Clinical trial results:
A Double-Blind, Doubly-Randomized, Placebo-Controlled Study of Intranasal Esketamine in an Adaptive Treatment Protocol to Assess Safety and Efficacy in Treatment-Resistant Depression

Summary

EudraCT number	2013-004005-11
Trial protocol	BE
Global end of trial date	25 September 2015

Results information

Result version number	v1 (current)
This version publication date	13 August 2016
First version publication date	13 August 2016

Trial information

Trial identification

Sponsor protocol code	ESKETINTRD2003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01998958
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen-Cilag International NV
Sponsor organisation address	Turnhoutseweg 30, Beerse, Belgium, 2340
Public contact	Clinical Registry Group, Janssen-Cilag International NV, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen-Cilag International NV, ClinicalTrialsEU@its.jnj.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 September 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to assess the efficacy and dose response of intranasal esketamine (Panel A: 28 mg, 56 mg, 84 mg; Panel B: 14 mg and 56 mg) compared with placebo in improving depressive symptoms in participants with treatment-resistant depression (TRD), as assessed by a change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) total score for the combined periods in the double-blind treatment phase.

Protection of trial subjects:

Safety evaluations included monitoring of adverse events (AEs), clinical laboratory tests (hematology, serum chemistry, and urinalysis), vital sign measurements, physical examination, height and body weight and electrocardiograms (ECG).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 January 2014
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	Belgium: 11
Country: Number of subjects enrolled	Japan: 41
Country: Number of subjects enrolled	United States: 56
Worldwide total number of subjects	108
EEA total number of subjects	11

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)	108

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment period: 28 January 2014 - 25 September 2015

Pre-assignment

Screening details:

A total of 126 participants were screened for entry in Panel A, of these 67 participants were randomized and received treatment. A total of 54 participants were screened for entry in Panel B, of these 41 participants were randomized and treated with treatment.

Period 1

Period 1 title	Double-Blind Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants in Panel A and B were self-administered intranasal placebo on Days 1 and 4 during the double-blind phase. Depending on response on Day 8, participants received intranasal placebo on Days 8 and 11 or were re-randomized to receive intranasal placebo or esketamine at a dose of 28 mg, 56 mg, or 84 mg (Panel A) or 14 mg or 56 mg (Panel B) on Day 8 and Day 11.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray
Routes of administration	Nasal use

Dosage and administration details:

Participants self-administered with placebo as an intranasal formulation 1 spray into each nostril at t=0, 5, and 10 minutes on each dosing day.

Arm title	Esketamine 56 milligrams (mg)/Esketamine 56 mg

Arm description:

Participants in Panel A and B were self-administered with intranasal esketamine 56 mg on Days 1, 4, 8, and 11 during the double-blind phase.

Arm type	Experimental
Investigational medicinal product name	Esketamine 56 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray
Routes of administration	Nasal use

Dosage and administration details:

Participants self-administered 1 to 6 sprays of esketamine 56 mg as an intranasal formulation into each nostril on Days 1, 4, 8, and 11.

Arm title	Esketamine 84 mg/Esketamine 84 mg

Arm description:

Participants in Panel A were self-administered intranasal esketamine 84 mg on Days 1, 4, 8, and 11 during the double-blind phase.

Arm type	Experimental

Investigational medicinal product name	Esketamine 84 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray
Routes of administration	Nasal use

Dosage and administration details:

Participants were self-administered 1 to 6 sprays of esketamine 84 mg as an intranasal formulation for up to 2 weeks (Days 1, 4, 8, 11).

Arm title	Placebo/Placebo

Arm description:

Participants in Panel A and B (who received placebo on Day 1 and 4 and responders [Quick Inventory of Depressive Symptomatology – 16-item Self Report {QIDS-SR16} total score less than 11]) were self-administered with Placebo on Day 8 and 11; non-responders (Quick Inventory of Depressive Symptomatology – 16-item Self Report [QIDS-SR16] total score greater than or equal to [>=] 11) on Day 8 were re-randomized to intranasal placebo or esketamine on Days 8 and 11 during the double-blind phase.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray
Routes of administration	Nasal use

Dosage and administration details:

Participants were self-administered 1 to 6 sprays of placebo as an intranasal formulation for up to 2 weeks (Days 1, 4, 8, and 11).

Arm title	Placebo/Esketamine 14 mg

Arm description:

Participants in Panel B (who received placebo on Day 1 and 4 and non-responders (Quick Inventory of Depressive Symptomatology – 16-item Self Report [QIDS-SR16] total score greater than or equal to (>=) 11) on Day 8) were self-administered intranasal esketamine 14 mg on Days 8, and 11 during the double-blind phase.

Arm type	Experimental
Investigational medicinal product name	Esketamine 14 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray
Routes of administration	Nasal use

Dosage and administration details:

Participants self-administered with esketamine 14 mg as an intranasal formulation into each nostril on Days 8 and 11.

Arm title	Placebo/Esketamine 28 mg

Arm description:

Participants in Panel A (who received placebo on Day 1 and 4 and non-responders [QIDS-SR16 total score >=11] on Day 8) were self-administered intranasal esketamine 28 mg on Days 8 and 11 during the double-blind phase.

Arm type	Experimental
Investigational medicinal product name	Esketamine 28 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray
Routes of administration	Nasal use

Dosage and administration details:

Participants were self-administered 1 to 6 sprays of esketamine 28 mg as an intranasal formulation on Day 8, 11.

Arm title	Placebo/Esketamine 56 mg

Arm description:

Participants in Panel A and B (who received placebo on Day 1 and 4 and non-responders [QIDS-SR16 total score >=11] on Day 8) were self-administered intranasal esketamine 56 mg on Day 8 and 11 during the double-blind phase.

Arm type	Experimental
Investigational medicinal product name	Esketamine 56 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray
Routes of administration	Nasal use

Dosage and administration details:

Participants were self-administered 1 to 6 sprays of esketamine 56 mg as an intranasal formulation on Days 8, and 11.

Arm title	Placebo/Esketamine 84 mg

Arm description:

Participants in Panel A (who received placebo on Day 1 and 4 and non-responders [QIDS-SR16 total score >=11] on Day 8) were self-administered intranasal esketamine 84 mg on Days 8 and 11 during the double-blind phase.

Arm type	Experimental
Investigational medicinal product name	Esketamine 84 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray
Routes of administration	Nasal use

Dosage and administration details:

Participants were self-administered 1 to 6 sprays of intranasal esketamine 84 mg on Days 8 and 11.

Arm title	Esketamine 14 mg/Esketamine 14 mg

Arm description:

Participants in Panel B were self-administered intranasal esketamine 14 mg on Days 1, 4, 8, and 11 during the double-blind phase.

Arm type	Experimental
Investigational medicinal product name	Esketamine 14 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray
Routes of administration	Nasal use

Dosage and administration details:

Participants were self-administered intranasal esketamine 14 mg on Days 1, 4, 8, and 11.

Arm title	Esketamine 28 mg

Arm description:

Participants in Panel A were self-administered intranasal esketamine 28 mg on Days 1, and 4 during the double-blind phase.

Arm type	Experimental
Investigational medicinal product name	Esketamine 28 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray
Routes of administration	Nasal use

Dosage and administration details:

Participants were self-administered 1 to 6 sprays of esketamine 28 mg as an intranasal formulation into each nostril.

Arm title	Esketamine 28 mg/ Esketamine 28 mg

Arm description:

Participants in Panel A were self-administered intranasal esketamine 28 mg on Days 1, 4, 8, and 11 during the double-blind phase.

Arm type	Experimental
Investigational medicinal product name	Esketamine 28 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray
Routes of administration	Nasal use

Dosage and administration details:

Participants were self-administered with esketamine 28 mg as an intranasal formulation on Days 1, 4, 8, and 11.

Number of subjects in period 1	Placebo	Esketamine 56 milligrams (mg)/Esketamine 56	Esketamine 84 mg/Esketamine 84 mg
Started	1	20	12
Completed	0	20	10
Not completed	1	0	2
Consent withdrawn by subject	-	-	1
Adverse event, non-fatal	-	-	1
Other	1	-	-
Lack of efficacy	-	-	-

Number of subjects in period 1	Placebo/Placebo	Placebo/Esketamine 14 mg	Placebo/Esketamine 28 mg
Started	23	5	8
Completed	23	5	8
Not completed	0	0	0
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	-	-	-
Other	-	-	-
Lack of efficacy	-	-	-

Number of subjects in period 1	Placebo/Esketamine 56 mg	Placebo/Esketamine 84 mg	Esketamine 14 mg/Esketamine 14 mg
Started	12	5	11
Completed	10	5	11
Not completed	2	0	0
Consent withdrawn by subject	1	-	-
Adverse event, non-fatal	1	-	-
Other	-	-	-
Lack of efficacy	-	-	-

Number of subjects in period 1	Esketamine 28 mg	Esketamine 28 mg/ Esketamine 28 mg

Started	3	8
Completed	0	8
Not completed	3	0
Consent withdrawn by subject	1	-
Adverse event, non-fatal	1	-
Other	-	-
Lack of efficacy	1	-

Period 2

Period 2 title	Open-label Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Esketamine

Arm description:

Participants were received intranasal esketamine with a starting dose of 56-mg on Day 15 and subsequent doses on Days 18, 22, 25, 32, 39, and 46 and on Days 18, 22, and 25 (the dose of esketamine was adjusted based on the Investigator's clinical judgement of efficacy and tolerability) in Panel A and Panel B respectively.

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

Dosage and administration details:

Participants were received intranasal esketamine with a starting dose of 56-mg on Day 15 and subsequent doses on Days 18, 22, 25, 32, 39, and 46 and on Days 18, 22, and 25 (the dose of esketamine was adjusted based on the Investigator's clinical judgement of efficacy and tolerability) in Panel A and Panel B respectively.

Number of subjects in period 2[1]	Esketamine
Started	96
Completed	80
Not completed	16
Consent withdrawn by subject	5
Adverse event, non-fatal	1
Other	6
Lost to follow-up	1
Lack of efficacy	3

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: 100 subjects were completed the double blind phase, However only 96 subjects were entered into open label treatment phase.

Baseline characteristics

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants in Panel A and B were self-administered intranasal placebo on Days 1 and 4 during the double-blind phase. Depending on response on Day 8, participants received intranasal placebo on Days 8 and 11 or were re-randomized to receive intranasal placebo or esketamine at a dose of 28 mg, 56 mg, or 84 mg (Panel A) or 14 mg or 56 mg (Panel B) on Day 8 and Day 11.

Reporting group title	Esketamine 56 milligrams (mg)/Esketamine 56 mg

Reporting group description:

Participants in Panel A and B were self-administered with intranasal esketamine 56 mg on Days 1, 4, 8, and 11 during the double-blind phase.

Reporting group title	Esketamine 84 mg/Esketamine 84 mg

Reporting group description:

Participants in Panel A were self-administered intranasal esketamine 84 mg on Days 1, 4, 8, and 11 during the double-blind phase.

Reporting group title	Placebo/Placebo

Reporting group description:

Participants in Panel A and B (who received placebo on Day 1 and 4 and responders [Quick Inventory of Depressive Symptomatology – 16-item Self Report {QIDS-SR16} total score less than 11]) were self-administered with Placebo on Day 8 and 11; non-responders (Quick Inventory of Depressive Symptomatology – 16-item Self Report [QIDS-SR16] total score greater than or equal to [>=] 11) on Day 8 were re-randomized to intranasal placebo or esketamine on Days 8 and 11 during the double-blind phase.

Reporting group title	Placebo/Esketamine 14 mg

Reporting group description:

Participants in Panel B (who received placebo on Day 1 and 4 and non-responders (Quick Inventory of Depressive Symptomatology – 16-item Self Report [QIDS-SR16] total score greater than or equal to (>=) 11) on Day 8) were self-administered intranasal esketamine 14 mg on Days 8, and 11 during the double-blind phase.

Reporting group title	Placebo/Esketamine 28 mg

Reporting group description:

Participants in Panel A (who received placebo on Day 1 and 4 and non-responders [QIDS-SR16 total score >=11] on Day 8) were self-administered intranasal esketamine 28 mg on Days 8 and 11 during the double-blind phase.

Reporting group title	Placebo/Esketamine 56 mg

Reporting group description:

Participants in Panel A and B (who received placebo on Day 1 and 4 and non-responders [QIDS-SR16 total score >=11] on Day 8) were self-administered intranasal esketamine 56 mg on Day 8 and 11 during the double-blind phase.

Reporting group title	Placebo/Esketamine 84 mg

Reporting group description:

Participants in Panel A (who received placebo on Day 1 and 4 and non-responders [QIDS-SR16 total score >=11] on Day 8) were self-administered intranasal esketamine 84 mg on Days 8 and 11 during the double-blind phase.

Reporting group title	Esketamine 14 mg/Esketamine 14 mg

Reporting group description:

Participants in Panel B were self-administered intranasal esketamine 14 mg on Days 1, 4, 8, and 11 during the double-blind phase.

Reporting group title	Esketamine 28 mg

Reporting group description:

Participants in Panel A were self-administered intranasal esketamine 28 mg on Days 1, and 4 during the double-blind phase.

Reporting group title	Esketamine 28 mg/ Esketamine 28 mg

Reporting group description:

Participants in Panel A were self-administered intranasal esketamine 28 mg on Days 1, 4, 8, and 11

during the double-blind phase.

Reporting group values	Placebo	Esketamine 56 milligrams (mg)/Esketamine 56	Esketamine 84 mg/Esketamine 84 mg
Number of subjects	1	20	12
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	1	20	12
From 65 to 84 years	0	0	0
85 years and over	0	0	0
Title for AgeContinuous Units: years			
arithmetic mean	52	44	49.8
standard deviation	± 0	± 9.55	± 9.29
Title for Gender Units: subjects			
Female	0	13	6
Male	1	7	6

Reporting group values	Placebo/Placebo	Placebo/Esketamine 14 mg	Placebo/Esketamine 28 mg
Number of subjects	23	5	8
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	23	5	8
From 65 to 84 years	0	0	0
85 years and over	0	0	0
Title for AgeContinuous Units: years			
arithmetic mean	45.1	50.6	42.1
standard deviation	± 6.84	± 9.37	± 12.17
Title for Gender Units: subjects			
Female	10	2	5
Male	13	3	3

Reporting group values	Placebo/Esketamine 56 mg	Placebo/Esketamine 84 mg	Esketamine 14 mg/Esketamine 14 mg
Number of subjects	12	5	11
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	12	5	11
From 65 to 84 years	0	0	0

85 years and over	0	0	0

Title for AgeContinuous			
Units: years			
arithmetic mean	42.4	45.4	42.2
standard deviation	± 9.25	± 10.31	± 9.43
Title for Gender			
Units: subjects			
Female	8	2	4
Male	4	3	7

Reporting group values	Esketamine 28 mg	Esketamine 28 mg/ Esketamine 28 mg	Total
Number of subjects	3	8	108
Title for AgeCategorical			
Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	3	8	108
From 65 to 84 years	0	0	0
85 years and over	0	0	0
Title for AgeContinuous			
Units: years			
arithmetic mean	48.7	39.6	
standard deviation	± 5.77	± 10.81	-
Title for Gender			
Units: subjects			
Female	1	4	55
Male	2	4	53

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants in Panel A and B were self-administered intranasal placebo on Days 1 and 4 during the double-blind phase. Depending on response on Day 8, participants received intranasal placebo on Days 8 and 11 or were re-randomized to receive intranasal placebo or esketamine at a dose of 28 mg, 56 mg, or 84 mg (Panel A) or 14 mg or 56 mg (Panel B) on Day 8 and Day 11.	
Reporting group title	Esketamine 56 milligrams (mg)/Esketamine 56 mg
Reporting group description:	
Participants in Panel A and B were self-administered with intranasal esketamine 56 mg on Days 1, 4, 8, and 11 during the double-blind phase.	
Reporting group title	Esketamine 84 mg/Esketamine 84 mg
Reporting group description:	
Participants in Panel A were self-administered intranasal esketamine 84 mg on Days 1, 4, 8, and 11 during the double-blind phase.	
Reporting group title	Placebo/Placebo
Reporting group description:	
Participants in Panel A and B (who received placebo on Day 1 and 4 and responders [Quick Inventory of Depressive Symptomatology – 16-item Self Report {QIDS-SR16} total score less than 11]) were self-administered with Placebo on Day 8 and 11; non-responders (Quick Inventory of Depressive Symptomatology – 16-item Self Report [QIDS-SR16] total score greater than or equal to [>=] 11) on Day 8 were re-randomized to intranasal placebo or esketamine on Days 8 and 11 during the double-blind phase.	
Reporting group title	Placebo/Esketamine 14 mg
Reporting group description:	
Participants in Panel B (who received placebo on Day 1 and 4 and non-responders (Quick Inventory of Depressive Symptomatology – 16-item Self Report [QIDS-SR16] total score greater than or equal to (>=) 11) on Day 8) were self-administered intranasal esketamine 14 mg on Days 8, and 11 during the double-blind phase.	
Reporting group title	Placebo/Esketamine 28 mg
Reporting group description:	
Participants in Panel A (who received placebo on Day 1 and 4 and non-responders [QIDS-SR16 total score >=11] on Day 8) were self-administered intranasal esketamine 28 mg on Days 8 and 11 during the double-blind phase.	
Reporting group title	Placebo/Esketamine 56 mg
Reporting group description:	
Participants in Panel A and B (who received placebo on Day 1 and 4 and non-responders [QIDS-SR16 total score >=11] on Day 8) were self-administered intranasal esketamine 56 mg on Day 8 and 11 during the double-blind phase.	
Reporting group title	Placebo/Esketamine 84 mg
Reporting group description:	
Participants in Panel A (who received placebo on Day 1 and 4 and non-responders [QIDS-SR16 total score >=11] on Day 8) were self-administered intranasal esketamine 84 mg on Days 8 and 11 during the double-blind phase.	
Reporting group title	Esketamine 14 mg/Esketamine 14 mg
Reporting group description:	
Participants in Panel B were self-administered intranasal esketamine 14 mg on Days 1, 4, 8, and 11 during the double-blind phase.	
Reporting group title	Esketamine 28 mg
Reporting group description:	
Participants in Panel A were self-administered intranasal esketamine 28 mg on Days 1, and 4 during the double-blind phase.	
Reporting group title	Esketamine 28 mg/ Esketamine 28 mg
Reporting group description:	
Participants in Panel A were self-administered intranasal esketamine 28 mg on Days 1, 4, 8, and 11	

during the double-blind phase.

Reporting group title	Esketamine

Reporting group description:

Participants were received intranasal esketamine with a starting dose of 56-mg on Day 15 and subsequent doses on Days 18, 22, 25, 32, 39, and 46 and on Days 18, 22, and 25 (the dose of esketamine was adjusted based on the Investigator's clinical judgement of efficacy and tolerability) in Panel A and Panel B respectively.

Subject analysis set title	Panel A: Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects who received Placebo in Panel A.

Subject analysis set title	Panel A: Esketamine 28 mg
Subject analysis set type	Intention-to-treat

Subject analysis set description:

subjects who received at least one dose of Intranasal Esketamine 28 mg in Panel A.

Subject analysis set title	Panel A: Esketamine 56mg
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subject who received at least one dose of Intranasal Esketamine 56 mg in Panel A.

Subject analysis set title	Panel A: Esketamine 84mg
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects who received at least one dose of Intranasal Esketamine 84mg in Panel A.

Subject analysis set title	Panel B: Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects who received Placebo in Panel B were included.

Subject analysis set title	Panel B: Esketamine 14mg
Subject analysis set type	Intention-to-treat

Subject analysis set description:

subjects who received Intranasal Esketamine 14mg in Panel B were included.

Subject analysis set title	Panel B: Esketamine 56 mg
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects who received Intranasal Esketamine 56 mg in Panel B were included.

Primary: Change From Baseline to the 1-week Endpoint in Montgomery Asberg Depression Rating Scale (MADRS) Total Score

End point title	Change From Baseline to the 1-week Endpoint in Montgomery Asberg Depression Rating Scale (MADRS) Total Score

End point description:

The MADRS is a clinician-rated scale designed to measure depression severity and to detect changes due to antidepressant treatment. The scale consists of 10 items, each of which is scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms), for a total possible score of 60. Higher scores represent a more severe condition. Intent-to-treat population included all participants randomly assigned to treatment in Period 1 and who were considered non-responders (Quick Inventory of Depressive Symptomatology – 16-item Self Report [QIDS-SR16] total score less than 11) to placebo treatment in Period 1 and were then randomly reassigned to a treatment group in Period 2.

End point type	Primary

End point timeframe:

Day 1 to Day 15

End point values	Panel A: Placebo	Panel A: Esketamine 28 mg	Panel A: Esketamine 56mg	Panel A: Esketamine 84mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	33	11	11	12
Units: Units on a scale				
least squares mean (standard error)				
Double-blind(DB): Period 1 (n=33,11,11,12,21,11,9)	-4.9 (± 1.74)	-9.8 (± 2.72)	-12.4 (± 2.66)	-15.3 (± 2.56)
DB: Period 2 (n= 6, 8, 9, 5, 5, 5, 3)	-4.5 (± 2.92)	-7.6 (± 2.49)	-8.9 (± 2.51)	-11.4 (± 2.68)

End point values	Panel B: Placebo	Panel B: Esketamine 14mg	Panel B: Esketamine 56 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	21	11	9	
Units: Units on a scale				
least squares mean (standard error)				
Double-blind(DB): Period 1 (n=33,11,11,12,21,11,9)	-6.6 (± 1.53)	-4.8 (± 2.13)	-10.3 (± 2.36)	
DB: Period 2 (n= 6, 8, 9, 5, 5, 5, 3)	-0.7 (± 3.32)	-6.6 (± 4.02)	-1.2 (± 6.04)	

Statistical analyses

Statistical analysis title	Statistical analyses: Panel A: 1
Comparison groups	Panel A: Esketamine 28 mg v Panel A: Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.021
Method	ANCOVA
Parameter estimate	Mean Difference
Point estimate	-4.2
Confidence interval	
level	90 %
sides	2-sided
lower limit	-7.67
upper limit	-0.79
Variability estimate	Standard error of the mean
Dispersion value	2.09

Statistical analysis title	Statistical analyses: Panel A: 2

Comparison groups	Panel A: Placebo v Panel A: Esketamine 56mg
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	ANCOVA
Parameter estimate	Mean Difference
Point estimate	-6.3
Confidence interval	
level	90 %
sides	2-sided
lower limit	-9.71
upper limit	-2.88
Variability estimate	Standard error of the mean
Dispersion value	2.07

Statistical analysis title	Statistical analyses: Panel A: 3
Comparison groups	Panel A: Placebo v Panel A: Esketamine 84mg
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean Difference
Point estimate	-9
Confidence interval	
level	90 %
sides	2-sided
lower limit	-12.53
upper limit	-5.52
Variability estimate	Standard error of the mean
Dispersion value	2.13

Statistical analysis title	Statistical analyses: Panel B: 1
Comparison groups	Panel B: Placebo v Panel B: Esketamine 14mg
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Consistency
Point estimate	-10.5
Confidence interval	
level	90 %
sides	2-sided
lower limit	-29.27
upper limit	8.23

Variability estimate	Standard error of the mean
Dispersion value	11.72

Statistical analysis title	Statistical analyses: Panel B: 2
Comparison groups	Panel B: Esketamine 56 mg v Panel B: Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Consistency
Point estimate	1.8
Confidence interval	
level	90 %
sides	2-sided
lower limit	-21.42
upper limit	24.94
Variability estimate	Standard error of the mean
Dispersion value	14.49

Secondary: Percentage of Participants With Sustained Response (>=50% Reduction From Baseline in MADRS Total Score) With Onset by Day 2 Through the end of the Double-blind Phase (Day 15)

End point title	Percentage of Participants With Sustained Response (>=50% Reduction From Baseline in MADRS Total Score) With Onset by Day 2 Through the end of the Double-blind Phase (Day 15)

End point description:

Sustained response was defined as at least 50% improvement from baseline in the MADRS total score with onset by Day 2 that is maintained to study Day 15. Intent-to-treat population included all participants randomly assigned to treatment in Period 1 and who were considered non-responders to placebo treatment in Period 1 and were then randomly reassigned to a treatment group in Period 2.

End point type	Secondary

End point timeframe:

Day 2 to Day 15

End point values	Panel A: Esketamine 28 mg	Panel A: Esketamine 56mg	Panel A: Esketamine 84mg	Panel B: Esketamine 14mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8	11	12	11
Units: participants	1	1	3	2

End point values	Panel B: Esketamine 56 mg			

Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: participants	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Responders (>=) 50 Percent (%) Reduction From Baseline in MADRS Total Score) at Each Visit

End point title	Percentage of Responders (>=) 50 Percent (%) Reduction From Baseline in MADRS Total Score) at Each Visit

End point description:

A subject was defined as a responder at a given timepoint if the percentage improvement from baseline (ie, reduction from baseline) in the subject's MADRS total score was greater than or equal to (> =) 50 %. Intent-to-treat population included all participants randomly assigned to treatment in Period 1 and who were considered non-responders to placebo treatment in Period 1 and were then randomly reassigned to a treatment group in Period 2. Here 'n' signifies the number of participants evaluated at this time point.

End point type	Secondary

End point timeframe:

Day 1 to Day 15

End point values	Panel A: Placebo	Panel A: Esketamine 28 mg	Panel A: Esketamine 56mg	Panel A: Esketamine 84mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	33	11	11	12
Units: Participants				
number (not applicable)				
Period 1 Day 1 DB: 2 h (n=33,11,11,12,21,11,9)	6	6	4	7
Period 1 Day 2 DB (n=33,11,11,12,21,11,9)	1	4	3	5
Period 1 Day 8 DB (n=33,11,11,12,21,11,9)	2	1	2	5
Period 2 Day 1 DB: 2 h (n=6,8,9,5,5,5,3)	1	1	2	2
Period 2 Day 2 DB (n=6,8,9,5,5,5,3)	0	0	1	2
Period 2 Day 8 DB (n=6,8,9,5,5,5,3)	0	1	0	1

End point values	Panel B: Placebo	Panel B: Esketamine 14mg	Panel B: Esketamine 56 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	21	11	9	
Units: Participants				
number (not applicable)				

Period 1 Day 1 DB: 2 h (n=33,11,11,12,21,11,9)	7	4	4	
Period 1 Day 2 DB (n=33,11,11,12,21,11,9)	6	4	4	
Period 1 Day 8 DB (n=33,11,11,12,21,11,9)	5	2	2	
Period 2 Day 1 DB: 2 h (n=6,8,9,5,5,5,3)	0	3	0	
Period 2 Day 2 DB (n=6,8,9,5,5,5,3)	0	4	0	
Period 2 Day 8 DB (n=6,8,9,5,5,5,3)	0	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Remitters (Proportion of Subjects in Remission MADRS Total Score ≤10) at Each Visit

End point title	Percentage of Remitters (Proportion of Subjects in Remission MADRS Total Score ≤10) at Each Visit

End point description:

A subject was defined as a remitter at a given timepoint if the subject's MADRS total score was less than or equal to 10. Here 'n' signifies the number of participants evaluated at this time point. Intent-to-treat population included all participants randomly assigned to treatment in Period 1 and who were considered non-responders to placebo treatment in Period 1 and were then randomly reassigned to a treatment group in Period 2.

End point type	Secondary

End point timeframe:

Day 1 to Day 15

End point values	Panel A: Placebo	Panel A: Esketamine 28 mg	Panel A: Esketamine 56mg	Panel A: Esketamine 84mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	33	11	11	12
Units: participants				
number (not applicable)				
Period 1 Day 1 DB: 2 h (n=33,11,11,12,21,11,9)	1	3	2	2
Period 1 Day 2 DB (n=33,11,11,12,21,11,9)	0	4	2	3
Period 1 Day 8 DB (n=33,11,11,12,21,11,9)	1	1	1	3
Period 2 Day 1 DB: 2 h (n=6,8,9,5,5,5,3)	1	1	0	2
Period 2 Day 2 DB (n=6,8,9,5,5,5,3)	0	0	0	1
Period 2 Day 8 DB (n=6,8,9,5,5,5,3)	0	1	0	1

End point values	Panel B: Placebo	Panel B: Esketamine	Panel B: Esketamine 56	

		14mg	mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	21	11	9	
Units: participants				
number (not applicable)				
Period 1 Day 1 DB: 2 h (n=33,11,11,12,21,11,9)	4	4	3	
Period 1 Day 2 DB (n=33,11,11,12,21,11,9)	4	3	3	
Period 1 Day 8 DB (n=33,11,11,12,21,11,9)	3	2	2	
Period 2 Day 1 DB: 2 h (n=6,8,9,5,5,5,3)	0	3	0	
Period 2 Day 2 DB (n=6,8,9,5,5,5,3)	0	4	0	
Period 2 Day 8 DB (n=6,8,9,5,5,5,3)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Quick Inventory of Depressive Symptomatology – 16-Item Self Report (QIDS-SR16)

End point title	Quick Inventory of Depressive Symptomatology – 16-Item Self Report (QIDS-SR16)

End point description:

The QIDS-SR16 is a patient reported measure designed to assess the severity of depressive symptoms. The QIDS-SR16 assesses all the criterion symptom domains designated by the DSM-IV to diagnose a major depressive episode. This assessment can be used to screen for depression, although it has been used predominantly as a measure of symptom severity. Intent-to-treat population included all participants randomly assigned to treatment in Period 1 and who were considered non-responders to placebo treatment in Period 1 and were then randomly reassigned to a treatment group in Period 2. Here 'n' signifies the number of participants evaluated at this time point.

End point type	Secondary

End point timeframe:

Day 1 to Day 15

End point values	Panel A: Placebo	Panel A: Esketamine 28 mg	Panel A: Esketamine 56mg	Panel A: Esketamine 84mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	33	11	11	12
Units: participants				
least squares mean (standard error)				
DB: Period 1 (n= 33, 11, 11, 12, 21, 11, 9)	-1.8 (± 0.93)	-4 (± 1.43)	-4.4 (± 1.43)	-4.2 (± 1.39)
DB: Period 2 (n=6, 8, 9, 5, 5, 5, 3)	-2 (± 1.5)	-3.1 (± 1.35)	-2 (± 1.41)	-3.3 (± 1.48)

End point values	Panel B: Placebo	Panel B: Esketamine 14mg	Panel B: Esketamine 56 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	21	11	9	
Units: participants				
least squares mean (standard error)				
DB: Period 1 (n= 33, 11, 11, 12, 21, 11, 9)	-1.1 (± 0.78)	-0.6 (± 1.1)	-3 (± 1.2)	
DB: Period 2 (n=6, 8, 9, 5, 5, 5, 3)	-2.1 (± 1.78)	-5.7 (± 1.78)	-1.5 (± 2.31)	

Statistical analyses

Statistical analysis title	Statistical analyses_Panel A_1
Comparison groups	Panel A: Placebo v Panel A: Esketamine 28 mg
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.069 [1]
Method	ANCOVA

Notes:

[1] - One sided P-value

Statistical analysis title	Statistical analyses_Panel A_3
Comparison groups	Panel A: Placebo v Panel A: Esketamine 84mg
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.046 [2]
Method	ANCOVA

Notes:

[2] - One sided P-value

Statistical analysis title	Statistical analyses_Panel A_2
Comparison groups	Panel A: Placebo v Panel A: Esketamine 56mg
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.096 [3]
Method	ANCOVA

Notes:

[3] - One sided P-value

Secondary: Change From Baseline in Severity of Illness Using the Clinical Global Impression Severity (CGI-S) Scale

End point title	Change From Baseline in Severity of Illness Using the Clinical Global Impression Severity (CGI-S) Scale

End point description:

The CGI-S rating scale is a 7-point global assessment that measures the clinician's impression of the

severity of illness exhibited by a participant. A rating of 1 is equivalent to "Normal, not at all ill" and a rating of 7 is equivalent to "Among the most extremely ill participants". Higher scores indicate worsening. Intent-to-treat population included all participants randomly assigned to treatment in Period 1 and who were considered non-responders to placebo treatment in Period 1 and were then randomly reassigned to a treatment group in Period 2. Here 'n' signifies the number of participants evaluated at this time point.

End point type	Secondary
End point timeframe:	
Day 1 to Day 15	

End point values	Panel A: Placebo	Panel A: Esketamine 28 mg	Panel A: Esketamine 56mg	Panel A: Esketamine 84mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	33	11	11	12
Units: participants				
median (full range (min-max))				
DB: Period 1 (n=33,11,11,12,21,11,9)	5 (1 to 6)	4 (3 to 5)	4 (1 to 5)	4 (1 to 6)
DB: Period 2 (n= 6, 8, 9, 5, 5, 5, 3)	5 (4 to 5)	4 (3 to 5)	5 (4 to 6)	4 (3 to 5)

End point values	Panel B: Placebo	Panel B: Esketamine 14mg	Panel B: Esketamine 56 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	21	11	9	
Units: participants				
median (full range (min-max))				
DB: Period 1 (n=33,11,11,12,21,11,9)	4 (1 to 6)	4 (2 to 6)	3 (3 to 6)	
DB: Period 2 (n= 6, 8, 9, 5, 5, 5, 3)	4 (3 to 6)	3 (3 to 4)	4 (4 to 5)	

Statistical analyses

Statistical analysis title	Statistical analyses_Panel A_1
Comparison groups	Panel A: Placebo v Panel A: Esketamine 28 mg
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	Statistical analyses_Panel A_2
Comparison groups	Panel A: Placebo v Panel A: Esketamine 56mg

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	Statistical analyses_Panel A_3
Comparison groups	Panel A: Placebo v Panel A: Esketamine 84mg
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	ANCOVA

Secondary: Change From Baseline in Severity of Illness Using the Patient Global Impression - Severity (PGI-S) Scale

End point title	Change From Baseline in Severity of Illness Using the Patient Global Impression - Severity (PGI-S) Scale

End point description:

The PGI-S is a 4-point scale that requires the participant to rate the severity of their illness at the time of assessment, relative to the participant's past experience. Considering their total experience, the patient assesses the severity of their depression illness at the time of rating as none, mild, moderate, or severe. Paper and pen format will be used for this study. Intent-to-treat population included all participants randomly assigned to treatment in Period 1 and who were considered non-responders to placebo treatment in Period 1 and were then randomly reassigned to a treatment group in Period 2. Here 'n' signifies the number of participants evaluated at this time point.

End point type	Secondary

End point timeframe:

Day 1 to Day 15

End point values	Panel A: Placebo	Panel A: Esketamine 28 mg	Panel A: Esketamine 56mg	Panel A: Esketamine 84mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	33	11	11	12
Units: participants				
median (full range (min-max))				
DB: Period 1 (n= 33, 11, 11, 12, 21, 11, 9)	3 (2 to 4)	3 (1 to 4)	3 (1 to 3)	3 (1 to 4)
DB: Period 2 (n= 6, 8, 9, 5, 5, 5, 3)	3 (2 to 4)	3 (2 to 4)	4 (2 to 4)	3 (2 to 4)

End point values	Panel B: Placebo	Panel B: Esketamine 14mg	Panel B: Esketamine 56 mg	

Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	21	11	9	
Units: participants				
median (full range (min-max))				
DB: Period 1 (n= 33, 11, 11, 12, 21, 11, 9)	3 (2 to 4)	3 (1 to 3)	3 (2 to 3)	
DB: Period 2 (n= 6, 8, 9, 5, 5, 5, 3)	3 (2 to 3)	3 (2 to 3)	3 (2 to 4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Anxiety Symptoms, as Measured by the Generalized Anxiety Disorder 7-Item (GAD-7) Scale

End point title	Change From Baseline in Anxiety Symptoms, as Measured by the Generalized Anxiety Disorder 7-Item (GAD-7) Scale

End point description:

The GAD-7 is a 7-item self-report assessment of severity of anxiety. Each item is scored on a 4-point scale (0-3), with a total score range of 0-30. The standard recall period used is 2 weeks, but in the current study we plan to use a 7-day recall. Intent-to-treat population included all participants randomly assigned to treatment in Period 1 and who were considered non-responders to placebo treatment in Period 1 and were then randomly reassigned to a treatment group in Period 2. Here 'n' signifies the number of participants evaluated at this time point.

End point type	Secondary

End point timeframe:

Day 1 to Day 15

End point values	Panel A: Placebo	Panel A: Esketamine 28 mg	Panel A: Esketamine 56mg	Panel A: Esketamine 84mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	33	11	11	12
Units: participants				
least squares mean (standard error)				
DB: Period 1 (n= 33, 11, 11, 12, 21, 11, 9)	-1.7 (± 0.88)	-1.5 (± 1.34)	-3.1 (± 1.34)	-5.1 (± 1.3)
DB: Period 2 (n= 6, 8, 9, 5, 5, 5, 3)	0.4 (± 1.02)	-1.6 (± 0.87)	1 (± 0.98)	-0.9 (± 1.02)

End point values	Panel B: Placebo	Panel B: Esketamine 14mg	Panel B: Esketamine 56 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	21	11	9	
Units: participants				
least squares mean (standard error)				
DB: Period 1 (n= 33, 11, 11, 12, 21, 11, 9)	-1.7 (± 0.68)	-1.9 (± 0.94)	-3.2 (± 1.03)	
DB: Period 2 (n= 6, 8, 9, 5, 5, 5, 3)	-2.7 (± 1.68)	-6.6 (± 1.68)	-0.7 (± 2.27)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

up to follow-up phase (8 weeks after last dose of drug administration)

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Placebo/Placebo

Reporting group description:

Participants in Panel A and B (who received placebo on Day 1 and 4 and responders [Quick Inventory of Depressive Symptomatology – 16-item Self Report {QIDS-SR16} total score less than 11]) were self-administered with Placebo on Day 8 and 11; non-responders (Quick Inventory of Depressive Symptomatology – 16-item Self Report [QIDS-SR16] total score greater than or equal to [>=] 11) on Day 8 were re-randomized to intranasal placebo or esketamine on Days 8 and 11 during the doubleblind phase.

Reporting group title	Placebo

Reporting group description:

Participants in Panel A and B were self-administered intranasal placebo on Days 1 and 4 during the double-blind phase. Depending on response on Day 8, participants received intranasal placebo on Days 8 and 11 or were re-randomized to receive intranasal placebo or esketamine at a dose of 28 mg, 56 mg, or 84 mg (Panel A) or 14 mg or 56 mg (Panel B) on Day 8 and Day 11.

Reporting group title	Placebo/Esketamine 14 mg

Reporting group description:

Participants in Panel B (who received placebo on Day 1 and 4 and non-responders (Quick Inventory of Depressive Symptomatology – 16-item Self Report [QIDS-SR16] total score greater than or equal to (>=) 11) on Day 8) were self-administered intranasal esketamine 14 mg on Days 8, and 11 during the double-blind phase and continued in the open label treatment phase for up to 2 weeks (Days 15, 18, 22, and 25). The dose of esketamine was adjusted based on the Investigator's clinical judgement of efficacy and tolerability.

Reporting group title	Placebo/Esketamine 28 mg

Reporting group description:

Participants in Panel A (who received placebo on Day 1 and 4 and non-responders [QIDS-SR16 total score >=11] on Day 8) were self-administered intranasal esketamine 28 mg on Days 8 and 11 during the double-blind phase and continued in the open label treatment phase for up to 9 weeks (Days 15, 18, 22, 25, 32, 39, 46, 60, and 74). The dose of esketamine was adjusted based on the Investigator's clinical judgement of efficacy and tolerability.

Reporting group title	Placebo/Esketamine 56 mg

Reporting group description:

Participants in Panel A and B (who received placebo on Day 1 and 4 and non-responders [QIDS-SR16 total score >=11] on Day 8) were self-administered intranasal esketamine 56 mg on Day 8 and 11 during the double-blind phase and continued in the open label treatment phase for up to 9 weeks in Panel A and up to 2 weeks in Panel B. The dose of esketamine was adjusted based on the Investigator's clinical judgement of efficacy and tolerability.

Reporting group title	Placebo/Esketamine 84 mg

Reporting group description:

Participants in Panel A (who received placebo on Day 1 and 4 and non-responders [QIDS-SR16 total score >=11] on Day 8) were self-administered intranasal esketamine 84 mg on Days 8 and 11 during the double-blind phase and continued in the open label treatment phase for up to 9 weeks (Days 15, 18, 22, 25, 32, 39, 46, 60, and 74). The dose of esketamine was adjusted based on the Investigator's clinical judgement of efficacy and tolerability.

Reporting group title	Esketamine 28 mg/Esketamine 28 mg

Reporting group description:

Participants in Panel A were self-administered intranasal esketamine 28 mg on Days 1, 4, 8, and 11 during the double-blind phase and in optional open-label phase intranasal esketamine on Days 15, 18, 22, 25, 32, 39, 46, 60, and 74. During the optional open-label phase, all participants were started

treatment with a 56-mg dose of intranasal esketamine on Day 15 (the dose of esketamine was adjusted based on the Investigator's clinical judgement of efficacy and tolerability).

Reporting group title	Esketamine 28 mg

Reporting group description:

Participants in Panel A were self-administered intranasal esketamine 28 mg on Days 1, and 4 during the double-blind phase.

Reporting group title	Esketamine 14 mg/Esketamine 14 mg

Reporting group description:

Participants in Panel B were self-administered intranasal esketamine 14 mg on Days 1, 4, 8, and 11 during the double-blind phase and intranasal esketamine on Days 15, 18, 22, and 25 during the optional open-label phase. During the optional open-label phase, participants were started with treatment with a 56-mg dose of intranasal esketamine on Day 15 (the dose of esketamine was adjusted based on the Investigator's clinical judgement of efficacy and tolerability).

Reporting group title	Esketamine 84 mg/Esketamine 84 mg

Reporting group description:

Participants in Panel A were self-administered intranasal esketamine 84 mg on Days 1, 4, 8, and 11 during the double-blind phase and in optional open-label phase intranasal esketamine for up to 9 weeks. During the optional open-label phase, all participants were started treatment with a 56-mg dose of intranasal esketamine on Day 15 (the dose of esketamine was adjusted based on the Investigator's clinical judgement of efficacy and tolerability).

Reporting group title	Esketamine 56 mg/Esketamine 56 mg

Reporting group description:

Participants in Panel A and B were self-administered intranasal esketamine 56 mg on Days 1, 4, 8, and 11 during the double-blind phase and in optional open-label phase intranasal esketamine for up to 9 weeks in Panel A and for up to 2 weeks in Panel B. During the optional open-label phase, all participants were started treatment with a 56-mg dose of intranasal esketamine on Day 15 (the dose of esketamine was adjusted based on the Investigator's clinical judgement of efficacy and tolerability).

Serious adverse events	Placebo/Placebo	Placebo	Placebo/Esketamine 14 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 23 (4.35%)	0 / 1 (0.00%)	0 / 5 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Gastrointestinal disorders			
Oesophagitis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo/Esketamine 28 mg	Placebo/Esketamine 56 mg	Placebo/Esketamine 84 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Gastrointestinal disorders			
Oesophagitis			

subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Esketamine 28 mg/Esketamine 28 mg	Esketamine 28 mg	Esketamine 14 mg/Esketamine 14 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Gastrointestinal disorders			
Oesophagitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Esketamine 84 mg/Esketamine 84 mg	Esketamine 56 mg/Esketamine 56 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Gastrointestinal disorders			
Oesophagitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo/Placebo	Placebo	Placebo/Esketamine 14 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 23 (65.22%)	1 / 1 (100.00%)	5 / 5 (100.00%)
Vascular disorders			
Hot Flush			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Hypertension			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Peripheral Coldness			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 23 (8.70%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	3	0	0
Chills			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Discomfort			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Energy Increased			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Feeling Abnormal			
subjects affected / exposed	1 / 23 (4.35%)	0 / 1 (0.00%)	2 / 5 (40.00%)
occurrences (all)	2	0	6
Feeling Drunk			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Feeling Hot			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Feeling Jittery			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Gait Disturbance			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hangover			

subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Injection Site Haemorrhage			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Pain			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Product Taste Abnormal			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Sluggishness			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Thirst			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Dry Throat			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hyperventilation			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nasal Congestion			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nasal Discomfort			

subjects affected / exposed	2 / 23 (8.70%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Nasal Dryness			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nasal Mucosal Disorder			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nasal Obstruction			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nasal Oedema			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nasal Pruritus			
subjects affected / exposed	0 / 23 (0.00%)	1 / 1 (100.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal Pain			
subjects affected / exposed	2 / 23 (8.70%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Pharyngeal Disorder			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Pharyngeal Hypoaesthesia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Sneezing			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Throat Irritation			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Upper-Airway Cough Syndrome			

subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Confusional State			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Daydreaming			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Dissociation			
subjects affected / exposed	0 / 23 (0.00%)	1 / 1 (100.00%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Dissociative Disorder			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Dysphoria			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Fear			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hallucination, Visual			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Illusion			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Merycism			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Somatic Hallucination			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Suspiciousness			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Thinking Abnormal			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Investigations			
Blood Pressure Diastolic Increased			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Blood Pressure Increased			
subjects affected / exposed	1 / 23 (4.35%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	4
Blood Pressure Systolic Increased			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Oxygen Saturation Decreased			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 23 (4.35%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Scratch			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Skin Abrasion			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Palpitations			
subjects affected / exposed	1 / 23 (4.35%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Sinus Bradycardia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Akathisia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Altered State of Consciousness			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Coordination Abnormal			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Disturbance in Attention			
subjects affected / exposed	1 / 23 (4.35%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	2 / 5 (40.00%)
occurrences (all)	0	0	3
Dizziness Postural			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Dysaesthesia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Dysgeusia			
subjects affected / exposed	6 / 23 (26.09%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	13	0	2
Dysgraphia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Dyskinesia			

subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	5 / 23 (21.74%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	8	0	0
Hypersomnia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypoaesthesia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	2	0	1
Loss of Consciousness			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Mental Impairment			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Psychomotor Hyperactivity			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Sedation			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Slow Speech			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	7 / 23 (30.43%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	12	0	2
Syncope			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Tremor			

subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Tunnel Vision			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Visual Field Defect			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Ear Congestion			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Vertigo			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Accommodation Disorder			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Conjunctival Hyperaemia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Vision Blurred			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Visual Impairment			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Abdominal Pain Upper			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			

subjects affected / exposed	1 / 23 (4.35%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Hypoaesthesia Oral			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	3 / 23 (13.04%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	8	0	1
Oral Discomfort			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Paraesthesia Oral			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Salivary Hypersecretion			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Dermatitis Contact			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hyperhidrosis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Scab			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Renal and urinary disorders			
Bladder Pain			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Micturition Urgency			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Polyuria			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Limb Discomfort			
subjects affected / exposed	1 / 23 (4.35%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Muscle Tightness			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Pain in Extremity			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Cystitis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased Appetite			

subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Placebo/Esketamine 28 mg	Placebo/Esketamine 56 mg	Placebo/Esketamine 84 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 8 (50.00%)	11 / 12 (91.67%)	5 / 5 (100.00%)
Vascular disorders			
Hot Flush			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypertension			
subjects affected / exposed	0 / 8 (0.00%)	3 / 12 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	7	0
Peripheral Coldness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Chills			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Discomfort			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Energy Increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Feeling Abnormal			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Feeling Drunk			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Feeling Hot			

subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Feeling Jittery			
subjects affected / exposed	1 / 8 (12.50%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Gait Disturbance			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Hangover			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Injection Site Haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Product Taste Abnormal			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Sluggishness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Thirst			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Dry Throat			

subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Hyperventilation			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Nasal Congestion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Nasal Discomfort			
subjects affected / exposed	0 / 8 (0.00%)	2 / 12 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	3	0
Nasal Dryness			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Nasal Mucosal Disorder			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Nasal Obstruction			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Nasal Oedema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Nasal Pruritus			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Oropharyngeal Pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	2
Pharyngeal Disorder			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Pharyngeal Hypoaesthesia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Rhinorrhoea			

subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Sneezing			
subjects affected / exposed	1 / 8 (12.50%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Throat Irritation			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	1 / 5 (20.00%)
occurrences (all)	0	2	1
Upper-Airway Cough Syndrome			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	1 / 5 (20.00%)
occurrences (all)	0	1	2
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Confusional State			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Daydreaming			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Dissociation			
subjects affected / exposed	0 / 8 (0.00%)	4 / 12 (33.33%)	1 / 5 (20.00%)
occurrences (all)	0	5	2
Dissociative Disorder			
subjects affected / exposed	1 / 8 (12.50%)	0 / 12 (0.00%)	1 / 5 (20.00%)
occurrences (all)	2	0	2
Dysphoria			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Fear			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Hallucination, Visual			
subjects affected / exposed	1 / 8 (12.50%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	2	1	0

Illusion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 12 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Merycism			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Somatic Hallucination			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Suspiciousness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Thinking Abnormal			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Investigations			
Blood Pressure Diastolic Increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Blood Pressure Increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Blood Pressure Systolic Increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Oxygen Saturation Decreased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Scratch			

subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Skin Abrasion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Palpitations			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Sinus Bradycardia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Akathisia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Altered State of Consciousness			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Coordination Abnormal			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Disturbance in Attention			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 8 (0.00%)	4 / 12 (33.33%)	3 / 5 (60.00%)
occurrences (all)	0	6	6
Dizziness Postural			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Dysaesthesia			

subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Dysgeusia			
subjects affected / exposed	1 / 8 (12.50%)	2 / 12 (16.67%)	3 / 5 (60.00%)
occurrences (all)	2	4	6
Dysgraphia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Dyskinesia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	2 / 8 (25.00%)	3 / 12 (25.00%)	1 / 5 (20.00%)
occurrences (all)	2	4	1
Hypersomnia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypoaesthesia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Loss of Consciousness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Mental Impairment			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Paraesthesia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Psychomotor Hyperactivity			
subjects affected / exposed	1 / 8 (12.50%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Sedation			
subjects affected / exposed	1 / 8 (12.50%)	0 / 12 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Slow Speech			

subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	0 / 8 (0.00%)	2 / 12 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	3	0
Syncope			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Tunnel Vision			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Visual Field Defect			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Ear Congestion			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Vertigo			
subjects affected / exposed	0 / 8 (0.00%)	2 / 12 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	4	0
Eye disorders			
Accommodation Disorder			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Conjunctival Hyperaemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Vision Blurred			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	2
Visual Impairment			

subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Abdominal Pain Upper			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypoaesthesia Oral			
subjects affected / exposed	0 / 8 (0.00%)	2 / 12 (16.67%)	1 / 5 (20.00%)
occurrences (all)	0	3	1
Nausea			
subjects affected / exposed	0 / 8 (0.00%)	2 / 12 (16.67%)	2 / 5 (40.00%)
occurrences (all)	0	2	2
Oral Discomfort			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Paraesthesia Oral			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Salivary Hypersecretion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Dermatitis Contact			

subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hyperhidrosis			
subjects affected / exposed	0 / 8 (0.00%)	2 / 12 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Pruritus			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Scab			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Bladder Pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Micturition Urgency			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Polyuria			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Limb Discomfort			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Muscle Tightness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Pain in Extremity			

subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Cystitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Esketamine 28 mg/Esketamine 28 mg	Esketamine 28 mg	Esketamine 14 mg/Esketamine 14 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 8 (75.00%)	2 / 3 (66.67%)	8 / 11 (72.73%)
Vascular disorders			
Hot Flush			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Hypertension			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Peripheral Coldness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Chills			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Discomfort			

subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Energy Increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Feeling Abnormal			
subjects affected / exposed	2 / 8 (25.00%)	0 / 3 (0.00%)	2 / 11 (18.18%)
occurrences (all)	2	0	8
Feeling Drunk			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Feeling Hot			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Feeling Jittery			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Gait Disturbance			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Hangover			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Injection Site Haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Malaise			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Product Taste Abnormal			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Pyrexia			

subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Sluggishness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Thirst			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Dry Throat			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Hyperventilation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Nasal Congestion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Nasal Discomfort			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Nasal Dryness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Nasal Mucosal Disorder			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Nasal Obstruction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Nasal Oedema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Nasal Pruritus			

subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Oropharyngeal Pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	2
Pharyngeal Disorder			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Pharyngeal Hypoaesthesia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Sneezing			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Throat Irritation			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Upper-Airway Cough Syndrome			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Confusional State			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Daydreaming			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Dissociation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0

Dissociative Disorder			
subjects affected / exposed	0 / 8 (0.00%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Dysphoria			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Fear			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Hallucination, Visual			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Illusion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Merycism			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Somatic Hallucination			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Suspiciousness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Thinking Abnormal			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Investigations			
Blood Pressure Diastolic Increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Blood Pressure Increased			

subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Blood Pressure Systolic Increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Oxygen Saturation Decreased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Scratch			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Skin Abrasion			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Palpitations			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Sinus Bradycardia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Nervous system disorders			
Akathisia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Altered State of Consciousness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Coordination Abnormal			

subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Disturbance in Attention			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	4 / 8 (50.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	16	0	2
Dizziness Postural			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Dysaesthesia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Dysgeusia			
subjects affected / exposed	2 / 8 (25.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	4	0	4
Dysgraphia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Dyskinesia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	3 / 8 (37.50%)	1 / 3 (33.33%)	2 / 11 (18.18%)
occurrences (all)	4	1	5
Hypersomnia			
subjects affected / exposed	2 / 8 (25.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Hypoaesthesia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	2 / 11 (18.18%)
occurrences (all)	1	0	4
Loss of Consciousness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Mental Impairment			

subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Psychomotor Hyperactivity			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Sedation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Slow Speech			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	2 / 11 (18.18%)
occurrences (all)	2	0	3
Syncope			
subjects affected / exposed	0 / 8 (0.00%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Tremor			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Tunnel Vision			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Visual Field Defect			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Ear Congestion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Vertigo			
subjects affected / exposed	1 / 8 (12.50%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	1	1	0

Eye disorders			
Accommodation Disorder			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Conjunctival Hyperaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Vision Blurred			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Visual Impairment			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Abdominal Pain Upper			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Hypoaesthesia Oral			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	2 / 8 (25.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	3	0	2
Oral Discomfort			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Paraesthesia Oral			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Salivary Hypersecretion			

subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Dermatitis Contact			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Hyperhidrosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Scab			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Bladder Pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Micturition Urgency			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Polyuria			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Limb Discomfort			

subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Muscle Tightness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Pain in Extremity			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Infections and infestations			
Cystitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	0 / 8 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1

Non-serious adverse events	Esketamine 84 mg/Esketamine 84 mg	Esketamine 56 mg/Esketamine 56 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 12 (83.33%)	18 / 20 (90.00%)	
Vascular disorders			
Hot Flush			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Hypertension			
subjects affected / exposed	1 / 12 (8.33%)	1 / 20 (5.00%)	
occurrences (all)	4	4	
Peripheral Coldness			
subjects affected / exposed	0 / 12 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	5	

General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Chills			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Discomfort			
subjects affected / exposed	0 / 12 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	3	
Energy Increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Feeling Abnormal			
subjects affected / exposed	1 / 12 (8.33%)	4 / 20 (20.00%)	
occurrences (all)	10	12	
Feeling Drunk			
subjects affected / exposed	0 / 12 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
Feeling Hot			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Feeling Jittery			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Gait Disturbance			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Hangover			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Injection Site Haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Malaise			

subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Product Taste Abnormal			
subjects affected / exposed	1 / 12 (8.33%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Pyrexia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Sluggishness			
subjects affected / exposed	0 / 12 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Thirst			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Dry Throat			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Hyperventilation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Nasal Congestion			
subjects affected / exposed	1 / 12 (8.33%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Nasal Discomfort			
subjects affected / exposed	1 / 12 (8.33%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Nasal Dryness			
subjects affected / exposed	1 / 12 (8.33%)	0 / 20 (0.00%)	
occurrences (all)	3	0	
Nasal Mucosal Disorder			

subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Nasal Obstruction			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Nasal Oedema			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Nasal Pruritus			
subjects affected / exposed	1 / 12 (8.33%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal Pain			
subjects affected / exposed	1 / 12 (8.33%)	1 / 20 (5.00%)	
occurrences (all)	1	2	
Pharyngeal Disorder			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Pharyngeal Hypoaesthesia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Rhinorrhoea			
subjects affected / exposed	0 / 12 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Sneezing			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Throat Irritation			
subjects affected / exposed	1 / 12 (8.33%)	0 / 20 (0.00%)	
occurrences (all)	10	0	
Upper-Airway Cough Syndrome			
subjects affected / exposed	1 / 12 (8.33%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	

Confusional State			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Daydreaming			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Dissociation			
subjects affected / exposed	3 / 12 (25.00%)	6 / 20 (30.00%)	
occurrences (all)	7	18	
Dissociative Disorder			
subjects affected / exposed	3 / 12 (25.00%)	1 / 20 (5.00%)	
occurrences (all)	8	3	
Dysphoria			
subjects affected / exposed	1 / 12 (8.33%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Fear			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Hallucination, Visual			
subjects affected / exposed	0 / 12 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
Illusion			
subjects affected / exposed	0 / 12 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Insomnia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Merycism			
subjects affected / exposed	1 / 12 (8.33%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Somatic Hallucination			
subjects affected / exposed	0 / 12 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Suspiciousness			
subjects affected / exposed	0 / 12 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	

Thinking Abnormal			
subjects affected / exposed	0 / 12 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	4	
Investigations			
Blood Pressure Diastolic Increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Blood Pressure Increased			
subjects affected / exposed	0 / 12 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	5	
Blood Pressure Systolic Increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Oxygen Saturation Decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Scratch			
subjects affected / exposed	0 / 12 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Skin Abrasion			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Palpitations			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Sinus Bradycardia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	

Nervous system disorders			
Akathisia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Altered State of Consciousness			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Coordination Abnormal			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Disturbance in Attention			
subjects affected / exposed	1 / 12 (8.33%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	5 / 12 (41.67%)	7 / 20 (35.00%)	
occurrences (all)	11	25	
Dizziness Postural			
subjects affected / exposed	0 / 12 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Dysaesthesia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Dysgeusia			
subjects affected / exposed	3 / 12 (25.00%)	4 / 20 (20.00%)	
occurrences (all)	8	13	
Dysgraphia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	4	
Dyskinesia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
Headache			
subjects affected / exposed	2 / 12 (16.67%)	4 / 20 (20.00%)	
occurrences (all)	2	5	
Hypersomnia			

subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Hypoaesthesia			
subjects affected / exposed	1 / 12 (8.33%)	4 / 20 (20.00%)	
occurrences (all)	1	15	
Loss of Consciousness			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Mental Impairment			
subjects affected / exposed	1 / 12 (8.33%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Paraesthesia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Psychomotor Hyperactivity			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Sedation			
subjects affected / exposed	0 / 12 (0.00%)	3 / 20 (15.00%)	
occurrences (all)	0	6	
Slow Speech			
subjects affected / exposed	1 / 12 (8.33%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Somnolence			
subjects affected / exposed	0 / 12 (0.00%)	3 / 20 (15.00%)	
occurrences (all)	0	9	
Syncope			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Tremor			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Tunnel Vision			
subjects affected / exposed	2 / 12 (16.67%)	0 / 20 (0.00%)	
occurrences (all)	7	0	
Visual Field Defect			

subjects affected / exposed	0 / 12 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	4	
Ear and labyrinth disorders			
Ear Congestion			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Vertigo			
subjects affected / exposed	1 / 12 (8.33%)	0 / 20 (0.00%)	
occurrences (all)	4	0	
Eye disorders			
Accommodation Disorder			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Conjunctival Hyperaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Vision Blurred			
subjects affected / exposed	1 / 12 (8.33%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Visual Impairment			
subjects affected / exposed	0 / 12 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Abdominal Pain Upper			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Diarrhoea			
subjects affected / exposed	1 / 12 (8.33%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Hypoaesthesia Oral			
subjects affected / exposed	1 / 12 (8.33%)	3 / 20 (15.00%)	
occurrences (all)	3	8	
Nausea			

subjects affected / exposed	3 / 12 (25.00%)	6 / 20 (30.00%)	
occurrences (all)	3	9	
Oral Discomfort			
subjects affected / exposed	0 / 12 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
Paraesthesia Oral			
subjects affected / exposed	0 / 12 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	4	
Salivary Hypersecretion			
subjects affected / exposed	0 / 12 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Stomatitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Vomiting			
subjects affected / exposed	0 / 12 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Dermatitis Contact			
subjects affected / exposed	1 / 12 (8.33%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Hyperhidrosis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Pruritus			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Scab			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Renal and urinary disorders			
Bladder Pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Micturition Urgency			

subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Polyuria			
subjects affected / exposed	0 / 12 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Limb Discomfort			
subjects affected / exposed	1 / 12 (8.33%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Muscle Tightness			
subjects affected / exposed	0 / 12 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
Myalgia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Pain in Extremity			
subjects affected / exposed	0 / 12 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Cystitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	0 / 12 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 December 2013	The purpose of this Amendment was: A new panel (Panel B) was added to evaluate the efficacy of intranasal esketamine in Japanese subjects with treatment-resistant depression (TRD); Text was added to indicate that review of the number of re-randomized and drop-out subjects at the end of Period 1 was a blinded Interactive Web Response System (IWRS) review; Clinical Global Assessment of Alertness was added to the safety evaluations to further assess the subject's level of alertness after dosing; Nasal tolerability questionnaire and Clinical Global Assessment of Alertness were added into the recommended order of assessments; Text revised to indicate that clinical assessment of major depressive disorder (MDD) used diagnostic criteria from Diagnostic and Statistical Manual of Mental Disorders (4th edition), text revised (DSM-IV-TR) instead of Diagnostic and Statistical Manual of Mental Disorders (5th edition) (DSM-5); Risk language used to describe enrollment criteria and prohibitions and restrictions was revised; Lower end of the age range was revised from 18 to 20 years of age to align Panels A and B; Rhinoplasty was added to the list of excluded anatomical or medical conditions in the exclusion criteria; Additional clarification and guidance for study procedures provided (eg, information regarding staff and equipment requirements for dosing, frequency of pulse oximetry monitoring, duration and recording of prestudy and concomitant therapies, study diary procedures, reasons for withdrawal, requirements for early termination visit, dose adjustment in open-label treatment phase, statistical analysis methods for safety data, prohibited therapies, tympanic temperature, completion of the MGH-ATRQ).
04 March 2014	The purpose of this Amendment was: Duration of the optional open-label treatment phase for Panel A was extended to allow exploration of the efficacy and safety of intranasal esketamine when the frequency of administration was tapered from twice per week to once per week to once every other week; Safety evaluation (ie, BPIC-SS assessment) was added to monitor subjects for symptoms of cystitis; Timing of the clinical laboratory tests was modified to ensure tests were performed over the extended duration of the open-label treatment phase; Text revised to specify that pharmacogenomic evaluations were only to be used for research releated to esketamine; Potential interim PK/PD analysis was added for Panel A; The PHQ-9 was added to the efficacy measures to provide data on this assessment in the event it is used as the self-report depression rating scale in further studies of intranasal esketamine in subjects with TRD; Text added to specify how the sleep and appetite items of the modified MADRS were to be handled; Respiratory rate was added to the list of vital sign assessments on all dosing days; Exclusion criteria were revised: to exclude subjects with a current or prior diagnosis of post-traumatic stress disorder (PTSD) or obsessive-compulsive disorder (OCD), to permit enrollment of subjects with signs and symptoms of rhinitis, to add a criterion that defined clinically significant ECG abnormalities that were exclusionary, to exclude subjects with a history or current symptoms of fibromyalgia, and to clarify timing of procedures related to exclusion criteria; Time and Events Schedule was revised: to add evaluation of potential withdrawal symptoms following last dose of study medication in the open-label treatment phase, to add a PK sample on Days 1 and 11, to include a definition of postdose, and to specify collection of past psychiatric and family psychiatric history.
28 April 2014	The purpose of this Amendment was to included the following changes; Objective cognitive assessments (Cogstate® computerized test battery and HVLT-R) were added to formally assess cognition in Panel A subjects receiving esketamine during the open-label treatment phase; Additional BPIC-SS assessment and urinalysis were added on Day 46 for Panel A; Prohibitions and restrictions of prestudy and concomitant therapies were revised to avoid potential impact of certain therapies on cognitive and/or efficacy assessments.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported