Clinical trial results:
Open-label Long-Term Extension Study for Participants With Treatment-Resistant Major Depressive Disorder Who are Continuing Esketamine Nasal Spray Treatment From Study 54135419TRD3013

Summary

EudraCT number	2020-004291-18
Trial protocol	DE BE CZ HU PL BG FI GR
Global end of trial date	22 July 2024

Results information

Result version number	v1 (current)
This version publication date	03 August 2025
First version publication date	03 August 2025

Trial information

Trial identification

Sponsor protocol code	54135419TRD4010

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04829318
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	24 September 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 July 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Main objective of the trial was to assess the long-term safety and tolerability of esketamine nasal spray in combination with a selective serotonin reuptake inhibitor/serotonin-norepinephrine reuptake inhibitor (SSRI/SNRI) in subjects who have completed 32 weeks of esketamine nasal spray treatment in Study 54135419TRD3013.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 April 2021
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	Argentina: 24
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Bulgaria: 9
Country: Number of subjects enrolled	Czechia: 25
Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	Germany: 19
Country: Number of subjects enrolled	Greece: 3
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Malaysia: 4
Country: Number of subjects enrolled	Poland: 69
Country: Number of subjects enrolled	Korea, Republic of: 6
Country: Number of subjects enrolled	South Africa: 6
Country: Number of subjects enrolled	Taiwan: 7
Country: Number of subjects enrolled	Türkiye: 6
Worldwide total number of subjects	183
EEA total number of subjects	130

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)	174
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 183 subjects who completed the maintenance phase (Week 32) of study 54135419TRD3013 were enrolled and treated in this study.

Pre-assignment

Screening details:

A total of 183 subjects who completed the maintenance phase (Week 32) of study 54135419TRD3013 were enrolled and treated in this study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Esketamine nasal spray + Oral Antidepressant (AD)

Arm description:

Subjects (who received esketamine nasal spray in study 54135419TRD3013 through Week 30 [every 2 weeks] or Week 31 [once weekly], and completed the maintenance phase at Week 32) received flexible dose of esketamine nasal spray 28 milligrams (mg) (1 spray per nostril at 0 minute), 56 mg (1 spray per nostril at 0 and 5 minutes) or 84 mg (1 spray per nostril at 0, 5 and 10 minutes) once weekly or every 2 weeks from Day 1 (Week 32 visit of Study 54135419TRD3013 until week 104 along with oral AD, serotonin-norepinephrine reuptake inhibitor/selective serotonin reuptake inhibitor (SSRI/SNRI) in this long-term extension (LTE) study. Time 0 minute signified time of first esketamine nasal spray administration to 1 nostril. Esketamine nasal devices contained a total of 28 mg esketamine per device (2 sprays). Only one device was used at a timepoint.

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

Dosage and administration details:

Subjects received flexible dose of esketamine nasal spray 28 mg, 56 mg or 84 mg once weekly or every 2 weeks from Day 1 up to Week 104.

Number of subjects in period 1	Esketamine nasal spray + Oral Antidepressant (AD)
Started	183
Treated with Esketamine 28 mg	2 [1]
Treated with Esketamine 56 mg	68 [2]
Treated with Esketamine 84 mg	113 [3]
Treated with oral AD	182
Completed	148
Not completed	35
Adverse event, serious fatal	1

Physician decision	1
Consent withdrawn by subject	19
Adverse event, non-fatal	6
Site terminated by sponsor	1
Unspecified	1
Lost to follow-up	1
Sponsor decision	5

Notes:

[1] - 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 reported subjects were planned to be included in this milestone.

[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 reported subjects were planned to be included in this milestone.

[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 reported subjects were planned to be included in this milestone.

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study
Reporting group description:	
Subjects (who received esketamine nasal spray in study 54135419TRD3013 through Week 30 [every 2 weeks] or Week 31 [once weekly], and completed the maintenance phase at Week 32) received flexible dose of esketamine nasal spray 28 milligrams (mg) (1 spray per nostril at 0 minute), 56 mg (1 spray per nostril at 0 and 5 minutes) or 84 mg (1 spray per nostril at 0, 5 and 10 minutes) once weekly or every 2 weeks from Day 1 (Week 32 visit of Study 54135419TRD3013 until week 104 along with oral AD, serotonin-norepinephrine reuptake inhibitor/selective serotonin reuptake inhibitor (SSRI/SNRI) in this long-term extension (LTE) study. Time 0 minute signified time of first esketamine nasal spray administration to 1 nostril. Esketamine nasal devices contained a total of 28 mg esketamine per device (2 sprays). Only one device was used at a timepoint.	

Reporting group values	Overall Study	Total	
Number of subjects	183	183	
Age categorical Units: Subjects			
In Utero	0	0	
Preterm newborn infants (gestional age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days - 23 months)	0	0	
Children (2 - 11 years)	0	0	
12 - 17 years	0	0	
Adults (18 - 64 years)	174	174	
From 65 - 84 years	9	9	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	44.6		
standard deviation	± 13.07	-	
Gender categorical Units: Subjects			
Male	55	55	
Female	128	128	

End points

End points reporting groups

Reporting group title	Esketamine nasal spray + Oral Antidepressant (AD)

Reporting group description:

Subjects (who received esketamine nasal spray in study 54135419TRD3013 through Week 30 [every 2 weeks] or Week 31 [once weekly], and completed the maintenance phase at Week 32) received flexible dose of esketamine nasal spray 28 milligrams (mg) (1 spray per nostril at 0 minute), 56 mg (1 spray per nostril at 0 and 5 minutes) or 84 mg (1 spray per nostril at 0, 5 and 10 minutes) once weekly or every 2 weeks from Day 1 (Week 32 visit of Study 54135419TRD3013 until week 104 along with oral AD, serotonin-norepinephrine reuptake inhibitor/selective serotonin reuptake inhibitor (SSRI/SNRI) in this long-term extension (LTE) study. Time 0 minute signified time of first esketamine nasal spray administration to 1 nostril. Esketamine nasal devices contained a total of 28 mg esketamine per device (2 sprays). Only one device was used at a timepoint.

Primary: Incidence Rate of Treatment-emergent Adverse Events (TEAEs)

End point title	Incidence Rate of Treatment-emergent Adverse Events

End point description:

Incidence rate of TEAEs were reported. AE Incidence rate was defined as incidence rate per 100 patient-months = (number of subjects with AE divided by sum of days at risk for AE) * 100*365.25/12. An AE was any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non investigational) product. An AE does not necessarily have a causal relationship with the intervention. A SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Any AE occurring at or after the initial administration of study intervention up to 30 days after last dose in Study 54135419TRD4010 was considered to be treatment emergent. TEAEs included both serious and non-serious adverse events. Safety analysis set was used.

End point type	Primary

End point timeframe:

From Day 1 of study 54135419TRD4010 up to 30 days after last dose of study drug at Week 104 (up to Week 108)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No inferential statistics was done. Only descriptive statistics was performed.

End point values	Esketamine nasal spray + Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	183			
Units: AEs per 100 patient-months				
number (confidence interval 95%)	17.33 (14.85 to 20.23)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects with Treatment-emergent Adverse Events (TEAEs)

End point title	Percentage of Subjects with Treatment-emergent Adverse Events (TEAEs)[2]

End point description:

Percentage of subjects with TEAEs were reported. An AE was any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non investigational) product. An AE does not necessarily have a causal relationship with the intervention. A SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Any AE occurring at or after the initial administration of study intervention up to 30 days after last dose in Study 54135419TRD4010 was considered to be treatment emergent. TEAEs included both serious and non-serious adverse events. Safety analysis set included all subjects who received at least 1 dose of esketamine anytime during the 54135419TRD4010 study.

End point type	Primary

End point timeframe:

From Day 1 of study 54135419TRD4010 up to 30 days after last dose of study drug at Week 104 (up to Week 108)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No inferential statistics was done. Only descriptive statistics was performed.

End point values	Esketamine nasal spray + Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	183			
Units: percentage of subjects				
number (not applicable)	88.0			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects with Treatment-emergent AEs of Special interest (AESIs)

End point title	Percentage of Subjects with Treatment-emergent AEs of Special interest (AESIs)[3]

End point description:

An AE was any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non investigational) product. An AE does not necessarily have a causal relationship with intervention. A SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Any AE occurring at or after the initial administration of study intervention up to 30 days after last dose in Study 54135419TRD4010 was considered to be treatment emergent. TEAEs included both serious and non-serious AEs. AEs of special interest were separately grouped by categories sedation, dissociation, suicidality, suggestive of abuse potential, cystitis and hepatic impairment. Safety analysis set was used.

End point type	Primary

End point timeframe:

From Day 1 of study 54135419TRD4010 up to 30 days after last dose of study drug at Week 104 (up to Week 108)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No inferential statistics was done. Only descriptive statistics was performed.

End point values	Esketamine nasal spray + Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	183			
Units: percentage of subjects				
number (not applicable)				
Sedation	16.9			
Dissociation	12.0			
Suicidality	3.8			
Suggestive of abuse potential	37.7			
Cystitis	0.5			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of of Subjects with TEAEs Leading to Death

End point title	Percentage of of Subjects with TEAEs Leading to Death[4]

End point description:

Percentage of subjects with TEAEs leading to death were reported. An AE was any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non investigational) product. An AE does not necessarily have a causal relationship with the intervention. A SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Any AE occurring at or after the initial administration of study intervention up to 30 days after last dose in Study 54135419TRD4010 was considered to be treatment emergent. TEAEs included both serious and non-serious adverse events. Safety analysis set included all subjects who received at least 1 dose of esketamine anytime during the 54135419TRD4010 study.

End point type	Primary

End point timeframe:

From Day 1 of study 54135419TRD4010 up to 30 days after last dose of study drug at Week 104 (up to Week 108)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No inferential statistics was done. Only descriptive statistics was performed.

End point values	Esketamine nasal spray + Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	183			
Units: percentage of subjects				

number (not applicable)	0.6			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects with Treatment-emergent Serious Adverse Events (TESAEs)

End point title	Percentage of Subjects with Treatment-emergent Serious Adverse Events (TESAEs)[5]

End point description:

Percentage of subjects with TESAEs were reported. An AE was any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non investigational) product. An AE does not necessarily have a causal relationship with the intervention. A SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Any AE occurring at or after the initial administration of study intervention up to 30 days after last dose in Study 54135419TRD4010 was considered to be treatment emergent. Safety analysis set included all subjects who received at least 1 dose of esketamine anytime during the 54135419TRD4010 study.

End point type	Primary

End point timeframe:

From Day 1 of study 54135419TRD4010 up to 30 days after last dose of study drug at Week 104 (up to Week 108)

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No inferential statistics was done. Only descriptive statistics was performed.

End point values	Esketamine nasal spray + Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	183			
Units: percentage of subjects				
number (not applicable)	6.0			

Statistical analyses

No statistical analyses for this end point

Primary: Incidence Rate of TEAEs Leading to Death

End point title	Incidence Rate of TEAEs Leading to Death[6]

End point description:

Incidence rate of TEAEs leading to death were reported. AE Incidence rate was defined as incidence rate per 100 patient-months = (number of subjects with AE divided by sum of days at risk for AE) * 100*365.25/12. An AE was any untoward medical occurrence in a clinical study subject administered a

medicinal (investigational or non investigational) product. An AE does not necessarily have a causal relationship with the intervention. A SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Any AE occurring at or after the initial administration of study intervention up to 30 days after last dose in Study 54135419TRD4010 was considered to be treatment emergent. TEAEs included both serious and non-serious adverse events. Safety analysis set was used.

End point type	Primary

End point timeframe:

From Day 1 of study 54135419TRD4010 up to 30 days after last dose of study drug at Week 104 (up to Week 108)

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No inferential statistics was done. Only descriptive statistics was performed.

End point values	Esketamine nasal spray + Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	183			
Units: AEs per 100 patient-months				
number (confidence interval 95%)	0.03 (0.00 to 0.18)			

Statistical analyses

No statistical analyses for this end point

Primary: Incidence Rate of Treatment-emergent Serious Adverse Events (TESAEs)

End point title	Incidence Rate of Treatment-emergent Serious Adverse Events (TESAEs)[7]

End point description:

Incidence rate of with TESAEs were reported. AE Incidence rate was defined as incidence rate per 100 patient-months = (number of subjects with AE divided by sum of days at risk for AE) * 100*365.25/12. An AE was any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non investigational) product. An AE does not necessarily have a causal relationship with the intervention. A SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Any AE occurring at or after the initial administration of study intervention up to 30 days after last dose in Study 54135419TRD4010 was considered to be treatment emergent. Safety analysis set was used.

End point type	Primary

End point timeframe:

From Day 1 of study 54135419TRD4010 up to 30 days after last dose of study drug at Week 104 (up to Week 108)

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No inferential statistics was done. Only descriptive statistics was performed.

End point values	Esketamine nasal spray + Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	183			
Units: AEs per 100 patient-months				
number (confidence interval 95%)	0.28 (0.16 to 0.51)			

Statistical analyses

No statistical analyses for this end point

Primary: Incidence Rate of Treatment-emergent AEs of Special interest (AESIs)

End point title	Incidence Rate of Treatment-emergent AEs of Special interest (AESIs)[8]

End point description:

AE Incidence rate: incidence rate per 100 patient-months=(number of subjects with AE divided by sum of days at risk for AE) * 100*365.25/12. AE: any untoward medical occurrence in clinical study subject administered a medicinal (investigational or non investigational) drug. An AE does not necessarily have a causal relationship with drug. SAE: AE resulting following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Any AE occurring at or after the initial drug administration up to 30 days after last dose in Study 54135419TRD4010 was considered to be treatment emergent. TEAEs included both serious and non-SAEs. AEs of special interest were grouped as categories sedation, dissociation, suicidality, suggestive of abuse potential, cystitis and hepatic impairment. Safety analysis set included was used.

End point type	Primary

End point timeframe:

From Day 1 of study 54135419TRD4010 up to 30 days after last dose of study drug at Week 104 (up to Week 108)

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No inferential statistics was done. Only descriptive statistics was performed.

End point values	Esketamine nasal spray + Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	183			
Units: AEs per 100 patient-months				
number (not applicable)				
Sedation	0.91			
Dissociation	0.61			
Suicidality	0.18			
Suggestive of abuse potential	2.63			
Cystitis	0.03			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Suicidal Ideation and Behavior in Study 54135419TRD4010 as Assessed by Columbia-suicide Severity Rating Scale (C-SSRS) Score

End point title	Number of Subjects with Suicidal Ideation and Behavior in Study 54135419TRD4010 as Assessed by Columbia-suicide Severity Rating Scale (C-SSRS) Score[9]

End point description:

C-SSRS score was defined as an assessment tool that evaluated suicidal ideation and behavior. Suicidal ideation (5 items): wish to be dead, non-specific active suicidal thoughts, active suicidal ideation with any methods (not plan) 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 (5 items): preparatory acts or behavior, aborted attempt, interrupted attempt, actual attempt (non-fatal), and suicide. The total score from 10 categories was summarized into 3 broad categories: No suicidal ideation or behavior (0), Suicidal ideation (1 to 5), Suicidal behavior (6 to 10). Total score ranged from 1 to 10. Higher scores indicated more severe suicidal ideation and behavior. Safety analysis set was analysed.

End point type	Primary

End point timeframe:

Baseline (Day 1 of Study 54135419TRD3013) up to Week 104 of Study 54135419TRD4010

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No inferential statistics was done. Only descriptive statistics was performed.

End point values	Esketamine nasal spray + Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	183			
Units: subjects				
No suicidal ideation or behavior	158			
Suicidal ideation	24			
Suicidal behavior	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with No Relapse and Without Discontinuation Until the end of the Prospective Observation Period at Week 104

End point title	Percentage of Subjects with No Relapse and Without Discontinuation Until the end of the Prospective Observation

	Period at Week 104

End point description:

Relapse was defined by any of the following: a) Worsening of depressive symptoms as indicated by Montgomery-Asberg Depression Rating Scale (MADRS) total score >=22 confirmed by 1 additional assessment of MADRS total score >=22 within the next 5 to 31 days. b) Any psychiatric hospitalization for: 1) worsening of depression, 2) suicide prevention or due to a suicide attempt for any of these events. c) Suicide attempt, completed suicide, or any other clinically relevant event determined per investigator's clinical judgment to be indicative of relapse of depressive illness, but for which subject was not hospitalized. MADRS scale consisted of 10 items, 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 0 to 60. Higher scores represented a more severe condition. Analysis population included subjects in Remission (MADRS total score of <=10.) at any time point during Study 54135419TRD3013.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of Study 54135419TRD3013) up to Week 104 of 54135419TRD4010

End point values	Esketamine nasal spray + Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	149			
Units: percentage of subjects				
number (not applicable)	79.2			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline of Study 54135419TRD3013 in Clinician-rated Montgomery-Asberg Depression Rating Scale (MADRS) Total Score

End point title	Change from Baseline of Study 54135419TRD3013 in Clinician-rated Montgomery-Asberg Depression Rating Scale (MADRS) Total Score

End point description:

Change from Baseline of Study 54135419TRD3013 in Clinician-rated MADRS total score were reported. MADRS was a clinician-rated scale designed to measure depression severity and to detect changes due to antidepressant treatment. The scale consists of 10 items , scored from 0 (item is not present or normal) to 6 (severe or continuous presence of symptoms), summed up for a total possible score range of 0 to 60. Higher scores represented a more severe condition. The MADRS evaluated reported sadness, apparent sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. Efficacy analysis set included all subjects who received at least 1 dose of esketamine anytime during the 54135419TRD4010 study. Here "N" (Number of subjects analysed) signifies subjects evaluable for this endpoint and "n" signifies subjects analysed at specified timepoints.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of Study 54135419TRD3013) up to weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, and 104 of study 54135419TRD4010

End point values	Esketamine nasal spray + Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	181			
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 4 (n=181)	-21.9 (± 8.10)			
Week 8 (n=177)	-21.8 (± 7.93)			
Week 12 (n=179)	-22.5 (± 7.25)			
Week 16 (n=175)	-22.8 (± 7.24)			
Week 20 n=176)	-22.3 (± 7.26)			
Week 24 (n=177)	-22.6 (± 6.82)			
Week 28 (n=173)	-22.4 (± 7.13)			
Week 32 (n=166)	-22.5 (± 7.16)			
Week 36 (n=163)	-22.5 (± 8.12)			
Week 40 (n=163)	-22.7 (± 7.03)			
Week 44 (n=159)	-22.9 (± 7.41)			
Week 48 (n=159)	-22.9 (± 7.19)			
Week 52 (n=151)	-22.6 (± 7.13)			
Week 56 (n=148)	-23.0 (± 6.88)			
Week 60 (n=152)	-23.1 (± 7.11)			
Week 64 (n=151)	-23.4 (± 7.52)			
Week 68 (n=148)	-23.2 (± 7.10)			
Week 72 (n=143)	-23.6 (± 6.98)			
Week 76 (n=138)	-23.8 (± 6.91)			
Week 80 (n=139)	-23.7 (± 7.19)			
Week 84 (n=137)	-23.6 (± 6.87)			
Week 88 (n=134)	-24.4 (± 6.78)			
Week 92 (n=136)	-24.3 (± 7.17)			
Week 96 (n=132)	-24.7 (± 6.57)			
Week 100 (n=130)	-24.9 (± 6.39)			
Week 104 (n=127)	-25.3 (± 6.69)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline of Study 54135419TRD3013 in Clinician-rated Montgomery-Asberg Depression Rating Scale (MADRS) Score Individual Items

End point title	Change from Baseline of Study 54135419TRD3013 in Clinician-rated Montgomery-Asberg Depression Rating Scale (MADRS) Score Individual Items

End point description:

Change from Baseline of Study 54135419TRD3013 in Clinician-rated MADRS Score Individual Items (apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, interest level, pessimistic thoughts, and suicidal thoughts) were reported. MADRS was 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. Efficacy analysis set included all subjects who received at

least 1 dose of esketamine anytime during the 54135419TRD4010 study. Here "N" (Number of subjects analysed) signifies subjects evaluable for this endpoint and "n" signifies subjects analysed at specified timepoints.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of Study 54135419TRD3013) up to weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, and 104 of study 54135419TRD4010

End point values	Esketamine nasal spray + Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	181			
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 4: Apparent Sadness (n=181)	-3.0 (± 1.38)			
Week 8: Apparent Sadness (n=177)	-3.0 (± 1.45)			
Week 12: Apparent Sadness (n=179)	-3.0 (± 1.34)			
Week 16: Apparent Sadness (n=175)	-3.1 (± 1.34)			
Week 20: Apparent Sadness (n=176)	-3.1 (± 1.31)			
Week 24: Apparent Sadness (n=177)	-2.9 (± 1.36)			
Week 28: Apparent Sadness (n=173)	-3.0 (± 1.33)			
Week 32: Apparent Sadness (n=166)	-3.0 (± 1.28)			
Week 36: Apparent Sadness (n=163)	-3.0 (± 1.42)			
Week 40: Apparent Sadness (n=163)	-3.0 (± 1.36)			
Week 44: Apparent Sadness (n=159)	-3.1 (± 1.38)			
Week 48: Apparent Sadness (n=159)	-3.1 (± 1.34)			
Week 52: Apparent Sadness (n=151)	-3.1 (± 1.32)			
Week 56: Apparent Sadness (n=148)	-3.1 (± 1.23)			
Week 60: Apparent Sadness (n=152)	-3.1 (± 1.24)			
Week 64: Apparent Sadness (n=151)	-3.2 (± 1.33)			
Week 68: Apparent Sadness (n=148)	-3.1 (± 1.23)			
Week 72: Apparent Sadness (n=143)	-3.2 (± 1.21)			
Week 76: Apparent Sadness (n=138)	-3.3 (± 1.22)			
Week 80: Apparent Sadness (n=139)	-3.3 (± 1.24)			
Week 84: Apparent Sadness (n=137)	-3.2 (± 1.15)			
Week 88: Apparent Sadness (n=134)	-3.4 (± 1.17)			
Week 92: Apparent Sadness (n=136)	-3.3 (± 1.20)			
Week 96: Apparent Sadness (n=132)	-3.3 (± 1.20)			
Week 100: Apparent Sadness (n=130)	-3.4 (± 1.13)			
Week 104: Apparent Sadness (n=127)	-3.5 (± 1.20)			
Week 4: Reported Sadness (n=181)	-3.1 (± 1.29)			
Week 8: Reported Sadness (n=177)	-3.0 (± 1.38)			
Week 12: Reported Sadness (n=179)	-3.0 (± 1.20)			
Week 16: Reported Sadness (n=175)	-3.1 (± 1.28)			
Week 20: Reported Sadness (n=176)	-3.1 (± 1.24)			
Week 24: Reported Sadness (n=177)	-3.1 (± 1.19)			
Week 28: Reported Sadness (n=173)	-3.0 (± 1.21)			
Week 32: Reported Sadness (n=166)	-3.1 (± 1.18)			

Week 36: Reported Sadness (n=163)	-3.0 (± 1.23)			
Week 40: Reported Sadness (n=163)	-3.2 (± 1.18)			
Week 44: Reported Sadness(n=159)	-3.1 (± 1.23)			
Week 48: Reported Sadness(n=159)	-3.1 (± 1.22)			
Week 52: Reported Sadness (n=151)	-3.1 (± 1.19)			
Week 56: Reported Sadness (n=148)	-3.2 (± 1.12)			
Week 60: Reported Sadness (n=152)	-3.3 (± 1.14)			
Week 64: Reported Sadness (n=151)	-3.3 (± 1.26)			
Week 68: Reported Sadness (n=148)	-3.2 (± 1.24)			
Week 72: Reported Sadness (n=143)	-3.2 (± 1.20)			
Week 76: Reported Sadness (n=138)	-3.3 (± 1.16)			
Week 80: Reported Sadness (n=139)	-3.3 (± 1.12)			
Week 84: Reported Sadness (n=137)	-3.3 (± 1.10)			
Week 88: Reported Sadness (n=134)	-3.3 (± 1.14)			
Week 92: Reported Sadness (n=136)	-3.3 (± 1.24)			
Week 96: Reported Sadness (n=132)	-3.4 (± 1.03)			
Week 100: Reported Sadness (n=130)	-3.4 (± 1.05)			
Week 104: Reported Sadness (n=127)	-3.5 (± 1.07)			
Week 4: Inner Tension (n=181)	-1.8 (± 1.19)			
Week 8: Inner Tension (n=177)	-1.8 (± 1.18)			
Week 12: Inner Tension (n=179)	-1.9 (± 1.20)			
Week 16: Inner Tension (n=175)	-1.9 (± 1.15)			
Week 20: Inner Tension (n=176)	-1.8 (± 1.19)			
Week 24: Inner Tension (n=177)	-1.9 (± 1.21)			
Week 28: Inner Tension (n=173)	-1.8 (± 1.23)			
Week 32: Inner Tension (n=166)	-1.9 (± 1.23)			
Week 36: Inner Tension (n=163)	-2.0 (± 1.07)			
Week 40: Inner Tension (n=163)	-1.8 (± 1.17)			
Week 44: Inner Tension (n=159)	-1.9 (± 1.20)			
Week 48: Inner Tension (n=159)	-2.0 (± 1.25)			
Week 52: Inner Tension (n=151)	-1.9 (± 1.16)			
Week 56: Inner Tension (n=148)	-2.0 (± 1.20)			
Week 60: Inner Tension (n=152)	-1.9 (± 1.32)			
Week 64: Inner Tension (n=151)	-2.0 (± 1.34)			
Week 68: Inner Tension (n=148)	-1.9 (± 1.26)			
Week 72: Inner Tension (n=143)	-2.0 (± 1.26)			
Week 76: Inner Tension (n=138)	-2.0 (± 1.22)			
Week 80: Inner Tension (n=139)	-2.1 (± 1.13)			
Week 84: Inner Tension (n=137)	-2.0 (± 1.28)			
Week 88: Inner Tension (n=134)	-2.0 (± 1.20)			
Week 92: Inner Tension (n=136)	-2.0 (± 1.16)			
Week 96: Inner Tension (n=132)	-2.0 (± 1.14)			
Week 100: Inner Tension (n=130)	-2.0 (± 1.18)			
Week 104: Inner Tension (n=127)	-2.1 (± 1.22)			
Week 4: Reduced Sleep (n=181)	-2.1 (± 1.72)			
Week 8: Reduced Sleep (n=177)	-2.2 (± 1.64)			
Week 12: Reduced Sleep (n=179)	-2.2 (± 1.63)			
Week 16: Reduced Sleep (n=175)	-2.2 (± 1.75)			
Week 20: Reduced Sleep (n=176)	-2.3 (± 1.72)			
Week 24: Reduced Sleep (n=177)	-2.2 (± 1.68)			
Week 28: Reduced Sleep (n=173)	-2.2 (± 1.72)			
Week 32: Reduced Sleep (n=166)	-2.3 (± 1.70)			

Week 36: Reduced Sleep (n=163)	-2.3 (± 1.81)			
Week 40: Reduced Sleep (n=163)	-2.3 (± 1.76)			
Week 44: Reduced Sleep (n=159)	-2.4 (± 1.61)			
Week 48: Reduced Sleep (n=159)	-2.3 (± 1.69)			
Week 52: Reduced Sleep (n=151)	-2.2 (± 1.64)			
Week 56: Reduced Sleep (n=148)	-2.2 (± 1.73)			
Week 60: Reduced Sleep (n=152)	-2.3 (± 1.62)			
Week 64: Reduced Sleep (n=151)	-2.2 (± 1.70)			
Week 68: Reduced Sleep (n=148)	-2.4 (± 1.82)			
Week 72: Reduced Sleep (n=143)	-2.3 (± 1.66)			
Week 76: Reduced Sleep (n=138)	-2.4 (± 1.67)			
Week 80: Reduced Sleep (n=139)	-2.3 (± 1.84)			
Week 84: Reduced Sleep (n=137)	-2.4 (± 1.73)			
Week 88: Reduced Sleep (n=134)	-2.5 (± 1.58)			
Week 92: Reduced Sleep (n=136)	-2.4 (± 1.70)			
Week 96: Reduced Sleep (n=132)	-2.5 (± 1.66)			
Week 100: Reduced Sleep (n=130)	-2.5 (± 1.66)			
Week 104: Reduced Sleep (n=127)	-2.6 (± 1.76)			
Week 4: Reduced Appetite (n=181)	-1.7 (± 1.78)			
Week 8: Reduced Appetite (n=177)	-1.7 (± 1.75)			
Week 12: Reduced Appetite (n=179)	-1.9 (± 1.68)			
Week 16: Reduced Appetite (n=175)	-2.0 (± 1.69)			
Week 20: Reduced Appetite (n=176)	-1.8 (± 1.74)			
Week 24: Reduced Appetite (n=177)	-1.9 (± 1.74)			
Week 28: Reduced Appetite (n=173)	-1.9 (± 1.74)			
Week 32: Reduced Appetite (n=166)	-1.9 (± 1.72)			
Week 36: Reduced Appetite (n=163)	-1.9 (± 1.81)			
Week 40: Reduced Appetite (n=163)	-1.9 (± 1.69)			
Week 44: Reduced Appetite (n=159)	-1.9 (± 1.81)			
Week 48: Reduced Appetite (n=159)	-1.9 (± 1.73)			
Week 52: Reduced Appetite (n=151)	-1.9 (± 1.78)			
Week 56: Reduced Appetite (n=148)	-1.9 (± 1.65)			
Week 60: Reduced Appetite (n=152)	-1.9 (± 1.68)			
Week 64: Reduced Appetite (n=151)	-2.0 (± 1.67)			
Week 68: Reduced Appetite (n=148)	-2.0 (± 1.69)			
Week 72: Reduced Appetite (n=143)	-2.0 (± 1.64)			
Week 76: Reduced Appetite (n=138)	-2.0 (± 1.62)			
Week 80: Reduced Appetite (n=139)	-1.9 (± 1.78)			
Week 84: Reduced Appetite (n=137)	-2.0 (± 1.70)			
Week 88: Reduced Appetite (n=134)	-2.0 (± 1.73)			
Week 92: Reduced Appetite (n=136)	-2.0 (± 1.67)			
Week 96: Reduced Appetite (n=132)	-2.1 (± 1.61)			
Week 100: Reduced Appetite (n=130)	-2.0 (± 1.69)			
Week 104: Reduced Appetite (n=127)	-2.1 (± 1.72)			
Week 4: Concentration Difficulties (n=181)	-2.2 (± 1.28)			
Week 8: Concentration Difficulties (n=177)	-2.3 (± 1.37)			
Week 12: Concentration Difficulties (n=179)	-2.3 (± 1.26)			
Week 16: Concentration Difficulties (n=175)	-2.3 (± 1.28)			

Week 20: Concentration Difficulties (n=176)	-2.2 (± 1.25)			
Week 24: Concentration Difficulties (n=177)	-2.3 (± 1.26)			
Week 28: Concentration Difficulties (n=173)	-2.2 (± 1.28)			
Week 32: Concentration Difficulties (n=166)	-2.2 (± 1.23)			
Week 36: Concentration Difficulties (n=163)	-2.3 (± 1.28)			
Week 40: Concentration Difficulties (n=163)	-2.3 (± 1.21)			
Week 44: Concentration Difficulties (n=159)	-2.3 (± 1.26)			
Week 48: Concentration Difficulties (n=159)	-2.4 (± 1.18)			
Week 52: Concentration Difficulties (n=151)	-2.4 (± 1.20)			
Week 56: Concentration Difficulties (n=148)	-2.4 (± 1.14)			
Week 60: Concentration Difficulties (n=152)	-2.3 (± 1.19)			
Week 64: Concentration Difficulties (n=151)	-2.4 (± 1.25)			
Week 68: Concentration Difficulties (n=148)	-2.4 (± 1.26)			
Week 72: Concentration Difficulties (n=143)	-2.4 (± 1.10)			
Week 76: Concentration Difficulties (n=138)	-2.5 (± 1.17)			
Week 80: Concentration Difficulties (n=139)	-2.4 (± 1.10)			
Week 84: Concentration Difficulties (n=137)	-2.4 (± 1.14)			
Week 88: Concentration Difficulties (n=134)	-2.6 (± 1.08)			
Week 92: Concentration Difficulties (n=136)	-2.6 (± 1.12)			
Week 96: Concentration Difficulties (n=132)	-2.5 (± 1.10)			
Week 100: Concentration Difficulties (n=130)	-2.6 (± 1.06)			
Week 104: Concentration Difficulties (n=127)	-2.6 (± 1.10)			
Week 4: Lassitude (n=181)	-2.5 (± 1.36)			
Week 8: Lassitude (n=177)	-2.4 (± 1.33)			
Week 12: Lassitude (n=179)	-2.5 (± 1.22)			
Week 16: Lassitude (n=175)	-2.5 (± 1.27)			
Week 20: Lassitude (n=176)	-2.6 (± 1.33)			
Week 24: Lassitude (n=177)	-2.6 (± 1.21)			
Week 28: Lassitude (n=173)	-2.6 (± 1.21)			
Week 32: Lassitude (n=166)	-2.5 (± 1.20)			
Week 36: Lassitude (n=163)	-2.6 (± 1.30)			
Week 40: Lassitude (n=163)	-2.5 (± 1.17)			
Week 44: Lassitude (n=159)	-2.6 (± 1.16)			
Week 48: Lassitude (n=159)	-2.6 (± 1.19)			
Week 52: Lassitude (n=151)	-2.6 (± 1.15)			
Week 56: Lassitude (n=148)	-2.6 (± 1.16)			
Week 60: Lassitude (n=152)	-2.6 (± 1.25)			

Week 64: Lassitude (n=151)	-2.6 (± 1.25)			
Week 68: Lassitude (n=148)	-2.6 (± 1.21)			
Week 72: Lassitude (n=143)	-2.7 (± 1.13)			
Week 76: Lassitude (n=138)	-2.6 (± 1.11)			
Week 80: Lassitude (n=139)	-2.8 (± 1.00)			
Week 84: Lassitude (n=137)	-2.6 (± 1.09)			
Week 88: Lassitude (n=134)	-2.8 (± 1.14)			
Week 92: Lassitude (n=136)	-2.7 (± 1.09)			
Week 96: Lassitude (n=132)	-2.8 (± 1.11)			
Week 100: Lassitude (n=130)	-2.9 (± 1.00)			
Week 104: Lassitude (n=127)	-2.9 (± 0.91)			
Week 4: Inability to Feel (n=181)	-2.7 (± 1.29)			
Week 8: Inability to Feel (n=177)	-2.6 (± 1.34)			
Week 12: Inability to Feel (n=179)	-2.7 (± 1.24)			
Week 16: Inability to Feel (n=175)	-2.8 (± 1.20)			
Week 20: Inability to Feel (n=176)	-2.6 (± 1.19)			
Week 24: Inability to Feel (n=177)	-2.8 (± 1.24)			
Week 28: Inability to Feel (n=173)	-2.7 (± 1.27)			
Week 32: Inability to Feel (n=166)	-2.8 (± 1.30)			
Week 36: Inability to Feel (n=163)	-2.8 (± 1.28)			
Week 40: Inability to Feel (n=163)	-2.8 (± 1.22)			
Week 44: Inability to Feel (n=159)	-2.8 (± 1.26)			
Week 48: Inability to Feel (n=159)	-2.7 (± 1.27)			
Week 52: Inability to Feel (n=151)	-2.7 (± 1.26)			
Week 56: Inability to Feel (n=148)	-2.8 (± 1.22)			
Week 60: Inability to Feel (n=152)	-2.9 (± 1.20)			
Week 64: Inability to Feel (n=151)	-2.9 (± 1.21)			
Week 68: Inability to Feel (n=148)	-2.8 (± 1.14)			
Week 72: Inability to Feel (n=143)	-2.8 (± 1.24)			
Week 76: Inability to Feel (n=138)	-2.8 (± 1.20)			
Week 80: Inability to Feel (n=139)	-2.9 (± 1.29)			
Week 84: Inability to Feel (n=137)	-2.9 (± 1.34)			
Week 88: Inability to Feel (n=134)	-2.9 (± 1.13)			
Week 92: Inability to Feel (n=136)	-3.0 (± 1.20)			
Week 96: Inability to Feel (n=132)	-3.0 (± 1.13)			
Week 100: Inability to Feel (n=130)	-3.0 (± 1.15)			
Week 104: Inability to Feel (n=127)	-3.0 (± 1.23)			
Week 4: Pessimistic Thoughts (n=181)	-2.0 (± 1.25)			
Week 8: Pessimistic Thoughts (n=177)	-2.0 (± 1.24)			
Week 12: Pessimistic Thoughts (n=179)	-2.1 (± 1.26)			
Week 16: Pessimistic Thoughts (n=175)	-2.1 (± 1.26)			
Week 20: Pessimistic Thoughts (n=176)	-2.0 (± 1.25)			
Week 24: Pessimistic Thoughts (n=177)	-2.1 (± 1.24)			
Week 28: Pessimistic Thoughts (n=173)	-2.1 (± 1.20)			
Week 32: Pessimistic Thoughts (n=166)	-2.1 (± 1.23)			
Week 36: Pessimistic Thoughts (n=163)	-2.0 (± 1.33)			
Week 40: Pessimistic Thoughts (n=163)	-2.1 (± 1.27)			
Week 44: Pessimistic Thoughts (n=159)	-2.1 (± 1.23)			
Week 48: Pessimistic Thoughts (n=159)	-2.1 (± 1.24)			
Week 52: Pessimistic Thoughts (n=151)	-2.0 (± 1.22)			
Week 56: Pessimistic Thoughts (n=148)	-2.0 (± 1.25)			
Week 60: Pessimistic Thoughts (n=152)	-2.1 (± 1.27)			

Week 64: Pessimistic Thoughts (n=151)	-2.1 (± 1.26)			
Week 68: Pessimistic Thoughts (n=148)	-2.1 (± 1.21)			
Week 72: Pessimistic Thoughts (n=143)	-2.1 (± 1.17)			
Week 76: Pessimistic Thoughts (n=138)	-2.1 (± 1.16)			
Week 80: Pessimistic Thoughts (n=139)	-2.1 (± 1.23)			
Week 84: Pessimistic Thoughts (n=137)	-2.1 (± 1.20)			
Week 88: Pessimistic Thoughts (n=134)	-2.1 (± 1.18)			
Week 92: Pessimistic Thoughts (n=136)	-2.1 (± 1.21)			
Week 96: Pessimistic Thoughts (n=132)	-2.2 (± 1.16)			
Week 100: Pessimistic Thoughts (n=130)	-2.2 (± 1.22)			
Week 104: Pessimistic Thoughts (n=127)	-2.2 (± 1.18)			
Week 4: Suicidal Thoughts (n=181)	-0.8 (± 1.05)			
Week 8: Suicidal Thoughts (n=177)	-0.7 (± 0.97)			
Week 12: Suicidal Thoughts (n=179)	-0.8 (± 1.05)			
Week 16: Suicidal Thoughts (n=175)	-0.8 (± 1.04)			
Week 20: Suicidal Thoughts (n=176)	-0.8 (± 1.01)			
Week 24: Suicidal Thoughts (n=177)	-0.8 (± 1.06)			
Week 28: Suicidal Thoughts (n=173)	-0.8 (± 1.02)			
Week 32: Suicidal Thoughts (n=166)	-0.8 (± 1.01)			
Week 36: Suicidal Thoughts (n=163)	-0.7 (± 1.13)			
Week 40: Suicidal Thoughts (n=163)	-0.8 (± 0.97)			
Week 44: Suicidal Thoughts (n=159)	-0.7 (± 0.91)			
Week 48: Suicidal Thoughts (n=159)	-0.8 (± 0.98)			
Week 52: Suicidal Thoughts (n=151)	-0.8 (± 0.98)			
Week 56: Suicidal Thoughts (n=148)	-0.8 (± 0.99)			
Week 60: Suicidal Thoughts (n=152)	-0.8 (± 0.97)			
Week 64: Suicidal Thoughts (n=151)	-0.8 (± 0.98)			
Week 68: Suicidal Thoughts (n=148)	-0.8 (± 0.98)			
Week 72: Suicidal Thoughts (n=143)	-0.8 (± 1.01)			
Week 76: Suicidal Thoughts (n=138)	-0.8 (± 1.01)			
Week 80: Suicidal Thoughts (n=139)	-0.8 (± 1.03)			
Week 84: Suicidal Thoughts (n=137)	-0.8 (± 0.97)			
Week 88: Suicidal Thoughts (n=134)	-0.8 (± 0.98)			
Week 92: Suicidal Thoughts (n=136)	-0.8 (± 0.97)			
Week 96: Suicidal Thoughts (n=132)	-0.8 (± 1.04)			
Week 100: Suicidal Thoughts (n=130)	-0.8 (± 1.03)			
Week 104: Suicidal Thoughts (n=127)	-0.8 (± 1.01)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline of Study 54135419TRD3013 in Clinical Global Impression -severity (CGI-S) Scale Score

End point title	Change from Baseline of Study 54135419TRD3013 in Clinical Global Impression -severity (CGI-S) Scale Score

End point description:

Change from Baseline of Study 54135419TRD3013 in CGI-S scale score were reported. The CGI-S provided an overall clinician-determined summary measure of the severity of the subject's illness that

took into account all available information, including knowledge of the subject's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the subject's ability to function. The CGI-S evaluated the severity of psychopathology on a scale of 1 to 7: where, 1 = normal (not 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 indicated improvement. Subjects with a score of zero were considered missing. Efficacy analysis set were used. Here "N" (Number of subjects analysed) signifies subjects evaluable for this endpoint and "n" signifies subjects analysed at specified timepoints.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of Study 54135419TRD3013) up to weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, and 104 of study 54135419TRD4010

End point values	Esketamine nasal spray + Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	181			
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 4 (n=181)	-2.5 (± 1.00)			
Week 8 (n=177)	-2.6 (± 1.02)			
Week 12 (n=179)	-2.6 (± 0.99)			
Week 16 (n=175)	-2.6 (± 0.96)			
Week 20 n=176)	-2.6 (± 0.96)			
Week 24 (n=174)	-2.7 (± 0.96)			
Week 28 (n=172)	-2.8 (± 0.96)			
Week 32 (n=166)	-2.7 (± 1.01)			
Week 36 (n=162)	-2.7 (± 0.99)			
Week 40 (n=162)	-2.9 (± 0.99)			
Week 44 (n=159)	-2.9 (± 0.98)			
Week 48 (n=158)	-2.9 (± 0.96)			
Week 52 (n=151)	-2.8 (± 1.00)			
Week 56 (n=148)	-2.9 (± 0.93)			
Week 60 (n=152)	-2.9 (± 0.96)			
Week 64 (n=150)	-2.9 (± 0.99)			
Week 68 (n=146)	-2.9 (± 0.93)			
Week 72 (n=142)	-2.9 (± 0.93)			
Week 76 (n=138)	-2.9 (± 0.93)			
Week 80 (n=139)	-2.9 (± 0.91)			
Week 84 (n=137)	-3.0 (± 0.86)			
Week 88 (n=133)	-3.0 (± 0.88)			
Week 92 (n=135)	-3.0 (± 0.88)			
Week 96 (n=132)	-3.1 (± 0.88)			
Week 100 (n=130)	-3.1 (± 0.87)			
Week 104 (n=123)	-3.1 (± 0.85)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline of Study 54135419TRD3013 in Patient Health Questionnaire (PHQ) 9-item Total Score

End point title	Change from Baseline of Study 54135419TRD3013 in Patient Health Questionnaire (PHQ) 9-item Total Score

End point description:

Change from Baseline of Study 54135419TRD3013 in PHQ 9-item total score were reported. The PHQ-9 was a validated 9-item, patient-reported outcome (PRO) measure to assess depressive symptoms. Each item was 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 were summed to a total score with a range of 0 to 27. Higher scores indicated greater severity of depressive symptoms. Efficacy analysis set was used. Here "N" (Number of subjects analysed) signifies subjects evaluable for this endpoint and "n" signifies subjects analysed at specified timepoints.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of Study 54135419TRD3013) up to weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, and 104 of study 54135419TRD4010

End point values	Esketamine nasal spray + Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	178			
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 4 (n=178)	-11.0 (± 5.80)			
Week 8 (n=174)	-10.9 (± 5.98)			
Week 12 (n=175)	-10.9 (± 5.73)			
Week 16 (n=173)	-11.2 (± 5.53)			
Week 20 n=171)	-11.3 (± 5.46)			
Week 24 (n=173)	-11.3 (± 5.19)			
Week 28 (n=172)	-11.5 (± 5.25)			
Week 32 (n=161)	-11.3 (± 5.71)			
Week 36 (n=158)	-11.6 (± 6.06)			
Week 40 (n=159)	-11.5 (± 5.55)			
Week 44 (n=155)	-11.9 (± 5.67)			
Week 48 (n=156)	-11.9 (± 5.61)			
Week 52 (n=149)	-11.4 (± 5.55)			
Week 56 (n=145)	-12.0 (± 5.19)			
Week 60 (n=150)	-11.9 (± 5.24)			
Week 64 (n=148)	-11.9 (± 5.18)			
Week 68 (n=145)	-11.9 (± 5.60)			
Week 72 (n=139)	-12.1 (± 5.00)			
Week 76 (n=135)	-12.2 (± 5.12)			
Week 80 (n=134)	-12.1 (± 5.28)			
Week 84 (n=134)	-11.9 (± 5.19)			
Week 88 (n=129)	-12.2 (± 5.21)			
Week 92 (n=133)	-12.5 (± 5.11)			

Week 96 (n=129)	-12.2 (± 5.10)			
Week 100 (n=127)	-12.7 (± 4.78)			
Week 104 (n=125)	-12.7 (± 4.97)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline of Study 54135419TRD3013 in European Quality of Life (EuroQol) 5 Dimension 5-Level (EQ-5D-5L): Health status index

End point title	Change from Baseline of Study 54135419TRD3013 in European Quality of Life (EuroQol) 5 Dimension 5-Level (EQ-5D-5L): Health status index

End point description:

Change from baseline of Study 54135419TRD3013 in EQ-5D-5LQuestionnaire Score: health status index was reported. The EQ-5D-5L descriptive system comprised the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each of the 5 dimensions were 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). The subject selected an answer for each of the 5 dimensions considering a response that best matched subject's health "today." Responses were used to generate health status index ranged from 0.148 to 0.949, anchored at 0 (dead) and 1 (full health). Positive change in score indicated improvement. Efficacy analysis set was used. Here "N" (Number of subjects analysed) signifies subjects evaluable for this endpoint and "n" signifies subjects analysed at specified timepoints.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of Study 54135419TRD3013) up to weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, and 104 of study 54135419TRD4010

End point values	Esketamine nasal spray + Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	178			
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 4 (n=177)	0.323 (± 0.2479)			
Week 8 (n=173)	0.320 (± 0.2518)			
Week 12 (n=178)	0.325 (± 0.2379)			
Week 16 (n=172)	0.322 (± 0.2568)			
Week 20 n=175)	0.336 (± 0.2444)			
Week 24 (n=175)	0.331 (± 0.2337)			
Week 28 (n=171)	0.323 (± 0.2415)			
Week 32 (n=163)	0.335 (± 0.2377)			

Week 36 (n=160)	0.341 (± 0.2512)			
Week 40 (n=161)	0.333 (± 0.2364)			
Week 44 (n=157)	0.343 (± 0.2576)			
Week 48 (n=158)	0.345 (± 0.2317)			
Week 52 (n=150)	0.332 (± 0.2374)			
Week 56 (n=146)	0.348 (± 0.2348)			
Week 60 (n=150)	0.364 (± 0.2322)			
Week 64 (n=150)	0.350 (± 0.2422)			
Week 68 (n=146)	0.337 (± 0.2546)			
Week 72 (n=142)	0.354 (± 0.2295)			
Week 76 (n=135)	0.357 (± 0.2440)			
Week 80 (n=138)	0.362 (± 0.2375)			
Week 84 (n=134)	0.350 (± 0.2295)			
Week 88 (n=133)	0.366 (± 0.2385)			
Week 92 (n=134)	0.367 (± 0.2275)			
Week 96 (n=130)	0.375 (± 0.2333)			
Week 100 (n=129)	0.387 (± 0.2321)			
Week 104 (n=125)	0.387 (± 0.2444)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline of Study 54135419TRD3013 in European Quality of Life (EuroQol) 5 Dimension 5-Level (EQ-5D-5L): Visual Analogue Scale (VAS)

End point title	Change from Baseline of Study 54135419TRD3013 in European Quality of Life (EuroQol) 5 Dimension 5-Level (EQ-5D-5L): Visual Analogue Scale (VAS)

End point description:

Change from baseline of Study 54135419TRD3013 in EQ-5D-5L: visual analogue scale were reported. EQ-VAS self-rating recorded the subject's own assessment of his/her overall health status at time of completion, on a scale of 0 (worst health you can imagine) to 100 (best health you can imagine). Positive change in score indicated improvement. Efficacy analysis set included all subjects who received at least 1 dose of esketamine anytime during the 54135419TRD4010 study. Here "N" (Number of subjects analysed) signifies subjects evaluable for this endpoint and "n" signifies subjects analysed at specified timepoints.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of Study 54135419TRD3013) up to weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, and 104 of study 54135419TRD4010

End point values	Esketamine nasal spray + Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	175			
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 4 (n=174)	27.35 (± 20.595)			
Week 8 (n=174)	26.24 (± 21.939)			
Week 12 (n=175)	26.74 (± 20.884)			
Week 16 (n=173)	27.98 (± 20.523)			
Week 20 n=174)	27.85 (± 20.143)			
Week 24 (n=174)	28.83 (± 20.438)			
Week 28 (n=172)	28.23 (± 21.006)			
Week 32 (n=162)	28.30 (± 21.119)			
Week 36 (n=159)	29.99 (± 19.901)			
Week 40 (n=160)	28.56 (± 21.210)			
Week 44 (n=156)	29.19 (± 21.259)			
Week 48 (n=156)	29.57 (± 21.717)			
Week 52 (n=149)	29.60 (± 21.419)			
Week 56 (n=145)	29.90 (± 20.828)			
Week 60 (n=150)	30.47 (± 20.423)			
Week 64 (n=149)	30.49 (± 20.352)			
Week 68 (n=146)	29.82 (± 20.195)			
Week 72 (n=141)	30.84 (± 20.252)			
Week 76 (n=134)	31.90 (± 19.866)			
Week 80 (n=137)	31.23 (± 20.512)			
Week 84 (n=133)	30.40 (± 19.697)			
Week 88 (n=132)	31.10 (± 20.469)			
Week 92 (n=133)	31.87 (± 20.228)			
Week 96 (n=130)	30.75 (± 19.759)			

Week 100 (n=128) Week 104 (n=125)	31.66 (± 18.887) 33.75 (± 19.356)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 1 of study 54135419TRD4010 up to 30 days after last dose of study drug at Week 104 (up to Week 108)

Adverse event reporting additional description:

Safety analysis set included all subjects who received at least 1 dose of esketamine anytime during the 54135419TRD4010 study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups

Reporting group title	Esketamine + Oral AD

Reporting group description:

Subjects (who received esketamine nasal spray in study 54135419TRD3013 through Week 30 [every 2 weeks] or Week 31 [once weekly],and completed the maintenance phase at Week 32) received flexible dose of esketamine nasal spray 28 milligrams (mg) (1 spray per nostril at 0 minute), 56 mg (1 spray per nostril at 0 and 5 minutes) or 84 mg (1 spray per nostril at 0, 5 and 105 minutes) once weekly or every 2 weeks from Day 1 (Week 32 visit of Study 54135419TRD3013 until week 104 along with oral AD, serotonin-norepinephrine reuptake inhibitor/selective serotonin reuptake inhibitor (SSRI/SNRI) in this long-term extension (LTE) study. Time 0 minute signified time of first esketamine nasal spray administration to 1 nostril. Esketamine nasal devices contained a total of 28 mg esketamine per device (2 sprays). Only one device was used at a timepoint.

Serious adverse events	Esketamine + Oral AD		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 183 (6.01%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Brain Neoplasm			
subjects affected / exposed	1 / 183 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Invasive Ductal Breast Carcinoma			
subjects affected / exposed	1 / 183 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Alcohol Poisoning			

subjects affected / exposed	1 / 183 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Multiple Injuries			
subjects affected / exposed	1 / 183 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac disorders			
Acute Coronary Syndrome			
subjects affected / exposed	1 / 183 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Psychomotor Hyperactivity			
subjects affected / exposed	1 / 183 (0.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Macular Hole			
subjects affected / exposed	1 / 183 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Suicidal Ideation			
subjects affected / exposed	1 / 183 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	1 / 183 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Goitre			

subjects affected / exposed	1 / 183 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	1 / 183 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Esketamine + Oral AD		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	145 / 183 (79.23%)		
Investigations			
Blood Pressure Increased			
subjects affected / exposed	13 / 183 (7.10%)		
occurrences (all)	64		
Nervous system disorders			
Dizziness			
subjects affected / exposed	50 / 183 (27.32%)		
occurrences (all)	1268		
Dysgeusia			
subjects affected / exposed	14 / 183 (7.65%)		
occurrences (all)	523		
Headache			
subjects affected / exposed	81 / 183 (44.26%)		
occurrences (all)	285		
Paraesthesia			
subjects affected / exposed	13 / 183 (7.10%)		
occurrences (all)	305		
Somnolence			
subjects affected / exposed	24 / 183 (13.11%)		
occurrences (all)	752		
Ear and labyrinth disorders			

Vertigo subjects affected / exposed occurrences (all)	32 / 183 (17.49%) 470		
Eye disorders Lacrimation Increased subjects affected / exposed occurrences (all)	10 / 183 (5.46%) 15		
Gastrointestinal disorders Abdominal Pain subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	15 / 183 (8.20%) 20 15 / 183 (8.20%) 22 37 / 183 (20.22%) 128 12 / 183 (6.56%) 18		
Respiratory, thoracic and mediastinal disorders Oropharyngeal Pain subjects affected / exposed occurrences (all) Rhinorrhoea subjects affected / exposed occurrences (all) Rhinalgia subjects affected / exposed occurrences (all) Sneezing subjects affected / exposed occurrences (all)	10 / 183 (5.46%) 11 13 / 183 (7.10%) 26 13 / 183 (7.10%) 18 14 / 183 (7.65%) 26		
Psychiatric disorders Dissociation			

subjects affected / exposed	19 / 183 (10.38%)		
occurrences (all)	515		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	11 / 183 (6.01%)		
occurrences (all)	14		
Back Pain			
subjects affected / exposed	20 / 183 (10.93%)		
occurrences (all)	28		
Infections and infestations			
Covid-19			
subjects affected / exposed	30 / 183 (16.39%)		
occurrences (all)	34		
Nasopharyngitis			
subjects affected / exposed	37 / 183 (20.22%)		
occurrences (all)	60		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 September 2022	The purpose of the amendment was to indicate that the bicarbonate assay (one of the protocol required clinical laboratory safety tests) was optional, to reduce patient burden. In addition, the window during which the additional assessment of MADRS total score were evaluated to confirm relapse was widened (from '14 to 28 days' to '5 to 31 days') to allow greater patient flexibility with undertaking this additional assessment and to align with the parent study (54135419TRD3013) and a previous relapse prevention study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported