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 (<=)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 (>=)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

No statistical analyses for this end point

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

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 (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)

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:

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.

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 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,

	EQ-VAS at LOCF

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	1 / 336 (0.30%)	40 / 334 (11.98%)	
occurrences (all)	1	405	
Dizziness			
subjects affected / exposed	28 / 336 (8.33%)	156 / 334 (46.71%)	
occurrences (all)	29	1509	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	34 / 336 (10.12%)	19 / 334 (5.69%)	
occurrences (all)	42	61	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	3 / 336 (0.89%)	63 / 334 (18.86%)	
occurrences (all)	3	411	
Eye disorders			
Vision blurred			
subjects affected / exposed	3 / 336 (0.89%)	21 / 334 (6.29%)	
occurrences (all)	4	177	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	5 / 336 (1.49%)	36 / 334 (10.78%)	
occurrences (all)	5	48	
Nausea			
subjects affected / exposed	12 / 336 (3.57%)	98 / 334 (29.34%)	
occurrences (all)	12	240	
Dry mouth			
subjects affected / exposed	22 / 336 (6.55%)	3 / 334 (0.90%)	
occurrences (all)	27	14	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 336 (0.30%)	20 / 334 (5.99%)	
occurrences (all)	1	46	
Dissociation			
subjects affected / exposed	2 / 336 (0.60%)	94 / 334 (28.14%)	
occurrences (all)	2	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) Nasopharyngitis subjects affected / exposed occurrences (all)	29 / 336 (8.63%) 31 11 / 336 (3.27%) 14	24 / 334 (7.19%) 24 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: