Clinical trial results:
A Randomized, Double-blind, Multicenter, Active-controlled Study of Intranasal Esketamine Plus an Oral Antidepressant for Relapse Prevention in Treatment-resistant Depression

Summary

EudraCT number	2014-004586-24
Trial protocol	DE BE PL ES HU CZ SK IT
Global end of trial date	15 February 2018

Results information

Result version number	v1 (current)
This version publication date	03 March 2019
First version publication date	03 March 2019

Trial information

Trial identification

Sponsor protocol code	ESKETINTRD3003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02493868
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	15 February 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose of the study was to assess the efficacy of intranasal esketamine + oral antidepressant compared with an oral antidepressant + intranasal placebo in delaying relapse of depressive symptoms in subjects with treatment-resistant depression (TRD) who were in stable remission after an induction and optimization course of intranasal esketamine + oral antidepressant.

Protection of trial subjects:

The 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.The safety assessments included clinical laboratory tests (hematology, serum chemistry, and urinalysis), vital sign measurements (temperature, pulse/heart rate, respiratory rate, and blood pressure), physical examinations, height, body weight, and neck circumference, electrocardiograms (ECGs), pulse oximetry, nasal examination.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 October 2015
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	Belgium: 14
Country: Number of subjects enrolled	Brazil: 64
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Czech Republic: 99
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Spain: 16
Country: Number of subjects enrolled	Estonia: 1
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Hungary: 35
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	Mexico: 35
Country: Number of subjects enrolled	Poland: 132
Country: Number of subjects enrolled	Slovakia: 7
Country: Number of subjects enrolled	Sweden: 16
Country: Number of subjects enrolled	Turkey: 53
Country: Number of subjects enrolled	United States: 190

Worldwide total number of subjects	705
EEA total number of subjects	358

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)	705
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Total of 705 subjects were enrolled. Out of which 437 (direct entry [DE] subjects) entered in induction (IND) phase and 268 subjects (150 transferred-entry [TE] subjects from study ESKETINTRD3001 [NCT02417064] and 118 subjects from study ESKETINTRD3002 [NCT02418585]) entered in this study in optimization (OP) phase.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	IND: Intranasal Esketamine + Oral AD (DE Subjects)

Arm description:

Subjects in open-label induction (IND) phase received 56 or 84 milligram intranasal esketamine solution twice weekly with open-label oral antidepressant (AD) (one of: duloxetine/escitalopram/sertraline/venlafaxine extended release [XR]) once daily for 4 weeks. Subjects who completed IND phase and met predefined response criteria entered optimization (OP) phase.

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

Dosage and administration details:

Subjects received 56 or 84 mg intranasal esketamine solution twice weekly.

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

Dosage and administration details:

Subjects received one of duloxetine/escitalopram/sertraline/venlafaxine XR oral antidepressant once daily.

Arm title	OP: Intranasal Esketamine + Oral AD (DE+TE Subjects)

Arm description:

Subjects received intranasal esketamine (same dose) solution once per week for first 4 weeks, then once per week/once every other week based on severity of depressive symptoms, and continued same oral AD from IND phase for 12 weeks. Subjects who completed and met the predefined remission/response criteria entered maintenance (MA) phase.

Arm type	Experimental

Investigational medicinal product name	Esketamine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray, solution
Routes of administration	Nasal use

Dosage and administration details:

Subjects received 56 or 84 mg intranasal esketamine solution once per week for first 4 weeks, then once per week/once every other week.

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

Dosage and administration details:

Subjects received one of duloxetine/escitalopram/sertraline/venlafaxine XR oral antidepressant once daily.

Arm title	OP: Oral AD + Intranasal Placebo (TE Subjects)

Arm description:

Optimization phase (transferred-entry subjects): Subjects received intranasal esketamine matching placebo solution once per week for the first 4 weeks, then once per week or once every other week depending on severity of depressive symptoms with open-label oral AD (one of: duloxetine/escitalopram/sertraline/venlafaxine XR), once daily for 12 weeks. Subjects who completed and met the predefined remission/response criteria entered MA phase.

Arm type	Placebo
Investigational medicinal product name	Oral Antidepressant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received one of duloxetine/escitalopram/sertraline/venlafaxine XR oral antidepressant once daily.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray, solution
Routes of administration	Nasal use

Dosage and administration details:

Subjects received intranasal esketamine matching placebo solution once per week for the first 4 weeks, then once per week or once every other week.

Arm title	MA: Intranasal Esketamine + Oral AD (DE+TE Subjects)

Arm description:

MA phase (DE+TE): subjects were randomized (at end of OP phase) to receive intranasal esketamine (same dose) once weekly/once every other week based on severity of depressive symptoms and continued same oral AD from IND phase.

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

Dosage and administration details:

Subjects received 56 or 84 mg intranasal esketamine solution once weekly or once every other week.

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

Dosage and administration details:

Subjects received one of duloxetine/escitalopram/sertraline/venlafaxine XR oral antidepressant once daily

Arm title	MA: Oral AD + Intranasal Placebo (DE+TE Subjects)

Arm description:

Maintenance phase (DE+TE subjects): Subjects (including randomized subjects from intranasal esketamine arm after OP phase and TE subjects who continued from previous phase in this group) to receive intranasal esketamine placebo with oral AD.

Arm type	Placebo
Investigational medicinal product name	Oral Antidepressant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received one of duloxetine/escitalopram/sertraline/venlafaxine XR oral antidepressant once daily.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray, solution
Routes of administration	Nasal use

Dosage and administration details:

Subjects received intranasal esketamine placebo once weekly or once every other week.

Arm title	FU: Intranasal Esketamine + Oral AD

Arm description:

Follow-up (FU) phase: subjects received no intranasal esketamine but continued oral AD for 2 weeks unless determined to not be clinically appropriate. Subjects who were non-responders at the end of IND phase or who were early terminated at any phase proceeded directly to FU phase.

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

Dosage and administration details:

Subjects received one of duloxetine/escitalopram/sertraline/venlafaxine XR oral antidepressant once daily.

Arm title	FU: Oral AD + Intranasal Placebo

Arm description:

FU Phase: subjects received oral AD for 2 weeks of the follow-up phase unless it was determined to not be clinically appropriate. Subjects who were non-responders in IND phase and who were in OP and MA phase at study termination proceeded directly to FU phase.

Arm type	Placebo

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

Dosage and administration details:

Subjects received one of duloxetine/escitalopram/sertraline/venlafaxine XR oral antidepressant once daily.

Number of subjects in period 1	IND: Intranasal Esketamine + Oral AD (DE Subjects)	OP: Intranasal Esketamine + Oral AD (DE+TE Subjects)	OP: Oral AD + Intranasal Placebo (TE Subjects)
Started	437	455	86
Completed	273	297	54
Not completed	164	158	32
Consent withdrawn by subject	15	8	3
Adverse Event	22	5	-
Non Compliance with Study Drug	-	-	-
Pregnancy	-	-	-
Subject did not meet crit for next phase	114	107	20
Unspecified	8	10	2
MADRS >= 22 for 2 Consecutive Visit	-	14	5
Lost to follow-up	1	2	1
PI Decision	-	-	-
Protocol deviation	2	4	1
Lack of efficacy	2	8	-

Number of subjects in period 1	MA: Intranasal Esketamine + Oral AD (DE+TE Subjects)	MA: Oral AD + Intranasal Placebo (DE+TE Subjects)	FU: Intranasal Esketamine + Oral AD
Started	152	199	481
Completed	139	177	470
Not completed	13	22	11
Consent withdrawn by subject	5	7	3
Adverse Event	1	4	-
Non Compliance with Study Drug	-	1	-
Pregnancy	1	-	-
Subject did not meet crit for next phase	-	-	-
Unspecified	4	9	2
MADRS >= 22 for 2 Consecutive Visit	-	-	-
Lost to follow-up	1	-	1

PI Decision	-	-	5
Protocol deviation	1	1	-
Lack of efficacy	-	-	-

Number of subjects in period 1	FU: Oral AD + Intranasal Placebo
Started	64
Completed	62
Not completed	2
Consent withdrawn by subject	-
Adverse Event	-
Non Compliance with Study Drug	-
Pregnancy	-
Subject did not meet crit for next phase	-
Unspecified	1
MADRS >= 22 for 2 Consecutive Visit	-
Lost to follow-up	-
PI Decision	1
Protocol deviation	-
Lack of efficacy	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	705	705	
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	705	705	
From 65 to 84 years	0	0	
85 years and over	0	0	
Title for AgeContinuous Units: years			
arithmetic mean	46.1		
standard deviation	± 11.10	-	
Title for Gender Units: subjects			
Female	457	457	
Male	248	248	

End points

End points reporting groups

Reporting group title	IND: Intranasal Esketamine + Oral AD (DE Subjects)

Reporting group description:

Subjects in open-label induction (IND) phase received 56 or 84 milligram intranasal esketamine solution twice weekly with open-label oral antidepressant (AD) (one of: duloxetine/escitalopram/sertraline/venlafaxine extended release [XR]) once daily for 4 weeks. Subjects who completed IND phase and met predefined response criteria entered optimization (OP) phase.

Reporting group title	OP: Intranasal Esketamine + Oral AD (DE+TE Subjects)

Reporting group description:

Subjects received intranasal esketamine (same dose) solution once per week for first 4 weeks, then once per week/once every other week based on severity of depressive symptoms, and continued same oral AD from IND phase for 12 weeks. Subjects who completed and met the predefined remission/response criteria entered maintenance (MA) phase.

Reporting group title	OP: Oral AD + Intranasal Placebo (TE Subjects)

Reporting group description:

Optimization phase (transferred-entry subjects): Subjects received intranasal esketamine matching placebo solution once per week for the first 4 weeks, then once per week or once every other week depending on severity of depressive symptoms with open-label oral AD (one of: duloxetine/escitalopram/sertraline/venlafaxine XR), once daily for 12 weeks. Subjects who completed and met the predefined remission/response criteria entered MA phase.

Reporting group title	MA: Intranasal Esketamine + Oral AD (DE+TE Subjects)

Reporting group description:

MA phase (DE+TE): subjects were randomized (at end of OP phase) to receive intranasal esketamine (same dose) once weekly/once every other week based on severity of depressive symptoms and continued same oral AD from IND phase.

Reporting group title	MA: Oral AD + Intranasal Placebo (DE+TE Subjects)

Reporting group description:

Maintenance phase (DE+TE subjects): Subjects (including randomized subjects from intranasal esketamine arm after OP phase and TE subjects who continued from previous phase in this group) to receive intranasal esketamine placebo with oral AD.

Reporting group title	FU: Intranasal Esketamine + Oral AD

Reporting group description:

Follow-up (FU) phase: subjects received no intranasal esketamine but continued oral AD for 2 weeks unless determined to not be clinically appropriate. Subjects who were non-responders at the end of IND phase or who were early terminated at any phase proceeded directly to FU phase.

Reporting group title	FU: Oral AD + Intranasal Placebo

Reporting group description:

FU Phase: subjects received oral AD for 2 weeks of the follow-up phase unless it was determined to not be clinically appropriate. Subjects who were non-responders in IND phase and who were in OP and MA phase at study termination proceeded directly to FU phase.

Subject analysis set title	Stable Remitters :Intranasal Esketamine + Oral AD
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects who were in stable remission at the end of the optimization phase and who received at least 1 dose of intranasal study drug and 1 dose of oral antidepressant during the maintenance phase.

Subject analysis set title	Stable Remitters: Oral AD + Intranasal Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects who were in stable remission at the end of the optimization phase and who received at least 1 dose of intranasal placebo and 1 dose of oral antidepressant during the maintenance phase.

Subject analysis set title	Stable Responders: Intranasal Esketamine + Oral AD
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects who were stable responders (but not stable remitters) at the end of the optimization phase and who received at least 1 dose of intranasal study drug and 1 dose of oral antidepressant during the

maintenance phase.

Subject analysis set title	Stable Responders: Oral AD + Intranasal Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects who were stable responders (but not stable remitters) at the end of the optimization phase and who received at least 1 dose of intranasal placebo and 1 dose of oral antidepressant during the maintenance phase.

Primary: Time to Relapse in Subjects with Stable Remission (Maintenance Phase)

End point title	Time to Relapse in Subjects with Stable Remission (Maintenance Phase)

End point description:

Relapse (any of following): MADRS total score >= 22 for 2 consecutive assessments separated by 5-15 days and/or hospitalization for worsening depression/any clinical event suggestive of relapse of depressive illness such as suicide attempt/completed suicide/hospitalization to prevent suicide; If hospitalized, start date of hospitalization will be date of relapse, if not then date of event will be used. Stable remission: MADRS total score <= 12 for at least 3 of last 4 weeks of OP phase, with 1 excursion total score > 12 or 1 missing assessment at OP week 13/14. FAS (stable remitters) = all randomized subjects who were in stable remission at end of OP phase and received at least 1 dose of study drug and oral AD in MA phase. '99999' = for esketamine arm that median time to relapse (time point at which cumulative survival function equals 0.5 or 50%) was not estimable, as group never reached 50%; 99999 (placebo arm) = upper limit of CI could not be estimated due to insufficient data.

End point type	Primary

End point timeframe:

Time from randomization to the first relapse during the maintenance phase (up to 92 Weeks)

End point values	Stable Remitters :Intranasal Esketamine + Oral AD	Stable Remitters: Oral AD + Intranasal Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	90	86		
Units: Days				
median (confidence interval 95%)	99999 (99999 to 99999)	273.0 (97.0 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Stable Remitters :Intranasal Esketamine + Oral AD v Stable Remitters: Oral AD + Intranasal Placebo
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.49

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	0.83

Secondary: Time to Relapse in Subjects with Stable Response (but not in Stable Remission) (Maintenance Phase)

End point title	Time to Relapse in Subjects with Stable Response (but not in Stable Remission) (Maintenance Phase)

End point description:

Relapse (any of following): MADRS total score >= 22 for 2 consecutive assessments separated by 5-15 days and/or hospitalization for worsening depression/any clinical event suggestive of relapse of depressive illness such as suicide attempt/completed suicide/hospitalization to prevent suicide; If hospitalized, start date of hospitalization will be date of relapse, if not then date of event will be used. MADRS: scale to measure depression severity and to detect changes due to AD treatment. It has 10 items, scored from 0-6 (not present/normal-severe/continuous symptoms), total score =60. Higher scores: more severe condition. Stable response: >= 50% reduction in MADRS total score from baseline (Day 1: IND phase [before first dose]) in each of last 2 weeks of OP phase, but no stable remission. FAS Stable responders: all randomized subjects who were stable responders (not stable remitters) at end of OP phase and who received at least 1 dose of intranasal study drug and oral AD in MA phase.

End point type	Secondary

End point timeframe:

Time from randomization to the first relapse during the maintenance phase (up to 92 Weeks)

End point values	Stable Responders: Intranasal Esketamine + Oral AD	Stable Responders: Oral AD + Intranasal Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	62	59		
Units: Days				
median (confidence interval 95%)	635.0 (264.0 to 635.0)	88.0 (46.0 to 196.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Montgomery-asberg Depression Rating Scale (MADRS) Total Score at Endpoint in Subjects with Stable Remission (Maintenance Phase)

End point title	Change from Baseline in Montgomery-asberg Depression Rating Scale (MADRS) Total Score at Endpoint in Subjects with Stable Remission (Maintenance Phase)

End point description:

MADRS: scale to measure depression severity and to detect changes due to AD treatment. It has 10 items, scored from 0-6 (not present/normal-severe/continuous symptoms), total score = 60. Higher scores: more severe condition. The change from baseline in MADRS total score (last observation carried

forward [LOCF] data), at endpoint was reported. The last post baseline observation was carried forward as the endpoint. FAS Stable remitters included all randomized subjects who were in stable remission at end of OP phase and received at least 1 dose of study drug and oral AD in MA phase. Here 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline and Endpoint (Up to 92 Weeks)

End point values	Stable Remitters :Intranasal Esketamine + Oral AD	Stable Remitters: Oral AD + Intranasal Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	89	86		
Units: Units on a scale				
arithmetic mean (standard deviation)	7.5 (± 11.59)	12.5 (± 13.63)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in MADRS Total Score at Endpoint in Subjects with Stable Response (but not in Stable Remission) (Maintenance Phase)

End point title	Change from Baseline in MADRS Total Score at Endpoint in Subjects with Stable Response (but not in Stable Remission) (Maintenance Phase)

End point description:

MADRS: scale to measure depression severity and to detect changes due to AD treatment. It has 10 items, scored from 0-6 (not present/normal-severe/continuous symptoms), total score = 60. Higher scores: more severe condition. The change from baseline in MADRS total score (LOCF data), at endpoint was reported. The last post baseline observation was carried forward as the endpoint. FAS Stable responders included all randomized subjects who were stable responders (but not stable remitters) at end of OP phase and who received at least 1 dose of intranasal study drug and oral AD in MA phase.

End point type	Secondary

End point timeframe:

Baseline and Endpoint (Up to 92 Weeks)

End point values	Stable Responders: Intranasal Esketamine + Oral AD	Stable Responders: Oral AD + Intranasal Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	62	59		
Units: Units on a scale				
arithmetic mean (standard deviation)	4.4 (± 11.38)	11.4 (± 12.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Patient Health Questionnaire-9 (PHQ-9) Total Score at Endpoint in Subjects with Stable Remission (Maintenance Phase)

End point title	Change from Baseline in Patient Health Questionnaire-9 (PHQ-9) Total Score at Endpoint in Subjects with Stable Remission (Maintenance Phase)

End point description:

PHQ-9 is a 9-item, self-report scale assessing depressive symptoms. Each item is rated on a 4-point scale (0 = Not at all, 1 = Several Days, 2 = More than half the days, and 3 = Nearly every day). The subject's item responses are summed to provide a total score (range of 0 to 27) with higher scores indicating greater severity of depressive symptoms. The severity of the PHQ-9 is categorized as follows: None-minimal (0-4), mild (5-9), moderate (10-14), moderately severe (15-19) and severe (20-27). The change from baseline in PHQ-9 total score, (LOCF data) at endpoint was reported. The last post baseline observation was carried forward as the endpoint. FAS Stable remitters included all randomized subjects who were in stable remission at end of OP phase and received at least 1 dose of study drug and oral AD in MA phase. Here 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline and Endpoint (Up to 92 Weeks)

End point values	Stable Remitters :Intranasal Esketamine + Oral AD	Stable Remitters: Oral AD + Intranasal Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	89	86		
Units: Units on a scale				
arithmetic mean (standard deviation)	3.3 (± 5.58)	5.9 (± 7.09)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in PHQ-9 Total Score at Endpoint in Subjects with Stable Response (but not in Stable Remission) (Maintenance Phase)

End point title	Change from Baseline in PHQ-9 Total Score at Endpoint in Subjects with Stable Response (but not in Stable Remission) (Maintenance Phase)

End point description:

PHQ-9 is a 9-item, self-report scale assessing depressive symptoms. Each item is rated on a 4-point

scale (0 = Not at all, 1 = Several Days, 2 = More than half the days, and 3 = Nearly every day). The subject's item responses are summed to provide a total score (range of 0 to 27) with higher scores indicating greater severity of depressive symptoms. The severity of the PHQ-9 is categorized as follows: None-minimal (0-4), mild (5-9), moderate (10-14), moderately severe (15-19) and severe (20-27). The change from baseline in PHQ-9 total score, (LOCF data) at endpoint was reported. The last post baseline observation was carried forward as the endpoint. FAS (Stable responders) included all randomized subjects who were stable responders (but not stable remitters) at end of OP phase and who received at least 1 dose of intranasal study drug and oral AD in MA phase. Here 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline and Endpoint (Up to 92 Weeks)

End point values	Stable Responders: Intranasal Esketamine + Oral AD	Stable Responders: Oral AD + Intranasal Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	61	58		
Units: Units on a scale				
arithmetic mean (standard deviation)	1.7 (± 5.02)	4.7 (± 5.48)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Clinical Global Impression-Severity (CGI-S) Score at Endpoint in Subjects with Stable Remission (Maintenance Phase)

End point title	Change from Baseline in Clinical Global Impression-Severity (CGI-S) Score at Endpoint in Subjects with Stable Remission (Maintenance Phase)

End point description:

CGI-S: clinician-determined summary measure of severity of subject's illness that considers all available information, including knowledge of subject's history, psychosocial circumstances, symptoms, behavior, impact of symptoms on ability to function. CGI-S evaluates severity of psychopathology on a scale of 0-7. Subject is assessed on severity of mental illness at time of rating as: 0=not assessed; 1=normal (not at all ill); 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=among most extremely ill patients. Change from baseline in CGI-S score, (LOCF data) at endpoint was reported. Last post baseline observation was carried forward as endpoint. FAS (Stable remitters) included all randomized subjects who were in stable remission at end of OP phase and received at least 1 dose of study drug and oral AD in MA phase. Here 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline and Endpoint (Up to 92 Weeks)

End point values	Stable Remitters :Intranasal Esketamine + Oral AD	Stable Remitters: Oral AD + Intranasal Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	89	86		
Units: Units on a scale				
median (full range (min-max))	0.0 (-3 to 4)	1.0 (-2 to 5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Clinical Global Impression-Severity Score at Endpoint in Subjects with Stable Response (but not in Stable Remission) (Maintenance Phase)

End point title	Change from Baseline in Clinical Global Impression-Severity Score at Endpoint in Subjects with Stable Response (but not in Stable Remission) (Maintenance Phase)

End point description:

CGI-S: clinician-determined summary measure of severity of subject's illness that considers information, including knowledge of subject's history, psychosocial circumstances, symptoms, behavior, impact of symptoms on ability to function. CGI-S evaluates severity of psychopathology on a scale of 0-7. Subject is assessed on severity of mental illness at time of rating as: 0=not assessed; 1=normal (not at all ill); 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=among most extremely ill patients. Change from baseline in CGI-S score, (LOCF data) at endpoint was reported. Last post baseline observation was carried forward as endpoint. FAS (Stable responders): all randomized subjects who were stable responders (but not stable remitters) at end of OP phase and who received at least 1 dose of intranasal study drug and oral AD in MA phase. 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline and Endpoint (Up to 92 Weeks)

End point values	Stable Responders: Intranasal Esketamine + Oral AD	Stable Responders: Oral AD + Intranasal Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	62	58		
Units: Units on a scale				
median (full range (min-max))	0.0 (-2 to 4)	1.0 (-3 to 5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Generalized Anxiety Disorder-7 Items (GAD-7) Total Score at Endpoint in Subjects with Stable Remission (Maintenance Phase)

End point title	Change from Baseline in Generalized Anxiety Disorder-7 Items (GAD-7) Total Score at Endpoint in Subjects with Stable Remission (Maintenance Phase)

End point description:

GAD-7 is brief and validated 7-item self-report assessment of overall anxiety. Subjects respond to each item using a 4-point scale with response categories: 0=not at all, 1=several days, 2=more than half the days, 3=nearly every day. Item responses are summed to yield total score with range of 0-21, higher scores indicate more anxiety. Severity of GAD-7 is categorized as: None (0-4), Mild (5-9), Moderate (10-14) and Severe (15 -21). Item responses are summed for total score (range of 0-21), higher scores indicating more anxiety. Change from baseline in GAD-7 total score, (LOCF data), at endpoint was reported. Last post baseline observation was carried forward as endpoint. FAS (Stable remitters) included all randomized subjects who were in stable remission at end of OP phase and received at least 1 dose of study drug and oral AD in MA phase. Here 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline and Endpoint (Up to 92 Weeks)

End point values	Stable Remitters :Intranasal Esketamine + Oral AD	Stable Remitters: Oral AD + Intranasal Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	89	86		
Units: Units on a scale				
arithmetic mean (standard deviation)	2.2 (± 4.45)	4.0 (± 5.93)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Generalized Anxiety Disorder-7 Items Total Score at Endpoint in Subjects with Stable Response (but not in Stable Remission) (Maintenance Phase)

End point title	Change from Baseline in Generalized Anxiety Disorder-7 Items Total Score at Endpoint in Subjects with Stable Response (but not in Stable Remission) (Maintenance Phase)

End point description:

GAD-7 is brief and validated 7-item self-report assessment of overall anxiety. Subjects respond to each item using a 4-point scale with response categories: 0=not at all, 1=several days, 2=more than half the days, 3=nearly every day. Item responses are summed to yield total score with range of 0-21, higher score means more anxiety. Severity of GAD-7 is categorized as: None (0-4), Mild (5-9), Moderate (10-14), Severe (15 -21). Item responses are summed for total score (range of 0-21), higher scores indicating more anxiety. Change from baseline in GAD-7 total score, (LOCF data), at endpoint was reported. Last post baseline observation was carried forward as endpoint. FAS (Stable responders) included all randomized subjects who were stable responders (but not stable remitters) at end of OP phase and who received at least 1 dose of intranasal study drug and oral AD in MA phase. Here 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline and Endpoint (Up to 92 Weeks)

End point values	Stable Responders: Intranasal Esketamine + Oral AD	Stable Responders: Oral AD + Intranasal Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	61	58		
Units: Units on a scale				
arithmetic mean (standard deviation)	1.4 (± 3.76)	2.6 (± 4.26)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in EuroQol-5 Dimension-5 Level (EQ-5D-5L) Sum Score at Endpoint in Subjects with Stable Remission (Maintenance Phase)

End point title	Change from Baseline in EuroQol-5 Dimension-5 Level (EQ-5D-5L) Sum Score at Endpoint in Subjects with Stable Remission (Maintenance Phase)

End point description:

EQ-5D-5L consists of EQ-5D-5L descriptive system and EQ VAS. EQ-5D-5L descriptive system has 5 dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. Each has 5 levels of perceived problems (1-no problem; 2-slight; 3-moderate; 4-severe; 5-extreme problems). Responses from all 5 dimensions answered by subject as per his/her health “today” were used to generate HIS, range=0-1.00 (dead-full health). EQ VAS self-rating records respondent’s own assessment of his/her overall health status at time of completion, scale range=0-100 (worst health-best health). Sum score range=0-100. sum score= (sum of the scores from the 5 dimensions minus 5) *5. Higher score indicates worst health state. FAS (Stable remitters) included all randomized subjects in stable remission at end of OP phase and received at least 1 dose of study drug and oral AD in MA phase. 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline and Endpoint (Up to 92 Weeks)

End point values	Stable Remitters :Intranasal Esketamine + Oral AD	Stable Remitters: Oral AD + Intranasal Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	88	86		
Units: Units on a scale				
arithmetic mean (standard deviation)	7.5 (± 11.87)	10.9 (± 14.74)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in EQ Visual Analogue Scale (EQ VAS) Score at Endpoint in Subjects with Stable Remission (Maintenance Phase)

End point title	Change from Baseline in EQ Visual Analogue Scale (EQ VAS) Score at Endpoint in Subjects with Stable Remission (Maintenance Phase)

End point description:

EQ VAS self-rating records respondent's own assessment of his/her overall health status at time of completion, scale range = 0-100 (worst health-best health). FAS (Stable remitters) included all randomized subjects who were in stable remission at end of OP phase and received at least 1 dose of study drug and oral AD in MA phase. Here 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline and Endpoint (Up to 92 Weeks)

End point values	Stable Remitters :Intranasal Esketamine + Oral AD	Stable Remitters: Oral AD + Intranasal Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	88	86		
Units: Units on a scale				
arithmetic mean (standard deviation)	-10.4 (± 20.29)	-16.1 (± 21.80)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in EQ-5D-5L Health Status Index (HSI) at Endpoint in Subjects with Stable Remission (Maintenance Phase)

End point title	Change from Baseline in EQ-5D-5L Health Status Index (HSI) at Endpoint in Subjects with Stable Remission (Maintenance Phase)

End point description:

EQ-5D-5L consists of EQ-5D-5L descriptive system and EQ VAS. EQ-5D-5L descriptive system has 5 dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. Each has 5 levels of perceived problems (1-no problem; 2-slight; 3-moderate; 4-severe; 5-extreme problems). Responses from all 5 dimensions answered by subject as per his/her health "today" were used to generate HSI. HSI range: 0-1.00 (dead-full health). FAS (Stable remitters) included all randomized subjects in stable remission at end of OP phase and received at least 1 dose of study drug and oral AD in MA phase. Here 'N' (number of subjects analyzed) included number of subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline and Endpoint (Up to 92 Weeks)

End point values	Stable Remitters :Intranasal Esketamine + Oral AD	Stable Remitters: Oral AD + Intranasal Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	88	86		
Units: Units on a scale				
arithmetic mean (standard deviation)	-0.067 (± 0.1180)	-0.096 (± 0.1484)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in EuroQol-5 Dimension-5 Level Sum Score at Endpoint in Subjects with Stable Response (but not in Stable Remission) (Maintenance Phase)

End point title	Change from Baseline in EuroQol-5 Dimension-5 Level Sum Score at Endpoint in Subjects with Stable Response (but not in Stable Remission) (Maintenance Phase)

End point description:

EQ-5D-5L consists of EQ-5D-5L descriptive system and EQ VAS. Descriptive system has 5 dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. Each has 5 levels of perceived problems (1-no problem; 2-slight; 3-moderate; 4-severe; 5-extreme problems). Responses from all 5 dimensions answered by subject as per his/her health "today" were used to generate HIS, range: 0-1.00 (dead-full health). EQ VAS self-rating records respondent's own assessment of his/her overall health status at time of completion, scale range=0-100 (worst health-best health). Sum score range=0-100. sum score= (sum score of 5 dimensions minus 5) *5. Higher score: worst health state. FAS (Stable responders): all randomized subjects who were stable responders (but not stable remitters) at end of OP phase and who received at least 1 dose of intranasal study drug and oral AD in MA phase. 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline and Endpoint (Up to 92 Weeks)

End point values	Stable Responders: Intranasal Esketamine + Oral AD	Stable Responders: Oral AD + Intranasal Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	61	58		
Units: Units on scale				
arithmetic mean (standard deviation)	3.0 (± 8.13)	8.4 (± 13.55)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in EQ-5D-5L EQ Visual Analogue Scale Score at Endpoint in Subjects with Stable Response (but not in Stable Remission) (Maintenance Phase)

End point title	Change from Baseline in EQ-5D-5L EQ Visual Analogue Scale Score at Endpoint in Subjects with Stable Response (but not in Stable Remission) (Maintenance Phase)

End point description:

EQ VAS self-rating records respondent's own assessment of his/her overall health status at time of completion, scale range=0-100 (worst health-best health). FAS (Stable responders) included all randomized subjects who were stable responders (but not stable remitters) at end of OP phase and who received at least 1 dose of intranasal study drug and oral AD in MA phase. Here 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline and Endpoint (Up to 92 Weeks)

End point values	Stable Responders: Intranasal Esketamine + Oral AD	Stable Responders: Oral AD + Intranasal Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	61	58		
Units: Units on a scale				
arithmetic mean (standard deviation)	-1.3 (± 15.55)	-13.8 (± 19.81)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in EQ-5D-5L Health Status Index at Endpoint in Subjects with Stable Response (but not in Stable Remission) (Maintenance Phase)

End point title	Change from Baseline in EQ-5D-5L Health Status Index at Endpoint in Subjects with Stable Response (but not in Stable Remission) (Maintenance Phase)

End point description:

EQ-5D-5L consists of EQ-5D-5L descriptive system and EQ VAS. EQ-5D-5L descriptive system has 5 dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. Each has 5 levels of perceived problems (1-no problem; 2-slight; 3-moderate; 4-severe; 5-extreme problems). Responses from all 5 dimensions answered by subject as per his/her health "today" were used to generate HSI. HSI range: 0-1.00 (dead-full health). FAS (Stable responders) included all randomized subjects who were stable responders (but not stable remitters) at end of OP phase and who received at least 1 dose of intranasal study drug and oral AD in MA phase. Here 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline and Endpoint (Up to 92 Weeks)

End point values	Stable Responders: Intranasal Esketamine + Oral AD	Stable Responders: Oral AD + Intranasal Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	61	58		
Units: Units on a scale				
arithmetic mean (standard deviation)	-0.023 (± 0.0753)	-0.073 (± 0.1383)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Sheehan Disability Scale (SDS) Total Score at Endpoint in Subjects with Stable Remission (Maintenance Phase)

End point title	Change from Baseline in Sheehan Disability Scale (SDS) Total Score at Endpoint in Subjects with Stable Remission (Maintenance Phase)

End point description:

SDS: 5-item questionnaire used for assessment of functional impairment and associated disability. First 3 items assess disruption of 1: work/school 2: social life 3: family life/home responsibilities on a 0-10 rating scale. It has 1 item for each day lost from school/work and when underproductive. First 3 items scores are summed to make total score of 0-30, higher score: greater impairment. Recall period is 7 days. Response: scores <=4 for each item, <=12 for total score. Remission: scores <=2 for each item, <=6 for total score. Change from baseline in SDS total Score, (LOCF data), at endpoint was reported. Last post baseline observation was carried forward as endpoint. FAS (Stable remitters) included all randomized subjects in stable remission at end of OP phase and received at least 1 dose of study drug and oral AD in MA phase. 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline and Endpoint (Up to 92 Weeks)

End point values	Stable Remitters :Intranasal Esketamine + Oral AD	Stable Remitters: Oral AD + Intranasal Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	82	77		
Units: Units on a scale				
arithmetic mean (standard deviation)	4.7 (± 7.34)	7.2 (± 10.44)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Sheehan Disability Total Score at Endpoint in

Subjects with Stable Response (but not in Stable Remission) (Maintenance Phase)

End point title	Change from Baseline in Sheehan Disability Total Score at Endpoint in Subjects with Stable Response (but not in Stable Remission) (Maintenance Phase)

End point description:

SDS: 5-item questionnaire for assessment of functional impairment and associated disability. First 3 items assess disruption of 1: work/school 2: social life 3: family life/home responsibilities on a 0-10 rating scale. It has 1 item for each day lost from school/work and when underproductive. First 3 items sum score gives total score of 0-30, higher score: greater impairment. Recall period is 7 days. Response: scores <=4 for each item, <=12 for total score. Remission: scores <=2 for each item, <=6 for total score. Change from baseline in SDS total Score, (LOCF data) at endpoint was reported. Last post baseline observation was carried forward as endpoint. FAS (Stable responders) included all randomized subjects who were stable responders (but not stable remitters) at end of OP phase and who received at least 1 dose of intranasal study drug and oral AD in MA phase. 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline and Endpoint (Up to 92 Weeks)

End point values	Stable Responders: Intranasal Esketamine + Oral AD	Stable Responders: Oral AD + Intranasal Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	58	53		
Units: Units on a scale				
arithmetic mean (standard deviation)	2.2 (± 6.63)	6.8 (± 7.64)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Approximately 2.4 years

Adverse event reporting additional description:

Safety analysis set included all subjects who received at least 1 dose of intranasal study medication or 1 dose of oral antidepressant in respective phase (Induction, Optimization, Maintenance). Follow-up analysis set included all subjects who entered the follow-up phase.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	IND: DE Subjects: Intranasal Esketamine + Oral AD

Reporting group description:

Subjects in open-label induction (IND) phase received 56 or 84 milligram intranasal esketamine solution twice weekly with open-label oral AD (one of: duloxetine/escitalopram/sertraline/venlafaxine extended release [XR]) once daily for 4 weeks.

Reporting group title	MA: Intranasal Esketamine + Oral AD (DE+TE Subjects)

Reporting group description:

Maintenance (MA) phase (both direct-entry and transferred-entry subjects): received 56 mg or 84 mg intranasal esketamine solution once per week for the first 4 weeks, then once per week or once every other week depending on severity of depressive symptoms with open-label oral AD (one of: duloxetine/escitalopram/sertraline/venlafaxine XR), once daily until relapse or study termination.

Reporting group title	OP: Intranasal Esketamine + Oral AD (DE+TE Subjects)

Reporting group description:

Subjects received intranasal esketamine (same dose) solution once per week for first 4 weeks, then once per week/once every other week based on severity of depressive symptoms, and continued same oral AD from IND phase for 12 weeks.

Reporting group title	MA: Oral AD + Intranasal Placebo (DE+TE Subjects)

Reporting group description:

Maintenance phase (both direct-entry and transferred-entry subjects): received intranasal esketamine matching placebo solution once per week for the first 4 weeks, then once per week or once every other week depending on severity of depressive symptoms with open-label oral AD (one of: duloxetine/escitalopram/sertraline/venlafaxine XR), until relapse or study termination.

Reporting group title	FU: Intranasal Esketamine + Oral AD

Reporting group description:

Subjects (who were non-responders in IND phase and who were in OP and MA phase at study termination) who received at least 1 dose of 56 mg or 84 mg intranasal esketamine participated in the follow-up (FU) phase. No intranasal esketamine was administered during FU phase. Subjects received oral AD for 2 weeks of the follow-up phase unless it was determined to not be clinically appropriate.

Reporting group title	FU: Oral AD + Intranasal Placebo

Reporting group description:

Subjects (who were non-responders in IND phase and who were in OP and MA phase at study termination) who received intranasal esketamine matching placebo with oral AD participated in the FU phase. Subjects received oral AD for 2 weeks of the follow-up phase unless it was determined to not be clinically appropriate.

Reporting group title	OP_TES: Oral AD + Intranasal Placebo

Reporting group description:

OP phase (transferred-entry subjects [TES]): received intranasal esketamine matching placebo solution once per week for the first 4 weeks, then once per week or once every other week depending on severity of depressive symptoms with open-label oral AD (one of: duloxetine/escitalopram/sertraline/venlafaxine XR), once daily for 12 weeks.

Reporting group title	MA_TES: Oral AD + Intranasal Placebo

Reporting group description:

Maintenance phase (transferred-entry subjects): Subjects were randomized (at the end of optimization phase) to intranasal esketamine matching placebo solution once per week for the first 4 weeks, then once per week or once every other week depending on severity of depressive symptoms with open-label oral AD (one of: duloxetine/escitalopram/sertraline/venlafaxine XR).

Serious adverse events	IND: DE Subjects: Intranasal Esketamine + Oral AD	MA: Intranasal Esketamine + Oral AD (DE+TE Subjects)	OP: Intranasal Esketamine + Oral AD (DE+TE Subjects)
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 437 (2.97%)	4 / 152 (2.63%)	11 / 455 (2.42%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Procedural Pain			
subjects affected / exposed	1 / 437 (0.23%)	0 / 152 (0.00%)	0 / 455 (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
Clavicle Fracture			
subjects affected / exposed	0 / 437 (0.00%)	0 / 152 (0.00%)	0 / 455 (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
Vascular disorders			
Hypertensive Crisis			
subjects affected / exposed	0 / 437 (0.00%)	0 / 152 (0.00%)	1 / 455 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic Hypotension			
subjects affected / exposed	1 / 437 (0.23%)	0 / 152 (0.00%)	0 / 455 (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
Cardiac disorders			
Sinus Tachycardia			
subjects affected / exposed	0 / 437 (0.00%)	0 / 152 (0.00%)	1 / 455 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Autonomic Nervous System Imbalance			
subjects affected / exposed	1 / 437 (0.23%)	0 / 152 (0.00%)	0 / 455 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 437 (0.00%)	0 / 152 (0.00%)	1 / 455 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lacunar Stroke			
subjects affected / exposed	1 / 437 (0.23%)	0 / 152 (0.00%)	0 / 455 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			
subjects affected / exposed	0 / 437 (0.00%)	0 / 152 (0.00%)	1 / 455 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	0 / 437 (0.00%)	0 / 152 (0.00%)	1 / 455 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sedation			
subjects affected / exposed	1 / 437 (0.23%)	0 / 152 (0.00%)	0 / 455 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Simple Partial Seizures			
subjects affected / exposed	1 / 437 (0.23%)	0 / 152 (0.00%)	0 / 455 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Ectopic Pregnancy			
subjects affected / exposed	0 / 437 (0.00%)	1 / 152 (0.66%)	0 / 455 (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

General disorders and administration site conditions			
Chest Pain			
subjects affected / exposed	0 / 437 (0.00%)	0 / 152 (0.00%)	1 / 455 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypothermia			
subjects affected / exposed	1 / 437 (0.23%)	0 / 152 (0.00%)	0 / 455 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Anal Fissure			
subjects affected / exposed	0 / 437 (0.00%)	0 / 152 (0.00%)	1 / 455 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis Acute			
subjects affected / exposed	0 / 437 (0.00%)	0 / 152 (0.00%)	1 / 455 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 437 (0.46%)	0 / 152 (0.00%)	0 / 455 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	3 / 437 (0.69%)	2 / 152 (1.32%)	1 / 455 (0.22%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disorientation			
subjects affected / exposed	1 / 437 (0.23%)	0 / 152 (0.00%)	0 / 455 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Major Depression			

subjects affected / exposed	0 / 437 (0.00%)	1 / 152 (0.66%)	0 / 455 (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
Mania			
subjects affected / exposed	0 / 437 (0.00%)	0 / 152 (0.00%)	0 / 455 (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
Panic Attack			
subjects affected / exposed	0 / 437 (0.00%)	0 / 152 (0.00%)	1 / 455 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal Ideation			
subjects affected / exposed	1 / 437 (0.23%)	0 / 152 (0.00%)	0 / 455 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 437 (0.23%)	0 / 152 (0.00%)	0 / 455 (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
Musculoskeletal and connective tissue disorders			
Intervertebral Disc Protrusion			
subjects affected / exposed	0 / 437 (0.00%)	0 / 152 (0.00%)	0 / 455 (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
Pain in Extremity			
subjects affected / exposed	0 / 437 (0.00%)	0 / 152 (0.00%)	1 / 455 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 437 (0.00%)	0 / 152 (0.00%)	1 / 455 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Sepsis			
subjects affected / exposed	0 / 437 (0.00%)	0 / 152 (0.00%)	1 / 455 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	MA: Oral AD + Intranasal Placebo (DE+TE Subjects)	FU: Intranasal Esketamine + Oral AD	FU: Oral AD + Intranasal Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 145 (0.69%)	3 / 481 (0.62%)	0 / 64 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Procedural Pain			
subjects affected / exposed	0 / 145 (0.00%)	0 / 481 (0.00%)	0 / 64 (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
Clavicle Fracture			
subjects affected / exposed	0 / 145 (0.00%)	0 / 481 (0.00%)	0 / 64 (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
Vascular disorders			
Hypertensive Crisis			
subjects affected / exposed	0 / 145 (0.00%)	0 / 481 (0.00%)	0 / 64 (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
Orthostatic Hypotension			
subjects affected / exposed	0 / 145 (0.00%)	0 / 481 (0.00%)	0 / 64 (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
Cardiac disorders			
Sinus Tachycardia			
subjects affected / exposed	0 / 145 (0.00%)	0 / 481 (0.00%)	0 / 64 (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			

Autonomic Nervous System Imbalance			
subjects affected / exposed	0 / 145 (0.00%)	0 / 481 (0.00%)	0 / 64 (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
Headache			
subjects affected / exposed	0 / 145 (0.00%)	0 / 481 (0.00%)	0 / 64 (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
Lacunar Stroke			
subjects affected / exposed	0 / 145 (0.00%)	0 / 481 (0.00%)	0 / 64 (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
Migraine			
subjects affected / exposed	0 / 145 (0.00%)	0 / 481 (0.00%)	0 / 64 (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
Paraesthesia			
subjects affected / exposed	0 / 145 (0.00%)	0 / 481 (0.00%)	0 / 64 (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
Sedation			
subjects affected / exposed	0 / 145 (0.00%)	0 / 481 (0.00%)	0 / 64 (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
Simple Partial Seizures			
subjects affected / exposed	0 / 145 (0.00%)	0 / 481 (0.00%)	0 / 64 (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
Pregnancy, puerperium and perinatal conditions			
Ectopic Pregnancy			
subjects affected / exposed	0 / 145 (0.00%)	0 / 481 (0.00%)	0 / 64 (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

General disorders and administration site conditions			
Chest Pain			
subjects affected / exposed	0 / 145 (0.00%)	1 / 481 (0.21%)	0 / 64 (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
Hypothermia			
subjects affected / exposed	0 / 145 (0.00%)	0 / 481 (0.00%)	0 / 64 (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
Gastrointestinal disorders			
Anal Fissure			
subjects affected / exposed	0 / 145 (0.00%)	0 / 481 (0.00%)	0 / 64 (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
Hepatobiliary disorders			
Cholecystitis Acute			
subjects affected / exposed	0 / 145 (0.00%)	0 / 481 (0.00%)	0 / 64 (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			
Anxiety			
subjects affected / exposed	0 / 145 (0.00%)	0 / 481 (0.00%)	0 / 64 (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			
subjects affected / exposed	1 / 145 (0.69%)	1 / 481 (0.21%)	0 / 64 (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
Disorientation			
subjects affected / exposed	0 / 145 (0.00%)	0 / 481 (0.00%)	0 / 64 (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 / 145 (0.00%)	0 / 481 (0.00%)	0 / 64 (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
Mania			
subjects affected / exposed	0 / 145 (0.00%)	1 / 481 (0.21%)	0 / 64 (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
Panic Attack			
subjects affected / exposed	0 / 145 (0.00%)	0 / 481 (0.00%)	0 / 64 (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	0 / 145 (0.00%)	0 / 481 (0.00%)	0 / 64 (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
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 145 (0.00%)	0 / 481 (0.00%)	0 / 64 (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
Musculoskeletal and connective tissue disorders			
Intervertebral Disc Protrusion			
subjects affected / exposed	0 / 145 (0.00%)	1 / 481 (0.21%)	0 / 64 (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
Pain in Extremity			
subjects affected / exposed	0 / 145 (0.00%)	0 / 481 (0.00%)	0 / 64 (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
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 145 (0.00%)	0 / 481 (0.00%)	0 / 64 (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

Sepsis			
subjects affected / exposed	0 / 145 (0.00%)	0 / 481 (0.00%)	0 / 64 (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	OP_TES: Oral AD + Intranasal Placebo	MA_TES: Oral AD + Intranasal Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 86 (0.00%)	1 / 54 (1.85%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Procedural Pain			
subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle Fracture			
subjects affected / exposed	0 / 86 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertensive Crisis			
subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic Hypotension			
subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Sinus Tachycardia			
subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Autonomic Nervous System Imbalance			

subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lacunar Stroke			
subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sedation			
subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Simple Partial Seizures			
subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Ectopic Pregnancy			
subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Chest Pain			
subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothermia			
subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Anal Fissure			
subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis Acute			
subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			
subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major Depression			

subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mania			
subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic Attack			
subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (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	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral Disc Protrusion			
subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in Extremity			
subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Sepsis			
subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (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	IND: DE Subjects: Intranasal Esketamine + Oral AD	MA: Intranasal Esketamine + Oral AD (DE+TE Subjects)	OP: Intranasal Esketamine + Oral AD (DE+TE Subjects)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	306 / 437 (70.02%)	114 / 152 (75.00%)	279 / 455 (61.32%)
Investigations			
Blood Pressure Increased			
subjects affected / exposed	34 / 437 (7.78%)	10 / 152 (6.58%)	26 / 455 (5.71%)
occurrences (all)	99	40	97
Nervous system disorders			
Dizziness			
subjects affected / exposed	97 / 437 (22.20%)	31 / 152 (20.39%)	61 / 455 (13.41%)
occurrences (all)	347	170	241
Dizziness Postural			
subjects affected / exposed	33 / 437 (7.55%)	10 / 152 (6.58%)	26 / 455 (5.71%)
occurrences (all)	188	98	168
Dysgeusia			
subjects affected / exposed	90 / 437 (20.59%)	41 / 152 (26.97%)	79 / 455 (17.36%)
occurrences (all)	429	494	529
Headache			
subjects affected / exposed	60 / 437 (13.73%)	27 / 152 (17.76%)	57 / 455 (12.53%)
occurrences (all)	86	77	91
Hypoaesthesia			
subjects affected / exposed	30 / 437 (6.86%)	9 / 152 (5.92%)	24 / 455 (5.27%)
occurrences (all)	102	179	115
Paraesthesia			
subjects affected / exposed	48 / 437 (10.98%)	11 / 152 (7.24%)	23 / 455 (5.05%)
occurrences (all)	161	82	85
Sedation			

subjects affected / exposed	43 / 437 (9.84%)	10 / 152 (6.58%)	19 / 455 (4.18%)
occurrences (all)	223	77	86
Somnolence			
subjects affected / exposed	65 / 437 (14.87%)	32 / 152 (21.05%)	63 / 455 (13.85%)
occurrences (all)	183	154	240
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	99 / 437 (22.65%)	38 / 152 (25.00%)	91 / 455 (20.00%)
occurrences (all)	385	260	406
Eye disorders			
Diplopia			
subjects affected / exposed	16 / 437 (3.66%)	9 / 152 (5.92%)	10 / 455 (2.20%)
occurrences (all)	39	31	34
Vision Blurred			
subjects affected / exposed	45 / 437 (10.30%)	24 / 152 (15.79%)	30 / 455 (6.59%)
occurrences (all)	148	217	170
Gastrointestinal disorders			
Hypoaesthesia Oral			
subjects affected / exposed	32 / 437 (7.32%)	20 / 152 (13.16%)	34 / 455 (7.47%)
occurrences (all)	87	144	156
Nausea			
subjects affected / exposed	94 / 437 (21.51%)	25 / 152 (16.45%)	48 / 455 (10.55%)
occurrences (all)	158	60	83
Paraesthesia Oral			
subjects affected / exposed	16 / 437 (3.66%)	8 / 152 (5.26%)	13 / 455 (2.86%)
occurrences (all)	61	15	35
Vomiting			
subjects affected / exposed	29 / 437 (6.64%)	10 / 152 (6.58%)	17 / 455 (3.74%)
occurrences (all)	39	15	26
Diarrhoea			
subjects affected / exposed	0 / 437 (0.00%)	0 / 152 (0.00%)	0 / 455 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Nasal Discomfort			
subjects affected / exposed	29 / 437 (6.64%)	11 / 152 (7.24%)	26 / 455 (5.71%)
occurrences (all)	95	94	98

Throat Irritation			
subjects affected / exposed	26 / 437 (5.95%)	8 / 152 (5.26%)	16 / 455 (3.52%)
occurrences (all)	100	75	97
Psychiatric disorders			
Anxiety			
subjects affected / exposed	31 / 437 (7.09%)	12 / 152 (7.89%)	11 / 455 (2.42%)
occurrences (all)	38	17	19
Confusional State			
subjects affected / exposed	13 / 437 (2.97%)	9 / 152 (5.92%)	9 / 455 (1.98%)
occurrences (all)	36	53	24
Dissociation			
subjects affected / exposed	82 / 437 (18.76%)	35 / 152 (23.03%)	73 / 455 (16.04%)
occurrences (all)	333	181	321
Musculoskeletal and connective tissue disorders			
Musculoskeletal Pain			
subjects affected / exposed	0 / 437 (0.00%)	0 / 152 (0.00%)	0 / 455 (0.00%)
occurrences (all)	0	0	0
Spinal Pain			
subjects affected / exposed	0 / 437 (0.00%)	0 / 152 (0.00%)	0 / 455 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	5 / 437 (1.14%)	11 / 152 (7.24%)	22 / 455 (4.84%)
occurrences (all)	6	16	23
Urinary Tract Infection			
subjects affected / exposed	0 / 437 (0.00%)	0 / 152 (0.00%)	0 / 455 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	MA: Oral AD + Intranasal Placebo (DE+TE Subjects)	FU: Intranasal Esketamine + Oral AD	FU: Oral AD + Intranasal Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 145 (31.03%)	14 / 481 (2.91%)	1 / 64 (1.56%)
Investigations			
Blood Pressure Increased			
subjects affected / exposed	5 / 145 (3.45%)	0 / 481 (0.00%)	0 / 64 (0.00%)
occurrences (all)	11	0	0
Nervous system disorders			

Dizziness			
subjects affected / exposed	7 / 145 (4.83%)	0 / 481 (0.00%)	1 / 64 (1.56%)
occurrences (all)	13	0	1
Dizziness Postural			
subjects affected / exposed	3 / 145 (2.07%)	0 / 481 (0.00%)	0 / 64 (0.00%)
occurrences (all)	6	0	0
Dysgeusia			
subjects affected / exposed	10 / 145 (6.90%)	0 / 481 (0.00%)	0 / 64 (0.00%)
occurrences (all)	125	0	0
Headache			
subjects affected / exposed	14 / 145 (9.66%)	8 / 481 (1.66%)	0 / 64 (0.00%)
occurrences (all)	23	11	0
Hypoaesthesia			
subjects affected / exposed	0 / 145 (0.00%)	0 / 481 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	0 / 145 (0.00%)	0 / 481 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Sedation			
subjects affected / exposed	1 / 145 (0.69%)	0 / 481 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	0
Somnolence			
subjects affected / exposed	3 / 145 (2.07%)	0 / 481 (0.00%)	0 / 64 (0.00%)
occurrences (all)	7	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	8 / 145 (5.52%)	2 / 481 (0.42%)	0 / 64 (0.00%)
occurrences (all)	26	3	0
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 145 (0.00%)	0 / 481 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Vision Blurred			
subjects affected / exposed	1 / 145 (0.69%)	0 / 481 (0.00%)	0 / 64 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal disorders			

Hypoaesthesia Oral			
subjects affected / exposed	0 / 145 (0.00%)	0 / 481 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	1 / 145 (0.69%)	2 / 481 (0.42%)	1 / 64 (1.56%)
occurrences (all)	2	3	1
Paraesthesia Oral			
subjects affected / exposed	1 / 145 (0.69%)	0 / 481 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	1 / 145 (0.69%)	0 / 481 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	0 / 145 (0.00%)	0 / 481 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Nasal Discomfort			
subjects affected / exposed	4 / 145 (2.76%)	0 / 481 (0.00%)	0 / 64 (0.00%)
occurrences (all)	19	0	0
Throat Irritation			
subjects affected / exposed	1 / 145 (0.69%)	0 / 481 (0.00%)	0 / 64 (0.00%)
occurrences (all)	7	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	5 / 145 (3.45%)	2 / 481 (0.42%)	0 / 64 (0.00%)
occurrences (all)	6	2	0
Confusional State			
subjects affected / exposed	0 / 145 (0.00%)	0 / 481 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Dissociation			
subjects affected / exposed	0 / 145 (0.00%)	0 / 481 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal Pain			
subjects affected / exposed	0 / 145 (0.00%)	0 / 481 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0

Spinal Pain			
subjects affected / exposed	0 / 145 (0.00%)	0 / 481 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	12 / 145 (8.28%)	1 / 481 (0.21%)	0 / 64 (0.00%)
occurrences (all)	18	1	0
Urinary Tract Infection			
subjects affected / exposed	0 / 145 (0.00%)	0 / 481 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	OP_TES: Oral AD + Intranasal Placebo	MA_TES: Oral AD + Intranasal Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 86 (46.51%)	37 / 54 (68.52%)	
Investigations			
Blood Pressure Increased			
subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 86 (6.98%)	0 / 54 (0.00%)	
occurrences (all)	0	0	
Dizziness Postural			
subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences (all)	0	0	
Dysgeusia			
subjects affected / exposed	8 / 86 (9.30%)	8 / 54 (14.81%)	
occurrences (all)	67	144	
Headache			
subjects affected / exposed	16 / 86 (18.60%)	12 / 54 (22.22%)	
occurrences (all)	40	24	
Hypoaesthesia			
subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences (all)	0	0	
Paraesthesia			

subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences (all)	0	0	
Sedation			
subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences (all)	0	0	
Somnolence			
subjects affected / exposed	5 / 86 (5.81%)	4 / 54 (7.41%)	
occurrences (all)	13	12	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences (all)	0	0	
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences (all)	0	0	
Vision Blurred			
subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Hypoaesthesia Oral			
subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences (all)	0	0	
Nausea			
subjects affected / exposed	0 / 86 (0.00%)	3 / 54 (5.56%)	
occurrences (all)	0	5	
Paraesthesia Oral			
subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences (all)	0	0	
Vomiting			
subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences (all)	0	0	
Diarrhoea			
subjects affected / exposed	0 / 86 (0.00%)	4 / 54 (7.41%)	
occurrences (all)	0	4	
Respiratory, thoracic and mediastinal disorders			

Nasal Discomfort			
subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences (all)	0	0	
Throat Irritation			
subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	5 / 86 (5.81%)	0 / 54 (0.00%)	
occurrences (all)	9	0	
Confusional State			
subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences (all)	0	0	
Dissociation			
subjects affected / exposed	0 / 86 (0.00%)	0 / 54 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal Pain			
subjects affected / exposed	0 / 86 (0.00%)	3 / 54 (5.56%)	
occurrences (all)	0	3	
Spinal Pain			
subjects affected / exposed	0 / 86 (0.00%)	3 / 54 (5.56%)	
occurrences (all)	0	14	
Infections and infestations			
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 86 (0.00%)	13 / 54 (24.07%)	
occurrences (all)	0	14	
Urinary Tract Infection			
subjects affected / exposed	0 / 86 (0.00%)	3 / 54 (5.56%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 January 2016	The overall reason for the amendment was to update and clarify the protocol based on ongoing feedback received during study initiation activities.
09 June 2016	The overall reason for the amendment was based on feedback received from investigators involved in the study, the subject entry criteria had been revised to improve recruitment.
04 April 2017	The overall reason for the amendment was to enhance the number of clinically valid subjects proceeding to the maintenance phase as stable remitters, the stable remission criteria had been revised.

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.

Esketamine's known transient dissociative, sedative effect difficult to blind, potential for treatment - emergent symptoms to have biased site staff who observed dosing was mitigated by independent, remote, blinded MADRS raters who assessed response.

Notes: