Clinical trial results:
A Double-blind, Randomized, Psychoactive Placebo-controlled, Study to Evaluate the Efficacy and Safety of 3 Fixed Doses (28 mg, 56 mg and 84 mg) of Intranasal Esketamine in Addition to Comprehensive Standard of Care for the Rapid Reduction of the Symptoms of Major Depressive Disorder, Including Suicidal Ideation, in Pediatric Subjects Assessed to be at Imminent Risk for Suicide

Summary

EudraCT number	2016-004422-42
Trial protocol	HU ES BE PL IT BG FR Outside EU/EEA
Global end of trial date	31 March 2023

Results information

Result version number	v1 (current)
This version publication date	15 October 2023
First version publication date	15 October 2023

Trial information

Trial identification

Sponsor protocol code	ESKETINSUI2002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03185819
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)	Yes
EMA paediatric investigation plan number(s)	EMEA-001428-PIP03-15
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 May 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 March 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to assess the efficacy of a single (first) dose of 3 fixed doses of intranasal esketamine (28 milligrams [mg], 56 mg, and 84 mg) compared with psychoactive placebo (oral midazolam) in rapidly reducing the symptoms of major depressive disorder (MDD), including suicidal ideation, in subjects 12 to less than (<) 18 years of age who were assessed to be at imminent risk for suicide.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 January 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Brazil: 11
Country: Number of subjects enrolled	Spain: 17
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Hungary: 8
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	United States: 87
Worldwide total number of subjects	147
EEA total number of subjects	49

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)	147
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 147 subjects were randomised, of which 146 subjects (safety analysis set) were involved in the analysis.

Period 1

Period 1 title	Double Blind Period (25 Days)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo + Midazolam + SOC

Arm description:

In double blind period, subjects with MDD who were at imminent risk for suicide received placebo nasal spray along with psychoactive oral midazolam 0.125 milligrams per kilogram (mg/kg) solution 2 times per week for 4 weeks. As local standard of care (SOC), subjects were hospitalized initially for recommended 5 days and received antidepressant (either fluoxetine, escitalopram or sertraline) daily at least through Day 25 and evidence-based psychological therapy for at least 81 days and close outpatient follow-up based on treating physician(s) clinical judgment. Subjects who completed the double-blind period entered the follow-up period.

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

Dosage and administration details:

Subjects received placebo nasal spray 2 times per week for 4 weeks.

Investigational medicinal product name	Antidepressant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received SOC antidepressant (either fluoxetine, escitalopram or sertraline) based on treating physician(s) clinical judgment daily at least through Day 25.

Investigational medicinal product name	Midazolam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Subjects received midazolam 0.125 mg/kg oral solution 2 times per week for 4 weeks.

Arm title	Esketamine 28 mg + Placebo + SOC

Arm description:

In double blind period, subjects with MDD who were at imminent risk for suicide received Esketamine 28

mg nasal spray along with oral placebo solution 2 times per week for 4 weeks. As SOC, subjects were hospitalized initially for recommended 5 days and received antidepressant (either fluoxetine, escitalopram or sertraline) daily at least through Day 25 and evidence-based psychological therapy for at least 81 days and close outpatient follow-up based on treating physician(s) clinical judgment. Subjects who completed the double-blind period entered the follow-up period.

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

Dosage and administration details:

Subjects received Esketamine 28 mg nasal spray 2 times per week for 4 weeks.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Subject received oral placebo solution 2 times per week for 4 weeks.

Investigational medicinal product name	Antidepressant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received SOC antidepressant (either fluoxetine, escitalopram or sertraline) based on treating physician(s) clinical judgment daily at least through Day 25.

Arm title	Esketamine 56 mg + Placebo + SOC

Arm description:

In double blind period, subjects with MDD who were at imminent risk for suicide received Esketamine 56 mg nasal spray along with oral placebo solution 2 times per week for 4 weeks. As local SOC, subjects were hospitalized initially for recommended 5 days and received antidepressant (either fluoxetine, escitalopram or sertraline) daily at least through Day 25 and evidence-based psychological therapy for at least 81 days and close outpatient follow-up based on treating physician(s) clinical judgment. Subjects who completed the double-blind period entered the follow-up period.

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

Dosage and administration details:

Subject received Esketamine 56 mg nasal spray 2 times per week for 4 weeks.

Investigational medicinal product name	Antidepressant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received SOC antidepressant (either fluoxetine, escitalopram or sertraline) based on treating physician(s) clinical judgment daily at least through Day 25.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Subject received oral placebo solution 2 times per week for 4 weeks.

Arm title	Esketamine 84 mg + Placebo + SOC

Arm description:

In double blind period, subjects with MDD who were at imminent risk for suicide received Esketamine 84 mg nasal spray along with oral placebo solution 2 times per week for 4 weeks. As local SOC, subjects were hospitalized initially for recommended 5 days and received antidepressant (either fluoxetine, escitalopram or sertraline) daily at least through Day 25 and evidence-based psychological therapy for at least 81 days and close outpatient follow-up based on treating physician(s) clinical judgment. Subjects who completed the double-blind period entered the follow-up period.

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

Dosage and administration details:

Subjects received Esketamine 84 mg nasal spray 2 times per week for 4 weeks.

Investigational medicinal product name	Antidepressant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received SOC antidepressant (either fluoxetine, escitalopram or sertraline) based on treating physician(s) clinical judgment daily at least through Day 25.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Subjects received oral placebo solution 2 times per week for 4 weeks.

Number of subjects in period 1[1]	Placebo + Midazolam + SOC	Esketamine 28 mg + Placebo + SOC	Esketamine 56 mg + Placebo + SOC
Started	63	29	31
Completed	59	29	29
Not completed	4	0	2
Adverse Event	1	-	-
Unspecified	1	-	1
Subject refused further study treatment	-	-	-
Withdrawal by parent/guardian	-	-	-
Lack of efficacy	2	-	1

Number of subjects in period 1[1]	Esketamine 84 mg + Placebo + SOC
Started	23
Completed	21
Not completed	2
Adverse Event	-
Unspecified	-
Subject refused further study treatment	1
Withdrawal by parent/guardian	1
Lack of efficacy	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 147 subjects were enrolled, of which 146 subjects received the drug and were included in the analysis.

Period 2

Period 2 title	Follow up Phase (6 months)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo + Midazolam + SOC

Arm description:

Subjects received Standard of Care (SOC) per clinical judgment. Subjects were followed for 6 months.

Arm type	Active comparator
Investigational medicinal product name	SOC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received SOC per clinical judgment and were followed for 6 months.

Arm title	Esketamine 28 mg + Placebo + SOC

Arm description:

Subjects received SOC per clinical judgment. Subjects were followed for 6 months.

Arm type	Experimental
Investigational medicinal product name	SOC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received SOC per clinical judgment and were followed for 6 months.

Arm title	Esketamine 56 mg + Placebo + SOC

Arm description:	
Subjects received SOC per clinical judgment. Subjects were followed for 6 months.	
Arm type	Experimental
Investigational medicinal product name	SOC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Subjects received SOC per clinical judgment and were followed for 6 months.	
Arm title	Esketamine 84 mg + Placebo + SOC
Arm description:	
Subjects received SOC per clinical judgment. Subjects were followed for 6 months.	
Arm type	Experimental
Investigational medicinal product name	SOC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Subjects received SOC per clinical judgment and were followed for 6 months.	

Number of subjects in period 2	Placebo + Midazolam + SOC	Esketamine 28 mg + Placebo + SOC	Esketamine 56 mg + Placebo + SOC
Started	59	29	29
Completed	48	24	21
Not completed	11	5	8
Consent withdrawn by subject	3	3	2
Physician decision	2	-	2
Adverse Event	-	1	-
Death	1	-	-
Requires treatment with ECT, TMS, ketamine	1	-	-
Unspecified	1	-	3
Lost to follow-up	2	1	-
Withdrawal by parent/guardian	1	-	1

Number of subjects in period 2	Esketamine 84 mg + Placebo + SOC
Started	21
Completed	18
Not completed	3
Consent withdrawn by subject	-
Physician decision	-
Adverse Event	-
Death	-

Requires treatment with ECT, TMS, ketamine	-
Unspecified	1
Lost to follow-up	2
Withdrawal by parent/guardian	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo + Midazolam + SOC
Reporting group description:	
In double blind period, subjects with MDD who were at imminent risk for suicide received placebo nasal spray along with psychoactive oral midazolam 0.125 milligrams per kilogram (mg/kg) solution 2 times per week for 4 weeks. As local standard of care (SOC), subjects were hospitalized initially for recommended 5 days and received antidepressant (either fluoxetine, escitalopram or sertraline) daily at least through Day 25 and evidence-based psychological therapy for at least 81 days and close outpatient follow-up based on treating physician(s) clinical judgment. Subjects who completed the double-blind period entered the follow-up period.	
Reporting group title	Esketamine 28 mg + Placebo + SOC
Reporting group description:	
In double blind period, subjects with MDD who were at imminent risk for suicide received Esketamine 28 mg nasal spray along with oral placebo solution 2 times per week for 4 weeks. As SOC, subjects were hospitalized initially for recommended 5 days and received antidepressant (either fluoxetine, escitalopram or sertraline) daily at least through Day 25 and evidence-based psychological therapy for at least 81 days and close outpatient follow-up based on treating physician(s) clinical judgment. Subjects who completed the double-blind period entered the follow-up period.	
Reporting group title	Esketamine 56 mg + Placebo + SOC
Reporting group description:	
In double blind period, subjects with MDD who were at imminent risk for suicide received Esketamine 56 mg nasal spray along with oral placebo solution 2 times per week for 4 weeks. As local SOC, subjects were hospitalized initially for recommended 5 days and received antidepressant (either fluoxetine, escitalopram or sertraline) daily at least through Day 25 and evidence-based psychological therapy for at least 81 days and close outpatient follow-up based on treating physician(s) clinical judgment. Subjects who completed the double-blind period entered the follow-up period.	
Reporting group title	Esketamine 84 mg + Placebo + SOC
Reporting group description:	
In double blind period, subjects with MDD who were at imminent risk for suicide received Esketamine 84 mg nasal spray along with oral placebo solution 2 times per week for 4 weeks. As local SOC, subjects were hospitalized initially for recommended 5 days and received antidepressant (either fluoxetine, escitalopram or sertraline) daily at least through Day 25 and evidence-based psychological therapy for at least 81 days and close outpatient follow-up based on treating physician(s) clinical judgment. Subjects who completed the double-blind period entered the follow-up period.	

Reporting group values	Placebo + Midazolam + SOC	Esketamine 28 mg + Placebo + SOC	Esketamine 56 mg + Placebo + SOC
Number of subjects	63	29	31
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	63	29	31
Adults (18-64 years)	0	0	0
From 65 to 84 years	0	0	0
85 years and over	0	0	0
Title for AgeContinuous Units: years			
arithmetic mean	15.2	14.9	14.8
standard deviation	± 1.45	± 1.33	± 1.52
Title for Gender Units: subjects			
Female	48	24	25
Male	15	5	6

Reporting group values	Esketamine 84 mg + Placebo + SOC	Total	
Number of subjects	23	146	
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	
Adolescents (12-17 years)	23	146	
Adults (18-64 years)	0	0	
From 65 to 84 years	0	0	
85 years and over	0	0	
Title for AgeContinuous Units: years			
arithmetic mean	14.3		
standard deviation	± 1.43	-	
Title for Gender Units: subjects			
Female	17	114	
Male	6	32	

End points

End points reporting groups

Reporting group title	Placebo + Midazolam + SOC

Reporting group description:

In double blind period, subjects with MDD who were at imminent risk for suicide received placebo nasal spray along with psychoactive oral midazolam 0.125 milligrams per kilogram (mg/kg) solution 2 times per week for 4 weeks. As local standard of care (SOC), subjects were hospitalized initially for recommended 5 days and received antidepressant (either fluoxetine, escitalopram or sertraline) daily at least through Day 25 and evidence-based psychological therapy for at least 81 days and close outpatient follow-up based on treating physician(s) clinical judgment. Subjects who completed the double-blind period entered the follow-up period.

Reporting group title	Esketamine 28 mg + Placebo + SOC

Reporting group description:

In double blind period, subjects with MDD who were at imminent risk for suicide received Esketamine 28 mg nasal spray along with oral placebo solution 2 times per week for 4 weeks. As SOC, subjects were hospitalized initially for recommended 5 days and received antidepressant (either fluoxetine, escitalopram or sertraline) daily at least through Day 25 and evidence-based psychological therapy for at least 81 days and close outpatient follow-up based on treating physician(s) clinical judgment. Subjects who completed the double-blind period entered the follow-up period.

Reporting group title	Esketamine 56 mg + Placebo + SOC

Reporting group description:

In double blind period, subjects with MDD who were at imminent risk for suicide received Esketamine 56 mg nasal spray along with oral placebo solution 2 times per week for 4 weeks. As local SOC, subjects were hospitalized initially for recommended 5 days and received antidepressant (either fluoxetine, escitalopram or sertraline) daily at least through Day 25 and evidence-based psychological therapy for at least 81 days and close outpatient follow-up based on treating physician(s) clinical judgment. Subjects who completed the double-blind period entered the follow-up period.

Reporting group title	Esketamine 84 mg + Placebo + SOC

Reporting group description:

In double blind period, subjects with MDD who were at imminent risk for suicide received Esketamine 84 mg nasal spray along with oral placebo solution 2 times per week for 4 weeks. As local SOC, subjects were hospitalized initially for recommended 5 days and received antidepressant (either fluoxetine, escitalopram or sertraline) daily at least through Day 25 and evidence-based psychological therapy for at least 81 days and close outpatient follow-up based on treating physician(s) clinical judgment. Subjects who completed the double-blind period entered the follow-up period.

Reporting group title	Placebo + Midazolam + SOC

Reporting group description:

Subjects received Standard of Care (SOC) per clinical judgment. Subjects were followed for 6 months.

Reporting group title	Esketamine 28 mg + Placebo + SOC

Reporting group description:

Subjects received SOC per clinical judgment. Subjects were followed for 6 months.

Reporting group title	Esketamine 56 mg + Placebo + SOC

Reporting group description:

Subjects received SOC per clinical judgment. Subjects were followed for 6 months.

Reporting group title	Esketamine 84 mg + Placebo + SOC

Reporting group description:

Subjects received SOC per clinical judgment. Subjects were followed for 6 months.

Subject analysis set title	Placebo + Midazolam + SOC
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects with MDD who were at imminent risk for suicide received placebo nasal spray along with psychoactive oral midazolam 0.125 milligrams per kilogram (mg/kg) solution 2 times per week for 4 weeks. As SOC, Subjects were hospitalized initially for recommended 5 days and received antidepressant (either fluoxetine, escitalopram or sertraline) daily at least through Day 25 and evidence-based psychological therapy for at least 81 days and close outpatient follow-up based on treating physician(s) clinical judgment. Subjects were followed for 6 months.

Subject analysis set title	Esketamine 28 mg + Placebo + SOC

Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects with MDD who were at imminent risk for suicide received Esketamine 28 mg nasal spray along with oral placebo solution 2 times per week for 4 weeks. As SOC, subjects were hospitalized initially for recommended 5 days and received antidepressant (either fluoxetine, escitalopram or sertraline) daily at least through Day 25 and evidence-based psychological therapy for at least 81 days and close outpatient follow-up based on treating physician(s) clinical judgment. Subjects were followed for 6 months.

Subject analysis set title	Esketamine 56 mg + Placebo + SOC
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects with MDD who were at imminent risk for suicide received Esketamine 56 mg nasal spray along with oral placebo solution 2 times per week for 4 weeks. As SOC, subjects were hospitalized initially for recommended 5 days and received antidepressant (either fluoxetine, escitalopram or sertraline) daily at least through Day 25 and evidence-based psychological therapy for at least 81 days and close outpatient follow-up based on treating physician(s) clinical judgment. Subjects were followed for 6 months.

Subject analysis set title	Esketamine 84 mg + Placebo + SOC
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects with MDD who were at imminent risk for suicide received Esketamine 84 mg nasal spray along with oral placebo solution 2 times per week for 4 weeks. As SOC, subjects were hospitalized initially for recommended 5 days and received antidepressant (either fluoxetine, escitalopram or sertraline) daily at least through Day 25 and evidence-based psychological therapy for at least 81 days and close outpatient follow-up based on treating physician(s) clinical judgment. Subjects were followed for 6 months.

Subject analysis set title	Pooled Esketamine 56 mg + Esketamine 84 mg
Subject analysis set type	Safety analysis

Subject analysis set description:

Pooled data of 'Esketamine 56 mg + Placebo + SOC' arm and 'Esketamine 84 mg + Placebo + SOC' arm was analysed.

Primary: Change From Baseline in Children’s Depression Rating Scale-Revised (CDRS-R) Total Score at 24 Hours Post First Dose

End point title	Change From Baseline in Children’s Depression Rating Scale-Revised (CDRS-R) Total Score at 24 Hours Post First Dose

End point description:

The CDRS-R is a validated 17- item, clinician-rated instrument developed to assess depressive symptomatology in children that measures the severity of a patient’s depressive symptoms. The 17-item included 14 best description items that were determined by CDRS-R raters based on their scores from interviewing of the subject and caregiver, and 3 nonverbal behaviour ratings. The item scores ranged from 1 to 5 or 1 to 7, with a possible total score ranging from 17 to 113. A higher score represented a more severe condition. Full efficacy analysis set for DB phase was defined as all randomized subjects who received at least 1 dose of double-blind study medication during the DB phase and have both a baseline and a post dose evaluation for the CDRS-R total score. Follow-up analysis set for follow-up phase was defined as all subjects who completed the double-blind phase and either entered the follow-up phase or have provided adverse event data after the double-blind phase.

End point type	Primary

End point timeframe:

Baseline (predose) on Day 1 to 24 hours post first dose

End point values	Placebo + Midazolam + SOC	Esketamine 28 mg + Placebo + SOC	Esketamine 56 mg + Placebo + SOC	Esketamine 84 mg + Placebo + SOC
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	63	28	31	23
Units: Units on a scale				
arithmetic mean (standard deviation)	-26.2 (± 16.72)	-29.6 (± 18.15)	-31.8 (± 12.92)	-30.3 (± 17.48)

End point values	Pooled Esketamine 56 mg + Esketamine 84 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	54			
Units: Units on a scale				
arithmetic mean (standard deviation)	-31.2 (± 14.90)			

Statistical analyses

Statistical analysis title	Pooled Esketamine Vs Midazolam + SOC
Comparison groups	Pooled Esketamine 56 mg + Esketamine 84 mg v Placebo + Midazolam + SOC
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.037
Method	ANCOVA
Parameter estimate	Difference of LS Means
Point estimate	-5.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.19
upper limit	-0.35
Variability estimate	Standard error of the mean
Dispersion value	2.74

Statistical analysis title	Esketamine 28 mg + SOC Vs Midazolam + SOC
Comparison groups	Placebo + Midazolam + SOC v Esketamine 28 mg + Placebo + SOC
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference of LS Means
Point estimate	-2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.08
upper limit	4.19

Variability estimate	Standard error of the mean
Dispersion value	3.35

Statistical analysis title	Esketamine 56 mg + SOC Vs Midazolam + SOC
Comparison groups	Placebo + Midazolam + SOC v Esketamine 56 mg + Placebo + SOC
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.072
Method	ANCOVA
Parameter estimate	Difference of LS Mean
Point estimate	-5.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.25
upper limit	0.53
Variability estimate	Standard error of the mean
Dispersion value	3.23

Statistical analysis title	Esketamine 84 mg + Placebo VS Midazolam + SOC
Comparison groups	Placebo + Midazolam + SOC v Esketamine 84 mg + Placebo + SOC
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.123
Method	ANCOVA
Parameter estimate	Difference of LS Mean
Point estimate	-5.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.91
upper limit	1.55
Variability estimate	Standard error of the mean
Dispersion value	3.65

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Double Blind Period: Until Day 25; Follow-up period: Up to 6 months

Adverse event reporting additional description:

Safety analysis set for DB period included all randomized subjects who received at least 1 dose of study medication during the double-blind period. Follow-up analysis set for follow-up period included subjects who completed the double-blind treatment period and either entered the follow-up period or provided AE data after the DB treatment period.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	DB: Placebo + Midazolam + SOC

Reporting group description:

In double blind (DB) period, subjects with MDD who were at imminent risk for suicide received placebo nasal spray along with psychoactive oral midazolam 0.125 milligrams per kilogram (mg/kg) solution 2 times per week for 4 weeks. As local standard of care (SOC), subjects were hospitalized initially for recommended 5 days and received antidepressant (either fluoxetine, escitalopram or sertraline) daily at least through Day 25 and evidence-based psychological therapy for at least 81 days and close outpatient follow-up based on treating physician(s) clinical judgment. Subjects who completed the double-blind period entered the follow-up (FU) period.

Reporting group title	DB: Esketamine 28 mg + Placebo + SOC

Reporting group description:

In DB period, subjects with MDD who were at imminent risk for suicide received Esketamine 28 mg nasal spray along with oral placebo solution 2 times per week for 4 weeks. As SOC, subjects were hospitalized initially for recommended 5 days and received antidepressant (either fluoxetine, escitalopram or sertraline) daily at least through Day 25 and evidence-based psychological therapy for at least 81 days and close outpatient follow-up based on treating physician(s) clinical judgment. Subjects who completed the double-blind period entered the follow-up period.

Reporting group title	DB: Esketamine 56 mg + Placebo + SOC

Reporting group description:

In DB period, subjects with MDD who were at imminent risk for suicide received Esketamine 56 mg nasal spray along with oral placebo solution 2 times per week for 4 weeks. As local SOC, subjects were hospitalized initially for recommended 5 days and received antidepressant (either fluoxetine, escitalopram or sertraline) daily at least through Day 25 and evidence-based psychological therapy for at least 81 days and close outpatient follow-up based on treating physician(s) clinical judgment. Subjects who completed the double-blind period entered the follow-up period.

Reporting group title	DB: Esketamine 84 mg + Placebo + SOC

Reporting group description:

In DB period, subjects with MDD who were at imminent risk for suicide received Esketamine 84 mg nasal spray along with oral placebo solution 2 times per week for 4 weeks. As local SOC, subjects were hospitalized initially for recommended 5 days and received antidepressant (either fluoxetine, escitalopram or sertraline) daily at least through Day 25 and evidence-based psychological therapy for at least 81 days and close outpatient follow-up based on treating physician(s) clinical judgment. Subjects who completed the double-blind period entered the follow-up period.

Reporting group title	FU: Placebo + Midazolam + SOC

Reporting group description:

Subjects received Standard of Care (SOC) per clinical judgment. Subjects were followed for 6 months.

Reporting group title	FU: Esketamine 28 mg + Placebo + SOC

Reporting group description:

Subjects received SOC per clinical judgment. Subjects were followed for 6 months.

Reporting group title	FU: Esketamine 56 mg + Placebo + SOC

Reporting group description:

Subjects received SOC per clinical judgment. Subjects were followed for 6 months.

Reporting group title	FU: Esketamine 84 mg + Placebo + SOC

Reporting group description:

Subjects received SOC per clinical judgment. Subjects were followed for 6 months.

Serious adverse events	DB: Placebo + Midazolam + SOC	DB: Esketamine 28 mg + Placebo + SOC	DB: Esketamine 56 mg + Placebo + SOC
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 63 (14.29%)	4 / 29 (13.79%)	7 / 31 (22.58%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Alcohol Poisoning			
subjects affected / exposed	0 / 63 (0.00%)	0 / 29 (0.00%)	0 / 31 (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
Humerus Fracture			
subjects affected / exposed	0 / 63 (0.00%)	0 / 29 (0.00%)	0 / 31 (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
Intentional Overdose			
subjects affected / exposed	0 / 63 (0.00%)	0 / 29 (0.00%)	0 / 31 (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
Pelvic Fracture			
subjects affected / exposed	0 / 63 (0.00%)	0 / 29 (0.00%)	0 / 31 (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
Nervous system disorders			
Psychomotor Hyperactivity			
subjects affected / exposed	0 / 63 (0.00%)	0 / 29 (0.00%)	0 / 31 (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
Status Migrainosus			

subjects affected / exposed	0 / 63 (0.00%)	0 / 29 (0.00%)	0 / 31 (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
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 63 (0.00%)	0 / 29 (0.00%)	0 / 31 (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
Anxiety			
subjects affected / exposed	1 / 63 (1.59%)	0 / 29 (0.00%)	0 / 31 (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
Depression Suicidal			
subjects affected / exposed	1 / 63 (1.59%)	1 / 29 (3.45%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 63 (0.00%)	0 / 29 (0.00%)	0 / 31 (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
Completed Suicide			
subjects affected / exposed	0 / 63 (0.00%)	0 / 29 (0.00%)	0 / 31 (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
Bipolar Disorder			
subjects affected / exposed	0 / 63 (0.00%)	0 / 29 (0.00%)	0 / 31 (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
Suicidal Ideation			
subjects affected / exposed	3 / 63 (4.76%)	3 / 29 (10.34%)	2 / 31 (6.45%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic Disorder			

subjects affected / exposed	0 / 63 (0.00%)	0 / 29 (0.00%)	0 / 31 (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
Major Depression			
subjects affected / exposed	0 / 63 (0.00%)	0 / 29 (0.00%)	0 / 31 (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
Intentional Self-Injury			
subjects affected / exposed	0 / 63 (0.00%)	0 / 29 (0.00%)	0 / 31 (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
Suicide Attempt			
subjects affected / exposed	5 / 63 (7.94%)	1 / 29 (3.45%)	5 / 31 (16.13%)
occurrences causally related to treatment / all	0 / 6	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Hiv Infection			
subjects affected / exposed	0 / 63 (0.00%)	0 / 29 (0.00%)	0 / 31 (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
Metabolism and nutrition disorders			
Food Refusal			
subjects affected / exposed	0 / 63 (0.00%)	0 / 29 (0.00%)	0 / 31 (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	DB: Esketamine 84 mg + Placebo + SOC	FU: Placebo + Midazolam + SOC	FU: Esketamine 28 mg + Placebo + SOC
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 23 (4.35%)	19 / 59 (32.20%)	10 / 29 (34.48%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Alcohol Poisoning			

subjects affected / exposed	0 / 23 (0.00%)	0 / 59 (0.00%)	0 / 29 (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
Humerus Fracture			
subjects affected / exposed	0 / 23 (0.00%)	0 / 59 (0.00%)	0 / 29 (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
Intentional Overdose			
subjects affected / exposed	0 / 23 (0.00%)	0 / 59 (0.00%)	0 / 29 (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
Pelvic Fracture			
subjects affected / exposed	0 / 23 (0.00%)	0 / 59 (0.00%)	0 / 29 (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
Nervous system disorders			
Psychomotor Hyperactivity			
subjects affected / exposed	0 / 23 (0.00%)	1 / 59 (1.69%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status Migrainosus			
subjects affected / exposed	0 / 23 (0.00%)	0 / 59 (0.00%)	0 / 29 (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
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 23 (0.00%)	2 / 59 (3.39%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	0 / 23 (0.00%)	0 / 59 (0.00%)	0 / 29 (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
Depression Suicidal			

subjects affected / exposed	0 / 23 (0.00%)	3 / 59 (5.08%)	2 / 29 (6.90%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 23 (0.00%)	1 / 59 (1.69%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Completed Suicide			
subjects affected / exposed	0 / 23 (0.00%)	1 / 59 (1.69%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Bipolar Disorder			
subjects affected / exposed	0 / 23 (0.00%)	0 / 59 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal Ideation			
subjects affected / exposed	0 / 23 (0.00%)	4 / 59 (6.78%)	5 / 29 (17.24%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic Disorder			
subjects affected / exposed	0 / 23 (0.00%)	0 / 59 (0.00%)	0 / 29 (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
Major Depression			
subjects affected / exposed	0 / 23 (0.00%)	1 / 59 (1.69%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional Self-Injury			
subjects affected / exposed	0 / 23 (0.00%)	2 / 59 (3.39%)	2 / 29 (6.90%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide Attempt			

subjects affected / exposed	1 / 23 (4.35%)	9 / 59 (15.25%)	3 / 29 (10.34%)
occurrences causally related to treatment / all	0 / 1	0 / 11	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Hiv Infection			
subjects affected / exposed	0 / 23 (0.00%)	1 / 59 (1.69%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Food Refusal			
subjects affected / exposed	0 / 23 (0.00%)	0 / 59 (0.00%)	0 / 29 (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	FU: Esketamine 56 mg + Placebo + SOC	FU: Esketamine 84 mg + Placebo + SOC	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 29 (27.59%)	7 / 21 (33.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Alcohol Poisoning			
subjects affected / exposed	0 / 29 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus Fracture			
subjects affected / exposed	0 / 29 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional Overdose			
subjects affected / exposed	0 / 29 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic Fracture			

subjects affected / exposed	0 / 29 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Psychomotor Hyperactivity			
subjects affected / exposed	0 / 29 (0.00%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status Migrainosus			
subjects affected / exposed	0 / 29 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 29 (0.00%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	0 / 29 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression Suicidal			
subjects affected / exposed	1 / 29 (3.45%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 29 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed Suicide			
subjects affected / exposed	0 / 29 (0.00%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bipolar Disorder			

subjects affected / exposed	0 / 29 (0.00%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal Ideation			
subjects affected / exposed	3 / 29 (10.34%)	3 / 21 (14.29%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic Disorder			
subjects affected / exposed	1 / 29 (3.45%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major Depression			
subjects affected / exposed	0 / 29 (0.00%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional Self-Injury			
subjects affected / exposed	0 / 29 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide Attempt			
subjects affected / exposed	5 / 29 (17.24%)	4 / 21 (19.05%)	
occurrences causally related to treatment / all	0 / 11	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Hiv Infection			
subjects affected / exposed	0 / 29 (0.00%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Food Refusal			
subjects affected / exposed	0 / 29 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	DB: Placebo + Midazolam + SOC	DB: Esketamine 28 mg + Placebo + SOC	DB: Esketamine 56 mg + Placebo + SOC
Total subjects affected by non-serious adverse events			
subjects affected / exposed	57 / 63 (90.48%)	26 / 29 (89.66%)	30 / 31 (96.77%)
Vascular disorders			
Hypotension			
subjects affected / exposed	4 / 63 (6.35%)	1 / 29 (3.45%)	2 / 31 (6.45%)
occurrences (all)	9	1	2
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 63 (1.59%)	0 / 29 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Feeling Drunk			
subjects affected / exposed	2 / 63 (3.17%)	1 / 29 (3.45%)	0 / 31 (0.00%)
occurrences (all)	2	6	0
Fatigue			
subjects affected / exposed	3 / 63 (4.76%)	1 / 29 (3.45%)	0 / 31 (0.00%)
occurrences (all)	9	4	0
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	3 / 63 (4.76%)	0 / 29 (0.00%)	1 / 31 (3.23%)
occurrences (all)	6	0	1
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	2 / 63 (3.17%)	2 / 29 (6.90%)	3 / 31 (9.68%)
occurrences (all)	3	5	3
Nasal Congestion			
subjects affected / exposed	3 / 63 (4.76%)	0 / 29 (0.00%)	2 / 31 (6.45%)
occurrences (all)	3	0	2
Nasal Discomfort			
subjects affected / exposed	2 / 63 (3.17%)	2 / 29 (6.90%)	3 / 31 (9.68%)
occurrences (all)	5	2	5
Oropharyngeal Pain			

subjects affected / exposed	3 / 63 (4.76%)	2 / 29 (6.90%)	1 / 31 (3.23%)
occurrences (all)	3	4	1
Pharyngeal Hypoaesthesia			
subjects affected / exposed	1 / 63 (1.59%)	1 / 29 (3.45%)	2 / 31 (6.45%)
occurrences (all)	1	3	3
Sneezing			
subjects affected / exposed	1 / 63 (1.59%)	2 / 29 (6.90%)	1 / 31 (3.23%)
occurrences (all)	1	2	1
Hiccups			
subjects affected / exposed	8 / 63 (12.70%)	1 / 29 (3.45%)	1 / 31 (3.23%)
occurrences (all)	8	1	1
Throat Irritation			
subjects affected / exposed	3 / 63 (4.76%)	2 / 29 (6.90%)	3 / 31 (9.68%)
occurrences (all)	4	4	3
Psychiatric disorders			
Disinhibition			
subjects affected / exposed	0 / 63 (0.00%)	2 / 29 (6.90%)	0 / 31 (0.00%)
occurrences (all)	0	8	0
Depression			
subjects affected / exposed	2 / 63 (3.17%)	0 / 29 (0.00%)	0 / 31 (0.00%)
occurrences (all)	2	0	0
Confusional State			
subjects affected / exposed	4 / 63 (6.35%)	1 / 29 (3.45%)	2 / 31 (6.45%)
occurrences (all)	12	2	2
Anxiety			
subjects affected / exposed	10 / 63 (15.87%)	3 / 29 (10.34%)	4 / 31 (12.90%)
occurrences (all)	15	3	5
Agitation			
subjects affected / exposed	1 / 63 (1.59%)	2 / 29 (6.90%)	1 / 31 (3.23%)
occurrences (all)	1	3	4
Aggression			
subjects affected / exposed	0 / 63 (0.00%)	0 / 29 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Dissociation			
subjects affected / exposed	11 / 63 (17.46%)	12 / 29 (41.38%)	12 / 31 (38.71%)
occurrences (all)	24	46	51

Euphoric Mood			
subjects affected / exposed	6 / 63 (9.52%)	6 / 29 (20.69%)	5 / 31 (16.13%)
occurrences (all)	12	17	22
Time Perception Altered			
subjects affected / exposed	1 / 63 (1.59%)	2 / 29 (6.90%)	0 / 31 (0.00%)
occurrences (all)	1	3	0
Suicidal Ideation			
subjects affected / exposed	2 / 63 (3.17%)	1 / 29 (3.45%)	0 / 31 (0.00%)
occurrences (all)	3	1	0
Intentional Self-Injury			
subjects affected / exposed	12 / 63 (19.05%)	6 / 29 (20.69%)	6 / 31 (19.35%)
occurrences (all)	19	9	12
Insomnia			
subjects affected / exposed	8 / 63 (12.70%)	4 / 29 (13.79%)	2 / 31 (6.45%)
occurrences (all)	16	4	7
Initial Insomnia			
subjects affected / exposed	0 / 63 (0.00%)	1 / 29 (3.45%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Illusion			
subjects affected / exposed	1 / 63 (1.59%)	0 / 29 (0.00%)	2 / 31 (6.45%)
occurrences (all)	1	0	2
Hallucination, Visual			
subjects affected / exposed	3 / 63 (4.76%)	1 / 29 (3.45%)	1 / 31 (3.23%)
occurrences (all)	7	1	1
Investigations			
Weight Increased			
subjects affected / exposed	2 / 63 (3.17%)	0 / 29 (0.00%)	0 / 31 (0.00%)
occurrences (all)	2	0	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 63 (1.59%)	0 / 29 (0.00%)	2 / 31 (6.45%)
occurrences (all)	1	0	3
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	1 / 63 (1.59%)	2 / 29 (6.90%)	3 / 31 (9.68%)
occurrences (all)	2	3	4
Dysgeusia			

subjects affected / exposed	15 / 63 (23.81%)	10 / 29 (34.48%)	8 / 31 (25.81%)
occurrences (all)	53	57	33
Memory Impairment			
subjects affected / exposed	4 / 63 (6.35%)	1 / 29 (3.45%)	3 / 31 (9.68%)
occurrences (all)	6	1	3
Hypoaesthesia			
subjects affected / exposed	2 / 63 (3.17%)	5 / 29 (17.24%)	8 / 31 (25.81%)
occurrences (all)	2	12	24
Headache			
subjects affected / exposed	18 / 63 (28.57%)	10 / 29 (34.48%)	13 / 31 (41.94%)
occurrences (all)	33	17	34
Dizziness			
subjects affected / exposed	27 / 63 (42.86%)	16 / 29 (55.17%)	16 / 31 (51.61%)
occurrences (all)	44	76	88
Sedation			
subjects affected / exposed	9 / 63 (14.29%)	2 / 29 (6.90%)	4 / 31 (12.90%)
occurrences (all)	45	2	7
Somnolence			
subjects affected / exposed	24 / 63 (38.10%)	10 / 29 (34.48%)	9 / 31 (29.03%)
occurrences (all)	123	36	34
Tremor			
subjects affected / exposed	1 / 63 (1.59%)	3 / 29 (10.34%)	2 / 31 (6.45%)
occurrences (all)	1	4	2
Syncope			
subjects affected / exposed	0 / 63 (0.00%)	0 / 29 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 63 (1.59%)	2 / 29 (6.90%)	2 / 31 (6.45%)
occurrences (all)	2	2	5
Eye disorders			
Vision Blurred			
subjects affected / exposed	1 / 63 (1.59%)	2 / 29 (6.90%)	4 / 31 (12.90%)
occurrences (all)	8	3	7
Gastrointestinal disorders			

Abdominal Pain Upper			
subjects affected / exposed	4 / 63 (6.35%)	3 / 29 (10.34%)	2 / 31 (6.45%)
occurrences (all)	5	3	2
Abdominal Pain			
subjects affected / exposed	1 / 63 (1.59%)	3 / 29 (10.34%)	0 / 31 (0.00%)
occurrences (all)	1	3	0
Hypoaesthesia Oral			
subjects affected / exposed	0 / 63 (0.00%)	6 / 29 (20.69%)	6 / 31 (19.35%)
occurrences (all)	0	19	29
Constipation			
subjects affected / exposed	2 / 63 (3.17%)	1 / 29 (3.45%)	2 / 31 (6.45%)
occurrences (all)	2	1	2
Diarrhoea			
subjects affected / exposed	3 / 63 (4.76%)	0 / 29 (0.00%)	1 / 31 (3.23%)
occurrences (all)	4	0	1
Dyspepsia			
subjects affected / exposed	1 / 63 (1.59%)	2 / 29 (6.90%)	1 / 31 (3.23%)
occurrences (all)	1	2	3
Vomiting			
subjects affected / exposed	4 / 63 (6.35%)	5 / 29 (17.24%)	7 / 31 (22.58%)
occurrences (all)	5	5	11
Nausea			
subjects affected / exposed	11 / 63 (17.46%)	8 / 29 (27.59%)	15 / 31 (48.39%)
occurrences (all)	13	19	43
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	0 / 63 (0.00%)	1 / 29 (3.45%)	2 / 31 (6.45%)
occurrences (all)	0	1	3
Rash			
subjects affected / exposed	0 / 63 (0.00%)	2 / 29 (6.90%)	0 / 31 (0.00%)
occurrences (all)	0	2	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 63 (1.59%)	0 / 29 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	0 / 63 (0.00%)	1 / 29 (3.45%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Muscular Weakness			
subjects affected / exposed	0 / 63 (0.00%)	2 / 29 (6.90%)	0 / 31 (0.00%)
occurrences (all)	0	2	0
Pain in Extremity			
subjects affected / exposed	2 / 63 (3.17%)	1 / 29 (3.45%)	1 / 31 (3.23%)
occurrences (all)	2	1	1
Infections and infestations			
Covid-19			
subjects affected / exposed	0 / 63 (0.00%)	0 / 29 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	2 / 63 (3.17%)	0 / 29 (0.00%)	2 / 31 (6.45%)
occurrences (all)	2	0	2
Influenza			
subjects affected / exposed	0 / 63 (0.00%)	0 / 29 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Gastroenteritis Viral			
subjects affected / exposed	1 / 63 (1.59%)	0 / 29 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	0 / 63 (0.00%)	3 / 29 (10.34%)	4 / 31 (12.90%)
occurrences (all)	0	4	4

Non-serious adverse events	DB: Esketamine 84 mg + Placebo + SOC	FU: Placebo + Midazolam + SOC	FU: Esketamine 28 mg + Placebo + SOC
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 23 (100.00%)	48 / 59 (81.36%)	21 / 29 (72.41%)
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 23 (0.00%)	0 / 59 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	0 / 23 (0.00%)	3 / 59 (5.08%)	0 / 29 (0.00%)
occurrences (all)	0	3	0
Feeling Drunk			
subjects affected / exposed	2 / 23 (8.70%)	0 / 59 (0.00%)	0 / 29 (0.00%)
occurrences (all)	3	0	0
Fatigue			
subjects affected / exposed	2 / 23 (8.70%)	2 / 59 (3.39%)	0 / 29 (0.00%)
occurrences (all)	3	2	0
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 23 (4.35%)	4 / 59 (6.78%)	0 / 29 (0.00%)
occurrences (all)	1	9	0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 23 (4.35%)	1 / 59 (1.69%)	0 / 29 (0.00%)
occurrences (all)	2	1	0
Nasal Congestion			
subjects affected / exposed	0 / 23 (0.00%)	1 / 59 (1.69%)	0 / 29 (0.00%)
occurrences (all)	0	1	0
Nasal Discomfort			
subjects affected / exposed	3 / 23 (13.04%)	0 / 59 (0.00%)	0 / 29 (0.00%)
occurrences (all)	9	0	0
Oropharyngeal Pain			
subjects affected / exposed	2 / 23 (8.70%)	2 / 59 (3.39%)	2 / 29 (6.90%)
occurrences (all)	2	2	3
Pharyngeal Hypoaesthesia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 59 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Sneezing			
subjects affected / exposed	1 / 23 (4.35%)	0 / 59 (0.00%)	0 / 29 (0.00%)
occurrences (all)	4	0	0
Hiccups			
subjects affected / exposed	0 / 23 (0.00%)	0 / 59 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Throat Irritation			

subjects affected / exposed	2 / 23 (8.70%)	0 / 59 (0.00%)	0 / 29 (0.00%)
occurrences (all)	3	0	0
Psychiatric disorders			
Disinhibition			
subjects affected / exposed	1 / 23 (4.35%)	0 / 59 (0.00%)	0 / 29 (0.00%)
occurrences (all)	2	0	0
Depression			
subjects affected / exposed	0 / 23 (0.00%)	2 / 59 (3.39%)	1 / 29 (3.45%)
occurrences (all)	0	3	1
Confusional State			
subjects affected / exposed	1 / 23 (4.35%)	0 / 59 (0.00%)	0 / 29 (0.00%)
occurrences (all)	1	0	0
Anxiety			
subjects affected / exposed	2 / 23 (8.70%)	7 / 59 (11.86%)	3 / 29 (10.34%)
occurrences (all)	6	16	6
Agitation			
subjects affected / exposed	1 / 23 (4.35%)	1 / 59 (1.69%)	1 / 29 (3.45%)
occurrences (all)	4	1	1
Aggression			
subjects affected / exposed	0 / 23 (0.00%)	3 / 59 (5.08%)	0 / 29 (0.00%)
occurrences (all)	0	4	0
Dissociation			
subjects affected / exposed	11 / 23 (47.83%)	1 / 59 (1.69%)	1 / 29 (3.45%)
occurrences (all)	58	1	1
Euphoric Mood			
subjects affected / exposed	5 / 23 (21.74%)	1 / 59 (1.69%)	0 / 29 (0.00%)
occurrences (all)	24	1	0
Time Perception Altered			
subjects affected / exposed	0 / 23 (0.00%)	0 / 59 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Suicidal Ideation			
subjects affected / exposed	0 / 23 (0.00%)	4 / 59 (6.78%)	2 / 29 (6.90%)
occurrences (all)	0	6	3
Intentional Self-Injury			
subjects affected / exposed	5 / 23 (21.74%)	21 / 59 (35.59%)	7 / 29 (24.14%)
occurrences (all)	7	33	19

Insomnia			
subjects affected / exposed	2 / 23 (8.70%)	1 / 59 (1.69%)	4 / 29 (13.79%)
occurrences (all)	3	1	4
Initial Insomnia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 59 (1.69%)	1 / 29 (3.45%)
occurrences (all)	0	1	1
Illusion			
subjects affected / exposed	2 / 23 (8.70%)	0 / 59 (0.00%)	0 / 29 (0.00%)
occurrences (all)	3	0	0
Hallucination, Visual			
subjects affected / exposed	2 / 23 (8.70%)	0 / 59 (0.00%)	0 / 29 (0.00%)
occurrences (all)	2	0	0
Investigations			
Weight Increased			
subjects affected / exposed	0 / 23 (0.00%)	5 / 59 (8.47%)	2 / 29 (6.90%)
occurrences (all)	0	5	2
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 59 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 59 (0.00%)	0 / 29 (0.00%)
occurrences (all)	2	0	0
Dysgeusia			
subjects affected / exposed	9 / 23 (39.13%)	0 / 59 (0.00%)	0 / 29 (0.00%)
occurrences (all)	39	0	0
Memory Impairment			
subjects affected / exposed	1 / 23 (4.35%)	0 / 59 (0.00%)	0 / 29 (0.00%)
occurrences (all)	1	0	0
Hypoaesthesia			
subjects affected / exposed	4 / 23 (17.39%)	0 / 59 (0.00%)	0 / 29 (0.00%)
occurrences (all)	7	0	0
Headache			
subjects affected / exposed	7 / 23 (30.43%)	12 / 59 (20.34%)	10 / 29 (34.48%)
occurrences (all)	18	20	14
Dizziness			

subjects affected / exposed	16 / 23 (69.57%)	3 / 59 (5.08%)	0 / 29 (0.00%)
occurrences (all)	58	5	0
Sedation			
subjects affected / exposed	2 / 23 (8.70%)	1 / 59 (1.69%)	0 / 29 (0.00%)
occurrences (all)	4	1	0
Somnolence			
subjects affected / exposed	8 / 23 (34.78%)	2 / 59 (3.39%)	0 / 29 (0.00%)
occurrences (all)	25	2	0
Tremor			
subjects affected / exposed	2 / 23 (8.70%)	2 / 59 (3.39%)	0 / 29 (0.00%)
occurrences (all)	2	3	0
Syncope			
subjects affected / exposed	1 / 23 (4.35%)	3 / 59 (5.08%)	1 / 29 (3.45%)
occurrences (all)	1	4	1
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 23 (8.70%)	0 / 59 (0.00%)	1 / 29 (3.45%)
occurrences (all)	7	0	1
Eye disorders			
Vision Blurred			
subjects affected / exposed	3 / 23 (13.04%)	1 / 59 (1.69%)	1 / 29 (3.45%)
occurrences (all)	12	1	1
Gastrointestinal disorders			
Abdominal Pain Upper			
subjects affected / exposed	3 / 23 (13.04%)	7 / 59 (11.86%)	1 / 29 (3.45%)
occurrences (all)	5	8	1
Abdominal Pain			
subjects affected / exposed	2 / 23 (8.70%)	2 / 59 (3.39%)	0 / 29 (0.00%)
occurrences (all)	3	2	0
Hypoaesthesia Oral			
subjects affected / exposed	5 / 23 (21.74%)	1 / 59 (1.69%)	0 / 29 (0.00%)
occurrences (all)	7	1	0
Constipation			
subjects affected / exposed	1 / 23 (4.35%)	2 / 59 (3.39%)	0 / 29 (0.00%)
occurrences (all)	1	2	0
Diarrhoea			

subjects affected / exposed	1 / 23 (4.35%)	6 / 59 (10.17%)	1 / 29 (3.45%)
occurrences (all)	3	7	1
Dyspepsia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 59 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	6 / 23 (26.09%)	4 / 59 (6.78%)	3 / 29 (10.34%)
occurrences (all)	7	5	3
Nausea			
subjects affected / exposed	13 / 23 (56.52%)	9 / 59 (15.25%)	3 / 29 (10.34%)
occurrences (all)	37	10	3
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 59 (0.00%)	0 / 29 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	0 / 23 (0.00%)	1 / 59 (1.69%)	0 / 29 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	2 / 23 (8.70%)	1 / 59 (1.69%)	0 / 29 (0.00%)
occurrences (all)	3	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 23 (8.70%)	3 / 59 (5.08%)	0 / 29 (0.00%)
occurrences (all)	2	3	0
Muscular Weakness			
subjects affected / exposed	1 / 23 (4.35%)	0 / 59 (0.00%)	0 / 29 (0.00%)
occurrences (all)	2	0	0
Pain in Extremity			
subjects affected / exposed	2 / 23 (8.70%)	0 / 59 (0.00%)	2 / 29 (6.90%)
occurrences (all)	2	0	2
Infections and infestations			
Covid-19			
subjects affected / exposed	0 / 23 (0.00%)	2 / 59 (3.39%)	0 / 29 (0.00%)
occurrences (all)	0	2	0

Nasopharyngitis			
subjects affected / exposed	1 / 23 (4.35%)	2 / 59 (3.39%)	2 / 29 (6.90%)
occurrences (all)	1	2	2
Influenza			
subjects affected / exposed	0 / 23 (0.00%)	3 / 59 (5.08%)	0 / 29 (0.00%)
occurrences (all)	0	3	0
Gastroenteritis Viral			
subjects affected / exposed	0 / 23 (0.00%)	1 / 59 (1.69%)	0 / 29 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	0 / 23 (0.00%)	4 / 59 (6.78%)	1 / 29 (3.45%)
occurrences (all)	0	4	1

Non-serious adverse events	FU: Esketamine 56 mg + Placebo + SOC	FU: Esketamine 84 mg + Placebo + SOC	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 29 (65.52%)	14 / 21 (66.67%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 29 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Feeling Drunk			
subjects affected / exposed	0 / 29 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Fatigue			
subjects affected / exposed	0 / 29 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	2 / 29 (6.90%)	1 / 21 (4.76%)	
occurrences (all)	2	1	
Respiratory, thoracic and mediastinal disorders			

Epistaxis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	2	
Nasal Congestion			
subjects affected / exposed	1 / 29 (3.45%)	1 / 21 (4.76%)	
occurrences (all)	1	2	
Nasal Discomfort			
subjects affected / exposed	0 / 29 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Oropharyngeal Pain			
subjects affected / exposed	0 / 29 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Pharyngeal Hypoaesthesia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Sneezing			
subjects affected / exposed	0 / 29 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Hiccups			
subjects affected / exposed	0 / 29 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Throat Irritation			
subjects affected / exposed	0 / 29 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			
Disinhibition			
subjects affected / exposed	0 / 29 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Depression			
subjects affected / exposed	0 / 29 (0.00%)	4 / 21 (19.05%)	
occurrences (all)	0	5	
Confusional State			
subjects affected / exposed	0 / 29 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Anxiety			

subjects affected / exposed	4 / 29 (13.79%)	3 / 21 (14.29%)	
occurrences (all)	4	11	
Agitation			
subjects affected / exposed	0 / 29 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Aggression			
subjects affected / exposed	0 / 29 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Dissociation			
subjects affected / exposed	1 / 29 (3.45%)	0 / 21 (0.00%)	
occurrences (all)	4	0	
Euphoric Mood			
subjects affected / exposed	0 / 29 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Time Perception Altered			
subjects affected / exposed	0 / 29 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Suicidal Ideation			
subjects affected / exposed	0 / 29 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Intentional Self-Injury			
subjects affected / exposed	3 / 29 (10.34%)	7 / 21 (33.33%)	
occurrences (all)	3	17	
Insomnia			
subjects affected / exposed	2 / 29 (6.90%)	0 / 21 (0.00%)	
occurrences (all)	3	0	
Initial Insomnia			
subjects affected / exposed	2 / 29 (6.90%)	0 / 21 (0.00%)	
occurrences (all)	3	0	
Illusion			
subjects affected / exposed	0 / 29 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Hallucination, Visual			
subjects affected / exposed	0 / 29 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Investigations			

Weight Increased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Dysgeusia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Memory Impairment			
subjects affected / exposed	0 / 29 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Hypoaesthesia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Headache			
subjects affected / exposed	7 / 29 (24.14%)	3 / 21 (14.29%)	
occurrences (all)	11	6	
Dizziness			
subjects affected / exposed	2 / 29 (6.90%)	0 / 21 (0.00%)	
occurrences (all)	2	0	
Sedation			
subjects affected / exposed	0 / 29 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Somnolence			
subjects affected / exposed	1 / 29 (3.45%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Tremor			
subjects affected / exposed	0 / 29 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Syncope			

subjects affected / exposed	1 / 29 (3.45%)	1 / 21 (4.76%)	
occurrences (all)	1	3	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 29 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Eye disorders			
Vision Blurred			
subjects affected / exposed	0 / 29 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Abdominal Pain Upper			
subjects affected / exposed	2 / 29 (6.90%)	1 / 21 (4.76%)	
occurrences (all)	3	1	
Abdominal Pain			
subjects affected / exposed	1 / 29 (3.45%)	2 / 21 (9.52%)	
occurrences (all)	1	3	
Hypoaesthesia Oral			
subjects affected / exposed	0 / 29 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Constipation			
subjects affected / exposed	2 / 29 (6.90%)	1 / 21 (4.76%)	
occurrences (all)	2	1	
Diarrhoea			
subjects affected / exposed	3 / 29 (10.34%)	2 / 21 (9.52%)	
occurrences (all)	3	2	
Dyspepsia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Vomiting			
subjects affected / exposed	0 / 29 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Nausea			
subjects affected / exposed	3 / 29 (10.34%)	1 / 21 (4.76%)	
occurrences (all)	11	1	
Skin and subcutaneous tissue disorders			

Hyperhidrosis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Rash			
subjects affected / exposed	0 / 29 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 29 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Muscular Weakness			
subjects affected / exposed	0 / 29 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Pain in Extremity			
subjects affected / exposed	1 / 29 (3.45%)	2 / 21 (9.52%)	
occurrences (all)	1	2	
Infections and infestations			
Covid-19			
subjects affected / exposed	2 / 29 (6.90%)	2 / 21 (9.52%)	
occurrences (all)	2	2	
Nasopharyngitis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Influenza			
subjects affected / exposed	1 / 29 (3.45%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis Viral			
subjects affected / exposed	0 / 29 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
Decreased Appetite			

subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 21 (4.76%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 April 2017	The overall reason for the amendment was to revise the protocol to address feedback from Health Authorities, improve clarity, enhance safety, and align the protocol with currently ongoing studies in a related population.
14 June 2017	The overall reason for the amendment (1) permit the initiation of standard of care antidepressant during the first 7 days of double-blind treatment, to reflect local standard of care in regions where it was not routine to initiate two medications simultaneously; (2) remove cognitive assessment at baseline and replace the Rey Auditory Verbal Learning Test (RAVLT) with the International Shopping List Test (ISLT); (3) expand description of safety evaluations; and (4) clarify within the Time & Events schedule the different recall periods for efficacy assessments used at certain study visits.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The study was designed as a Phase 2 study and thus limited by the relatively small sample size per treatment arm.

Notes: