300 mg/day were based on individual subject evaluation no earlier than Day 22.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Quetiapine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

In adult subjects aged 18 to 64 years, the initial dose is 50 mg/day on Days 1-2, 150 mg/day on Days 3-4 [lowest effective dose]; a further dose increase to 300 mg/day on Day 5 and onward will be based on individual subject evaluation. In elderly subjects aged 65 to 74 years, the initial dose is 50 mg/day on Days 1-3, 100 mg/day on Days 4-7, and 150 mg/day on Day 8; a further dose increase to 300 mg/day will be based on individual subject evaluation no earlier than Day 22.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Only assessor was blinded in this trial.

| Number of subjects in period 1 | Esketamine Nasal Spray + Oral Antidepressant (AD) | Quetiapine Extended Release (XR) + Oral AD |
|---------------------------------------|--|---|
| Started | 336 | 340 |
| Treated (Safety Analysis Set) | 334 | 336 |
| Completed Treatment | 258 ^[2] | 203 ^[3] |
| Completed | 274 | 232 |
| Not completed | 62 | 108 |
| Adverse event, serious fatal | 1 | 1 |
| Consent withdrawn by subject | 45 | 69 |
| Physician decision | 5 | 9 |
| Adverse event, non-fatal | 4 | 10 |
| Unspecified | 3 | 10 |
| Lost to follow-up | 4 | 9 |

Notes:

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Only specified number of subjects completed treatment in the respective arms.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Only specified number of subjects completed treatment in the respective arms.

Baseline characteristics

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | Esketamine Nasal Spray + Oral Antidepressant (AD) |
|-----------------------|---|

Reporting group description:

Subjects received treatment with esketamine nasal spray (28 milligrams [mg] [initial dose for elderly subjects aged 65 to 74 years and adults of Japanese ancestry], 56 mg [initial dose for adult subjects aged 18 to 64 years], or 84 mg [maximum dose esketamine nasal spray]) twice-weekly with a flexible dose regimen from Day 1 until Week 4, once weekly from Week 5 to Week 8 and once-weekly or once every 2 weeks from Week 9 to Week 32 in combination with continuing serotonin-norepinephrine reuptake inhibitor/selective serotonin reuptake inhibitor (SSRI/SNRI).

| | |
|-----------------------|--|
| Reporting group title | Quetiapine Extended Release (XR) + Oral AD |
|-----------------------|--|

Reporting group description:

Subjects continued to take their current SSRI/SNRI augmented with quetiapine XR as per the Summary of Product Characteristics (SmPC) (or local equivalent, if applicable) at an initial dose of 50 mg/day on Days 1-2, 150 mg/day on Days 3-4 (lowest effective dose) in adult subjects aged 18 to 64 years; a further dose increase to 300 mg/day on Day 5 and onward were based on individual subject evaluation. In elderly subjects aged 65 to 74 years, the initial dose was 50 mg/day on Days 1-3, 100 mg/day on Days 4-7, and 150 mg/day on Day 8; a further dose increase to 300 mg/day were based on individual subject evaluation no earlier than Day 22.

| Reporting group values | Esketamine Nasal Spray + Oral Antidepressant (AD) | Quetiapine Extended Release (XR) + Oral AD | Total |
|--|---|--|-------|
| Number of subjects | 336 | 340 | 676 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 317 | 322 | 639 |
| From 65-84 years | 19 | 18 | 37 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous Units: years | | | |
| arithmetic mean | 44.3 | 45.7 | |
| standard deviation | ± 13.6 | ± 13.38 | - |
| Sex: Female, Male Units: Subjects | | | |
| Female | 225 | 222 | 447 |
| Male | 111 | 118 | 229 |

End points

End points reporting groups

| | |
|---|---|
| Reporting group title | Esketamine Nasal Spray + Oral Antidepressant (AD) |
| Reporting group description: Subjects received treatment with esketamine nasal spray (28 milligrams [mg] [initial dose for elderly subjects aged 65 to 74 years and adults of Japanese ancestry], 56 mg [initial dose for adult subjects aged 18 to 64 years], or 84 mg [maximum dose esketamine nasal spray]) twice-weekly with a flexible dose regimen from Day 1 until Week 4, once weekly from Week 5 to Week 8 and once-weekly or once every 2 weeks from Week 9 to Week 32 in combination with continuing serotonin-norepinephrine reuptake inhibitor/selective serotonin reuptake inhibitor (SSRI/SNRI). | |
| Reporting group title | Quetiapine Extended Release (XR) + Oral AD |
| Reporting group description: Subjects continued to take their current SSRI/SNRI augmented with quetiapine XR as per the Summary of Product Characteristics (SmPC) (or local equivalent, if applicable) at an initial dose of 50 mg/day on Days 1-2, 150 mg/day on Days 3-4 (lowest effective dose) in adult subjects aged 18 to 64 years; a further dose increase to 300 mg/day on Day 5 and onward were based on individual subject evaluation. In elderly subjects aged 65 to 74 years, the initial dose was 50 mg/day on Days 1-3, 100 mg/day on Days 4-7, and 150 mg/day on Day 8; a further dose increase to 300 mg/day were based on individual subject evaluation no earlier than Day 22. | |

Primary: Percentage of Subjects with Remission as Assessed by the Montgomery-Asberg Depression Rating Scale (MADRS) Score at Week 8

| | |
|---|--|
| End point title | Percentage of Subjects with Remission as Assessed by the Montgomery-Asberg Depression Rating Scale (MADRS) Score at Week 8 |
| End point description: Percentage of subjects with remission as assessed by the MADRS at week 8 was reported. The MADRS is a clinician-rated scale designed to measure depression severity and to detect changes due to antidepressant treatment. The scale consists of 10 items, each of which is scored from 0 (item is not present or is normal) to 6 (severe or continuous presence of the symptoms), for a total possible score of 60. Higher scores represent a more severe condition. The MADRS evaluates apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, interest level, pessimistic thoughts, and suicidal thoughts. A subject was defined as being in remission if the MADRS total score was less than or equal to (\leq)10 and no treatment or study discontinuation before Week 8. The full analysis set (FAS) included all randomised subjects. | |
| End point type | Primary |
| End point timeframe: Week 8 | |

| End point values | Esketamine Nasal Spray + Oral Antidepressant (AD) | Quetiapine Extended Release (XR) + Oral AD | | |
|-------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 336 | 340 | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 27.1 | 17.6 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Esketamine Nasal Spray + Oral Antidepressant (AD) v Quetiapine Extended Release (XR) + Oral AD |
| Number of subjects included in analysis | 676 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.003 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 9.44 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.19 |
| upper limit | 15.68 |

Secondary: Percentage of Subjects With Both Remission at Week 8 and Relapse-free at Week 32

| | |
|-----------------|--|
| End point title | Percentage of Subjects With Both Remission at Week 8 and Relapse-free at Week 32 |
|-----------------|--|

End point description:

Percentage of subjects with both remission at Week 8 and relapse-free at Week 32 was reported. A subject was defined as being in remission if the MADRS total score was ≤ 10 and no treatment or study discontinuation before Week 8. A relapse is defined by any of following: a) Worsening of depressive symptoms as indicated by MADRS total score greater than or equal to (\geq) 22 confirmed by 1 additional assessment of MADRS total score ≥ 22 within the next 5 to 15 days. The date of the second MADRS assessment was used for the date of relapse; b) Any psychiatric hospitalisation for: worsening of depression, suicide prevention or suicide attempt, the start date of hospitalisation was the date of relapse; c) Suicide attempt, completed suicide, or any other clinically relevant event determined by investigator's judgment to be indicative of relapse of depressive illness, but without hospitalised. The FAS includes all randomised subjects.

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

End point timeframe:

Week 32

| End point values | Esketamine Nasal Spray + Oral Antidepressant (AD) | Quetiapine Extended Release (XR) + Oral AD | | |
|-------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 336 | 340 | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 21.7 | 14.1 | | |

Statistical analyses

Secondary: Change from Baseline in Clinician-rated Overall MADRS Score

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|-----------------|---|
| End point title | Change from Baseline in Clinician-rated Overall MADRS Score |
|-----------------|---|

End point description:

Change from baseline in clinician-rated overall MADRS score was reported. The MADRS is a clinician-rated scale designed to measure depression severity and to detect changes due to antidepressant treatment. The scale consists of 10 items, each of which is scored from 0 (item is not present or is normal) to 6 (severe or continuous presence of the symptoms), summed up for a total possible score range of 0 to 60. Higher scores represent a more severe condition. The MADRS evaluates apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, interest level, pessimistic thoughts, and suicidal thoughts. The FAS included all randomised subjects. Here, 'N' (number of subjects analysed) signifies subjects evaluable for this endpoint. Here, 'n' (number analysed) signifies subjects evaluable for this endpoint at specified time points.

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

End point timeframe:

Baseline, Weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32

| End point values | Esketamine Nasal Spray + Oral Antidepressant (AD) | Quetiapine Extended Release (XR) + Oral AD | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 325 | 326 | | |
| Units: Unit on scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 1 (n=325, 326) | -5.3 (± 5.71) | -3.7 (± 4.65) | | |
| Week 2 (n=324, 315) | -9.0 (± 6.87) | -6.1 (± 6.52) | | |
| Week 4 (n=317, 295) | -12.8 (± 7.50) | -9.8 (± 7.32) | | |
| Week 6 (n=312, 285) | -14.9 (± 8.27) | -12.2 (± 8.11) | | |
| Week 8 (n=300, 265) | -16.4 (± 8.67) | -14.3 (± 8.26) | | |
| Week 10 (n=288, 242) | -18.2 (± 8.32) | -16.2 (± 7.38) | | |
| Week 12 (n=285, 235) | -18.4 (± 8.26) | -16.7 (± 8.16) | | |
| Week 14 (n=280, 232) | -19.0 (± 8.06) | -17.1 (± 8.06) | | |
| Week 16 (n=277, 223) | -19.6 (± 8.16) | -17.8 (± 8.23) | | |
| Week 18 (n=267, 219) | -19.9 (± 8.59) | -18.1 (± 8.36) | | |
| Week 20 (n=269, 214) | -20.1 (± 8.75) | -19.1 (± 8.11) | | |
| Week 22 (n=263, 214) | -20.6 (± 8.32) | -19.5 (± 8.04) | | |
| Week 24 (n=259, 209) | -21.0 (± 8.58) | -20.1 (± 7.96) | | |
| Week 26 (n=257, 206) | -21.2 (± 8.19) | -20.0 (± 8.18) | | |
| Week 28 (n=252, 205) | -21.5 (± 8.33) | -20.8 (± 8.33) | | |
| Week 30 (n=250, 200) | -21.8 (± 8.66) | -20.6 (± 8.39) | | |
| Week 32 (n=255, 203) | -22.2 (± 8.12) | -20.5 (± 8.58) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Clinician-rated Overall MADRS Score at last observation carried forward (LOCF)

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|-----------------|--|
| End point title | Change from Baseline in Clinician-rated Overall MADRS Score at last observation carried forward (LOCF) |
|-----------------|--|

End point description:

Change from baseline in clinician-rated overall MADRS score at LOCF was reported. The MADRS is to measure depression severity and to detect changes due to antidepressant treatment. The scale consists of 10 items, each of which is scored from 0 (item is not present or is normal) to 6 (severe or continuous presence of the symptoms), summed up for a total possible score range of 0 to 60. Higher scores represent a more severe condition. The MADRS evaluates apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, interest level, pessimistic thoughts, and suicidal thoughts. LOCF is defined as the subjects who had a missing value or who stopped treatment at a specific time point had their last non-missing value carried forward. The FAS included all randomised subjects. Here, 'N' (number of subjects analysed) signifies subjects evaluable for this endpoint. Here, 'n' (number analysed) signifies subjects evaluable for this endpoint at specified time points.

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

End point timeframe:

Baseline, LOCF at Weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32

| End point values | Esketamine Nasal Spray + Oral Antidepressant (AD) | Quetiapine Extended Release (XR) + Oral AD | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 327 | 330 | | |
| Units: Units on scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 1 (n=325, 326) | -5.3 (± 5.71) | -3.7 (± 4.65) | | |
| Week 2 (n=327, 330) | -9.0 (± 6.86) | -5.8 (± 6.53) | | |
| Week 4 (n=327, 330) | -12.6 (± 7.63) | -8.9 (± 7.70) | | |
| Week 6 (n=327, 330) | -14.5 (± 8.47) | -10.7 (± 8.78) | | |
| Week 8 (n=327, 330) | -15.7 (± 9.07) | -12.0 (± 9.30) | | |
| Week 10 (n=327, 330) | -16.9 (± 9.15) | -12.8 (± 9.24) | | |
| Week 12 (n=327, 330) | -17.1 (± 9.22) | -13.1 (± 9.82) | | |
| Week 14 (n=327, 330) | -17.6 (± 9.08) | -13.2 (± 9.88) | | |
| Week 16 (n=327, 330) | -18.1 (± 9.24) | -13.7 (± 10.17) | | |
| Week 18 (n=327, 330) | -18.1 (± 9.60) | -13.8 (± 10.26) | | |
| Week 20 (n=327, 330) | -18.2 (± 9.80) | -14.3 (± 10.46) | | |
| Week 22 (n=327, 330) | -18.7 (± 9.83) | -14.6 (± 10.56) | | |
| Week 24 (n=327, 330) | -18.8 (± 9.88) | -14.8 (± 10.77) | | |
| Week 26 (n=327, 330) | -19.0 (± 9.76) | -14.9 (± 10.76) | | |
| Week 28 (n=327, 330) | -19.1 (± 9.88) | -15.2 (± 11.08) | | |
| Week 30 (n=327, 330) | -19.2 (± 10.10) | -15.2 (± 11.11) | | |
| Week 32 (n=327, 330) | -19.6 (± 9.94) | -15.1 (± 11.18) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Clinician-rated Overall Severity of Depressive Illness as assessed by Clinical Global Impression - Severity (CGI-S) Scale Score

| | |
|-----------------|---|
| End point title | Change from Baseline in Clinician-rated Overall Severity of Depressive Illness as assessed by Clinical Global Impression - Severity (CGI-S) Scale Score |
|-----------------|---|

End point description:

Change from baseline in clinician-rated overall severity of depressive illness as assessed by CGI-S scale score was reported. The CGI-S evaluates the severity of psychopathology on a scale of 1 to 7. Considering total clinical experience, a subject is assessed on severity of mental illness at the time of rating according to: 1 = normal (not at all ill); 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill subjects. Negative change in score indicates improvement. The FAS included all randomised subjects. Here, 'N' (number of subjects analysed) signifies subjects evaluable for this endpoint. Here, 'n' (number analysed) signifies subjects evaluable for this endpoint at specified time points.

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

End point timeframe:

Baseline, Weeks 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32

| End point values | Esketamine Nasal Spray + Oral Antidepressant (AD) | Quetiapine Extended Release (XR) + Oral AD | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 326 | 327 | | |
| Units: Units on scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 1 (n=326, 327) | -0.3 (± 0.58) | -0.2 (± 0.53) | | |
| Week 2 (n=324, 314) | -0.7 (± 0.79) | -0.5 (± 0.77) | | |
| Week 3 (n=313, 302) | -1.0 (± 0.88) | -0.7 (± 0.83) | | |
| Week 4 (n=317, 296) | -1.3 (± 0.94) | -1.0 (± 0.95) | | |
| Week 8 (n=300, 265) | -1.7 (± 0.98) | -1.4 (± 1.05) | | |
| Week 12 (n=286, 238) | -1.9 (± 1.00) | -1.7 (± 1.07) | | |
| Week 16 (n=280, 229) | -2.1 (± 1.05) | -1.9 (± 1.15) | | |
| Week 20 (n=270, 218) | -2.2 (± 1.04) | -2.0 (± 1.22) | | |
| Week 24 (n=260, 213) | -2.3 (± 1.06) | -2.1 (± 1.22) | | |
| Week 28 (n=255, 208) | -2.4 (± 1.02) | -2.2 (± 1.19) | | |
| Week 32 (n=255, 203) | -2.5 (± 1.05) | -2.3 (± 1.21) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Clinician-rated Overall Severity of Depressive Illness as assessed by CGI-S Scale Score at LOCF

| | |
|-----------------|---|
| End point title | Change from Baseline in Clinician-rated Overall Severity of Depressive Illness as assessed by CGI-S Scale Score at LOCF |
|-----------------|---|

End point description:

Change from baseline in clinician-rated overall severity of depressive illness as assessed by CGI-S scale score at LOCF was reported. The CGI-S evaluates the severity of psychopathology on a scale of 1 to 7. Considering total clinical experience, a subject is assessed on severity of mental illness at the time of rating according to: 1 = normal (not at all ill); 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill subjects. LOCF is defined as the subjects who had a missing value or who stopped treatment at a specific time point had their last non-missing value carried forward. The FAS included all randomised subjects. Here, 'N' (number of subjects analysed) signifies subjects evaluable for this endpoint.

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

End point timeframe:

Baseline, LOCF at Weeks 2, 3, 4, 8, 12, 16, 20, 24, 28, 32

| End point values | Esketamine Nasal Spray + Oral Antidepressant (AD) | Quetiapine Extended Release (XR) + Oral AD | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 327 | 331 | | |
| Units: Units on scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 2 | -0.7 (± 0.79) | -0.5 (± 0.75) | | |
| Week 3 | -1.0 (± 0.88) | -0.7 (± 0.84) | | |
| Week 4 | -1.3 (± 0.95) | -0.9 (± 0.96) | | |
| Week 8 | -1.6 (± 1.02) | -1.2 (± 1.10) | | |
| Week 12 | -1.8 (± 1.09) | -1.3 (± 1.18) | | |
| Week 16 | -1.9 (± 1.16) | -1.4 (± 1.26) | | |
| Week 20 | -2.0 (± 1.17) | -1.5 (± 1.32) | | |
| Week 24 | -2.1 (± 1.22) | -1.5 (± 1.35) | | |
| Week 28 | -2.1 (± 1.22) | -1.6 (± 1.36) | | |
| Week 32 | -2.2 (± 1.27) | -1.6 (± 1.40) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Clinician-rated Overall Severity of Depressive Illness as assessed by Clinical Global Impression - Change (CGI-C) Scale Score

| | |
|-----------------|---|
| End point title | Clinician-rated Overall Severity of Depressive Illness as assessed by Clinical Global Impression - Change (CGI-C) Scale Score |
|-----------------|---|

End point description:

Clinician-rated overall severity of depressive illness as assessed by CGI-C scale score was reported. The CGI-C evaluates the total improvement whether or not due entirely to drug treatment on a scale of 1 to 7. Compared to the condition at baseline, a subject is assessed on how much he/she has changed, according to: 1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; 7 = very much worse. Higher scores indicate more severity. The FAS included all randomised subjects. Here, 'N' (number of subjects analysed) signifies subjects evaluable for this endpoint. Here, 'n' (number analysed) signifies subjects evaluable for this endpoint at specified time points.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Weeks 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32 | |

| End point values | Esketamine Nasal Spray + Oral Antidepressant (AD) | Quetiapine Extended Release (XR) + Oral AD | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 326 | 327 | | |
| Units: Units on scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 1 (n=326, 327) | 3.3 (± 0.77) | 3.6 (± 0.72) | | |
| Week 2 (n=324, 314) | 2.9 (± 0.87) | 3.3 (± 0.85) | | |
| Week 3 (n=313, 302) | 2.7 (± 0.83) | 3.1 (± 0.84) | | |
| Week 4 (n=317, 296) | 2.4 (± 0.85) | 2.9 (± 0.96) | | |
| Week 8 (n=300, 265) | 2.1 (± 0.84) | 2.4 (± 0.93) | | |
| Week 12 (n=286, 239) | 2.0 (± 0.85) | 2.3 (± 0.89) | | |
| Week 16 (n=280, 229) | 1.9 (± 0.87) | 2.2 (± 0.99) | | |
| Week 20 (n=270, 218) | 1.8 (± 0.85) | 2.1 (± 0.92) | | |
| Week 24 (n=260, 213) | 1.8 (± 0.85) | 2.0 (± 0.84) | | |
| Week 28 (n=255, 208) | 1.7 (± 0.84) | 2.0 (± 0.91) | | |
| Week 32 (n=255, 203) | 1.6 (± 0.81) | 1.9 (± 0.88) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects in Clinician-rated Overall Severity of Depressive Illness as assessed by CGI-C Scale Score at LOCF

| | |
|-----------------|---|
| End point title | Number of Subjects in Clinician-rated Overall Severity of Depressive Illness as assessed by CGI-C Scale Score at LOCF |
|-----------------|---|

End point description:

Number of subjects in clinician-rated overall severity of depressive illness as assessed by CGI-C scale score at LOCF was reported. The CGI-C evaluates the total improvement whether or not due entirely to drug treatment on a scale of 1 to 7. Compared to the condition at baseline, a subject is assessed on how much he/she has changed, according to: 1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; 7 = very much worse. Higher scores indicate more severity. LOCF is defined as the subjects who had a missing value or who stopped treatment at a specific time point had their last non-missing value carried forward. The FAS included all randomised subjects. Here, 'N' (number of subjects analysed) signifies subjects evaluable for this endpoint. Here, 'n' (number analysed) signifies subjects evaluable for this endpoint at specified

categories and time points.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, LOCF at Weeks 2, 3, 4, 8, 12, 16, 20, 24, 28, 32 | |

| End point values | Esketamine Nasal Spray + Oral Antidepressant (AD) | Quetiapine Extended Release (XR) + Oral AD | | |
|-------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 327 | 331 | | |
| Units: Subjects | | | | |
| Very much improved at Week 2 | 6 | 4 | | |
| Much improved at Week 2 | 97 | 39 | | |
| Minimally improved at Week 2 | 141 | 149 | | |
| No change at Week 2 | 75 | 108 | | |
| Minimally worse at Week 2 | 6 | 26 | | |
| Much worse at Week 2 | 1 | 5 | | |
| Very much worse at Week 2 | 1 | 0 | | |
| Very much improved at Week 3 | 14 | 8 | | |
| Much improved at Week 3 | 126 | 57 | | |
| Minimally improved at Week 3 | 135 | 159 | | |
| No change at Week 3 | 45 | 81 | | |
| Minimally worse at Week 3 | 6 | 20 | | |
| Much worse at Week 3 | 0 | 6 | | |
| Very much worse at Week 3 | 1 | 0 | | |
| Very much improved at Week 4 | 41 | 17 | | |
| Much improved at Week 4 | 150 | 83 | | |
| Minimally improved at Week 4 | 102 | 152 | | |
| No change at Week 4 | 29 | 52 | | |
| Minimally worse at Week 4 | 4 | 17 | | |
| Much worse at Week 4 | 0 | 10 | | |
| Very much worse at Week 4 | 1 | 0 | | |
| Very much improved at Week 8 | 68 | 38 | | |
| Much improved at Week 8 | 165 | 118 | | |
| Minimally improved at Week 8 | 68 | 105 | | |
| No change at Week 8 | 18 | 44 | | |
| Minimally worse at Week 8 | 5 | 16 | | |
| Much worse at Week 8 | 2 | 10 | | |
| Very much worse at Week 8 | 1 | 0 | | |
| Very much improved at Week 12 | 83 | 45 | | |
| Much improved at Week 12 | 156 | 120 | | |
| Minimally improved at Week 12 | 53 | 92 | | |
| No change at Week 12 | 24 | 47 | | |
| Minimally worse at Week 12 | 9 | 18 | | |
| Much worse at Week 12 | 1 | 9 | | |
| Very much worse at Week 12 | 1 | 0 | | |
| Very much improved at Week 16 | 100 | 55 | | |
| Much improved at Week 16 | 136 | 111 | | |

| | | | | |
|-------------------------------|-----|-----|--|--|
| Minimally improved at Week 16 | 58 | 84 | | |
| No change at Week 16 | 25 | 49 | | |
| Minimally worse at Week 16 | 5 | 23 | | |
| Much worse at Week 16 | 2 | 9 | | |
| Very much worse at Week 16 | 1 | 0 | | |
| Very much improved at Week 20 | 106 | 61 | | |
| Much improved at Week 20 | 137 | 110 | | |
| Minimally improved at Week 20 | 55 | 83 | | |
| No change at Week 20 | 19 | 49 | | |
| Minimally worse at Week 20 | 7 | 19 | | |
| Much worse at Week 20 | 2 | 9 | | |
| Very much worse at Week 20 | 1 | 0 | | |
| Very much improved at Week 24 | 123 | 64 | | |
| Much improved at Week 24 | 123 | 109 | | |
| Minimally improved at Week 24 | 48 | 86 | | |
| No change at Week 24 | 25 | 44 | | |
| Minimally worse at Week 24 | 6 | 19 | | |
| Much worse at Week 24 | 1 | 9 | | |
| Very much worse at Week 24 | 1 | 0 | | |
| Very much improved at Week 28 | 127 | 71 | | |
| Much improved at Week 28 | 121 | 104 | | |
| Minimally improved at Week 28 | 46 | 80 | | |
| No change at Week 28 | 24 | 48 | | |
| Minimally worse at Week 28 | 7 | 19 | | |
| Much worse at Week 28 | 1 | 9 | | |
| Very much worse at Week 28 | 1 | 0 | | |
| Very much improved at Week 32 | 148 | 82 | | |
| Much improved at Week 32 | 103 | 96 | | |
| Minimally improved at Week 32 | 42 | 81 | | |
| No change at Week 32 | 28 | 43 | | |
| Minimally worse at Week 32 | 4 | 20 | | |
| Much worse at Week 32 | 1 | 9 | | |
| Very much worse at Week 32 | 1 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Subject-Reported Depressive Symptoms as assessed by Patient Health Questionnaire (PHQ) 9-item Total Score

| | |
|-----------------|---|
| End point title | Change from Baseline in Subject-Reported Depressive Symptoms as assessed by Patient Health Questionnaire (PHQ) 9-item Total Score |
|-----------------|---|

End point description:

Change from baseline in subject-reported depressive symptoms as assessed by PHQ 9-item total score was reported. The PHQ-9 is a validated 9-item, patient-reported outcome (PRO) measure to assess 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 FAS included all randomized subjects. Here, 'N' (number of subjects analysed) signifies participants evaluable for this endpoint. Here, 'n' (number

analysed) signifies subjects evaluable for this endpoint at specified time points.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32 | |

| End point values | Esketamine Nasal Spray + Oral Antidepressant (AD) | Quetiapine Extended Release (XR) + Oral AD | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 319 | 310 | | |
| Units: Units on scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 2 (n=319, 310) | -4.9 (± 4.90) | -3.1 (± 4.62) | | |
| Week 4 (n=310, 291) | -6.7 (± 5.25) | -5.0 (± 5.06) | | |
| Week 6 (n=305, 278) | -8.1 (± 5.37) | -6.1 (± 5.64) | | |
| Week 8 (n=295, 254) | -8.9 (± 5.74) | -7.4 (± 5.58) | | |
| Week 10 (n=282, 236) | -9.6 (± 5.37) | -8.4 (± 5.58) | | |
| Week 12 (n=278, 227) | -9.8 (± 5.78) | -8.7 (± 5.65) | | |
| Week 14 (n=273, 224) | -10.2 (± 5.49) | -8.5 (± 5.76) | | |
| Week 16 (n=274, 216) | -10.5 (± 5.50) | -9.2 (± 5.77) | | |
| Week 18 (n=260, 212) | -10.6 (± 5.79) | -9.3 (± 5.74) | | |
| Week 20 (n=264, 209) | -10.4 (± 5.64) | -9.4 (± 5.97) | | |
| Week 22 (n=261, 209) | -10.7 (± 5.74) | -9.5 (± 5.87) | | |
| Week 24 (n=257, 206) | -10.6 (± 5.84) | -9.7 (± 6.08) | | |
| Week 26 (n=255, 201) | -10.9 (± 5.88) | -9.7 (± 6.21) | | |
| Week 28 (n=250, 201) | -10.9 (± 6.16) | -10.0 (± 6.23) | | |
| Week 30 (n=248, 197) | -11.2 (± 6.39) | -10.1 (± 6.08) | | |
| Week 32 (n=253, 198) | -11.4 (± 6.40) | -10.5 (± 6.01) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Subject-Reported Depressive Symptoms as assessed by PHQ 9-item Total Score at LOCF

| | |
|-----------------|--|
| End point title | Change from Baseline in Subject-Reported Depressive Symptoms as assessed by PHQ 9-item Total Score at LOCF |
|-----------------|--|

End point description:

Change from baseline in subject-reported depressive symptoms as assessed by PHQ 9-item total score at LOCF was reported. The PHQ-9 is a validated 9-item, PRO measure to assess 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 PHQ-9 is categorized as: None-minimal (0-4), Mild (5-9), Moderate (10-14), Moderately Severe (15-19) and Severe (20-27). LOCF is defined as subjects who had a missing value or who stopped treatment at a specific time point had their last non-missing value carried forward. The FAS included all randomized subjects. Here, 'N' (number of subjects analysed) signifies participants evaluable for this endpoint. Here, 'n' (number analysed) signifies subjects evaluable for this endpoint at specified time points.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, LOCF at Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32 | |

| End point values | Esketamine Nasal Spray + Oral Antidepressant (AD) | Quetiapine Extended Release (XR) + Oral AD | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 322 | 316 | | |
| Units: Units on scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 2 (n=319, 310) | -4.9 (± 4.90) | -3.1 (± 4.62) | | |
| Week 4 (n=320, 314) | -6.6 (± 5.33) | -4.7 (± 5.06) | | |
| Week 6 (n=320, 315) | -7.8 (± 5.51) | -5.6 (± 5.69) | | |
| Week 8 (n=322, 315) | -8.5 (± 5.94) | -6.3 (± 5.86) | | |
| Week 10 (n=322, 316) | -9.0 (± 5.75) | -7.0 (± 5.90) | | |
| Week 12 (n=322, 316) | -9.1 (± 6.13) | -7.1 (± 6.07) | | |
| Week 14 (n=322, 316) | -9.3 (± 5.93) | -6.9 (± 6.12) | | |
| Week 16 (n=322, 316) | -9.6 (± 5.98) | -7.4 (± 6.20) | | |
| Week 18 (n=322, 316) | -9.5 (± 6.26) | -7.3 (± 6.21) | | |
| Week 20 (n=322, 316) | -9.4 (± 6.12) | -7.4 (± 6.32) | | |
| Week 22 (n=322, 316) | -9.7 (± 6.27) | -7.5 (± 6.31) | | |
| Week 24 (n=322, 316) | -9.5 (± 6.35) | -7.5 (± 6.47) | | |
| Week 26 (n=322, 316) | -9.7 (± 6.46) | -7.5 (± 6.56) | | |
| Week 28 (n=322, 316) | -9.7 (± 6.66) | -7.6 (± 6.64) | | |
| Week 30 (n=322, 316) | -9.9 (± 6.85) | -7.6 (± 6.61) | | |
| Week 32 (n=322, 316) | -10.1 (± 6.94) | -8.0 (± 6.70) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Subject-Reported Functional Impairment and Associated Disability as assessed by Sheehan Disability Scale (SDS) Total Score

| | |
|-----------------|--|
| End point title | Change from Baseline in Subject-Reported Functional Impairment and Associated Disability as assessed by Sheehan Disability Scale (SDS) Total Score |
|-----------------|--|

End point description:

Change from baseline in subject-reported functional impairment and associated disability as assessed by SDS total score was reported. The SDS is a validated PRO measure consisting of a 5-item questionnaire that has been widely used and accepted for assessment of functional impairment and associated disability. The first 3 items assess disruption of (1) work/school, (2) social life, and (3) family life/home responsibilities using a rating scale from 0 to 10. The scores for the first 3 items are summed to create a total score of 0 to 30, where higher score indicates greater impairment. It also has 1 item assessing days lost from school or work and 1 item assessing days of underproductivity. The FAS included all randomised subjects. Here, 'N' (number of subjects analysed) signifies subjects evaluable for this endpoint. Here, 'n' (number analysed) signifies subjects evaluable for this endpoint at specified time points.

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

End point timeframe:

Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32

| End point values | Esketamine Nasal Spray + Oral Antidepressant (AD) | Quetiapine Extended Release (XR) + Oral AD | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 310 | 303 | | |
| Units: Units on scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (n=307, 298) | -5.9 (± 6.58) | -4.1 (± 5.89) | | |
| Week 8 (n=309, 303) | -8.2 (± 7.06) | -5.8 (± 7.45) | | |
| Week 12 (n=310, 303) | -9.0 (± 7.59) | -6.8 (± 7.59) | | |
| Week 16 (n=310, 303) | -9.8 (± 7.47) | -7.0 (± 7.99) | | |
| Week 20 (n=310, 303) | -9.9 (± 7.75) | -7.0 (± 7.97) | | |
| Week 24 (n=310, 303) | -10.0 (± 8.13) | -7.6 (± 8.37) | | |
| Week 28 (n=310, 303) | -10.4 (± 8.21) | -7.9 (± 8.69) | | |
| Week 32 (n=310, 303) | -11.1 (± 8.56) | -8.2 (± 8.78) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Participant-reported Functional Impairment and Associated Disability as assessed by SDS Total Score at LOCF

| | |
|-----------------|---|
| End point title | Change from Baseline in Participant-reported Functional Impairment and Associated Disability as assessed by SDS Total Score at LOCF |
|-----------------|---|

End point description:

Change from baseline in subject-reported functional impairment and associated disability as assessed by SDS total score at LOCF was reported. The SDS is a validated PRO measure consisting of a 5-item questionnaire for assessment of functional impairment and associated disability. The first 3 items assess disruption of (1) work/school, (2) social life, and (3) family life/home responsibilities using a rating scale from 0 to 10. The scores for the first 3 items are summed to create a total score of 0 to 30, where higher score indicates greater impairment. LOCF is defined as the subjects who had a missing value or who stopped treatment at a specific time point had their last non-missing value carried forward. The FAS included all randomised subjects. Here, 'N' (number of subject analysed) signifies subjects evaluable for this endpoint. Here, 'n' (number analysed) signifies subjects evaluable for this endpoint at specified time points.

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

End point timeframe:

Baseline, LOCF at Weeks 4, 8, 12, 16, 20, 24, 28, 32

| End point values | Esketamine Nasal Spray + Oral Antidepressant (AD) | Quetiapine Extended Release (XR) + Oral AD | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 310 | 303 | | |
| Units: Units on scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (n=307, 298) | -5.9 (± 6.58) | -4.1 (± 5.89) | | |
| Week 8 (n=309, 303) | -8.2 (± 7.06) | -5.8 (± 7.45) | | |
| Week 12 (n=310, 303) | -9.0 (± 7.59) | -6.8 (± 7.59) | | |
| Week16 (n=310, 303) | -9.8 (± 7.47) | -7.0 (± 7.99) | | |
| Week 20 (n=310, 303) | -9.9 (± 7.75) | -7.0 (± 7.97) | | |
| Week 24 (n=310, 303) | -10.0 (± 8.13) | -7.6 (± 8.37) | | |
| Week 28 (n=310, 303) | -10.4 (± 8.21) | -7.9 (± 8.69) | | |
| Week 32 (n=310, 303) | -11.1 (± 8.56) | -8.2 (± 8.78) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Subject-Reported Health-related Quality of Life (HRQL) and Health Status as Assessed by 36-item Short-Form Health Survey (SF-36) Domain Scores

| | |
|--|--|
| End point title | Change from Baseline in Subject-Reported Health-related Quality of Life (HRQL) and Health Status as Assessed by 36-item Short-Form Health Survey (SF-36) Domain Scores |
| End point description: | |
| <p>Change from baseline in subject-reported HRQL and health status as assessed by SF-36 domain scores was reported. The SF-36 consists of 8 subscales (physical function, role limitations due to physical problems, pain, general health perception, vitality, social function, role limitations due to emotional problems, and mental health). subjects self-report on items in a subscale that have between 2-6 choices per item using likert-type responses (for example: none of the time, some of the time, etc.). Summations of item scores of the same subscale give the subscale scores, which are transformed into a range from 0 to 100; zero= worst HRQL, 100=best HRQL. Higher scores indicate better health status. The FAS included all randomised subjects. Here, 'N' (number of subjects analysed) signifies subjects evaluable for this endpoint. Here, 'n' (number analysed) signifies subjects evaluable for this endpoint at specified categories with time points.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32 | |

| End point values | Esketamine Nasal Spray + Oral Antidepressant (AD) | Quetiapine Extended Release (XR) + Oral AD | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 317 | 306 | | |
| Units: Units on scale | | | | |
| arithmetic mean (standard deviation) | | | | |

| | | | | |
|---|----------------|----------------|--|--|
| Physical Functioning Week 4 (n=310, 295) | 3.5 (± 7.16) | 2.2 (± 6.85) | | |
| Physical Functioning Week 8 (n=287, 250) | 5.4 (± 7.64) | 3.8 (± 8.19) | | |
| Physical Functioning Week 12 (n=274, 228) | 5.8 (± 8.29) | 4.7 (± 8.00) | | |
| Physical Functioning Week 16 (n=268, 216) | 6.2 (± 8.36) | 5.2 (± 8.42) | | |
| Physical Functioning Week 20 (n=258, 207) | 6.1 (± 8.62) | 5.1 (± 8.87) | | |
| Physical Functioning Week 24 (n=252, 197) | 6.2 (± 9.01) | 5.9 (± 9.23) | | |
| Physical Functioning Week 28 (n=246, 197) | 6.4 (± 8.68) | 6.2 (± 9.51) | | |
| Physical Functioning Week 32 (n=250, 195) | 6.8 (± 8.79) | 6.4 (± 9.58) | | |
| Role-Physical Week 4 (n=314, 299) | 5.7 (± 9.57) | 3.1 (± 9.75) | | |
| Role-Physical Week 8 (n=291, 251) | 7.5 (± 10.49) | 6.1 (± 11.67) | | |
| Role-Physical Week 12 (n=276, 229) | 8.8 (± 10.59) | 7.1 (± 11.38) | | |
| Role-Physical Week 16 (n=272, 218) | 10.0 (± 11.60) | 8.3 (± 12.47) | | |
| Role-Physical Week 20 (n=264, 206) | 10.0 (± 11.75) | 8.2 (± 12.34) | | |
| Role-Physical Week 24 (n=256, 203) | 10.4 (± 11.97) | 9.2 (± 12.50) | | |
| Role-Physical Week 28 (n=250, 199) | 10.9 (± 11.92) | 8.8 (± 12.62) | | |
| Role-Physical Week 32 (n=250, 196) | 11.7 (± 11.97) | 9.4 (± 12.39) | | |
| Body Pain Week 4 (n=315, 306) | 3.7 (± 9.05) | 2.3 (± 8.50) | | |
| Body Pain Week 8 (n=294, 254) | 4.5 (± 10.04) | 4.0 (± 8.85) | | |
| Body Pain Week 12 (n=280, 235) | 5.1 (± 9.93) | 5.3 (± 9.71) | | |
| Body Pain Week 16 (n=275, 224) | 5.6 (± 10.05) | 5.5 (± 10.52) | | |
| Body Pain Week 20 (n=265, 215) | 5.7 (± 11.14) | 6.0 (± 10.41) | | |
| Body Pain Week 24 (n=255, 209) | 6.2 (± 10.68) | 6.1 (± 10.64) | | |
| Body Pain Week 28 (n=251, 204) | 6.2 (± 11.32) | 6.3 (± 11.34) | | |
| Body Pain Week 32 (n=252, 201) | 6.7 (± 11.03) | 7.2 (± 11.62) | | |
| General Health Week 4 (n=315, 302) | 5.3 (± 7.85) | 3.3 (± 7.45) | | |
| General Health Week 8 (n=289, 252) | 7.2 (± 8.63) | 5.7 (± 8.50) | | |
| General Health Week 12 (n=278, 232) | 7.9 (± 8.79) | 6.4 (± 9.02) | | |
| General Health Week 16 (n=274, 221) | 8.8 (± 9.09) | 7.3 (± 9.55) | | |
| General Health Week 20 (n=267, 212) | 9.0 (± 9.30) | 7.2 (± 9.71) | | |
| General Health Week 24 (n=255, 207) | 9.5 (± 9.73) | 7.7 (± 10.05) | | |
| General Health Week 28 (n=249, 200) | 10.1 (± 9.71) | 8.8 (± 10.38) | | |
| General Health Week 32 (n=253, 198) | 10.6 (± 10.25) | 9.7 (± 10.33) | | |
| Vitality Week 4 (n=317, 301) | 8.7 (± 9.13) | 5.2 (± 7.75) | | |
| Vitality Week 8 (n=293, 249) | 11.3 (± 10.04) | 9.2 (± 9.44) | | |
| Vitality Week 12 (n=277, 230) | 12.4 (± 10.36) | 10.8 (± 9.79) | | |
| Vitality Week 16 (n=276, 220) | 13.1 (± 10.69) | 12.1 (± 9.88) | | |
| Vitality Week 20 (n=267, 210) | 13.2 (± 10.67) | 12.6 (± 10.64) | | |
| Vitality Week 24 (n=251, 206) | 13.4 (± 10.83) | 12.9 (± 11.26) | | |
| Vitality Week 28 (n=251, 203) | 14.2 (± 11.25) | 13.9 (± 11.19) | | |
| Vitality Week 32 (n=251, 198) | 15.2 (± 11.64) | 14.0 (± 11.34) | | |
| Social Functioning Week 4 (n=304, 300) | 7.1 (± 10.32) | 5.0 (± 8.83) | | |
| Social Functioning Week 8 (n=284, 251) | 11.2 (± 11.42) | 8.7 (± 9.59) | | |
| Social Functioning Week 12 (n=274, 231) | 12.4 (± 11.29) | 10.2 (± 10.45) | | |
| Social Functioning Week 16 (n=269, 220) | 13.5 (± 10.92) | 11.2 (± 11.24) | | |

| | | | | |
|---|----------------|----------------|--|--|
| Social Functioning Week 20 (n=258, 208) | 13.6 (± 11.65) | 11.7 (± 10.73) | | |
| Social Functioning Week 24 (n=247, 206) | 14.3 (± 11.55) | 12.5 (± 11.75) | | |
| Social Functioning Week 28 (n=241, 198) | 15.3 (± 11.26) | 13.3 (± 11.15) | | |
| Social Functioning Week 32 (n=245, 197) | 16.1 (± 11.34) | 13.8 (± 11.47) | | |
| Role-Emotional Week 4 (n=316, 305) | 8.6 (± 9.62) | 5.3 (± 9.53) | | |
| Role-Emotional Week 8 (n=293, 254) | 12.7 (± 10.67) | 10.1 (± 11.30) | | |
| Role-Emotional Week 12 (n=280, 235) | 13.8 (± 10.70) | 12.2 (± 11.48) | | |
| Role-Emotional Week 16 (n=277, 224) | 15.4 (± 11.30) | 13.2 (± 12.07) | | |
| Role-Emotional Week 20 (n=268, 213) | 15.8 (± 11.26) | 13.4 (± 11.14) | | |
| Role-Emotional Week 24 (n=257, 209) | 16.0 (± 11.79) | 14.7 (± 11.71) | | |
| Role-Emotional Week 28 (n=252, 204) | 17.3 (± 12.44) | 15.0 (± 11.58) | | |
| Role-Emotional Week 32 (n=252, 201) | 18.1 (± 12.49) | 14.9 (± 12.62) | | |
| Mental Health Week 4 (n=311, 297) | 9.8 (± 9.77) | 6.7 (± 9.34) | | |
| Mental Health Week 8 (n=287, 248) | 13.5 (± 10.37) | 11.6 (± 10.78) | | |
| Mental Health Week 12 (n=278, 231) | 15.0 (± 10.50) | 13.3 (± 10.84) | | |
| Mental Health Week 16 (n=267, 217) | 16.1 (± 11.04) | 14.3 (± 11.01) | | |
| Mental Health Week 20 (n=266, 209) | 16.5 (± 10.90) | 14.7 (± 11.36) | | |
| Mental Health Week 24 (n=251, 204) | 16.6 (± 11.69) | 15.3 (± 11.45) | | |
| Mental Health Week 28 (n=246, 200) | 17.6 (± 11.40) | 16.5 (± 12.16) | | |
| Mental Health Week 32 (n=251, 195) | 18.4 (± 11.89) | 17.0 (± 12.05) | | |
| Physical component summary Week 4 (n=276,259) | 2.4 (± 6.52) | 1.1 (± 6.51) | | |
| Physical component summary Week 8 (n=257,222) | 3.1 (± 7.38) | 2.3 (± 7.58) | | |
| Physical component summary Week 12 (n=250,201) | 3.5 (± 7.93) | 2.9 (± 7.88) | | |
| Physical component summary Week 16 (n=242,191) | 4.0 (± 8.10) | 3.3 (± 8.43) | | |
| Physical component summary Week 20 (n=241,183) | 3.7 (± 8.32) | 3.3 (± 8.87) | | |
| Physical component summary Week 24 (n=228,181) | 4.1 (± 8.21) | 3.7 (± 9.24) | | |
| Physical component summary Week 28 (n=221,178) | 4.0 (± 8.48) | 3.9 (± 9.61) | | |
| Physical component summary Week 32 (n=232,176) | 4.4 (± 8.85) | 4.3 (± 9.36) | | |
| Mental component summary scale Week 4 (n=276,259) | 10.7 (± 10.06) | 7.2 (± 9.44) | | |
| Mental component summary scale Week 8 (n=257,222) | 15.1 (± 11.20) | 12.4 (± 11.15) | | |
| Mental component summary scale Week 12 (n=250,201) | 16.5 (± 11.22) | 15.2 (± 11.59) | | |
| Mental component summary scale Week 16 (n=242,191) | 18.0 (± 12.07) | 16.1 (± 12.01) | | |
| Mental component summary scale Week 20 (n=241, 183) | 18.4 (± 12.14) | 16.7 (± 11.90) | | |
| Mental component summary scale Week 24 (n=228,181) | 18.5 (± 12.74) | 17.8 (± 12.53) | | |
| Mental component summary scale Week 28 (n=221,178) | 20.0 (± 12.70) | 18.0 (± 13.28) | | |
| Mental component summary scale Week 32 (n=232,176) | 20.9 (± 13.05) | 18.9 (± 13.33) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Subject-Reported HRQL and Health Status as Assessed by SF-36 Domain Scores at LOCF

| | |
|--|--|
| End point title | Change from Baseline in Subject-Reported HRQL and Health Status as Assessed by SF-36 Domain Scores at LOCF |
| End point description: | |
| Change from baseline in subject-reported HRQL and health status as assessed by SF-36 domain scores at LOCF was reported. SF-36 consists of 8 subscales (physical function, role limitations due to physical problems, pain, general health perception, vitality, social function, role limitations due to emotional problems, and mental health). Subjects self-report on items in a subscale that has between 2-6 choices per item. Summations of item scores of the same subscale give the subscale scores, which are in a range of 0 to 100; zero= worst, 100=best. Higher scores indicate better health status. LOCF is defined as subjects who had a missing value or who stopped treatment at a specific time point had their last non-missing value carried forward. The FAS included all randomised subjects. Here, 'N' (number of subjects analysed) signifies subjects evaluable for this endpoint. Here, 'n' (number analysed) signifies subjects evaluable for this endpoint at specified categories with time points. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, LOCF at Weeks 8, 12, 16, 20, 24, 28, 32 | |

| End point values | Esketamine Nasal Spray + Oral Antidepressant (AD) | Quetiapine Extended Release (XR) + Oral AD | | |
|---|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 319 | 308 | | |
| Units: Units on scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Physical Functioning Week 8 (n=308, 300) | 5.1 (± 7.61) | 3.2 (± 8.15) | | |
| Physical Functioning Week 12 (n=308, 299) | 5.3 (± 8.22) | 3.9 (± 7.96) | | |
| Physical Functioning Week 16 (n=307, 298) | 5.6 (± 8.33) | 4.2 (± 8.27) | | |
| Physical Functioning Week 20 (n=306, 300) | 5.5 (± 8.63) | 4.0 (± 8.48) | | |
| Physical Functioning Week 24 (n=309, 295) | 5.6 (± 8.83) | 4.4 (± 8.84) | | |
| Physical Functioning Week 28 (n=309, 298) | 5.6 (± 8.71) | 4.5 (± 8.97) | | |
| Physical Functioning Week 32 (n=312, 300) | 6.0 (± 8.77) | 4.6 (± 9.05) | | |
| Role-Physical Week 8 (n=315, 302) | 7.4 (± 10.51) | 5.3 (± 11.50) | | |
| Role-Physical Week 12 (n=313, 301) | 8.3 (± 10.87) | 5.7 (± 11.31) | | |
| Role-Physical Week 16 (n=313, 302) | 9.3 (± 11.49) | 6.2 (± 12.23) | | |

| | | | | |
|---|----------------|----------------|--|--|
| Role-Physical Week 20 (n=314, 298) | 9.1 (± 11.69) | 6.3 (± 12.09) | | |
| Role-Physical Week 24 (n=316, 301) | 9.2 (± 11.93) | 6.9 (± 12.48) | | |
| Role-Physical Week 28 (n=316, 301) | 9.4 (± 12.00) | 6.8 (± 12.36) | | |
| Role-Physical Week 32 (n=315, 303) | 10.2 (± 12.21) | 7.2 (± 12.29) | | |
| Body Pain Week 8 (n=318, 306) | 4.4 (± 9.84) | 3.5 (± 8.79) | | |
| Body Pain Week 12 (n=317, 307) | 4.8 (± 9.99) | 4.2 (± 9.51) | | |
| Body Pain Week 16 (n=317, 308) | 5.2 (± 10.14) | 4.3 (± 10.02) | | |
| Body Pain Week 20 (n=316, 308) | 5.2 (± 10.85) | 4.5 (± 10.05) | | |
| Body Pain Week 24 (n=316, 307) | 5.6 (± 10.45) | 4.4 (± 10.26) | | |
| Body Pain Week 28 (n=318, 307) | 5.4 (± 11.01) | 4.5 (± 10.78) | | |
| Body Pain Week 32 (n=318, 308) | 6.0 (± 10.93) | 5.0 (± 11.10) | | |
| General Health Week 8 (n=313, 303) | 6.9 (± 8.85) | 4.9 (± 8.19) | | |
| General Health Week 12 (n=315, 304) | 7.4 (± 9.19) | 5.1 (± 8.68) | | |
| General Health Week 16 (n=316, 305) | 8.0 (± 9.41) | 5.6 (± 9.20) | | |
| General Health Week 20 (n=318, 306) | 8.1 (± 9.60) | 5.5 (± 9.37) | | |
| General Health Week 24 (n=316, 306) | 8.2 (± 10.08) | 5.6 (± 9.57) | | |
| General Health Week 28 (n=316, 304) | 8.6 (± 10.19) | 6.1 (± 10.01) | | |
| General Health Week 32 (n=319, 306) | 9.2 (± 10.78) | 6.7 (± 10.18) | | |
| Vitality Week 8 (n=317, 299) | 11.1 (± 10.08) | 7.8 (± 9.46) | | |
| Vitality Week 12 (n=314, 301) | 11.7 (± 10.48) | 8.7 (± 9.98) | | |
| Vitality Week 16 (n=317, 303) | 12.3 (± 10.81) | 9.5 (± 10.26) | | |
| Vitality Week 20 (n=317, 301) | 12.3 (± 10.94) | 9.6 (± 10.77) | | |
| Vitality Week 24 (n=311, 303) | 12.2 (± 11.04) | 9.6 (± 11.34) | | |
| Vitality Week 28 (n=316, 305) | 12.8 (± 11.43) | 10.1 (± 11.53) | | |
| Vitality Week 32 (n=315, 304) | 13.8 (± 11.99) | 10.4 (± 11.65) | | |
| Social Functioning Week 8 (n=308, 300) | 10.7 (± 11.31) | 7.6 (± 9.72) | | |
| Social Functioning Week 12 (n=310, 301) | 11.4 (± 11.29) | 8.6 (± 10.47) | | |
| Social Functioning Week 16 (n=310, 302) | 12.2 (± 11.24) | 9.0 (± 11.22) | | |
| Social Functioning Week 20 (n=307, 299) | 12.3 (± 11.91) | 9.1 (± 10.92) | | |
| Social Functioning Week 24 (n=306, 302) | 12.7 (± 11.81) | 9.5 (± 11.63) | | |
| Social Functioning Week 28 (n=306, 299) | 13.0 (± 12.09) | 9.8 (± 11.49) | | |
| Social Functioning Week 32 (n=309, 302) | 14.0 (± 12.35) | 10.3 (± 11.71) | | |
| Role-Emotional Week 8 (n=315, 304) | 12.0 (± 10.75) | 8.6 (± 11.30) | | |
| Role-Emotional Week 12 (n=315, 306) | 12.7 (± 10.89) | 9.8 (± 11.82) | | |
| Role-Emotional Week 16 (n=317, 307) | 14.2 (± 11.53) | 10.3 (± 12.32) | | |
| Role-Emotional Week 20 (n=317, 305) | 14.3 (± 11.77) | 10.4 (± 11.67) | | |
| Role-Emotional Week 24 (n=316, 306) | 14.3 (± 12.15) | 11.2 (± 12.22) | | |
| Role-Emotional Week 28 (n=317, 306) | 15.2 (± 12.91) | 11.2 (± 12.30) | | |
| Role-Emotional Week 32 (n=316, 307) | 16.0 (± 13.16) | 11.2 (± 12.96) | | |
| Mental Health Week 8 (n=310, 298) | 12.9 (± 10.76) | 9.8 (± 11.04) | | |
| Mental Health Week 12 (n=313, 301) | 14.0 (± 11.09) | 10.6 (± 11.44) | | |
| Mental Health Week 16 (n=306, 298) | 14.7 (± 11.63) | 10.9 (± 11.85) | | |
| Mental Health Week 20 (n=313, 299) | 15.0 (± 11.64) | 11.2 (± 12.07) | | |
| Mental Health Week 24 (n=308, 299) | 14.8 (± 12.24) | 11.5 (± 12.23) | | |
| Mental Health Week 28 (n=308, 300) | 15.5 (± 12.35) | 12.2 (± 13.01) | | |
| Mental Health Week 32 (n=312, 299) | 16.3 (± 12.90) | 12.6 (± 13.08) | | |
| Physical component summary Week 8 (n=276,262) | 3.1 (± 7.28) | 2.1 (± 7.27) | | |

| | | | | |
|--|----------------|----------------|--|--|
| Physical component summary Week 12 (n=280,260) | 3.3 (± 7.95) | 2.4 (± 7.46) | | |
| Physical component summary Week 16 (n=275,260) | 3.7 (± 8.01) | 2.6 (± 7.82) | | |
| Physical component summary Week 20 (n=282,259) | 3.3 (± 8.17) | 2.6 (± 8.15) | | |
| Physical component summary Week 24 (n=278,263) | 3.5 (± 8.05) | 2.8 (± 8.41) | | |
| Physical component summary Week 28 (n=276,262) | 3.4 (± 8.28) | 2.9 (± 8.59) | | |
| Physical component summary Week 32 (n=286,265) | 4.0 (± 8.62) | 3.2 (± 8.41) | | |
| Mental component summary scale Week 8 (n=276,262) | 14.5 (± 11.33) | 10.7 (± 11.27) | | |
| Mental component summary scale Week 12 (n=280,260) | 15.4 (± 11.52) | 12.2 (± 12.15) | | |
| Mental component summary scale Week 16 (n=275,260) | 16.6 (± 12.39) | 12.5 (± 12.66) | | |
| Mental component summary scale Week 20 (n=282,259) | 16.9 (± 12.68) | 12.9 (± 12.60) | | |
| Mental component summary scale Week 24 (n=278,263) | 16.8 (± 13.11) | 13.4 (± 13.19) | | |
| Mental component summary scale Week 28 (n=276,262) | 17.7 (± 13.49) | 13.6 (± 13.77) | | |
| Mental component summary scale Week 32 (n=286,265) | 18.8 (± 14.03) | 14.3 (± 14.04) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Subject-Reported Quality of Life as assessed by Quality of Life in Depression Scale (QLDS) Total Score

| | |
|-----------------|--|
| End point title | Change from Baseline in Subject-Reported Quality of Life as assessed by Quality of Life in Depression Scale (QLDS) Total Score |
|-----------------|--|

End point description:

Change from baseline in subject-reported quality of life as assessed by QLDS total score was reported. The QLDS is a disease-specific validated PRO measure which assesses the impact that depression has on a subject's quality of life. It is a 34-item self-rated questionnaire which consists of dichotomous response questions, with the response being either True/Not True. Each statement on the QLDS is given a score of "1" or "0". A score of "1" is indicative of adverse quality of life. All item scores are summed to give a total score that ranges from 0 (good quality of life) to 34 (very poor quality of life). The FAS included all randomised subjects. Here, 'N' (number of subjects analysed) signifies subjects evaluable for this endpoint. Here, 'n' (number analysed) signifies subjects evaluable for this endpoint at specified time points.

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

End point timeframe:

Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32

| End point values | Esketamine Nasal Spray + Oral Antidepressant (AD) | Quetiapine Extended Release (XR) + Oral AD | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 315 | 300 | | |
| Units: Units on Scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (n=315, 300) | -8.9 (± 8.83) | -5.6 (± 7.43) | | |
| Week 8 (n=292, 253) | -12.0 (± 9.36) | -9.1 (± 9.31) | | |
| Week 12 (n=281, 234) | -13.5 (± 9.30) | -10.9 (± 9.52) | | |
| Week 16 (n=277, 221) | -14.2 (± 9.39) | -11.6 (± 9.39) | | |
| Week 20 (n=264, 212) | -14.3 (± 9.50) | -12.1 (± 9.74) | | |
| Week 24 (n=256, 205) | -14.9 (± 9.44) | -12.8 (± 9.64) | | |
| Week 28 (n=249, 201) | -15.6 (± 9.42) | -13.7 (± 9.51) | | |
| Week 32 (n=252, 198) | -16.0 (± 9.55) | -14.2 (± 9.96) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Subject-Reported Quality of Life as assessed by QLDS Total Score at LOCF

| | |
|-----------------|--|
| End point title | Change from Baseline in Subject-Reported Quality of Life as assessed by QLDS Total Score at LOCF |
|-----------------|--|

End point description:

Change from baseline in subject-reported quality of life as assessed by QLDS total score was reported. QLDS is a disease-specific validated PRO measure which assesses the impact that depression has on a subject's quality of life. It is a 34-item self-rated questionnaire which consists of dichotomous response questions, with the response being either True/Not True. Each statement on the QLDS is given a score of "1" or "0". A score of "1" is indicative of adverse quality of life. All item scores are summed to give a total score that ranges from 0 (good quality of life) to 34 (very poor quality of life). LOCF is defined as the subjects who had a missing value or who stopped treatment at a specific time point had their last non-missing value carried forward. The FAS included all randomised subjects. Here, 'N' (number of subjects analysed) signifies subjects evaluable for this endpoint. Here, 'n' (number analysed) signifies subjects evaluable for this endpoint at specified time points.

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

End point timeframe:

Baseline, LOCF at Weeks 4, 8, 12, 16, 20, 24, 28, 32

| End point values | Esketamine Nasal Spray + Oral Antidepressant (AD) | Quetiapine Extended Release (XR) + Oral AD | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 318 | 305 | | |
| Units: Units on scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (n=315, 300) | -8.9 (± 8.83) | -5.6 (± 7.43) | | |
| Week 8 (n=318, 305) | -11.3 (± 9.59) | -8.1 (± 9.22) | | |

| | | | | |
|----------------------|-----------------|-----------------|--|--|
| Week 12 (n=318, 305) | -12.3 (± 9.73) | -9.0 (± 9.62) | | |
| Week 16 (n=318, 305) | -13.0 (± 9.86) | -9.3 (± 9.80) | | |
| Week 20 (n=318, 305) | -13.0 (± 9.93) | -9.5 (± 10.02) | | |
| Week 24 (n=318, 305) | -13.3 (± 9.98) | -9.8 (± 10.18) | | |
| Week 28 (n=318, 305) | -13.6 (± 10.06) | -10.3 (± 10.26) | | |
| Week 32 (n=318, 305) | -14.1 (± 10.29) | -10.5 (± 10.59) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Subject-Reported European Quality of Life (EuroQol) Group, 5 Dimension, 5-Level (EQ-5D-5L)

| | |
|-----------------|--|
| End point title | Change from Baseline in Subject-Reported European Quality of Life (EuroQol) Group, 5 Dimension, 5-Level (EQ-5D-5L) |
|-----------------|--|

End point description:

Change from baseline in subject-reported EuroQol group EQ-5D-5L was reported. The EQ-5D-5L is a validated standardized instrument for use as a measure of health outcome, primarily designed for self-completion by respondents. The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each of the 5 dimensions is divided into 5 levels of perceived problems (level 1 = no problem, level 2 = slight problems, level 3 = moderate problems, level 4 = severe problems, level 5 = extreme problems). Score is transformed and results in a total score range -0.594 to 1.000; higher score indicates a better health state. The FAS included all randomised subjects. Here, 'N' (number of subjects analysed) signifies subjects evaluable for this endpoint. Here, 'n' (number analysed) signifies subjects evaluable for this endpoint at specified time points.

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

End point timeframe:

Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32

| End point values | Esketamine Nasal Spray + Oral Antidepressant (AD) | Quetiapine Extended Release (XR) + Oral AD | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 318 | 306 | | |
| Units: Units on Scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (n=318, 306) | 0.177 (± 0.2354) | 0.124 (± 0.2280) | | |
| Week 8 (n=296, 258) | 0.234 (± 0.2655) | 0.206 (± 0.2463) | | |
| Week 12 (n=282, 237) | 0.276 (± 0.2405) | 0.227 (± 0.2367) | | |
| Week 16 (n=277, 225) | 0.284 (± 0.2445) | 0.232 (± 0.2431) | | |
| Week 20 (n=268, 214) | 0.294 (± 0.2399) | 0.238 (± 0.2423) | | |
| Week 24 (n=258, 209) | 0.297 (± 0.2498) | 0.259 (± 0.2489) | | |

| | | | | |
|----------------------|------------------|------------------|--|--|
| Week 28 (n=250, 205) | 0.303 (± 0.2584) | 0.262 (± 0.2492) | | |
| Week 32 (n=254, 200) | 0.317 (± 0.2636) | 0.279 (± 0.2581) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Subject-Reported EuroQol Group EQ-5D-5L at LOCF

| | |
|-----------------|---|
| End point title | Change from Baseline in Subject-Reported EuroQol Group EQ-5D-5L at LOCF |
|-----------------|---|

End point description:

Change from baseline in subject-reported EuroQol group EQ-5D-5L at LOCF was reported. The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each of the 5 dimensions is divided into 5 levels of perceived problems (level 1 = no problem, level 2 = slight problems, level 3 = moderate problems, level 4 = severe problems, level 5 = extreme problems). Score is transformed and results in a total score range - 0.594 to 1.000; higher score indicates a better health state. LOCF is defined as the subjects who had a missing value or who stopped treatment at a specific time point had their last non-missing value carried forward. The FAS included all randomised subjects. Here, 'N' (number of subjects analysed) signifies subjects evaluable for this endpoint. Here, 'n' (number analysed) signifies subjects evaluable for this endpoint at specified time points.

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

End point timeframe:

Baseline, LOCF at Weeks 4, 8, 12, 16, 20, 24, 28, 32

| End point values | Esketamine Nasal Spray + Oral Antidepressant (AD) | Quetiapine Extended Release (XR) + Oral AD | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 320 | 308 | | |
| Units: Units on scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (n=318, 306) | 0.177 (± 0.2354) | 0.124 (± 0.2280) | | |
| Week 8 (n=320, 308) | 0.221 (± 0.2681) | 0.175 (± 0.2510) | | |
| Week 12 (n=320, 308) | 0.247 (± 0.2552) | 0.187 (± 0.2523) | | |
| Week 16 (n=320, 308) | 0.255 (± 0.2580) | 0.188 (± 0.2595) | | |
| Week 20 (n=320, 308) | 0.261 (± 0.2600) | 0.187 (± 0.2590) | | |
| Week 24 (n=320, 308) | 0.264 (± 0.2627) | 0.196 (± 0.2671) | | |
| Week 28 (n=320, 308) | 0.266 (± 0.2739) | 0.195 (± 0.2664) | | |
| Week 32 (n=320, 308) | 0.280 (± 0.2806) | 0.207 (± 0.2739) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Participant-reported EuroQol Group, Visual Analogue Scale (EQ-VAS)

| | |
|-----------------|--|
| End point title | Change from Baseline in Participant-reported EuroQol Group, Visual Analogue Scale (EQ-VAS) |
|-----------------|--|

End point description:

Change from baseline in subject-reported EuroQol group EQ-VAS was reported. The EQ-VAS is a vertical visual analogue scale that takes values between 100 (best imaginable health) and 0 (worst imaginable health), on which subjects provide a global assessment of their health. The FAS included all randomised subjects. Here, 'N' (number of subjects analysed) signifies subjects evaluable for this endpoint. Here, 'n' (number analysed) signifies subjects evaluable for this endpoint at specified time points.

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

End point timeframe:

Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32

| End point values | Esketamine Nasal Spray + Oral Antidepressant (AD) | Quetiapine Extended Release (XR) + Oral AD | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 317 | 308 | | |
| Units: Units on scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (n=317, 308) | 13.3 (± 18.43) | 9.7 (± 17.83) | | |
| Week 8 (n=293, 256) | 18.9 (± 19.84) | 16.1 (± 19.64) | | |
| Week 12 (n=280, 238) | 20.9 (± 20.98) | 17.2 (± 20.73) | | |
| Week 16 (n=275, 225) | 21.9 (± 20.14) | 20.2 (± 22.14) | | |
| Week 20 (n=267, 215) | 22.3 (± 21.20) | 19.6 (± 21.59) | | |
| Week 24 (n=257, 208) | 23.6 (± 20.95) | 21.8 (± 21.60) | | |
| Week 28 (n=251, 205) | 25.2 (± 20.95) | 23.2 (± 22.11) | | |
| Week 32 (n=252, 201) | 24.9 (± 21.65) | 24.5 (± 22.64) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Participant-reported EuroQol Group, EQ-VAS at LOCF

| | |
|-----------------|---|
| End point title | Change from Baseline in Participant-reported EuroQol Group, |
|-----------------|---|

End point description:

Change from baseline in subject-reported EuroQol group EQ-VAS at LOCF was reported. The EQ-VAS is a vertical visual analogue scale that takes values between 100 (best imaginable health) and 0 (worst imaginable health), on which subjects provide a global assessment of their health. LOCF is defined as the subjects who had a missing value or who stopped treatment at a specific time point had their last non-missing value carried forward. The FAS included all randomised subjects. Here, 'N' (number of subjects analysed) signifies subjects evaluable for this endpoint. Here, 'n' (number analysed) signifies subjects evaluable for this endpoint at specified time points.

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

End point timeframe:

| |
|--|
| Baseline, LOCF at Weeks 4, 8, 12, 16, 20, 24, 28, 32 |
|--|

| End point values | Esketamine Nasal Spray + Oral Antidepressant (AD) | Quetiapine Extended Release (XR) + Oral AD | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 318 | 310 | | |
| Units: Units on scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (n=317, 308) | 13.3 (± 18.43) | 9.7 (± 17.83) | | |
| Week 8 (n=318, 310) | 18.2 (± 19.94) | 14.0 (± 20.42) | | |
| Week 12 (n=318, 310) | 19.4 (± 21.04) | 14.4 (± 21.19) | | |
| Week 16 (n=318, 310) | 20.2 (± 20.37) | 16.1 (± 22.42) | | |
| Week 20 (n=318, 310) | 20.4 (± 21.34) | 15.4 (± 22.19) | | |
| Week 24 (n=318, 310) | 21.3 (± 21.34) | 16.9 (± 22.64) | | |
| Week 28 (n=318, 310) | 21.9 (± 21.78) | 17.3 (± 23.10) | | |
| Week 32 (n=318, 310) | 22.3 (± 22.47) | 18.0 (± 23.59) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Subject-Reported Work Productivity as assessed by Work Productivity and Activity Impairment (WPAI): Depression Questionnaire

| | |
|-----------------|--|
| End point title | Change from Baseline in Subject-Reported Work Productivity as assessed by Work Productivity and Activity Impairment (WPAI): Depression Questionnaire |
|-----------------|--|

End point description:

Change from baseline in subject-reported work productivity as assessed by WPAI: depression questionnaire was reported. The WPAI-D questionnaire is a validated short instrument that assesses impairment in work and other regular activities over the past 7 days. The WPAI yields four types of scores: (a) Absenteeism; (b) Presenteeism; (c) Work productivity loss; (d) Activity Impairment. The first three scores were derived only for respondents who were working (should be missing for non-working), but the last score was applicable for all respondents. Each score ranges from 0 to 100 with higher scores indicating greater impairment and less productivity. The FAS included all randomised subjects. Here, 'N' (number of subjects analysed) signifies subjects evaluable for this endpoint. Here, 'n' (number analysed) signifies subjects evaluable for this endpoint at specified time points.

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

End point timeframe:

Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32

| End point values | Esketamine Nasal Spray + Oral Antidepressant (AD) | Quetiapine Extended Release (XR) + Oral AD | | |
|--|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 308 | 303 | | |
| Units: Units on scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Absenteeism Week 4 (n=115, 112) | -11.9 (± 20.745) | -8.37 (± 25.790) | | |
| Absenteeism Week 8 (n=108, 91) | -19.02 (± 30.205) | -13.62 (± 31.059) | | |
| Absenteeism Week 12 (n=106, 72) | -21.87 (± 34.711) | -17.25 (± 31.340) | | |
| Absenteeism Week 16 (n=105, 74) | -22.85 (± 33.023) | -14.24 (± 37.823) | | |
| Absenteeism Week 20 (n=102, 78) | -27.88 (± 32.107) | -18.70 (± 35.310) | | |
| Absenteeism Week 24 (n=104, 72) | -26.83 (± 32.909) | -21.03 (± 34.459) | | |
| Absenteeism Week 28 (n=97, 73) | -27.16 (± 35.825) | -17.90 (± 31.254) | | |
| Absenteeism Week 32 (n=102, 67) | -28.90 (± 32.066) | -16.68 (± 29.394) | | |
| Presenteeism Week 4 (n=120, 115) | -21.75 (± 25.558) | -9.13 (± 21.948) | | |
| Presenteeism Week 8 (n=112, 102) | -31.70 (± 25.144) | -16.86 (± 27.140) | | |
| Presenteeism Week 12 (n=108, 87) | -35.46 (± 27.998) | -23.22 (± 29.942) | | |
| Presenteeism Week 16 (n=102, 80) | -36.96 (± 28.556) | -24.50 (± 31.898) | | |
| Presenteeism Week 20 (n=99, 82) | -39.80 (± 26.263) | -26.34 (± 33.389) | | |
| Presenteeism Week 24 (n=99, 81) | -42.83 (± 27.332) | -31.60 (± 30.922) | | |
| Presenteeism Week 28 (n=100, 79) | -43.00 (± 28.762) | -33.29 (± 34.445) | | |
| Presenteeism Week 32 (n=99, 80) | -47.58 (± 26.691) | -33.88 (± 33.621) | | |
| Work productivity loss Week 4 (n=120, 115) | -20.94 (± 25.759) | -9.46 (± 23.374) | | |
| Work productivity loss Week 8 (n=112, 102) | -32.91 (± 26.244) | -18.21 (± 29.156) | | |
| Work productivity loss Week 12 (n=108, 87) | -36.68 (± 29.247) | -25.62 (± 35.135) | | |
| Work productivity loss Week 16 (n=102, 80) | -38.13 (± 30.490) | -24.50 (± 34.089) | | |
| Work productivity loss Week 20 (n=99, 82) | -41.11 (± 28.643) | -26.57 (± 32.885) | | |
| Work productivity loss Week 24 (n=99, 81) | -45.31 (± 29.000) | -30.63 (± 34.087) | | |
| Work productivity loss Week 28 (n=100, 79) | -44.40 (± 32.098) | -32.61 (± 33.836) | | |

| | | | | |
|---|-------------------|-------------------|--|--|
| Work productivity loss Week 32 (n=99, 80) | -50.20 (± 29.176) | -35.48 (± 35.915) | | |
| Activity Impairment Week 4 (n=308, 303) | -20.29 (± 23.702) | -13.43 (± 20.846) | | |
| Activity Impairment Week 8 (n=287, 254) | -30.31 (± 27.410) | -24.25 (± 24.187) | | |
| Activity Impairment Week 12 (n=275, 233) | -33.96 (± 27.218) | -28.28 (± 25.555) | | |
| Activity Impairment Week 16 (n=270, 221) | -35.07 (± 27.291) | -30.95 (± 27.444) | | |
| Activity Impairment Week 20 (n=260, 214) | -33.88 (± 28.770) | -30.93 (± 27.698) | | |
| Activity Impairment Week 24 (n=248, 206) | -36.69 (± 29.742) | -36.84 (± 27.000) | | |
| Activity Impairment Week 28 (n=244, 202) | -40.00 (± 29.828) | -37.62 (± 28.500) | | |
| Activity Impairment Week 32 (n=245, 196) | -41.92 (± 30.299) | -39.59 (± 27.190) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Subject-Reported Work Productivity as assessed by WPAI: Depression Questionnaire at LOCF

| | |
|-----------------|--|
| End point title | Change from Baseline in Subject-Reported Work Productivity as assessed by WPAI: Depression Questionnaire at LOCF |
|-----------------|--|

End point description:

Change from baseline in subject-reported work productivity as assessed by WPAI: depression questionnaire at LOCF was reported. The WPAI yields four types of scores: (a) Absenteeism; (b) Presenteeism; (c) Work productivity loss; (d) Activity Impairment. The first three scores were derived only for respondents who were working (should be missing for non-working), but the last score was applicable for all respondents. Each score ranges from 0 to 100 with higher scores indicating greater impairment and less productivity. LOCF is defined as the subjects who had a missing value or who stopped treatment at a specific time point had their last non-missing value carried forward. The FAS included all randomised subjects. Here, 'N' (number of subjects analysed) signifies subjects evaluable for this endpoint. Here, 'n' (number analysed) signifies subjects evaluable for this endpoint at specified time points.

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

End point timeframe:

Baseline, LOCF at Weeks 4, 8, 12, 16, 20, 24, 28, 32

| End point values | Esketamine Nasal Spray + Oral Antidepressant (AD) | Quetiapine Extended Release (XR) + Oral AD | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 310 | 307 | | |
| Units: Units on scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Absenteeism Week 4 (n=115, 112) | -11.95 (± 20.745) | -8.37 (± 25.790) | | |

| | | | | |
|---|-------------------|-------------------|--|--|
| Absenteeism Week 8 (n=120, 107) | -18.28 (± 29.417) | -12.38 (± 30.369) | | |
| Absenteeism Week 12 (n=120, 103) | -20.23 (± 33.590) | -15.17 (± 31.835) | | |
| Absenteeism Week 16 (n=122, 107) | -21.35 (± 31.806) | -14.14 (± 37.534) | | |
| Absenteeism Week 20 (n=124, 114) | -25.45 (± 31.628) | -16.04 (± 37.769) | | |
| Absenteeism Week 24 (n=126, 111) | -24.41 (± 32.403) | -16.28 (± 37.672) | | |
| Absenteeism Week 28 (n=122, 114) | -23.88 (± 34.623) | -14.14 (± 35.849) | | |
| Absenteeism Week 32 (n=128, 108) | -26.10 (± 31.903) | -13.90 (± 36.104) | | |
| Presenteeism Week 4 (n=120, 115) | -21.75 (± 25.558) | -9.13 (± 21.948) | | |
| Presenteeism Week 8 (n=127, 122) | -29.45 (± 26.437) | -14.84 (± 27.067) | | |
| Presenteeism Week 12 (n=129, 125) | -33.57 (± 28.745) | -17.44 (± 29.997) | | |
| Presenteeism Week 16 (n=130, 128) | -35.00 (± 29.075) | -19.84 (± 31.322) | | |
| Presenteeism Week 20 (n=130, 128) | -36.08 (± 28.598) | -21.41 (± 32.862) | | |
| Presenteeism Week 24 (n=131, 128) | -36.87 (± 29.641) | -22.19 (± 32.189) | | |
| Presenteeism Week 28 (n=131, 128) | -37.40 (± 30.924) | -23.83 (± 34.757) | | |
| Presenteeism Week 32 (n=132, 128) | -40.53 (± 30.700) | -23.44 (± 35.526) | | |
| Work productivity loss Week 4 (n=120, 115) | -20.94 (± 25.759) | -9.46 (± 23.374) | | |
| Work productivity loss Week 8 (n=127, 122) | -30.59 (± 26.789) | -15.35 (± 30.059) | | |
| Work productivity loss Week 12 (n=129, 125) | -34.46 (± 29.333) | -19.27 (± 33.905) | | |
| Work productivity loss Week 16 (n=130, 128) | -36.35 (± 30.531) | -20.75 (± 33.545) | | |
| Work productivity loss Week 20 (n=130, 128) | -37.59 (± 30.354) | -22.58 (± 34.117) | | |
| Work productivity loss Week 24 (n=131, 128) | -39.02 (± 31.482) | -22.54 (± 34.635) | | |
| Work productivity loss Week 28 (n=131, 128) | -39.09 (± 33.271) | -23.85 (± 35.152) | | |
| Work productivity loss Week 32 (n=132, 128) | -43.42 (± 32.638) | -24.89 (± 37.870) | | |
| Activity Impairment Week 4 (n=308, 303) | -20.29 (± 23.702) | -13.43 (± 20.846) | | |
| Activity Impairment Week 8 (n=310, 306) | -28.84 (± 27.412) | -20.39 (± 24.599) | | |
| Activity Impairment Week 12 (n=310, 306) | -31.10 (± 27.778) | -22.81 (± 26.264) | | |
| Activity Impairment Week 16 (n=310, 307) | -31.84 (± 28.413) | -23.68 (± 28.014) | | |
| Activity Impairment Week 20 (n=310, 307) | -30.84 (± 29.983) | -23.62 (± 28.185) | | |
| Activity Impairment Week 24 (n=310, 307) | -32.45 (± 31.207) | -26.71 (± 28.821) | | |
| Activity Impairment Week 28 (n=310, 307) | -34.87 (± 31.804) | -27.07 (± 29.965) | | |
| Activity Impairment Week 32 (n=310, 307) | -36.65 (± 32.357) | -28.40 (± 29.930) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Treatment-emergent Adverse Events (TEAEs)

| | |
|-----------------|---|
| End point title | Number of Subjects with Treatment-emergent Adverse Events (TEAEs) |
|-----------------|---|

End point description:

An AE is any untoward medical occurrence in a subject participating in a clinical study that does not necessarily have a causal relationship with the pharmaceutical/ biological agent under study. TEAEs are those events if they started after administration of the first dose and until 14 days for non serious TEAEs and or until 30 days for serious TEAEs after the last dose of study medication. The safety analysis set included all randomised subjects who received at least 1 dose of any study intervention.

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

End point timeframe:

Up to Week 35

| End point values | Esketamine Nasal Spray + Oral Antidepressant (AD) | Quetiapine Extended Release (XR) + Oral AD | | |
|-----------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 334 | 336 | | |
| Units: Subjects | 307 | 262 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with TEAEs of Special Interest

| | |
|-----------------|---|
| End point title | Number of Subjects with TEAEs of Special Interest |
|-----------------|---|

End point description:

Number of subjects with TEAEs of special interest were reported. It included significant TEAEs that were judged to be of special interest because of clinical importance, known or suspected class effects, or based on nonclinical signals. Events such as sedation, depersonalisation/derealisation disorder, depression suicidal, aggression, allergic cystitis, cholestasis and jaundice of hepatic origin, and many more were considered as TEAEs of special interest. The safety analysis set included all randomised subjects who received at least 1 dose of any study intervention.

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

End point timeframe:

Up to Week 35

| End point values | Esketamine Nasal Spray + Oral Antidepressant (AD) | Quetiapine Extended Release (XR) + Oral AD | | |
|-----------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 334 | 336 | | |
| Units: Subjects | 223 | 140 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Suicidal Ideation or Behavior as Assessed by Columbia-Suicide Severity Rating Scale (C-SSRS) Score

| | |
|-----------------|--|
| End point title | Number of Subjects with Suicidal Ideation or Behavior as Assessed by Columbia-Suicide Severity Rating Scale (C-SSRS) Score |
|-----------------|--|

End point description:

Number of subjects with suicidal ideation or behavior as assessed by C-SSRS score was reported. The C-SSRS evaluates suicidal ideation and behavior. Suicidal ideation consists of: wish to be dead, non-specific active suicidal thoughts, active suicidal ideation with any methods without intention to act, active suicidal ideation with some intent to act without specific plan, and active suicidal ideation with specific plan and intent. Suicidal behavior consists of: preparatory acts, aborted attempt, interrupted attempt, actual attempt, and completed suicide. The maximum score assigned for each subject was summarized as follows: No suicidal ideation or behavior (0), Suicidal ideation (1-5), Suicidal behavior (6-10). Higher scores indicate more severe suicidal ideation. The safety analysis set was used. Here, 'N' (number of subjects analysed) signifies subjects evaluable for this endpoint. Here, 'n' (number analysed) signifies subjects evaluable for this endpoint at specified time points.

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

End point timeframe:

Weeks 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32

| End point values | Esketamine Nasal Spray + Oral Antidepressant (AD) | Quetiapine Extended Release (XR) + Oral AD | | |
|---------------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 317 | 295 | | |
| Units: Subjects | | | | |
| Suicidal Ideation Week 1 (n=277, 282) | 22 | 25 | | |
| Suicidal Behavior Week 1 (n=277, 282) | 0 | 0 | | |
| Suicidal Ideation Week 2 (n=278, 274) | 21 | 32 | | |
| Suicidal Behavior Week 2 (n=278, 274) | 0 | 1 | | |
| Suicidal Ideation Week 3 (n=271, 265) | 19 | 17 | | |
| Suicidal Behavior Week 3 (n=271, 265) | 0 | 0 | | |
| Suicidal Ideation Week 4 (n=317, 295) | 22 | 27 | | |

| | | | | |
|--|----|----|--|--|
| Suicidal Behavior Week 4 (n=317, 295) | 0 | 0 | | |
| Suicidal Ideation Week 8 (n=300, 265) | 21 | 18 | | |
| Suicidal Behavior Week 8 (n=300, 265) | 0 | 0 | | |
| Suicidal Ideation Week 12 (n=286, 239) | 13 | 14 | | |
| Suicidal Behavior Week 12 (n=286, 239) | 0 | 0 | | |
| Suicidal Ideation Week 16 (n=280, 229) | 12 | 12 | | |
| Suicidal Behavior Week 16 (n=280, 229) | 1 | 1 | | |
| Suicidal Ideation Week 20 (n=270, 218) | 15 | 14 | | |
| Suicidal Behavior Week 20 (n=270, 218) | 0 | 0 | | |
| Suicidal Ideation Week 24 (n=260, 213) | 14 | 9 | | |
| Suicidal Behavior Week 24 (n=260, 213) | 0 | 0 | | |
| Suicidal Ideation Week 28 (n=255, 208) | 8 | 5 | | |
| Suicidal Behavior Week 28 (n=255, 208) | 0 | 0 | | |
| Suicidal Ideation Week 32 (n=250, 203) | 7 | 4 | | |
| Suicidal Behavior Week 32 (n=250, 203) | 0 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality and serious adverse events: until 30 days after last dose (up to Week 35); Non-serious AEs: until 14 days after last dose (up to Week 33)

Adverse event reporting additional description:

The safety analysis set included all randomised subjects who received at least 1 dose of any study intervention.

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 25.0 |

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Quetiapine Extended Release (XR) + Oral AD |
|-----------------------|--|

Reporting group description:

Subjects continued to take their current SSRI/SNRI augmented with quetiapine XR as per the Summary of Product Characteristics (SmPC) (or local equivalent, if applicable) at an initial dose of 50 mg/day on Days 1-2, 150 mg/day on Days 3-4 (lowest effective dose) in adult subjects aged 18 to 64 years; a further dose increase to 300 mg/day on Day 5 and onward were based on individual subject evaluation. In elderly subjects aged 65 to 74 years, the initial dose was 50 mg/day on Days 1-3, 100 mg/day on Days 4-7, and 150 mg/day on Day 8; a further dose increase to 300 mg/day were based on individual subject evaluation no earlier than Day 22.

| | |
|-----------------------|---|
| Reporting group title | Esketamine Nasal Spray + Oral Antidepressant (AD) |
|-----------------------|---|

Reporting group description:

Subjects received treatment with esketamine nasal spray (28 milligrams [mg] [initial dose for elderly subjects aged 65 to 74 years and adults of Japanese ancestry], 56 mg [initial dose for adult subjects aged 18 to 64 years], or 84 mg [maximum dose esketamine nasal spray]) twice-weekly with a flexible dose regimen from Day 1 until Week 4, once weekly from Week 5 to Week 8 and once-weekly or once every 2 weeks from Week 9 to Week 32 in combination with continuing serotonin-norepinephrine reuptake inhibitor/selective serotonin reuptake inhibitor (SSRI/SNRI).

| Serious adverse events | Quetiapine Extended Release (XR) + Oral AD | Esketamine Nasal Spray + Oral Antidepressant (AD) | |
|---|--|---|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 17 / 336 (5.06%) | 19 / 334 (5.69%) | |
| number of deaths (all causes) | 1 | 1 | |
| number of deaths resulting from adverse events | | | |
| Injury, poisoning and procedural complications | | | |
| Tendon rupture | | | |
| subjects affected / exposed | 0 / 336 (0.00%) | 1 / 334 (0.30%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 336 (0.00%) | 1 / 334 (0.30%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 336 (0.00%) | 1 / 334 (0.30%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 336 (0.30%) | 0 / 334 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 336 (0.00%) | 1 / 334 (0.30%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Generalised tonic-clonic seizure | | | |
| subjects affected / exposed | 1 / 336 (0.30%) | 0 / 334 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Lymphadenopathy mediastinal | | | |
| subjects affected / exposed | 1 / 336 (0.30%) | 0 / 334 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 0 / 336 (0.00%) | 1 / 334 (0.30%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Eye disorders | | | |
| Retinal detachment | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 336 (0.00%) | 1 / 334 (0.30%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 336 (0.30%) | 0 / 334 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 336 (0.00%) | 1 / 334 (0.30%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Nasal turbinate hypertrophy | | | |
| subjects affected / exposed | 1 / 336 (0.30%) | 0 / 334 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Major depression | | | |
| subjects affected / exposed | 1 / 336 (0.30%) | 1 / 334 (0.30%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Somatic symptom disorder | | | |
| subjects affected / exposed | 0 / 336 (0.00%) | 2 / 334 (0.60%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Suicidal ideation | | | |
| subjects affected / exposed | 3 / 336 (0.89%) | 1 / 334 (0.30%) | |
| occurrences causally related to treatment / all | 3 / 3 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Suicide attempt | | | |
| subjects affected / exposed | 1 / 336 (0.30%) | 2 / 334 (0.60%) | |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Depression | | | |
| subjects affected / exposed | 3 / 336 (0.89%) | 2 / 334 (0.60%) | |
| occurrences causally related to treatment / all | 4 / 4 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Conversion disorder | | | |
| subjects affected / exposed | 1 / 336 (0.30%) | 0 / 334 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anxiety | | | |
| subjects affected / exposed | 2 / 336 (0.60%) | 0 / 334 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Alcoholism | | | |
| subjects affected / exposed | 0 / 336 (0.00%) | 1 / 334 (0.30%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 336 (0.00%) | 1 / 334 (0.30%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 336 (0.30%) | 0 / 334 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COVID-19 | | | |
| subjects affected / exposed | 0 / 336 (0.00%) | 1 / 334 (0.30%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cystitis | | | |
| subjects affected / exposed | 1 / 336 (0.30%) | 0 / 334 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Pilonidal disease | | | |
| subjects affected / exposed | 0 / 336 (0.00%) | 1 / 334 (0.30%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Quetiapine Extended Release (XR) + Oral AD | Esketamine Nasal Spray + Oral Antidepressant (AD) | |
|---|--|---|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 216 / 336 (64.29%) | 289 / 334 (86.53%) | |
| Investigations | | | |
| Blood pressure increased | | | |
| subjects affected / exposed | 4 / 336 (1.19%) | 28 / 334 (8.38%) | |
| occurrences (all) | 4 | 135 | |
| Weight increased | | | |
| subjects affected / exposed | 42 / 336 (12.50%) | 9 / 334 (2.69%) | |
| occurrences (all) | 42 | 9 | |
| Nervous system disorders | | | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 1 / 336 (0.30%) | 19 / 334 (5.69%) | |
| occurrences (all) | 2 | 112 | |
| Paraesthesia | | | |
| subjects affected / exposed | 2 / 336 (0.60%) | 37 / 334 (11.08%) | |
| occurrences (all) | 2 | 219 | |
| Sedation | | | |
| subjects affected / exposed | 29 / 336 (8.63%) | 22 / 334 (6.59%) | |
| occurrences (all) | 43 | 136 | |
| Somnolence | | | |
| subjects affected / exposed | 78 / 336 (23.21%) | 50 / 334 (14.97%) | |
| occurrences (all) | 110 | 570 | |
| Headache | | | |
| subjects affected / exposed | 43 / 336 (12.80%) | 82 / 334 (24.55%) | |
| occurrences (all) | 63 | 169 | |
| Dysgeusia | | | |

| | | | |
|--|-------------------------|----------------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 336 (0.30%) 1 | 40 / 334 (11.98%) 405 | |
| Dizziness subjects affected / exposed occurrences (all) | 28 / 336 (8.33%) 29 | 156 / 334 (46.71%) 1509 | |
| General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) | 34 / 336 (10.12%) 42 | 19 / 334 (5.69%) 61 | |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 3 / 336 (0.89%) 3 | 63 / 334 (18.86%) 411 | |
| Eye disorders Vision blurred subjects affected / exposed occurrences (all) | 3 / 336 (0.89%) 4 | 21 / 334 (6.29%) 177 | |
| Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all) | 5 / 336 (1.49%) 5 | 36 / 334 (10.78%) 48 | |
| Nausea subjects affected / exposed occurrences (all) | 12 / 336 (3.57%) 12 | 98 / 334 (29.34%) 240 | |
| Dry mouth subjects affected / exposed occurrences (all) | 22 / 336 (6.55%) 27 | 3 / 334 (0.90%) 14 | |
| Psychiatric disorders Confusional state subjects affected / exposed occurrences (all) | 1 / 336 (0.30%) 1 | 20 / 334 (5.99%) 46 | |
| Dissociation subjects affected / exposed occurrences (all) | 2 / 336 (0.60%) 2 | 94 / 334 (28.14%) 825 | |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|---|------------------------|------------------------|--|
| Back pain subjects affected / exposed occurrences (all) | 9 / 336 (2.68%) 11 | 17 / 334 (5.09%) 26 | |
| Infections and infestations COVID-19 subjects affected / exposed occurrences (all) | 29 / 336 (8.63%) 31 | 24 / 334 (7.19%) 24 | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 11 / 336 (3.27%) 14 | 21 / 334 (6.29%) 27 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 08 October 2020 | The overall reason for the amendment was to address the impact that the Coronavirus Disease 2019 (COVID-19) pandemic may have had on the conduct of this study and to address comments made by regional health authorities on the protocol. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

To minimize potential bias, the MADRS was performed by an independent on-site rater who was blinded to the subject's treatment, and who was not involved in any other study assessments or treatment decisions.

Notes: