Clinical trial results:
An Open-label Long-term Extension Safety Study of Esketamine Nasal Spray in Treatment-resistant Depression

Summary

EudraCT number	2015-003578-34
Trial protocol	DE GB BE ES PL HU CZ SK LT AT FI BG IT
Global end of trial date	30 December 2022

Results information

Result version number	v1 (current)
This version publication date	14 January 2024
First version publication date	14 January 2024

Trial information

Trial identification

Sponsor protocol code	54135419TRD3008

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02782104
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Research & Development, LLC
Sponsor organisation address	920 Route 202 South, Raritan, New Jersey, United States, 08869
Public contact	Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 December 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 December 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to assess the long term safety and tolerability of esketamine nasal spray in subjects with treatment-resistant depression (TRD).

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 Practice and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 June 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Türkiye: 24
Country: Number of subjects enrolled	Taiwan: 22
Country: Number of subjects enrolled	United States: 328
Country: Number of subjects enrolled	South Africa: 48
Country: Number of subjects enrolled	Argentina: 71
Country: Number of subjects enrolled	Australia: 16
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Belgium: 18
Country: Number of subjects enrolled	Bulgaria: 50
Country: Number of subjects enrolled	Brazil: 100
Country: Number of subjects enrolled	Canada: 15
Country: Number of subjects enrolled	Czechia: 90
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Spain: 41
Country: Number of subjects enrolled	Estonia: 9
Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	France: 23
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Hungary: 20
Country: Number of subjects enrolled	Italy: 8

Country: Number of subjects enrolled	Korea, Republic of: 7
Country: Number of subjects enrolled	Lithuania: 2
Country: Number of subjects enrolled	Mexico: 46
Country: Number of subjects enrolled	Malaysia: 9
Country: Number of subjects enrolled	Poland: 101
Country: Number of subjects enrolled	Slovakia: 9
Country: Number of subjects enrolled	Sweden: 65
Worldwide total number of subjects	1148
EEA total number of subjects	454

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)	1026
From 65 to 84 years	122
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 1148 subjects were enrolled in the study out of which 458 subjects entered in the induction (IND) phase and 1110 subjects entered in the optimization/maintenance (OP/MA) phase. Of the 458 subjects who participated in the IND phase, 420 subjects continued to the OP/MA phase.

Period 1

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

Arms

Arm title	Esketamine Nasal Spray

Arm description:

Subjects who entered the induction phase (IND) from studies ESKETINTRD3001, ESKETINTRD3002, ESKETINTRD3003, ESKETINTRD3004, or ESKETINTRD3006 received esketamine nasal spray twice per week on Day 1 for 4 weeks as a flexible dose regimen (56 milligrams [mg] or 84 mg for subjects less than [<]65 years; 28 mg, 56mg or 84mg for subjects greater than or equal to [>=]65 years). Subjects who entered the optimization and maintenance (OP/MA) phase from the IND phase of study 54135419TRD3008, continued on the same dose of esketamine from the IND phase, weekly. Subjects who entered from studies ESKETINTRD3001, ESKETINTRD3002, ESKETINTRD3003, ESKETINTRD3004, or 54135419TRD3006 were administered esketamine nasal spray, 56mg or 84mg, once weekly. Subjects who entered study ESKETINTRD3005 received esketamine nasal spray (28mg in Week 1; 28 or 56mg in Week 2; and 28, 56 or 84mg in Weeks 3 and 4) once weekly.

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:

Induction Phase: Esketamine was self-administered twice per week for 4 weeks as a flexible dose regimen (56 mg or 84 mg for subjects < 65 years; 28 mg, 56 mg or 84 mg for subjects >= 65 years). OP/MA Phase: Esketamine was self-administered weekly, every 2 weeks or every 4 weeks (28 mg in Week 1; 28 or 56 mg in Week 2; and 28, 56 or 84 mg in Weeks 3 and 4).

Number of subjects in period 1	Esketamine Nasal Spray
Started	1148
IND Phase	458 [1]
OP/MA Phase	1110
Completed	680
Not completed	468
Adverse event, serious fatal	9
Consent withdrawn by subject	63

Adverse event, non-fatal	73
Other	215
Pregnancy	6
Non-compliance with study drug	2
Lost to follow-up	23
Induction day 28 non-responder	9
Lack of efficacy	61
Protocol deviation	7

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 included in IND phase.

Baseline characteristics

Reporting groups	
Reporting group title	Esketamine Nasal Spray

Reporting group description:

Subjects who entered the induction phase (IND) from studies ESKETINTRD3001, ESKETINTRD3002, ESKETINTRD3003, ESKETINTRD3004, or ESKETINTRD3006 received esketamine nasal spray twice per week on Day 1 for 4 weeks as a flexible dose regimen (56 milligrams [mg] or 84 mg for subjects less than [<]65 years; 28 mg, 56mg or 84mg for subjects greater than or equal to [>=]65 years). Subjects who entered the optimization and maintenance (OP/MA) phase from the IND phase of study 54135419TRD3008, continued on the same dose of esketamine from the IND phase, weekly. Subjects who entered from studies ESKETINTRD3001, ESKETINTRD3002, ESKETINTRD3003, ESKETINTRD3004, or 54135419TRD3006 were administered esketamine nasal spray, 56mg or 84mg, once weekly. Subjects who entered study ESKETINTRD3005 received esketamine nasal spray (28mg in Week 1; 28 or 56mg in Week 2; and 28, 56 or 84mg in Weeks 3 and 4) once weekly.

Reporting group values	Esketamine Nasal Spray	Total	
Number of subjects	1148	1148	
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	1026	1026	
From 65 to 84 years	122	122	
85 years and over	0	0	
Title for AgeContinuous Units: years			
arithmetic mean	49.6		
standard deviation	± 12.28	-	
Title for Gender Units: subjects			
Female	764	764	
Male	384	384	

End points

End points reporting groups

Reporting group title	Esketamine Nasal Spray

Reporting group description:

Subjects who entered the induction phase (IND) from studies ESKETINTRD3001, ESKETINTRD3002, ESKETINTRD3003, ESKETINTRD3004, or ESKETINTRD3006 received esketamine nasal spray twice per week on Day 1 for 4 weeks as a flexible dose regimen (56 milligrams [mg] or 84 mg for subjects less than [<]65 years; 28 mg, 56mg or 84mg for subjects greater than or equal to [>=]65 years). Subjects who entered the optimization and maintenance (OP/MA) phase from the IND phase of study 54135419TRD3008, continued on the same dose of esketamine from the IND phase, weekly. Subjects who entered from studies ESKETINTRD3001, ESKETINTRD3002, ESKETINTRD3003, ESKETINTRD3004, or 54135419TRD3006 were administered esketamine nasal spray, 56mg or 84mg, once weekly. Subjects who entered study ESKETINTRD3005 received esketamine nasal spray (28mg in Week 1; 28 or 56mg in Week 2; and 28, 56 or 84mg in Weeks 3 and 4) once weekly.

Subject analysis set title	Esketamine Nasal Spray (IND Phase)
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects who entered induction phase (IND) from studies ESKETINTRD3001, ESKETINTRD3002, ESKETINTRD3003, ESKETINTRD3004, or ESKETINTRD3006 received esketamine nasal spray twice per week on Day 1 for 4 weeks as a flexible dose regimen (56 milligrams [mg] or 84 mg for subjects less than [<] 65 years; 28 mg, 56 mg or 84 mg for subjects greater than or equal to [>=] 65 years).

Subject analysis set title	Esketamine Nasal Spray (OP/MA Phase)
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects who entered the OP/MA phase from the IND phase of study 54135419TRD3008, continued on the same dose of esketamine from the IND phase, weekly. Subjects who entered from studies ESKETINTRD3001, ESKETINTRD3002, ESKETINTRD3003, ESKETINTRD3004, or ESKETINTRD3006 were administered esketamine nasal spray, 56 mg or 84 mg, once weekly. Subjects who entered study ESKETINTRD3005 were received esketamine nasal spray (28 mg in Week 1; 28 or 56 mg in Week 2; and 28, 56 or 84 mg in Weeks 3 and 4) once weekly in optimisation and maintenance phase (OP/MP). After Week 4 (starting at Week 5), based on the Investigator's clinical judgment, the dose of esketamine for all subjects was adjusted based upon efficacy and tolerability.

Primary: Change From Study Baseline in Computerized Cognitive Battery Domain Score: Detection Test (DET) Score

End point title	Change From Study Baseline in Computerized Cognitive Battery Domain Score: Detection Test (DET) Score[1]

End point description:

This battery is a series of computerized cognition tests (detection, identification, one card learning, one back and groton maze learning) designed to measure reaction time, visual learning and memory, and executive function/sequencing. The DET is a measure of psychomotor function and uses a well-validated simple reaction time. In this outcome measure, speed of performance of subjects (calculated as mean of the logarithmic base 10 transformed reaction times) for correct responses was reported. Total score ranged from 2 to 3.3 log 10 milliseconds (msec). Lower score indicated better performance. Higher change from baseline indicated better performance. All enrolled analysis set included all subjects who were eligible to enter this study and received at least 1 dose of intranasal study medication. Here, 'N' (number analysed) signifies number of subjects analysed for this endpoint.

End point type	Primary

End point timeframe:

IND Phase: Baseline up to 4 weeks; OP/MA Phase: Baseline up to 78 months

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: Descriptive statistics was done, no inferential statistical analysis was performed.

End point values	Esketamine Nasal Spray (IND Phase)	Esketamine Nasal Spray (OP/MA Phase)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	420	1085		
Units: log10 msec				
arithmetic mean (standard deviation)	0.0218 (± 0.10516)	-0.0065 (± 0.13526)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Study Baseline in Computerized Cognitive Battery Domain Score: Identification Test (IDN) Score

End point title	Change From Study Baseline in Computerized Cognitive Battery Domain Score: Identification Test (IDN) Score[2]

End point description:

This battery is a series of computerized cognition tests (detection, identification, one card learning, one back and groton maze learning) designed to measure reaction time, visual learning and memory, and executive function/sequencing. IDN test is a measure of visual attention (choice reaction time) and scored for speed of response (mean of the log10 transformed reaction times for correct responses). Total score ranged from 2 to 3.3 log 10 msec. Lower score indicated better performance. Higher change from baseline indicated better performance. All enrolled analysis set included all subjects who were eligible to enter this study and received at least 1 dose of intranasal study medication. Here, 'N' (number analysed) signifies number of subjects analysed for this endpoint.

End point type	Primary

End point timeframe:

IND Phase: Baseline up to 4 weeks; OP/MA Phase: Baseline up to 78 months

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: Descriptive statistics was done, no inferential statistical analysis was performed.

End point values	Esketamine Nasal Spray (IND Phase)	Esketamine Nasal Spray (OP/MA Phase)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	422	1084		
Units: log10 msec				
arithmetic mean (standard deviation)	0.0074 (± 0.07819)	-0.0185 (± 0.09893)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Study Baseline in Computerized Cognitive Battery Domain Score: One Back Test (ONB) Score

End point title	Change From Study Baseline in Computerized Cognitive Battery Domain Score: One Back Test (ONB) Score[3]

End point description:

The ONB is a measure of working memory and scored for speed of correct response (mean of the log10-transformed reaction times for correct responses). Total score ranges from 2 to 3.54 log10 msec. Lower score indicated better performance. Higher change from baseline indicated better performance. All enrolled analysis set included all subjects who were eligible to enter this study and received at least 1 dose of intranasal study medication. Here, 'N' (number analysed) signifies number of subjects analysed for this endpoint.

End point type	Primary

End point timeframe:

IND Phase: Baseline up to 4 weeks; OP/MA Phase: Baseline up to 78 months

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: Descriptive statistics was done, no inferential statistical analysis was performed.

End point values	Esketamine Nasal Spray (IND Phase)	Esketamine Nasal Spray (OP/MA Phase)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	429	1084		
Units: log10 msec				
arithmetic mean (standard deviation)	0.0086 (± 0.08096)	0.0198 (± 0.10329)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Study Baseline in Computerized Cognitive Battery Domain Score: One Card Learning Test (OCL) Score

End point title	Change From Study Baseline in Computerized Cognitive Battery Domain Score: One Card Learning Test (OCL) Score[4]

End point description:

This battery is a series of computerized cognition tests (detection, identification, one card learning, one back and groton maze learning) designed to measure reaction time, visual learning and memory, and executive function/sequencing. OCL test is a measure of visual episodic memory and visual recall test scored using arcsine transformation of the percentage of correct responses (CR). The range for OCL is 0 to 100 percent (%) accuracy; presented as an arcsin transformation, the range is 0 to 1.57. Higher score indicated better performance. Higher change from baseline indicated better performance. All enrolled analysis set included all subjects who were eligible to enter this study and received at least 1 dose of intranasal study medication. Here, 'N' (number analysed) signifies number of subjects analysed for this endpoint.

End point type	Primary

End point timeframe:

IND Phase: Baseline up to 4 weeks; OP/MA Phase: Baseline up to 78 months

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: Descriptive statistics was done, no inferential statistical analysis was performed.

End point values	Esketamine Nasal Spray (IND Phase)	Esketamine Nasal Spray (OP/MA Phase)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	429	1084		
Units: Arcsine (sqrt of percentage of [CR])				
arithmetic mean (standard deviation)	0.0170 (± 0.12356)	0.0397 (± 0.15364)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Study Baseline in Hopkins Verbal Learning Test-Revised (HVLT-R) Score

End point title	Change From Study Baseline in Hopkins Verbal Learning Test-Revised (HVLT-R) Score[5]

End point description:

The HVLT-R measures performance in verbal memory, learning, and long-term recall in which a list of words is read up to three times. Approximately 20-25 minutes later, a delayed recall trial and a recognition trial are completed. Delayed recall: free recall of any words remembered. The recognition trial: 24 words, including the 12 target words and 12 false-positives. When scoring the HVLT, the 3 learning trials are combined to calculate a total recall score (0-36); the delayed recall trial creates the delayed recall score (0-12); the total number of true-positive errors (0-12); and the range of recognition discrimination index is comprised by subtracting the total number of false positives from the total number of true positives. A higher score indicated higher cognition. All enrolled analysis set: who were eligible to enter this study and received at least 1 dose of intranasal study medication. Here, 'N' (number analysed) signifies number of subjects analysed for this endpoint.

End point type	Primary

End point timeframe:

IND Phase: Baseline up to 4 weeks; OP/MA Phase: Baseline up to 78 months

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: Descriptive statistics was done, no inferential statistical analysis was performed.

End point values	Esketamine Nasal Spray (IND Phase)	Esketamine Nasal Spray (OP/MA Phase)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	444	1091		
Units: score on a scale				
arithmetic mean (standard deviation)				
Total Recall (n=444,1091)	-0.1 (± 4.05)	0.8 (± 5.05)		
Delayed Recall (n=439,1091)	0.3 (± 3.81)	0.3 (± 2.03)		
Total Number of True Positives (n=443,1091)	0.1 (± 2.54)	-0.0 (± 2.70)		
Recognition Discrimination Index (n=443,1091)	-0.1 (± 2.88)	-0.1 (± 3.10)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Study Baseline in Computerized Cognitive Battery Domain Score: Groton Maze Learning Test (GMLT) Score

End point title	Change From Study Baseline in Computerized Cognitive Battery Domain Score: Groton Maze Learning Test (GMLT) Score[6]

End point description:

This battery is a series of computerized cognition tests (detection, identification, one card learning, one back and groton maze learning) designed to measure reaction time, visual learning and memory, and executive function/sequencing. GMLT measures executive function; maze/sequencing test, scored for total number of errors. Total score ranges from 0 to 999 number of errors. Lower score indicated better performance. Higher change from baseline indicated better performance. All enrolled analysis set included all subjects who were eligible to enter this study and received at least 1 dose of intranasal study medication. Here, 'N' (number analysed) signifies number of subjects analysed for this endpoint.

End point type	Primary

End point timeframe:

IND Phase: Baseline up to 4 weeks; OP/MA Phase: Baseline up to 78 months

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: Descriptive statistics was done, no inferential statistical analysis was performed.

End point values	Esketamine Nasal Spray (IND Phase)	Esketamine Nasal Spray (OP/MA Phase)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	415	1072		
Units: Number of Errors				
arithmetic mean (standard deviation)	1.5 (± 17.80)	5.1 (± 22.52)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Based on Columbia-Suicide Severity Rating Scale (C-SSRS) Score

End point title	Percentage of Subjects Based on Columbia-Suicide Severity Rating Scale (C-SSRS) Score[7]

End point description:

C-SSRS: interview-based instrument to systematically assess suicidal ideation (SI) and behavior, to assess whether subject experienced any of following: completed suicide, suicide attempt (response of "yes" on "actual attempt"), preparatory acts toward imminent suicidal behavior ("yes" on "preparatory acts or behavior", "aborted attempt" or "interrupted attempt"), suicidal ideation ("yes" on "wish to be dead", "non-specific active suicidal thoughts", "active SI with methods without intent to act or some intent to act, without or with specific plan and intent), any self-injurious behavior with no suicidal intent ("yes" on "has subject engaged in non-suicidal self-injurious behavior"). Here, percentage of subjects with >=1 positive behavior, subjects with >=1 positive ideations; no event were reported. Full analysis set: all subjects who received at least 1 dose of study medication in this study. Here, 'N' (number analysed): number of subjects analysed for this endpoint.

End point type	Primary

End point timeframe:

IND Phase: Baseline up to 4 weeks; OP/MA Phase: Baseline up to 78 months

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: Descriptive statistics was done, no inferential statistical analysis was performed.

End point values	Esketamine Nasal Spray (IND Phase)	Esketamine Nasal Spray (OP/MA Phase)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	456	1109		
Units: Percentage of subjects				
number (not applicable)				
Baseline: No event	79.8	94.8		
Baseline: Suicidal ideation	20.2	5.2		
Baseline: Suicidal behavior	0	0		
Most Severe Post Baseline: No event	77.4	70.2		
Most Severe Post Baseline: Suicidal ideation	22.6	27.8		
Most Severe Post Baseline: Suicidal behavior	0	2.0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Treatment Emergent Adverse Events (TEAEs)

End point title	Number of Subjects with Treatment Emergent Adverse Events (TEAEs)[8]

End point description:

An adverse event (AE) was any untoward medical occurrence in a clinical study subject administered a pharmaceutical (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the intervention. Any AE occurring at or after the initial administration of study intervention up to end of study was considered as treatment-emergent. All enrolled analysis set included all subjects who were eligible to enter this study and received at least 1 dose of intranasal study medication.

End point type	Primary

End point timeframe:

IND Phase: up to 4 weeks; OP/MA Phase: up to 78 months

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: Descriptive statistics was done, no inferential statistical analysis was performed.

End point values	Esketamine Nasal Spray (IND Phase)	Esketamine Nasal Spray (OP/MA Phase)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	458	1110		
Units: Subjects	346	1052		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Heart Rate

End point title	Change From Baseline in Heart Rate[9]

End point description:

Change from baseline (predose) in heart rate were reported. Full analysis set included subjects who received at least 1 dose of intranasal study medication in this study.

End point type	Primary

End point timeframe:

IND Phase: Baseline up to 4 weeks; OP/MA Phase: Baseline up to 78 months

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: Descriptive statistics was done, no inferential statistical analysis was performed.

End point values	Esketamine Nasal Spray (IND Phase)	Esketamine Nasal Spray (OP/MA Phase)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	458	1110		
Units: beats per minute				
arithmetic mean (standard deviation)	0.4 (± 9.52)	0.8 (± 10.47)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Systolic and Diastolic Blood Pressure

End point title	Change From Baseline in Systolic and Diastolic Blood

End point description:

Change from baseline in systolic and diastolic blood pressure were reported. Full analysis set included subjects who received at least 1 dose of intranasal study medication in this study.

End point type	Primary

End point timeframe:

IND Phase: Baseline up to 4 weeks; OP/MA Phase: baseline up to 78 months

Notes:

[10] - 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: Descriptive statistics was done, no inferential statistical analysis was performed.

End point values	Esketamine Nasal Spray (IND Phase)	Esketamine Nasal Spray (OP/MA Phase)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	458	1110		
Units: millimeters of mercury (mmHg)				
arithmetic mean (standard deviation)				
Systolic Blood pressure	0.4 (± 10.72)	5.8 (± 12.68)		
Diastolic Blood pressure	0.3 (± 7.47)	2.7 (± 8.78)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Respiratory Rate

End point title	Change From Baseline in Respiratory Rate[11]

End point description:

Change from baseline in respiratory rate were reported. Full analysis set included subjects who received at least 1 dose of intranasal study medication in this study.

End point type	Primary

End point timeframe:

IND Phase: Baseline up to 4 weeks; OP/MA Phase: Baseline up to 78 months

Notes:

[11] - 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: Descriptive statistics was done, no inferential statistical analysis was performed.

End point values	Esketamine Nasal Spray (IND Phase)	Esketamine Nasal Spray (OP/MA Phase)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	458	1110		
Units: breaths per minute				
arithmetic mean (standard deviation)	-0.1 (± 2.51)	-0.4 (± 2.83)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Blood Oxygen Saturation

End point title	Change From Baseline in Blood Oxygen Saturation[12]

End point description:

Change from baseline in blood oxygen saturation (predose) were reported. Full analysis set included subjects who received at least 1 dose of intranasal study medication in this study.

End point type	Primary

End point timeframe:

IND Phase: Baseline up to 4 weeks; OP/MA Phase: Baseline up to 78 months

Notes:

[12] - 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: Descriptive statistics was done, no inferential statistical analysis was performed.

End point values	Esketamine Nasal Spray (IND Phase)	Esketamine Nasal Spray (OP/MA Phase)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	458	1110		
Units: percent (%)				
arithmetic mean (standard deviation)	-0.1 (± 1.54)	-0.1 (± 1.63)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Montgomery Asberg Depression Rating Scale (MADRS) Total Score

End point title	Change From Baseline in Montgomery Asberg Depression Rating Scale (MADRS) Total Score

End point description:

MADRS measures depression severity, detects changes due to AD treatment. It consists 10 items (evaluate apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, interest level, pessimistic thoughts, suicidal thoughts), scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms), summed for a total possible score of 0 to 60. Higher scores indicate more severe condition. Negative change in score indicates improvement. Missing data was imputed using last observation carried forward (LOCF) method. Full analysis set included all subjects who received at least 1 dose of intranasal study medication in this study. Here, 'N' (number analysed) signifies number of subjects analysed for this endpoint.

End point type	Secondary

End point timeframe:

IND Phase: Baseline up to 4 weeks; OP/MA Phase: Baseline up to 78 months

End point values	Esketamine Nasal Spray (IND Phase)	Esketamine Nasal Spray (OP/MA Phase)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	455	1110		
Units: Score on a Scale				
arithmetic mean (standard deviation)	-12.8 (± 9.73)	0.2 (± 9.93)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Subject-Reported Depressive Symptoms Using the Patient Health Questionnaire - 9 (PHQ-9) Total Score

End point title	Change From Baseline in Subject-Reported Depressive Symptoms Using the Patient Health Questionnaire - 9 (PHQ-9) Total Score

End point description:

Change from baseline in PHQ-9 total score were reported. The PHQ-9 was a 9-item, patient-reported

outcome measure to assess depressive symptoms. The scale scores each of the 9 symptom domains of the Diagnostic and Statistical Manual of Mental Disorders. 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 provide a total score (range of 0 to 27) with higher scores indicating greater severity of depressive symptoms. Full analysis set included all subjects who received at least 1 dose of intranasal study medication in this study. Here, 'N' (number analysed) signifies number of subjects analysed for this endpoint.

End point type	Secondary

End point timeframe:

IND Phase: Baseline up to 4 weeks; OP/MA Phase: Baseline up to 78 months

End point values	Esketamine Nasal Spray (IND Phase)	Esketamine Nasal Spray (OP/MA Phase)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	453	1109		
Units: Score on a scale				
arithmetic mean (standard deviation)	-5.8 (± 5.84)	0.6 (± 6.22)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Clinical Global Impression-severity (CGI-S) Score

End point title	Change From Baseline in Clinical Global Impression-severity (CGI-S) Score

End point description:

The CGI-S provides an overall clinician-determined summary measure of the severity of the subject's illness that takes 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 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 subject. Negative change in score indicates improvement. Full analysis set: all subjects who received at least 1 dose of intranasal study medication in this study. Here, 'N' (number analysed): number of subjects analysed for this endpoint.

End point type	Secondary

End point timeframe:

IND Phase: Baseline up to 4 weeks; OP/MA Phase: Baseline up to 78 months

End point values	Esketamine Nasal Spray (IND Phase)	Esketamine Nasal Spray (OP/MA Phase)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	456	1110		
Units: Score on a scale				
median (full range (min-max))	-1.0 (-5.0 to 1)	0.0 (-5 to 4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Subject-Reported Health-related Quality of Life as Assessed by EuroQol-5 Dimension-5 Level (EQ-5D-5L) Valuation Index Score (VAS)

End point title	Change From Baseline in Subject-Reported Health-related Quality of Life as Assessed by EuroQol-5 Dimension-5 Level (EQ-5D-5L) Valuation Index Score (VAS)

End point description:

Change from baseline in subject-reported health-related quality of life as assessed by EQ-5D-5L VAS was reported. The EQ-5D-5L is a standardized 2-part instrument for use as a measure of health outcome, primarily designed for self-completion by respondents. It essentially consists of the EQ-5D-5L descriptive system and the EQ-VAS. EQ-VAS self-rating records the respondent'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 indicates improvement. Full analysis set: who received at least 1 dose of intranasal study medication in this study. Here, 'N' (number analysed) signifies number of subjects analysed for this endpoint.

End point type	Secondary

End point timeframe:

IND Phase: Baseline up to 4 weeks; OP/MA Phase: Baseline up to 78 months

End point values	Esketamine Nasal Spray (IND Phase)	Esketamine Nasal Spray (OP/MA Phase)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	454	1110		
Units: Score on a scale				
arithmetic mean (standard deviation)	13.0 (± 18.05)	0.7 (± 18.95)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Sheehan Disability Scale (SDS) Total Score

End point title	Change From Baseline in Sheehan Disability Scale (SDS) Total Score

End point description:

Change from baseline in SDS total score were reported. The SDS, a patient-reported outcome measure, was a 5 item questionnaire which had been widely used and accepted for assessment of functional and associated disability impairment. The first three items assessed disruption of (1) work/school, (2) social life, and (3) family life/home responsibilities using a 0-10 rating scale. The score for the first three items were summed to create a total score of 0-30 where a higher score indicated greater impairment. Full analysis set included all subjects who received at least 1 dose of intranasal study medication in this

study. Here, 'N' (number analysed) signifies number of subjects analysed for this endpoint.

End point type	Secondary

End point timeframe:

IND Phase: Baseline up to 4 weeks; OP/MA Phase: Baseline up to 78 months

End point values	Esketamine Nasal Spray (IND Phase)	Esketamine Nasal Spray (OP/MA Phase)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	384	1067		
Units: Score on a scale				
arithmetic mean (standard deviation)	-6.4 (± 7.13)	-0.1 (± 8.35)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Subject- Reported Health Related Quality of Life Using the Quality of Life in Depression Scale (QLDS)

End point title	Change From Baseline in Subject- Reported Health Related Quality of Life Using the Quality of Life in Depression Scale (QLDS)

End point description:

Change from baseline in subject- reported health related quality of life using the QLDS. The QLDS is a disease-specific validated patient-reported outcome (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). A higher score indicates a more severe condition. Full analysis set included all subjects who received at least 1 dose of intranasal study medication in this study. Here, 'N' (number analysed) signifies number of subjects analysed for this endpoint .

End point type	Secondary

End point timeframe:

IND Phase: Baseline up to 4 weeks; OP/MA Phase: Baseline up to 78 months

End point values	Esketamine Nasal Spray (IND Phase)	Esketamine Nasal Spray (OP/MA Phase)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	293	537		
Units: Score on a scale				
arithmetic mean (standard deviation)	-8.2 (± 8.47)	0.1 (± 9.47)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline as Assessed by EQ 5D-5L: Sum Score

End point title	Change From Baseline as Assessed by EQ 5D-5L: Sum Score

End point description:

EQ-5D-5L consists of EQ-5D-5L descriptive system and EQ-VAS. EQ-5D-5L descriptive system comprises of mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each has 5 levels of perceived problems (1-no problem, 2-slight problems, 3-moderate problems, 4-severe problems, 5-extreme problems). Sum score ([sum of the scores from the 5 dimensions – 5]*5) ranges from 0 to 100. Higher score indicates worst health state. Full analysis set: all subjects who received at least 1 dose of intranasal study medication in this study. Here, 'N' (number analysed): number of subjects analysed for this endpoint.

End point type	Secondary

End point timeframe:

IND Phase: Baseline up to 4 weeks; OP/MA Phase: Baseline up to 78 months

End point values	Esketamine Nasal Spray (IND Phase)	Esketamine Nasal Spray (OP/MA Phase)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	454	1110		
Units: Score on a scale				
arithmetic mean (standard deviation)	-10.4 (± 12.81)	2.9 (± 15.88)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

IND Phase: Baseline up to 4 weeks; OP/MA Phase: Baseline up to 78 months

Adverse event reporting additional description:

All enrolled analysis set included all subjects who were eligible to enter this study and received at least 1 dose of intranasal study medication.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Esketamine Nasal Spray (IND Phase)

Reporting group description:

Subjects who entered IND from studies ESKETINTRD3001, ESKETINTRD3002, ESKETINTRD3003, ESKETINTRD3004, or ESKETINTRD3006 received esketamine nasal spray twice per week on Day 1 for 4 weeks as a flexible dose regimen (56 milligrams [mg] or 84 mg for subjects less than [<] 65 years; 28 mg, 56 mg or 84 mg for subjects greater than or equal to [>=] 65 years).

Reporting group title	Esketamine Nasal Spray (OP/MA Phase)

Reporting group description:

Subjects who entered the OP/MA phase from the IND phase of study ESKETINTRD3008 continued on the same dose of esketamine from the IND phase weekly. Subjects who entered from studies ESKETINTRD3001, ESKETINTRD3002, ESKETINTRD3003, ESKETINTRD3004, or ESKETINTRD3006 were administered esketamine nasal spray, 56 mg or 84 mg, once weekly. Subjects who entered study ESKETINTRD3005 were received esketamine nasal spray (28 mg in Week 1; 28 or 56 mg in Week 2; and 28, 56 or 84 mg in Weeks 3 and 4) once weekly in optimization and maintenance (OP/MP) phase. After Week 4 (starting at Week 5), based on the Investigator's clinical judgment, the dose of esketamine for all subjects was adjusted based upon efficacy and tolerability.

Serious adverse events	Esketamine Nasal Spray (IND Phase)	Esketamine Nasal Spray (OP/MA Phase)	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 458 (1.09%)	212 / 1110 (19.10%)	
number of deaths (all causes)	1	8	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung Adenocarcinoma			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive Breast Carcinoma			

subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clear Cell Renal Cell Carcinoma			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangiocarcinoma			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast Neoplasm			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast Cancer			
subjects affected / exposed	0 / 458 (0.00%)	2 / 1110 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic Neuroendocrine Tumour			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoma			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic Syndrome			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal Squamous Cell Carcinoma			

subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian Germ Cell Teratoma			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal Cancer			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional Cell Carcinoma			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous Cell Carcinoma			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small Intestine Adenocarcinoma			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate Cancer			
subjects affected / exposed	0 / 458 (0.00%)	2 / 1110 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pituitary Tumour Benign			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Orthostatic Hypotension			

subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive Emergency			
subjects affected / exposed	1 / 458 (0.22%)	0 / 1110 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory Collapse			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Arterial Occlusive Disease			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic Dissection			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Spinal Fusion Surgery			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mammoplasty			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Female Sterilisation			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominoplasty			

subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Fatigue			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic Reaction			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Rectocele			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heavy Menstrual Bleeding			

subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epididymal Cyst			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometriosis			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical Dysplasia			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast Hyperplasia			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal Prolapse			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary Embolism			
subjects affected / exposed	0 / 458 (0.00%)	2 / 1110 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax Spontaneous			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal Septum Deviation			

subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal Polyps			
subjects affected / exposed	0 / 458 (0.00%)	2 / 1110 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Disorder			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea Exertional			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis Chronic			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	0 / 458 (0.00%)	2 / 1110 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Oedema			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sleep Apnoea Syndrome			

subjects affected / exposed	0 / 458 (0.00%)	2 / 1110 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillar Hypertrophy			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal Cord Thickening			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Persistent Depressive Disorder			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adjustment Disorder			
subjects affected / exposed	0 / 458 (0.00%)	2 / 1110 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Affect Lability			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	0 / 458 (0.00%)	5 / 1110 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mania			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major Depression			

subjects affected / exposed	0 / 458 (0.00%)	3 / 1110 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression Suicidal			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 458 (0.00%)	18 / 1110 (1.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 23	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conversion Disorder			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional State			
subjects affected / exposed	0 / 458 (0.00%)	2 / 1110 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed Suicide			
subjects affected / exposed	1 / 458 (0.22%)	0 / 1110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Suicide Attempt			
subjects affected / exposed	0 / 458 (0.00%)	15 / 1110 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal Ideation			
subjects affected / exposed	0 / 458 (0.00%)	11 / 1110 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic Disorder			

subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device Breakage			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood Pressure Diastolic Increased			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial Necrosis Marker Increased			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Hand Fracture			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol Poisoning			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Animal Bite			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle Fracture			

subjects affected / exposed	0 / 458 (0.00%)	2 / 1110 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exposure During Pregnancy			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Face Injury			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 458 (0.00%)	2 / 1110 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur Fracture			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional Hernia			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist Fracture			

subjects affected / exposed	0 / 458 (0.00%)	2 / 1110 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament Rupture			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb Injury			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Limb Fracture			
subjects affected / exposed	0 / 458 (0.00%)	3 / 1110 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus Injury			
subjects affected / exposed	0 / 458 (0.00%)	2 / 1110 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple Injuries			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Muscle Rupture			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 458 (0.00%)	2 / 1110 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic Fracture			

subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius Fracture			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road Traffic Accident			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin Laceration			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic Vertebral Fracture			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia Fracture			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic Intracranial Haemorrhage			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional Overdose			
subjects affected / exposed	0 / 458 (0.00%)	3 / 1110 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Myocardial Bridging			

subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	0 / 458 (0.00%)	5 / 1110 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Myocardial Infarction			
subjects affected / exposed	0 / 458 (0.00%)	2 / 1110 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary Artery Disease			
subjects affected / exposed	0 / 458 (0.00%)	2 / 1110 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary Artery Stenosis			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial Effusion			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial Infarction			

subjects affected / exposed	0 / 458 (0.00%)	4 / 1110 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Dysarthria			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular Accident			
subjects affected / exposed	0 / 458 (0.00%)	2 / 1110 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid Artery Aneurysm			
subjects affected / exposed	0 / 458 (0.00%)	2 / 1110 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Akathisia			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of Consciousness			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic Stroke			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial Aneurysm			

subjects affected / exposed	0 / 458 (0.00%)	2 / 1110 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiplegia			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 458 (0.00%)	3 / 1110 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial Paralysis			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic Encephalopathy			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient Ischaemic Attack			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Occipital Neuralgia			

subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo Positional			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	0 / 458 (0.00%)	2 / 1110 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 458 (0.00%)	2 / 1110 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastric Polyps			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	0 / 458 (0.00%)	2 / 1110 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus Hernia			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal Perforation			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal Hernia			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large Intestine Polyp			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Gastrointestinal Haemorrhage			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis Acute			
subjects affected / exposed	0 / 458 (0.00%)	2 / 1110 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis Relapsing			

subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical Hernia			
subjects affected / exposed	0 / 458 (0.00%)	2 / 1110 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 458 (0.00%)	10 / 1110 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile Duct Stone			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary Obstruction			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 458 (0.00%)	3 / 1110 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 458 (0.00%)	6 / 1110 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic Kidney Disease			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder Outlet Obstruction			

subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Kidney Injury			
subjects affected / exposed	0 / 458 (0.00%)	2 / 1110 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Incontinence			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Artery Stenosis			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Failure			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress Urinary Incontinence			
subjects affected / exposed	0 / 458 (0.00%)	2 / 1110 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral Stenosis			
subjects affected / exposed	0 / 458 (0.00%)	2 / 1110 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urge Incontinence			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Bladder Polyp			

subjects affected / exposed	1 / 458 (0.22%)	0 / 1110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Retention			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back Pain			
subjects affected / exposed	2 / 458 (0.44%)	2 / 1110 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical Spinal Stenosis			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facet Joint Syndrome			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral Disc Degeneration			
subjects affected / exposed	0 / 458 (0.00%)	2 / 1110 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral Disc Disorder			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral Disc Protrusion			

subjects affected / exposed	0 / 458 (0.00%)	3 / 1110 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 458 (0.00%)	3 / 1110 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylolisthesis			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator Cuff Syndrome			
subjects affected / exposed	0 / 458 (0.00%)	2 / 1110 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pharyngitis Streptococcal			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 458 (0.00%)	3 / 1110 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis Staphylococcal			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Covid-19			
subjects affected / exposed	0 / 458 (0.00%)	9 / 1110 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 2	
Covid-19 Pneumonia			

subjects affected / exposed	0 / 458 (0.00%)	2 / 1110 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cystitis			
subjects affected / exposed	0 / 458 (0.00%)	2 / 1110 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis Salmonella			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Infection			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 458 (0.00%)	2 / 1110 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large Intestine Infection			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising Fasciitis			

subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis Media Chronic			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess Limb			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 458 (0.00%)	7 / 1110 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 2	
Pyelonephritis			
subjects affected / exposed	0 / 458 (0.00%)	2 / 1110 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal Infection			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			
subjects affected / exposed	0 / 458 (0.00%)	3 / 1110 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative Wound Infection			

subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic Ketoacidosis			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 458 (0.00%)	2 / 1110 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obesity			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 Diabetes Mellitus			
subjects affected / exposed	0 / 458 (0.00%)	1 / 1110 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Esketamine Nasal Spray (IND Phase)	Esketamine Nasal Spray (OP/MA Phase)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	318 / 458 (69.43%)	1010 / 1110 (90.99%)	
Investigations			
Blood Pressure Increased			
subjects affected / exposed	35 / 458 (7.64%)	157 / 1110 (14.14%)	
occurrences (all)	118	1100	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 458 (0.22%)	71 / 1110 (6.40%)	
occurrences (all)	1	92	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 458 (0.22%)	79 / 1110 (7.12%)	
occurrences (all)	3	239	
Nervous system disorders			
Dizziness Postural			
subjects affected / exposed	22 / 458 (4.80%)	57 / 1110 (5.14%)	
occurrences (all)	104	1773	
Dizziness			
subjects affected / exposed	95 / 458 (20.74%)	365 / 1110 (32.88%)	
occurrences (all)	364	9860	
Dysgeusia			
subjects affected / exposed	77 / 458 (16.81%)	217 / 1110 (19.55%)	
occurrences (all)	351	7165	
Hypoaesthesia			
subjects affected / exposed	44 / 458 (9.61%)	102 / 1110 (9.19%)	
occurrences (all)	166	2375	
Migraine			
subjects affected / exposed	3 / 458 (0.66%)	56 / 1110 (5.05%)	
occurrences (all)	3	162	
Paraesthesia			
subjects affected / exposed	24 / 458 (5.24%)	92 / 1110 (8.29%)	
occurrences (all)	47	622	
Sedation			

subjects affected / exposed	25 / 458 (5.46%)	84 / 1110 (7.57%)	
occurrences (all)	111	1333	
Somnolence			
subjects affected / exposed	43 / 458 (9.39%)	253 / 1110 (22.79%)	
occurrences (all)	128	6649	
Headache			
subjects affected / exposed	70 / 458 (15.28%)	401 / 1110 (36.13%)	
occurrences (all)	128	2727	
General disorders and administration site conditions			
Feeling Drunk			
subjects affected / exposed	25 / 458 (5.46%)	47 / 1110 (4.23%)	
occurrences (all)	139	2403	
Fatigue			
subjects affected / exposed	20 / 458 (4.37%)	145 / 1110 (13.06%)	
occurrences (all)	29	393	
Pyrexia			
subjects affected / exposed	2 / 458 (0.44%)	84 / 1110 (7.57%)	
occurrences (all)	2	107	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	77 / 458 (16.81%)	198 / 1110 (17.84%)	
occurrences (all)	373	10231	
Eye disorders			
Diplopia			
subjects affected / exposed	15 / 458 (3.28%)	58 / 1110 (5.23%)	
occurrences (all)	42	944	
Vision Blurred			
subjects affected / exposed	35 / 458 (7.64%)	116 / 1110 (10.45%)	
occurrences (all)	131	1667	
Gastrointestinal disorders			
Hypoaesthesia Oral			
subjects affected / exposed	38 / 458 (8.30%)	83 / 1110 (7.48%)	
occurrences (all)	128	1766	
Diarrhoea			

subjects affected / exposed	12 / 458 (2.62%)	184 / 1110 (16.58%)	
occurrences (all)	12	350	
Constipation			
subjects affected / exposed	6 / 458 (1.31%)	59 / 1110 (5.32%)	
occurrences (all)	6	87	
Abdominal Pain Upper			
subjects affected / exposed	6 / 458 (1.31%)	80 / 1110 (7.21%)	
occurrences (all)	6	147	
Abdominal Pain			
subjects affected / exposed	4 / 458 (0.87%)	70 / 1110 (6.31%)	
occurrences (all)	4	126	
Paraesthesia Oral			
subjects affected / exposed	26 / 458 (5.68%)	69 / 1110 (6.22%)	
occurrences (all)	58	917	
Toothache			
subjects affected / exposed	2 / 458 (0.44%)	84 / 1110 (7.57%)	
occurrences (all)	2	138	
Vomiting			
subjects affected / exposed	17 / 458 (3.71%)	176 / 1110 (15.86%)	
occurrences (all)	20	462	
Nausea			
subjects affected / exposed	82 / 458 (17.90%)	356 / 1110 (32.07%)	
occurrences (all)	165	1945	
Respiratory, thoracic and mediastinal disorders			
Throat Irritation			
subjects affected / exposed	26 / 458 (5.68%)	60 / 1110 (5.41%)	
occurrences (all)	118	1722	
Rhinorrhoea			
subjects affected / exposed	7 / 458 (1.53%)	65 / 1110 (5.86%)	
occurrences (all)	11	257	
Oropharyngeal Pain			
subjects affected / exposed	11 / 458 (2.40%)	95 / 1110 (8.56%)	
occurrences (all)	15	182	
Nasal Discomfort			

subjects affected / exposed	23 / 458 (5.02%)	93 / 1110 (8.38%)	
occurrences (all)	66	1045	
Cough			
subjects affected / exposed	6 / 458 (1.31%)	114 / 1110 (10.27%)	
occurrences (all)	6	207	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	30 / 458 (6.55%)	197 / 1110 (17.75%)	
occurrences (all)	61	736	
Depression			
subjects affected / exposed	1 / 458 (0.22%)	73 / 1110 (6.58%)	
occurrences (all)	1	126	
Insomnia			
subjects affected / exposed	16 / 458 (3.49%)	149 / 1110 (13.42%)	
occurrences (all)	16	232	
Dissociation			
subjects affected / exposed	100 / 458 (21.83%)	272 / 1110 (24.50%)	
occurrences (all)	460	7112	
Musculoskeletal and connective tissue disorders			
Pain in Extremity			
subjects affected / exposed	1 / 458 (0.22%)	79 / 1110 (7.12%)	
occurrences (all)	1	142	
Myalgia			
subjects affected / exposed	6 / 458 (1.31%)	84 / 1110 (7.57%)	
occurrences (all)	9	120	
Back Pain			
subjects affected / exposed	5 / 458 (1.09%)	226 / 1110 (20.36%)	
occurrences (all)	5	433	
Arthralgia			
subjects affected / exposed	9 / 458 (1.97%)	182 / 1110 (16.40%)	
occurrences (all)	10	322	
Infections and infestations			
Urinary Tract Infection			

subjects affected / exposed	7 / 458 (1.53%)	176 / 1110 (15.86%)	
occurrences (all)	7	417	
Upper Respiratory Tract Infection			
subjects affected / exposed	6 / 458 (1.31%)	142 / 1110 (12.79%)	
occurrences (all)	6	274	
Sinusitis			
subjects affected / exposed	1 / 458 (0.22%)	74 / 1110 (6.67%)	
occurrences (all)	1	107	
Nasopharyngitis			
subjects affected / exposed	13 / 458 (2.84%)	267 / 1110 (24.05%)	
occurrences (all)	14	629	
Influenza			
subjects affected / exposed	3 / 458 (0.66%)	133 / 1110 (11.98%)	
occurrences (all)	3	197	
Gastroenteritis			
subjects affected / exposed	2 / 458 (0.44%)	72 / 1110 (6.49%)	
occurrences (all)	3	94	
Covid-19			
subjects affected / exposed	0 / 458 (0.00%)	134 / 1110 (12.07%)	
occurrences (all)	0	147	
Bronchitis			
subjects affected / exposed	0 / 458 (0.00%)	71 / 1110 (6.40%)	
occurrences (all)	0	107	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 December 2016	The purpose of the amendment was to update the entry pathways from other Phase 3 esketamine protocols into this protocol and made other administrative changes to the protocol.
21 August 2017	The purpose of the amendment was to allow the investigator to adjust the frequency of intranasal dosing sessions to every 2 weeks instead of every 4 weeks, depending on the subject's depressive symptomatology, in order to allow greater flexibility with the aim of preventing depression relapse and to review machine read ECG tracing where initiation of treatment or safety follow-up was time-critical or if action needed to be taken for safety reasons; to clarify the rationale for removal of the Mini Mental State Examination to more clearly outline the clinical rationale; to clarify that pulse oximetry was to be performed at all intranasal dosing sessions; corrected erroneous text relating to the MADRS assessment that was no longer relevant; and permitted benzodiazepine medication during the study.
24 April 2019	The purpose of the amendment was to extend the study to collect data characterizing the safety risks of long-term effects of esketamine on cognitive function and urinary symptoms (cystitis); and to update categories of treatment-emergent adverse events (TEAEs) of special interest. Updated Attachment 1 of the protocol (Prohibited Concomitant Medications With Esketamine Nasal Spray Study Medication) with new guidelines.
05 October 2020	The purpose of the amendment was following the conclusion post-marketing requirement of the Food and Drug Administration (FDA) for 3 years of US data at the end of 2020, the sponsor extended the study duration to allow for ongoing subjects to continue to receive esketamine treatment if clinically warranted and until it was available in the subject's respective country, or December 2022, whichever was earlier. The number/frequency of assessments was therefore reduced to mimic clinical practice and reduce burden on sites and subjects while ensuring adequate clinical oversight and monitoring of subject safety.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported