Clinical trial results:
An Open-label, Long-term, Safety and Efficacy Study of Intranasal Esketamine in Treatment-resistant Depression. Safety and Sustenance of Esketamine Treatment Response with Repeated Doses at Intervals Determined by Symptom Severity (SUSTAIN-2)

Summary

EudraCT number	2014-004587-38
Trial protocol	SE BE DE ES GB AT PL BG LT FI IT
Global end of trial date	28 October 2017

Results information

Result version number	v1 (current)
This version publication date	10 November 2018
First version publication date	10 November 2018

Trial information

Trial identification

Sponsor protocol code	ESKETINTRD3004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02497287
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen-Cilag International NV
Sponsor organisation address	Turnhoutseweg 30, Beerse, Belgium, 2340
Public contact	Janssen-Cilag International NV, Clinical Registry Group, ClinicalTrialsEU@its.jnj.com
Scientific contact	Janssen-Cilag International NV, Clinical Registry Group, 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	28 October 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to assess the long-term safety and tolerability of intranasal esketamine plus a newly initiated oral antidepressant in subjects with treatment resistant depression (TRD), with special attention to the following: potential effects on cognitive function; potential treatment-emergent symptoms of cystitis and/or lower urinary tract symptoms; potential withdrawal and/or rebound symptoms following cessation of intranasal esketamine treatment.

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. Screening safety evaluation included the following clinical laboratory tests: hematology, serum chemistry, urinalysis, lipid panel, serum and urine pregnancy testing (for women of childbearing potential only), urine drug screen, alcohol breath test, thyroid-stimulating hormone (TSH), free thyroxine (FT4), creatinine clearance, glycated hemoglobin (HbA1c) test, serum follicle stimulating hormone (FSH) level test. Safety assessments in the study included single, 12-lead electrocardiogram (ECG), vital signs, pulse oximetry, physical examination, height, body weight and neck circumference, nasal examinations, nasal symptom questionnaire, columbia suicide severity rating scale (C-SSRS), clinician administered dissociative states scale (CADSS), positive-symptom subscale of the brief psychiatric rating scale (BPRS+), modified observer's assessment of alertness/sedation (MOAA/S), clinical global assessment of discharge readiness (CGADR), physician withdrawal checklist, 20-item (PWC-20), bladder pain/interstitial cystitis symptom score (BPIC-SS), cognition testing.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 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	Argentina: 106
Country: Number of subjects enrolled	Australia: 23
Country: Number of subjects enrolled	Austria: 16
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Bulgaria: 94
Country: Number of subjects enrolled	Brazil: 52
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Spain: 42
Country: Number of subjects enrolled	Finland: 2
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	United Kingdom: 12

Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Korea, Republic of: 26
Country: Number of subjects enrolled	Mexico: 10
Country: Number of subjects enrolled	Malaysia: 19
Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	Sweden: 90
Country: Number of subjects enrolled	Turkey: 31
Country: Number of subjects enrolled	Taiwan: 33
Country: Number of subjects enrolled	United States: 147
Country: Number of subjects enrolled	South Africa: 64
Worldwide total number of subjects	802
EEA total number of subjects	291

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)	624
From 65 to 84 years	176
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 802 subjects were enrolled in this study. Direct-entry subjects (691) and transferred-entry subjects (111) from study ESKETINTRD3005 were assigned to esketamine plus oral antidepressant.

Period 1

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

Arms

Arm title	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)

Arm description:

Subjects enrolled directly or were non-responders in the double blind, placebo-controlled study in elderly (TRD3005) self-administered Esk in induction (IND) phase twice per week for 4 weeks as flexible dose regimen. Subjects who met the response criteria at the end of IND phase, entered Optimization/Maintenance (OP/MA) phase and received Esk nasal spray at the same dose as in the end of IND phase from week 5 to 52 in OP/MA phase. Subjects who responded in the TRD3005 study joined the OP/MA phase and received intranasal Esk at a dose of 28 mg, flexible dose until week 8. Direct entry subjects initiated new oral antidepressant (O.A) (duloxetine, escitalopram, sertraline, or venlafaxine extended release [XR]) on Day 1 of IND Phase and continued during IND and OP/MA phase. The dose of O.A was increased according to titration schedule provided in the protocol. Transfer entry subjects continued to administer the same O.A which was initiated during the TRD3005 study.

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

Dosage and administration details:

In the Induction phase, direct-entry subjects and non-responders from the TRD3005 study self-administered Esk twice per week for 4 weeks as a flexible dose regimen (56 or 84 mg for those less than [<]65 years; 28 mg, 56 mg or 84 mg for those greater than or equal to [>]=65 years old until Day 11 and 15, respectively, after which the dose remained to be stable for the remainder of the study. The transfer-entry responder subjects from TRD3005 joined the study in the OP/MA phase and received Esk at the starting dose of 28 mg which could be further up-titrated until week 8; from week 9, the dose remained stable until the end of the study. Subjects in OP/MA Phase received the weekly sessions of intranasal Esk for week 5 to 8 and received either weekly or every other week dosing depending on the MADRS score which was assessed monthly from week 9 to 52.

Investigational medicinal product name	Duloxetine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gastro-resistant capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Direct entry subjects who were < 65 years old, administered duloxetine at a dose of 60mg/day during of the study period. Subjects >=65 years old administered duloxetine at a dose of 30 mg/day with a maximum dose of 60mg/day.

Investigational medicinal product name	Escitalopram
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Direct entry subjects who were < 65 years old, administered Escitalopram at a dose of 10 mg/day during Week 1 of the Induction Phase, and from Week 2 to Week 52 of the study administered Escitalopram at a dose of 20 mg/day. Subjects >=65 years old administered Escitalopram at a dose of 10 mg/day during the entire Induction and Optimization/Maintenance phase.

Investigational medicinal product name	Sertraline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Direct entry subjects <65 years old received 50 mg during week 1, 100 mg during Week 2 and 150 mg during Week 3 and 4 of the Induction Phase and during Optimization/Maintenance phase. Transferred entry subjects received 150 mg dose during their entire participation in the study. The dose could be reduced due to tolerability.

Investigational medicinal product name	Venlafaxine XR Extended Release
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Prolonged-release capsule
Routes of administration	Oral use

Dosage and administration details:

Direct entry subjects who were < 65 years old received AD Venlafaxine XR at increasing doses during the Induction Phase (75 mg/day during Week 1, 150 mg/day during week 2, and 225 mg/day during week 3 and 4 of the Induction phase) and continued to administer 225 mg/day during the Optimization/Maintenance phase. Subjects who were >=65 years old received AD Venlafaxine XR (37.5 mg/day during Week 1, 75 mg/day during Week 2 and 150 mg/day during weeks 3 and 4) during open-label Induction Phase. All subjects continued to administer Venlafaxine XR at a dose of 225 mg/day during the OP/MA phase.

Number of subjects in period 1	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)
Started	802
Induction phase (IND)	779
Optimization/maintenance phase	603
Follow-up phase	357
Completed	150
Not completed	652
Adverse event, serious fatal	2
Study terminated by sponsor	331
Adverse event, serious non-fatal	16
Consent withdrawn by subject	52
Did not meet criteria to enter op/ma phase	84
Adverse event, non-fatal	61
Other	34
Pregnancy	2

Non-compliance with study drug	2
Missed assessment	3
Lost to follow-up	15
Protocol deviation	4
Lack of efficacy	46

Baseline characteristics

Reporting groups

Reporting group title	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)

Reporting group description:

Subjects enrolled directly or were non-responders in the double blind, placebo-controlled study in elderly (TRD3005) self-administered Esk in induction (IND) phase twice per week for 4 weeks as flexible dose regimen. Subjects who met the response criteria at the end of IND phase, entered Optimization/Maintenance (OP/MA) phase and received Esk nasal spray at the same dose as in the end of IND phase from week 5 to 52 in OP/MA phase. Subjects who responded in the TRD3005 study joined the OP/MA phase and received intranasal Esk at a dose of 28 mg, flexible dose until week 8. Direct entry subjects initiated new oral antidepressant (O.A) (duloxetine, escitalopram, sertraline, or venlafaxine extended release [XR]) on Day 1 of IND Phase and continued during IND and OP/MA phase. The dose of O.A was increased according to titration schedule provided in the protocol. Transfer entry subjects continued to administer the same O.A which was initiated during the TRD3005 study.

Reporting group values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)	Total	
Number of subjects	802	802	
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	624	624	
From 65 to 84 years	176	176	
85 years and over	2	2	
Title for AgeContinuous Units: years			
arithmetic mean	52.2		
standard deviation	± 13.69	-	
Title for Gender Units: subjects			
Female	502	502	
Male	300	300	

End points

End points reporting groups

Reporting group title	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)

Reporting group description:

Subjects enrolled directly or were non-responders in the double blind, placebo-controlled study in elderly (TRD3005) self-administered Esk in induction (IND) phase twice per week for 4 weeks as flexible dose regimen. Subjects who met the response criteria at the end of IND phase, entered Optimization/Maintenance (OP/MA) phase and received Esk nasal spray at the same dose as in the end of IND phase from week 5 to 52 in OP/MA phase. Subjects who responded in the TRD3005 study joined the OP/MA phase and received intranasal Esk at a dose of 28 mg, flexible dose until week 8. Direct entry subjects initiated new oral antidepressant (O.A) (duloxetine, escitalopram, sertraline, or venlafaxine extended release [XR]) on Day 1 of IND Phase and continued during IND and OP/MA phase. The dose of O.A was increased according to titration schedule provided in the protocol. Transfer entry subjects continued to administer the same O.A which was initiated during the TRD3005 study.

Primary: Percentage of Subjects With Treatment-Emergent Adverse Events (TEAEs)

End point title	Percentage of Subjects With Treatment-Emergent Adverse Events (TEAEs)[1]

End point description:

An adverse event is any untoward medical occurrence in a clinical study which subject administered a medicinal (investigational or non-investigational) product and does not necessarily have a causal relationship with the treatment. A TEAE defined as an event that was new in onset or increased in severity following treatment initiation. The TEAEs for the induction (IND) phase were those events with an onset date/time on or after the start of study medication, which occurred on or before the end of the IND phase and for the optimization/maintenance (OP/MA) phase were those events with an onset date/time on or after the start of OP/MA study medication, which occurred on or before the end of the optimization/maintenance phase. All enrolled analysis set include all transferred-entry and direct-entry subjects who were not screen failures and received at least one dose of intranasal study medication or 1 dose of oral antidepressant.

End point type	Primary

End point timeframe:

Screening up to Follow up period (Maximum 60 Weeks)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was an open-label, single-arm study. There were no pre-planned inferential statistical analyses.

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	802			
Units: percentage of subjects				
number (not applicable)	90.1			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Cystitis, Urinary Tract Infections, Urinary Tract Symptom, Renal and Urinary Disorders

End point title	Percentage of Subjects With Cystitis, Urinary Tract Infections, Urinary Tract Symptom, Renal and Urinary Disorders[2]

End point description:

Percentage of subjects with cystitis, urinary tract infections, urinary tract symptom, renal and urinary disorders was evaluated. Cystitis and urinary tract infections are selected MedDRA preferred terms, "urinary tract symptoms" refers to any preferred term (PT) in the group of selected PTs; and "renal and urinary disorders" refers to a MedDRA System Organ Class (SOC). All enrolled analysis set include all subjects enrolled into the study, including transferred-entry subjects from study ESKETINTRD3005 and received at least 1 dose of intranasal study medication or 1 dose of oral antidepressant medication.

End point type	Primary

End point timeframe:

Screening to follow up phase (Maximum 60 Weeks)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was an open-label, single-arm study. There were no pre-planned inferential statistical analyses.

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	802			
Units: percentage of subjects				
number (not applicable)				
Cystitis	0.6			
Urinary tract infections	8.1			
Renal and urinary disorders	10.5			
Urinary tract symptoms	17.0			

Statistical analyses

No statistical analyses for this end point

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

End point title	Change From Baseline in Cognitive Test Battery: Detection Test (DET) Score[3]

End point description:

The DET is a measure of psychomotor function and uses a well-validated simple reaction time. Lower score indicates better performance. Higher change from baseline indicates better performance. All enrolled analysis set include all subjects enrolled into the study, including transferred-entry subjects from study ESKETINTRD3005 and received at least 1 dose of intranasal study medication or 1 dose of oral antidepressant medication. Here, 'N' (number of subjects analysed) signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline up to the End-point (last post-baseline assessment value during 52 weeks of Optimization/Maintenance [OP/MA] period)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was an open-label, single-arm study. There were no pre-planned inferential statistical analyses.

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	561			
Units: log10 millisecond (msec)				
arithmetic mean (standard deviation)	-0.0028 (± 0.12744)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Change From Baseline in Cognitive Test Battery: Identification Test (IDN) Score[4]

End point description:

IDN test is a measure of visual attention, uses a validated choice reaction time and scored for speed of response (mean of the log10 transformed reaction times for correct responses). Lower score indicates better performance. Higher change from baseline indicates better performance. All enrolled analysis set include all subjects enrolled into the study, including transferred-entry subjects from study ESKETINTRD3005 and received at least 1 dose of intranasal study medication or 1 dose of oral antidepressant medication. Here, 'N' (number of subjects analysed) signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline up to the End-point (last post-baseline assessment value during 52 weeks of OP/MA period)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was an open-label, single-arm study. There were no pre-planned inferential statistical analyses.

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	561			
Units: log10 msec				
arithmetic mean (standard deviation)	-0.0083 (± 0.09656)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Change From Baseline in Cognitive Test Battery: One Card Learning Test (OCL) Score[5]

End point description:

OCL test is a measure of visual episodic memory and visual recall test scored using arcsine transformation of the percentage of correct responses. Higher score indicates better performance. Higher change from baseline indicates better performance. All enrolled analysis set include all subjects enrolled into the study, including transferred-entry subjects from study ESKETINTRD3005 and received at least 1 dose of intranasal study medication or 1 dose of oral antidepressant medication. Here, 'N' (number of subjects analysed) signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline up to the End-point (last post-baseline assessment value during 52 weeks of OP/MA period)

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was an open-label, single-arm study. There were no pre-planned inferential statistical analyses.

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	561			
Units: Arcsine ([sqrt] proportion of CR)				
arithmetic mean (standard deviation)	0.0502 (± 0.13149)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Change From Baseline in Cognitive Test Battery: One Back Test (ONB) Score[6]

End point description:

The ONB is a measure of working memory and scored for speed of correct response (mean of the log10-transformed reaction times for correct responses). Lower score indicates better performance. Higher change from baseline indicates better performance. All enrolled analysis set include all subjects enrolled into the study, including transferred-entry subjects from study ESKETINTRD3005 and received at least 1 dose of intranasal study medication or 1 dose of oral antidepressant medication. Here, 'N' (number of subjects analysed) signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline up to the End-point (last post-baseline assessment value during 52 weeks of OP/MA period)

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was an open-label, single-arm study. There were no pre-planned inferential statistical analyses.

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	563			
Units: log10 msec				
arithmetic mean (standard deviation)	0.0177 (± 0.10026)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Change From Baseline in Cognitive Test Battery: Groton Maze Learning Test (GMLT) Score[7]

End point description:

GMLT measures executive function; maze/sequencing test, scored for total number of errors. Lower score indicates better performance. Higher change from baseline indicates better performance. All enrolled analysis set: all subjects enrolled into the study, including transferred-entry subjects from study ESKETINTRD3005and received at least 1 dose of oral AD medication. 'N' (number of subjects analysed); subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline up to the End-point (last post-baseline assessment value during 52 weeks of OP/MA period)

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was an open-label, single-arm study. There were no pre-planned inferential statistical analyses.

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	506			
Units: Number of Errors				
arithmetic mean (standard deviation)	6.9 (± 25.36)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Change From Baseline in Hopkins Verbal Learning Test-Revised (HVLT-R) Score: Total Recall[8]

End point description:

HVLT-R, a measure of verbal learning and memory, is a 12-item word list recall test. It includes 3 learning trials, a 24-word recognition list (including 12 target and 12 foil words), and a delayed recall trial (20-minute). Test administrator read instructions and word lists aloud, and recorded words recalled/ recognized by the subject. Scores included learning, delayed recall, and recognition scores. HVLT-R is a well-validated and widely used measure of verbal episodic memory. HVLT-R Score (Total Recall) is used to measure the verbal learning. Higher score indicate better performance. Higher change from baseline indicates better performance. All enrolled analysis set include all subjects enrolled into the study, including transferred-entry subjects from study ESKETINTRD3005 and received at least 1 dose of intranasal study medication or 1 dose of oral antidepressant medication. Here, 'N' (number of subjects analysed) signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline up to the End-point (last post-baseline assessment value during 52 weeks of OP/MA period)

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was an open-label, single-arm study. There were no pre-planned inferential statistical analyses.

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	569			
Units: Number correct				
arithmetic mean (standard deviation)	2.8 (± 4.74)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Change From Baseline in Hopkins Verbal Learning Test-Revised (HVLT-R) Score: Delayed Recall[9]

End point description:

HVLT-R, a measure of verbal learning and memory, is a 12-item word list recall test. It includes 3 learning trials, a 24-word recognition list (including 12 target and 12 foil words), a delayed recall trial (20-minute). Test administrator read instructions and word lists aloud, and recorded words recalled/ recognized by the subject. Scores included learning, delayed recall, recognition scores. HVLT-R is a well-validated and widely used measure of verbal episodic memory. The test measure total number of words recalled after a 20 minute delay. Higher score indicate better performance. Higher change from baseline indicates better performance. All enrolled analysis set include all subjects enrolled into the study, including transferred-entry subjects from study ESKETINTRD3005 and received at least 1 dose of intranasal study medication or 1 dose of oral antidepressant medication. Here, 'N' (number of subjects analysed) signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline up to the End-point (last post-baseline assessment value during 52 weeks of OP/MA period)

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was an open-label, single-arm study. There were no pre-planned inferential statistical analyses.

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	569			
Units: Number correct				
arithmetic mean (standard deviation)	0.8 (± 2.31)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Change From Baseline in Hopkins Verbal Learning Test-Revised (HVLT-R) Score: True Positives[10]

End point description:

HVLT-R, a measure of verbal learning and memory, is a 12-item word list recall test. It includes 3 learning trials, a 24-word recognition list (including 12 target and 12 foil words), a delayed recall trial (20-minute). Test administrator read instructions and word lists aloud, and recorded words recalled/ recognized by the subject. Scores included learning, delayed recall, recognition scores. The HVLT-R is a well-validated and widely used measure of verbal episodic memory. The test measures total number of true positives (words recognized) after a 20 minute delay. Higher score indicate better performance. Higher change from baseline is better performance. All enrolled analysis set include all subjects enrolled into the study, including transferred-entry subjects from study ESKETINTRD3005 and received at least 1 dose of intranasal study medication or 1 dose of oral AD medication. Here, 'N' (number of subjects analysed) signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline up to the End-point (last post-baseline assessment value during 52 weeks of OP/MA period)

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was an open-label, single-arm study. There were no pre-planned inferential statistical analyses.

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	568			
Units: Units on a Scale				
arithmetic mean (standard deviation)	0.3 (± 2.83)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Change From Baseline in Hopkins Verbal Learning Test-Revised (HVLT-R) Score: Recognition Discrimination Index[11]

End point description:

HVLT-R, a measure of verbal learning, memory, is a 12-item word list recall test. It includes 3 learning trials, a 24-word recognition list (12 target and 12 foil words), a delayed recall trial (20-minute). Test administrator read instructions, word lists aloud, recorded words recalled/ recognized by the subject. Scores included learning, delayed recall, recognition scores. HVLT-R is a well-validated and measures verbal episodic memory. Test measures total number of true positives (words recognized) minus total number of false positives after a 20 minute delay. Higher score indicates better performance. Higher change from baseline is better performance. All enrolled analysis set include all subjects enrolled into the study, including transferred-entry subjects from study ESKETINTRD3005 and received at least 1 dose of intranasal study medication or 1 dose of oral AD medication. Here, 'N' (number of subjects analysed) signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline up to the End-point (last post-baseline assessment value during 52 weeks of OP/MA period)

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was an open-label, single-arm study. There were no pre-planned inferential statistical analyses.

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	568			
Units: Units on a Scale				
arithmetic mean (standard deviation)	0.5 (± 3.16)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Endpoint in Montgomery Asberg Depression Rating Scale (MADRS) Total Score During Induction (IND) Phase

End point title	Change From Baseline to Endpoint in Montgomery Asberg Depression Rating Scale (MADRS) Total Score During Induction (IND) Phase

End point description:

MADRS measures depression severity, detects changes due to AD treatment. It consists 10 items (evaluate apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, interest level, pessimistic thoughts, suicidal thoughts), scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms), total possible score of 60. Mean change (standard deviation [SD]) in MADRS total score from baseline to endpoint was evaluated. Higher scores indicate more severe condition. Negative change in score indicates improvement. Missing data was imputed using LOCF method, last post baseline observation during the phase was carried forward as the "End Point". Full (IND) analysis set included all subjects who received at least 1 dose of intranasal study medication or 1 dose of oral AD in open-label IND phase (for direct-entry and transferred-entry non-responder subjects). 'N' (number of subjects analysed); subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to the End-point (last post-baseline assessment value during 4 weeks of IND period)

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	756			
Units: Units on a Scale				
arithmetic mean (standard deviation)	-16.4 (± 8.76)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Endpoint in MADRS Total Score During Optimization/Maintenance (OP/MA) Phase

End point title	Change From Baseline to Endpoint in MADRS Total Score During Optimization/Maintenance (OP/MA) Phase

End point description:

MADRS measure depression severity, detects changes due to AD treatment. It evaluates 10 items: apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, interest level, pessimistic thoughts, suicidal thoughts, each of which is scored from 0 (item is not present or is normal) to 6 (severe or continuous presence of the symptoms), a total possible score of 60. The mean change (SD) in MADRS total score from baseline (OP/MA) to the endpoint (52 weeks) was evaluated. Higher scores represent a more severe condition. Negative change in score indicates improvement. Missing data was imputed using LOCF method and the last post baseline observation during the phase was carried forward as the "End Point". Full (OP/MA) analysis set included all subjects who received at least 1 dose of intranasal study medication or 1 dose of oral AD in the OP/MA phase. Here, 'N' (number of subjects analysed) signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (OP/MA) up to the End-point (last post-baseline assessment value during 52 weeks of OP/MA period)

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	603			
Units: Units on a Scale				
arithmetic mean (standard deviation)	0.3 (± 8.12)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Endpoint in Patient Health Questionnaire - 9 (PHQ-9) Total Score During IND Phase

End point title	Change From Baseline to Endpoint in Patient Health Questionnaire - 9 (PHQ-9) Total Score During IND Phase

End point description:

PHQ-9 is a 9-item, self-report scale assessing depressive symptoms. Each item was rated on a 4-point scale (0 = Not at all, 1 = Several Days, 2 = More than half the days, and 3 = Nearly every day), with a total score range of 0-27. The mean change (SD) in PHQ-9 total score from baseline (IND) to the endpoint (4 weeks) was evaluated. A higher score indicates greater severity of depression. Negative change in score indicates improvement. Missing data was imputed using LOCF method and the last post baseline observation during the phase was carried forward as the "End Point". The full (IND) analysis set included all subjects who received at least 1 dose of intranasal study medication or 1 dose of oral antidepressant in the open-label IND phase (for direct-entry and transferred-entry non-responder subjects). Here, 'N' (number of subjects analysed) signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to the End-point (last post-baseline assessment value during 4 weeks of IND period)

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	746			
Units: Unit on a Scale				
arithmetic mean (standard deviation)	-8.9 (± 6.67)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Endpoint in PHQ-9 Total Score During OP/MA Phase

End point title	Change From Baseline to Endpoint in PHQ-9 Total Score During OP/MA 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), with a total score range of 0-27. The mean change (SD) in PHQ-9 total score from baseline (OP/MA) to the endpoint (52 weeks) was evaluated. A higher score indicates greater severity of depression. Negative change in score indicates improvement. Missing data was imputed using LOCF method and the last post baseline observation during the phase was carried forward as the "End Point". The full (OP/MA) analysis set include all subjects who received at least 1 dose of intranasal study medication or 1 dose of oral antidepressant in the OP/MA phase. Here, 'N' (number of subjects analysed) signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (OP/MA) up to the End-point (last post-baseline assessment value during 52 weeks of OP/MA period)

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	603			
Units: Units on a Scale				
arithmetic mean (standard deviation)	-0.2 (± 5.65)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Endpoint in Clinical Global Impression of Severity (CGI-S) Scale Score During IND Phase

End point title	Change From Baseline to Endpoint in Clinical Global Impression of Severity (CGI-S) Scale Score During IND Phase

End point description:

CGI-S measures severity of subject's illness that include knowledge of subject's history, psychosocial circumstances, symptoms, behavior, impact of symptoms on subject's ability to function. Scale ranges from 0 - 7, were 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 the most extremely ill patients. Median change (range) in CGI-S score from baseline (IND) to endpoint (4 weeks) was evaluated. Negative change in score indicates improvement. Missing data was imputed using LOCF method and the last post baseline observation during the phase was carried forward as "End Point". Full (IND) analysis set included all subjects who received at least 1 dose of intranasal study medication or 1 dose of oral AD in the open-label IND phase (for direct-entry and transferred-entry non-responder subjects). Here, 'N' (number of subjects analysed) signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to the End-point (last post-baseline assessment value during 4 weeks of IND period)

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	763			
Units: Units on a Scale				
median (full range (min-max))	-2.0 (-6 to 2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Endpoint in CGI-S Scale Score During OP/MA Phase

End point title	Change From Baseline to Endpoint in CGI-S Scale Score During OP/MA Phase

End point description:

The CGI-S measures the severity of the subject's illness that include knowledge of the subject's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the subject's ability to function. The CGI-S evaluates the severity of psychopathology on a scale of 0 to 7, where 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 the most extremely ill patients. The median change (range) in CGI-S score from baseline (OP/MA) to the endpoint (52 weeks) was evaluated. Negative change in score indicates improvement. Missing data was imputed using LOCF method and the last post baseline observation during the phase was carried forward as the "End Point". The full (OP/MA) analysis set included all subjects who received at least 1 dose of intranasal study medication or 1 dose of oral antidepressant in the OP/MA phase.

End point type	Secondary

End point timeframe:

Baseline (OP/MA) up to the End-point (last post-baseline assessment value during 52 weeks of OP/MA period)

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	603			
Units: Units on a Scale				
median (full range (min-max))	0.0 (-3 to 4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Endpoint in Generalized Anxiety Disorder

(GAD-7) Total Score During IND Phase

End point title	Change From Baseline to Endpoint in Generalized Anxiety Disorder (GAD-7) Total Score During IND Phase

End point description:

GAD-7 is brief, 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, and 3=nearly every day. Item responses are summed to yield total score ranges from 0-21, higher scores indicate more anxiety. Negative change in score indicates improvement. Severity of GAD-7 is categorized as: None (0-4), Mild (5-9), Moderate (10-14), Severe (15 -21). Mean change (SD) in GAD-7 total score from baseline (IND) to endpoint (4 weeks) was evaluated. Missing data was imputed using LOCF method, last post baseline observation during the phase was carried forward as "End Point". Full (IND) analysis set: all subjects who received at least 1 dose of intranasal study drug or 1 dose of oral AD in the open-label IND phase (for direct-entry and transferred-entry non-responder subjects). Here, 'N' (number of subjects analysed): subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to the End-point (last post-baseline assessment value during 4 weeks of IND period)

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	724			
Units: Units on a Scale				
arithmetic mean (standard deviation)	-5.9 (± 5.85)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Endpoint in GAD-7 Total Score During OP/MA Phase

End point title	Change From Baseline to Endpoint in GAD-7 Total Score During OP/MA 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, and 3=nearly every day. Item responses are summed to yield a total score ranges from 0-21, higher scores indicate more anxiety. Negative change in score indicates improvement. Severity of the GAD-7 is categorized as follows: None (0-4), Mild (5-9), Moderate (10-14), Severe (15 -21). Mean change (SD) in GAD-7 total score from baseline (OP/MA) to endpoint (52 weeks) was evaluated. Missing data was imputed using LOCF method and the last post baseline observation during the phase was carried forward as the "End Point". Full (OP/MA) analysis set included all subjects who received at least 1 dose of intranasal study medication or 1 dose of oral antidepressant in the OP/MA phase. Here, 'N' (number of subjects analysed) signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (OP/MA) up to the End-point (last post-baseline assessment value during 52 weeks of OP/MA period)

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	574			
Units: Units on a Scale				
arithmetic mean (standard deviation)	0.2 (± 4.23)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Endpoint in Health-Related Quality of Life and Health Status as European Quality of Life (EuroQol) Group, 5-Dimension, 5-Level (EQ 5D-5L) During IND Phase

End point title	Change From Baseline to Endpoint in Health-Related Quality of Life and Health Status as European Quality of Life (EuroQol) Group, 5-Dimension, 5-Level (EQ 5D-5L) During IND Phase

End point description:

EQ-5D-5L measures health outcome self-completed by respondents. It consists of EQ visual analogue scale (EQ VAS), EQ-5D-5L descriptive system. It comprises of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. Each has 5 levels (1-no problem, 2-slight problems, 3-moderate problems, 4-severe problems, 5-extreme problems). Health Status Index range is -0.148 - 0.949, is anchored at 0 (dead) and 1 (full health), EQ-VAS score from 0 (worst health you can imagine) to 100 (best health you can imagine), Sum score from 0 - 100, Sum score=(sum of scores from 5 dimensions minus 5)*5". Mean change (SD) in EQ-5D health status index score from baseline (IND) to endpoint (4 weeks) was evaluated. Full (IND) analysis set: all subjects who received at least 1 dose of intranasal study drug or 1 dose of oral AD in the open-label IND phase (direct-entry, transferred-entry non-responder subjects). 'n' signifies those subjects who were evaluable for each category.

End point type	Secondary

End point timeframe:

Baseline up to the End-point (last post-baseline assessment value during 4 weeks of IND period)

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	746			
Units: Units on a Scale				
arithmetic mean (standard deviation)				
Health Status Index (n= 745)	0.190 (± 0.2138)			
EQ VAS Score (n= 746)	17.0 (± 21.69)			
Sum Score (n= 745)	-15.3 (± 16.26)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Endpoint in Health-Related Quality of Life and Health Status as EQ 5D-5L During OP/MA Phase

End point title	Change From Baseline to Endpoint in Health-Related Quality of Life and Health Status as EQ 5D-5L During OP/MA Phase

End point description:

EQ-5D-5L measures health outcome self-completed by respondents. It consists of EQ visual analogue scale (EQ VAS), EQ-5D-5L descriptive system. It comprises of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. Each has 5 levels (1-no problem, 2-slight problems, 3-moderate problems, 4-severe problems, 5-extreme problems). Health Status Index range is -0.148 - 0.949, is anchored at 0 (dead) and 1 (full health), EQ-VAS score from 0 (worst health) to 100 (best health), Sum score from 0-100, Sum score=(sum of the scores from the 5 dimensions minus 5)*5". Mean change (SD) in EQ-5D health status index score from baseline (OP/MA) to endpoint (52 weeks) was evaluated. Full (OP/MA) analysis set: all subjects who received at least 1 dose of intranasal study drug or 1 dose of oral AD in OP/MA phase. 'N' (number of subjects analysed) signifies: subjects who were evaluable for this endpoint, 'n' signifies those subjects who were evaluable for each category.

End point type	Secondary

End point timeframe:

Baseline (OP/MA) up to the End-point (last post-baseline assessment value during 52 weeks of OP/MA period)

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	603			
Units: Units on a Scale				
arithmetic mean (standard deviation)				
Health Status Index	-0.009 (± 0.1411)			
EQ VAS Score	1.6 (± 18.51)			
Sum Score	-0.7 (± 13.19)			

Statistical analyses

No statistical analyses for this end point

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

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

	Score During IND Phase

End point description:

SDS was a 5 item questionnaire used for assessment of functional impairment and associated disability. The first three items assess disruption of (1) work/school, (2) social life, (3) family life/home responsibilities using a 0-10 rating scale. Score for the first three items are summed to create a total score of 0-30, higher score indicates greater impairment and a negative change in score indicates improvement. Mean change (SD) in SDS total score from baseline (IND) to the endpoint (4 weeks) was evaluated. Missing data was imputed using LOCF method and the last post baseline observation during the phase was carried forward as the "End Point". Full (IND) analysis set: all subjects who received at least 1 dose of intranasal study medication or 1 dose of oral antidepressant in the open-label IND phase (for direct-entry and transferred-entry non-responder subjects). Here, 'N' (number of subjects analysed) signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to the End-point (last post-baseline assessment value during 4 weeks of IND period)

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	626			
Units: Units on a Scale				
arithmetic mean (standard deviation)	-9.3 (± 7.86)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Functional Impairment and Associated Disability Using Sheehan Disability Scale Total Score During OP/MA Phase

End point title	Change From Baseline in Functional Impairment and Associated Disability Using Sheehan Disability Scale Total Score During OP/MA Phase

End point description:

SDS was a subject-reported outcome measure and was a 5 item questionnaire used for assessment of functional impairment and associated disability. The first three items assess disruption of (1) work/school, (2) social life, and (3) family life/home responsibilities using a 0-10 rating scale. The score for the first three items are summed to create a total score of 0-30 where a higher score indicates greater impairment and a negative change in score indicates improvement. The mean change (SD) in SDS total score from baseline (OP/MA) to the endpoint (52 weeks) was evaluated. Missing data was imputed using LOCF method and the last post baseline observation during the phase was carried forward as the "End Point". Full (OP/MA) analysis set included all subjects who received at least 1 dose of intranasal study medication or 1 dose of oral antidepressant in the OP/MA phase. Here, 'N' (number of subjects analysed) signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (OP/MA) up to the End-point (last post-baseline assessment value during 52 weeks of OP/MA period)

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	541			
Units: Units on a Scale				
arithmetic mean (standard deviation)	-1.6 (± 8.25)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Response Rate Over Time Who Achieved Greater Than or Equal to (>=) 50 Percent (%) Reduction From Baseline in MADRS Total Score During IND Phase

End point title	Percentage of Subjects With Response Rate Over Time Who Achieved Greater Than or Equal to (>=) 50 Percent (%) Reduction From Baseline in MADRS Total Score During IND Phase

End point description:

Response rate over time is defined as percentage of subjects with >= 50 % reduction from baseline (IND phase) in the MADRS total score. Missing data was imputed using LOCF method and the last post baseline observation during the phase was carried forward as the "End Point". Full (IND) analysis set included all subjects who received at least 1 dose of intranasal study medication or 1 dose of oral antidepressant in the open-label IND phase (for direct-entry and transferred-entry non-responder subjects). Here, 'n' signifies those subjects who were evaluable at specific time point for this endpoint.

End point type	Secondary

End point timeframe:

Day 8, 15, 22 and End-point (last post-baseline assessment value during 4 weeks of IND period)

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	756			
Units: Percentage of subjects				
number (not applicable)				
Day 8 (n=739)	11.6			
Day 15 (n=751)	25.0			
Day 22 (n=753)	42.8			
End point (n=756)	78.4			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Response Rate Over Time Who Achieved >= 50 % Reduction From Baseline in PHQ-9 Total Score During IND Phase

End point title	Percentage of Subjects With Response Rate Over Time Who Achieved >= 50 % Reduction From Baseline in PHQ-9 Total Score During IND Phase

End point description:

Response rate over time is defined as percentage of subjects with >= 50 % reduction from baseline (IND phase) in PHQ-9 total score. Missing data was imputed using LOCF method and the last post baseline observation during the phase was carried forward as the "End Point". The full (IND) analysis set include all subjects who received at least 1 dose of intranasal study medication or 1 dose of oral antidepressant in the open-label IND phase (for direct-entry and transferred-entry non-responder subjects). Here, 'n' signifies those subjects who were evaluable at specific time point for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to the End-point (last post-baseline assessment value during 4 Week IND period)

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	746			
Units: percentage of subjects				
number (not applicable)				
Day 15 (n=724)	37.2			
End point (n=744)	62.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Remission Rate Over Time With MADRS Total Score Less Than or Equal to (<=) 12 During IND Phase

End point title	Percentage of Subjects With Remission Rate Over Time With MADRS Total Score Less Than or Equal to (<=) 12 During IND Phase

End point description:

Remission rate over time is defined as percentage of subjects with MADRS total score <= 12. Missing data was imputed using LOCF method and the last post baseline observation during the phase was carried forward as the "End Point". The full (IND) analysis set included all subjects who received at least 1 dose of intranasal study medication or 1 dose of oral antidepressant in the open-label IND phase (for direct-entry and transferred-entry non-responder subjects). Here, 'n' signifies those subjects who were evaluable at specific time point for this endpoint.

End point type	Secondary

End point timeframe:

Day 8, 15, 22 and End-point (last post-baseline assessment value during 4 weeks of IND period)

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	756			
Units: percentage of subjects				
number (not applicable)				
Day 8 (n=739)	7.3			
Day 15 (n=751)	15.6			
Day 22 (n=753)	27.2			
End point (n=756)	47.2			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Remission Rate Over Time With PHQ-9 Total Score <= 4 During IND Phase

End point title	Percentage of Subjects With Remission Rate Over Time With PHQ-9 Total Score <= 4 During IND Phase

End point description:

Remission rate over time is defined as percentage of subjects with PHQ-9 total score less than or equals to 4. Missing data was imputed using LOCF method and the last post baseline observation during the phase was carried forward as the "End Point". The full (IND) analysis set included all subjects who received at least 1 dose of intranasal study medication or 1 dose of oral antidepressant in the open-label IND phase (for direct-entry and transferred-entry non-responder subjects). Here, 'n' signifies those subjects who were evaluable at specific time point for this endpoint.

End point type	Secondary

End point timeframe:

Day 15 and End-point (last post-baseline assessment value during 4 weeks of IND period)

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	746			
Units: percentage of subjects				
number (not applicable)				
Day 15 (n=726)	12.7			
Endpoint (n=746)	26.9			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With an Increase Score From Predose at Any Time in Clinician-Administered Dissociative States Scale (CADSS) During IND Phase

End point title	Percentage of Subjects With an Increase Score From Predose at Any Time in Clinician-Administered Dissociative States Scale (CADSS) During IND Phase

End point description:

The CADSS used to measure present-state dissociative symptoms, and to assess treatment-emergent dissociative symptoms. It comprises 23 subjective items divided into 3 components: depersonalization, derealization, and amnesia. Subjects responses are coded on a 5-point scale (0 = "Not at all", 1 = "Mild", 2 = "Moderate", 3 = 'Severe" and 4 = "Extreme"). All enrolled analysis set include all subjects enrolled into the study, including transferred-entry subjects from study ESKETINTRD3005 and received at least 1 dose of intranasal study medication or 1 dose of oral antidepressant medication. Here, 'N' (number of subjects analysed) signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline of each dosing session (predose) , up to the last post-dose measurement (1.5 hours) from the start of Induction Phase to End of Induction phase (week 4)

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	775			
Units: percentage of subjects				
number (not applicable)	92.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With an Increase Score From Predose at Any Time in CADSS During OP/MA Phase

End point title	Percentage of Subjects With an Increase Score From Predose at Any Time in CADSS During OP/MA Phase

End point description:

The CADSS used to measure present-state dissociative symptoms, and to assess treatment-emergent dissociative symptoms. It comprises 23 subjective items divided into 3 components: depersonalization, derealization, and amnesia. Subjects responses are coded on a 5-point scale (0 = "Not at all", 1 = "Mild", 2 = "Moderate", 3 = 'Severe" and 4 = "Extreme"). All enrolled analysis set include all subjects

enrolled into the study, including transferred-entry subjects from study ESKETINTRD3005 and received at least 1 dose of intranasal study medication or 1 dose of oral antidepressant medication. Here, 'N' (number of subjects analysed) signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline of each dosing session (predose) , up to the last post-dose measurement (1.5 hours) from the start of Induction Phase to End of Optimization/Maintenance Phase (week 52)

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	603			
Units: percentage of subjects				
number (not applicable)	86.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Treatment-Emergent Acute Hypertension (Systolic and Diastolic) During IND and OP/MA Phases

End point title	Percentage of Subjects With Treatment-Emergent Acute Hypertension (Systolic and Diastolic) During IND and OP/MA Phases

End point description:

Percentage of subjects with treatment-emergent acute hypertension (Systolic Blood Pressure >= 180 mm Hg or Diastolic Blood Pressure >= 110 mm Hg) during IND and OP/MA Phases was evaluated. All enrolled analysis set include all subjects enrolled into the study, including transferred-entry subjects from study ESKETINTRD3005 and received at least 1 dose of intranasal study medication or 1 dose of oral antidepressant medication.

End point type	Secondary

End point timeframe:

Screening up to OP/MA phase (Week 52)

End point values	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)			
Subject group type	Reporting group			
Number of subjects analysed	802			
Units: percentage of subjects				
number (not applicable)				
Systolic BP >=180	2.2			
Diastolic BP >=110	2.4			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Screening up to follow up phase (Week 60)

Adverse event reporting additional description:

There were 2 deaths resulting from adverse events.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)

Reporting group description:

Subjects enrolled directly or were non-responders in the double blind, placebo-controlled study in elderly (TRD3005) self-administered Esk in induction (IND) phase twice per week for 4 weeks as flexible dose regimen. Subjects who met the response criteria at the end of IND phase, entered Optimization/Maintenance (OP/MA) phase and received Esk nasal spray at the same dose as in the end of IND phase from week 5 to 52 in OP/MA phase. Subjects who responded in the TRD3005 study joined the OP/MA phase and received intranasal Esk at a dose of 28 mg, flexible dose until week 8. Direct entry subjects initiated new oral antidepressant (O.A) (duloxetine, escitalopram, sertraline, or venlafaxine extended release [XR]) on Day 1 of IND Phase and continued during IND and OP/MA phase. The dose of O.A was increased according to titration schedule provided in the protocol. Transfer entry subjects continued to administer the same O.A which was initiated during the TRD3005 study.

Serious adverse events	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)		
Total subjects affected by serious adverse events			
subjects affected / exposed	55 / 802 (6.86%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Ovarian Cancer			
subjects affected / exposed	1 / 802 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Abortion Spontaneous			
subjects affected / exposed	1 / 802 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration			

site conditions				
Pyrexia				
subjects affected / exposed	1 / 802 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Menorrhagia				
subjects affected / exposed	1 / 802 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute Respiratory Failure				
subjects affected / exposed	1 / 802 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Psychiatric disorders				
Alcohol Abuse				
subjects affected / exposed	1 / 802 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Anxiety				
subjects affected / exposed	2 / 802 (0.25%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Completed Suicide				
subjects affected / exposed	1 / 802 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Delirium				
subjects affected / exposed	1 / 802 (0.12%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Delusion				

subjects affected / exposed	1 / 802 (0.12%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	8 / 802 (1.00%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 0		
Depression Suicidal			
subjects affected / exposed	1 / 802 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intentional Self-Injury			
subjects affected / exposed	1 / 802 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Major Depression			
subjects affected / exposed	1 / 802 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Suicidal Ideation			
subjects affected / exposed	6 / 802 (0.75%)		
occurrences causally related to treatment / all	1 / 6		
deaths causally related to treatment / all	0 / 0		
Suicide Attempt			
subjects affected / exposed	6 / 802 (0.75%)		
occurrences causally related to treatment / all	1 / 6		
deaths causally related to treatment / all	0 / 0		
Investigations			
Transaminases Increased			
subjects affected / exposed	1 / 802 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			

Costochondral Separation			
subjects affected / exposed	1 / 802 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fibula Fracture			
subjects affected / exposed	1 / 802 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Overdose			
subjects affected / exposed	1 / 802 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Foot Fracture			
subjects affected / exposed	1 / 802 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Poisoning			
subjects affected / exposed	1 / 802 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Toxicity to Various Agents			
subjects affected / exposed	1 / 802 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac Failure Acute			
subjects affected / exposed	1 / 802 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 802 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Psychomotor Hyperactivity			
subjects affected / exposed	1 / 802 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Anal Incontinence			
subjects affected / exposed	1 / 802 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colitis Microscopic			
subjects affected / exposed	1 / 802 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhoids			
subjects affected / exposed	1 / 802 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Large Intestinal Obstruction			
subjects affected / exposed	1 / 802 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophageal Ulcer			
subjects affected / exposed	1 / 802 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	1 / 802 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Stress Urinary Incontinence			
subjects affected / exposed	1 / 802 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Tubulointerstitial Nephritis			
subjects affected / exposed	1 / 802 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vesical Fistula			
subjects affected / exposed	1 / 802 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 802 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Back Pain			
subjects affected / exposed	1 / 802 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	1 / 802 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Synovial Cyst			
subjects affected / exposed	1 / 802 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 802 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	2 / 802 (0.25%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Dengue Fever			
subjects affected / exposed	1 / 802 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatitis B			
subjects affected / exposed	1 / 802 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	1 / 802 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary Tract Infection			
subjects affected / exposed	1 / 802 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis Acute			
subjects affected / exposed	1 / 802 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Intranasal Esketamine (Esk) Plus Oral Antidepressant (AD)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	653 / 802 (81.42%)		
Investigations			
Blood Pressure Increased			
subjects affected / exposed	75 / 802 (9.35%)		
occurrences (all)	219		
Nervous system disorders			
Dizziness			
subjects affected / exposed	264 / 802 (32.92%)		
occurrences (all)	1663		

Dizziness Postural subjects affected / exposed occurrences (all)	67 / 802 (8.35%) 532		
Dysgeusia subjects affected / exposed occurrences (all)	95 / 802 (11.85%) 602		
Headache subjects affected / exposed occurrences (all)	200 / 802 (24.94%) 480		
Hypoaesthesia subjects affected / exposed occurrences (all)	95 / 802 (11.85%) 592		
Paraesthesia subjects affected / exposed occurrences (all)	58 / 802 (7.23%) 176		
Sedation subjects affected / exposed occurrences (all)	71 / 802 (8.85%) 280		
Somnolence subjects affected / exposed occurrences (all)	134 / 802 (16.71%) 708		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	63 / 802 (7.86%) 97		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	88 / 802 (10.97%) 516		
Eye disorders Vision Blurred subjects affected / exposed occurrences (all)	60 / 802 (7.48%) 199		
Gastrointestinal disorders Diarrhoea			

subjects affected / exposed	60 / 802 (7.48%)		
occurrences (all)	79		
Hypoaesthesia Oral			
subjects affected / exposed	73 / 802 (9.10%)		
occurrences (all)	251		
Nausea			
subjects affected / exposed	201 / 802 (25.06%)		
occurrences (all)	422		
Vomiting			
subjects affected / exposed	87 / 802 (10.85%)		
occurrences (all)	144		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	70 / 802 (8.73%)		
occurrences (all)	125		
Dissociation			
subjects affected / exposed	221 / 802 (27.56%)		
occurrences (all)	1466		
Insomnia			
subjects affected / exposed	63 / 802 (7.86%)		
occurrences (all)	105		
Infections and infestations			
Influenza			
subjects affected / exposed	43 / 802 (5.36%)		
occurrences (all)	47		
Urinary Tract Infection			
subjects affected / exposed	65 / 802 (8.10%)		
occurrences (all)	89		
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	82 / 802 (10.22%)		
occurrences (all)	120		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 June 2015	The overall reason for the amendment was to allow for the use of a 28 milligram (mg) dose throughout the study, based on pharmacokinetic data from study ESKETINTRD1012 in elderly subjects.
17 February 2016	The overall reason for this amendment was to update and/or clarify protocol content based on ongoing feedback received during the study initiation activities. In addition, key protocol entry criteria for direct entry subjects have been added for transferred entry subjects, in order to confirm that subject's, who completed ESKETINTRD3005, continue to meet the criteria at entry to the ESKETINTRD3004 study.
06 June 2016	The overall reason for the amendment was to modify entry criteria with respect to PR interval based on Phase 1 and Phase 2 data, to add the information about the long-term safety study 54135419TRD3008; to implement changes and align language being applied across all Phase 3 studies in the esketamine development program; to correct errors and make minor clarifications in the text of the inclusion and exclusion criteria.
06 July 2016	The overall reason for the amendment was to remove the exclusion criteria for subjects aged ≥ 65 years with first degree AV block.

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 treatment was open-label with no comparator group. Based on predefined criteria related to achieving the required number of exposures at 6 and 12 months, not all enrolled subjects completed the full planned duration of the study.

Notes: