Clinical trial results:
A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized Study To Evaluate the Efficacy, Safety and Tolerability of E2027 in Subjects With Dementia With Lewy Bodies

Summary

EudraCT number	2017-003728-64
Trial protocol	DE GB ES IT
Global end of trial date	15 April 2020

Results information

Result version number	v1 (current)
This version publication date	24 June 2022
First version publication date	24 June 2022

Trial information

Trial identification

Sponsor protocol code	E2027-G000-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03467152
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eisai Ltd.
Sponsor organisation address	European Knowledge Centre, Mosquito Way, Hatfield, Hertfordshire, United Kingdom, AL10 9SN
Public contact	Eisai Medical Information, Eisai Ltd., +1 888-274-2378, esi_medinfo@eisai.com
Scientific contact	Eisai Medical Information, Eisai Ltd., +1 888-274-2378, esi_medinfo@eisai.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 April 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 April 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This main objective of the trial is to compare E2027 (herein referred to as Irsenontrine) to placebo on the cognitive endpoint of Montreal Cognitive Assessment (MoCA) and the global clinical endpoint of Clinician's Interview Based Impression of Change Plus (CIBIC-Plus) Caregiver Input in subject with dementia with Lewy bodies after 12 weeks of treatment.

Protection of trial subjects:

This study was conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following: - Principles of the World Medical Association Declaration of Helsinki (World Medical Association, 2008) - International Council on Harmonisation (ICH) E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use - Title 21 of the United States (US) Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and Institutional Review Board (IRB) regulations and applicable sections of US 21 CFR Part 312 - European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country. All suspected unexpected serious adverse reactions were reported, as required, to the Competent Authorities of all involved EU member states. - Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP Subject Information and Informed Consent.

Background therapy:

-

Evidence for comparator:

-

Actual start date of recruitment	04 May 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	European Union: 62
Country: Number of subjects enrolled	Japan: 67
Country: Number of subjects enrolled	United States: 67
Worldwide total number of subjects	196
EEA total number of subjects	0

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)	17
From 65 to 84 years	179
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subject took part in the study at 65 investigative sites in the United States, Japan, United Kingdom, France, Spain, Germany, and Italy from 04 May 2018 to 15 April 2020.

Pre-assignment

Screening details:

A total of 320 subjects were screened and enrolled (signed informed consent form), of which 120 were screen failures and 200 were randomized out of which 196 were treated. An additional 6 subjects were randomized but were not treated and included in this study due to closure of a site resulting from serious compliance issues.

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, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received Irsenontrine-matched placebo capsule, orally, once daily for 12 weeks.

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

Dosage and administration details:

Subjects received Irsenontrine-matched placebo capsule, orally, once daily for 12 weeks.

Arm title	Irsenontrine 50 mg

Arm description:

Subjects received Irsenontrine 50 milligram (mg), capsule, once daily for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Irsenontrine
Investigational medicinal product code	
Other name	E2027
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received Irsenontrine 50 mg, capsule, once daily for 12 weeks.

Number of subjects in period 1	Placebo	Irsenontrine 50 mg
Started	97	99
Completed	84	89
Not completed	13	10
Consent withdrawn by subject	5	5
Others	3	-
Adverse event, non-fatal	4	5
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received Irsenontrine-matched placebo capsule, orally, once daily for 12 weeks.	
Reporting group title	Irsenontrine 50 mg
Reporting group description:	
Subjects received Irsenontrine 50 milligram (mg), capsule, once daily for 12 weeks.	

Reporting group values	Placebo	Irsenontrine 50 mg	Total
Number of subjects	97	99	196
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	9	8	17
From 65-84 years	88	91	179
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	73.8	75.3	
standard deviation	± 6.60	± 6.44	-
Gender categorical Units: Subjects			
Female	36	37	73
Male	61	62	123
Race (NIH/OMB) Units: Subjects			
Asian	33	34	67
Black or African American	1	1	2
White	48	55	103
Unknown or Not Reported	15	9	24
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	11	17	28
Not Hispanic or Latino	73	76	149
Unknown or Not Reported	13	6	19

Subject analysis sets	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety analysis set included the group of subjects who received at least 1 dose of study drug and had at least 1 post randomization safety assessment.

Reporting group values	Safety Analysis Set		
Number of subjects	196		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	74.5		
standard deviation	± 6.54		
Gender categorical Units: Subjects			
Female	73		
Male	123		
Race (NIH/OMB) Units: Subjects			
Asian	67		
Black or African American	2		
White	103		
Unknown or Not Reported	24		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	28		
Not Hispanic or Latino	149		
Unknown or Not Reported	19		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received Irsenontrine-matched placebo capsule, orally, once daily for 12 weeks.	
Reporting group title	Irsenontrine 50 mg
Reporting group description:	
Subjects received Irsenontrine 50 milligram (mg), capsule, once daily for 12 weeks.	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety analysis set included the group of subjects who received at least 1 dose of study drug and had at least 1 post randomization safety assessment.	

Primary: Change From Baseline in the Montreal Cognitive Assessment (MoCA) Total Score at Week 12 of Treatment

End point title	Change From Baseline in the Montreal Cognitive Assessment (MoCA) Total Score at Week 12 of Treatment
End point description:	
The MoCA scale is used for detecting cognitive impairment, the scores range between 0 to 30 points; a score of 26 or above was considered normal. Higher values represent a better outcome. The full analysis set (FAS) included the group of randomized subjects who received at least 1 dose of study drug, had baseline and at least 1 post randomization coprimary efficacy measurement. Here number of subjects analysed were subjects evaluable for the endpoint and number analysed "n" were the subject who were evaluable for the endpoint for given time points.	
End point type	Primary
End point timeframe:	
Baseline and Week 12	

End point values	Placebo	Irsenontrine 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	96		
Units: Score on a Scale				
arithmetic mean (standard deviation)				
Baseline	13.9 (± 5.40)	13.8 (± 5.18)		
Change at Week12(n=81,87)	-0.6 (± 2.63)	-0.4 (± 3.41)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Irsenontrine 50 mg

Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6909
Method	Mixed Models for Repeated Measures(MMRM)

Primary: Clinician’s Interview Based Impression of Change Plus Caregiver Input (CIBIC-Plus) Scale at Week 12 of Treatment

End point title	Clinician’s Interview Based Impression of Change Plus Caregiver Input (CIBIC-Plus) Scale at Week 12 of Treatment

End point description:

The CIBIC-Plus scale is designed to measure various domains that describe subject function: general, mental/cognitive state, behavior, and activities of daily living. It is a semi-structured global rating derived from a comprehensive interview with the subject and caregiver or informant by an independent rater who has no access to the source data or other psychometric test scores conducted post-randomization as part of the protocol. The CIBIC-Plus was a 7-point scale and scores were: 1 (marked improvement), 2 (moderate improvement), 3 (minimal improvement), 4 (no change), 5 (minimal worsening), 6 (moderate worsening), and 7 (marked worsening). Higher values represent a worse outcome. The FAS included the group of randomized subjects who received at least 1 dose of study drug, had baseline and at least 1 post randomization coprimary efficacy measurement. Here number of subjects analysed were the subjects who were evaluable for the endpoint.

End point type	Primary

End point timeframe:

Week 12

End point values	Placebo	Irsenontrine 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	89		
Units: Subjects				
Marked improvement	0	0		
Moderate improvement	5	3		
Minimal improvement	13	18		
No change	32	32		
Minimal worsening	30	28		
Moderate worsening	6	8		
Marked worsening	0	0		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Irsenontrine 50 mg

Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8251
Method	Generalized Linear Mixed Models (GLMM)
Parameter estimate	Odds ratio (OR)
Point estimate	1.018
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.695
upper limit	1.492

Secondary: Clinician's Global Impression of Change-In Dementia With Lewy Bodies (CGIC-DLB) Scale at Week 12 of Treatment

End point title	Clinician's Global Impression of Change-In Dementia With Lewy Bodies (CGIC-DLB) Scale at Week 12 of Treatment

End point description:

The CGIC-DLB scale provided an overall clinician-determined summary measure of change from the subject's clinical status that takes into account all available information from the efficacy endpoints (which include cognitive function, non-cognitive symptoms, behavior, and the impact of the symptoms on the subject's ability to function) and safety data. The FAS included the group of randomized subjects who received at least 1 dose of study drug, had baseline and at least 1 post randomization coprimary efficacy measurement. Here number of subjects analysed were the subjects who were evaluable for the endpoint.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	Irsenontrine 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	90		
Units: Subjects				
Marked improvement	1	0		
Moderate improvement	3	10		
Minimal improvement	20	15		
No change	36	30		
Minimal worsening	22	27		
Moderate worsening	1	8		
Marked worsening	0	0		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Irsenontrine 50 mg

Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3003
Method	Generalized Linear Mixed Models (GLMM)
Parameter estimate	Odds ratio (OR)
Point estimate	0.853
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.584
upper limit	1.247

Secondary: Mean Change From Baseline in the Cognitive Fluctuation Inventory (CFI) Score at Week 12 of Treatment

End point title	Mean Change From Baseline in the Cognitive Fluctuation Inventory (CFI) Score at Week 12 of Treatment

End point description:

The CFI scale assessed cognitive fluctuation. It evaluates fluctuation in various domains including attention, ability to perform daily functions, orientation, verbal communication and behavior. The score was based on frequency and severity with a score range of 0 to 12. The scale also assessed the degree of caregiver or informant distress engendered by the symptoms. Higher scores indicating greater impairment. The FAS included the group of randomized subjects who received at least 1 dose of study drug, had baseline and at least 1 post randomization coprimary efficacy measurement. Here number of subjects analysed are the subjects who were evaluable for the endpoint and number analysed "n" were the subjects who were evaluable for the endpoint for given time points.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	Irsenontrine 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	96		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline	3.4 (± 2.68)	3.1 (± 2.48)		
Change at Week12(n=86,89)	0.1 (± 3.20)	0.3 (± 3.25)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Irsenontrine 50 mg

Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9198
Method	Mixed Models for Repeated Measures(MMRM)

Secondary: Mean Change From Baseline in the Mini-Mental State Examination (MMSE) Total Score Week 12 of Treatment

End point title	Mean Change From Baseline in the Mini-Mental State Examination (MMSE) Total Score Week 12 of Treatment

End point description:

The MMSE is a 30-point scale that measured orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing. The total score ranges from 0 (most impaired) to 30 (no impairment). The lower score means severe cognitive deficit and higher score indicates better function. The FAS included the group of randomized subjects who received at least 1 dose of study drug, had baseline and at least 1 post randomization coprimary efficacy measurement. Here number of subjects analysed are the subjects who were evaluable for the endpoint and number analysed "n" were the subjects who were evaluable for the endpoint for given time points.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	Irsenontrine 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	96		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline	21.0 (± 3.63)	21.1 (± 3.22)		
Change at Week12(n=85,92)	-1.1 (± 3.63)	-1.7 (± 3.58)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Irsenontrine 50 mg
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2909
Method	ANCOVA

Secondary: Mean Change from Baseline in the Neuropsychiatric Inventory (NPI-12) Total Score at Week 12 of Treatment

End point title	Mean Change from Baseline in the Neuropsychiatric Inventory

	(NPI-12) Total Score at Week 12 of Treatment

End point description:

The NPI-12 scale assessed the frequency and severity of 12 neuropsychiatric symptoms commonly described in dementia subjects: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, motor disturbance, nighttime behaviors, and appetite/eating changes. The scale also assessed the degree of caregiver or informant distress engendered by each of the symptoms. The sum of the composite scores for the 12 domains yielded the NPI-12 total score. NPI-12 total score ranged from 0 (minimum severity) to 144 (maximum severity); higher score indicates greater neuropsychiatric disturbance. FAS was included. Here number of subjects analysed are the subjects who were evaluable for the endpoint and number analysed "n" were the subjects who were evaluable for the endpoint for given time points.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	Irsenontrine 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	96		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline	17.6 (± 14.32)	19.1 (± 16.07)		
Change at Week12(n=86,89)	-0.2 (± 11.07)	-2.0 (± 15.36)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Irsenontrine 50 mg
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6127
Method	Mixed Models for Repeated Measures(MMRM)

Secondary: Change from Baseline in NPI-4 Subscore at Week 12

End point title	Change from Baseline in NPI-4 Subscore at Week 12

End point description:

The NPI scale assesses the frequency and severity of 12 neuropsychiatric symptoms commonly described in dementia subjects: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, motor disturbance, nighttime behaviors, and appetite/eating changes. NPI-4 is the subscore covering the domains of delusions, hallucinations, apathy and depression. NPI-4 total subscore ranged from 0 to 48, with higher scores indicating a greater neuropsychiatric disturbance. The FAS included the group of randomized Subjects who received at least 1 dose of study drug, had baseline and at least 1 post randomization coprimary efficacy measurement. Here number of subjects analysed are the subjects who were evaluable for the endpoint and number analysed "n" were the subjects who were evaluable for the endpoint for given time points.

End point type	Secondary

End point timeframe: Baseline and Week 12

End point values	Placebo	Irsenontrine 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	96		
Units: Score on scale				
arithmetic mean (standard deviation)				
Baseline	8.2 (± 6.40)	8.6 (± 7.18)		
Change at Week 12 (n=86,89)	-0.4 (± 5.15)	-0.6 (± 6.79)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Irsenontrine 50 mg
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.878
Method	Mixed Models for Repeated Measures(MMRM)

Secondary: Change from Baseline in NPI-10 Subscore at Week 12

End point title	Change from Baseline in NPI-10 Subscore at Week 12

End point description:

The NPI-10 assessed range of behaviors seen in dementia for both frequency and severity. It is a 10 item questionnaire with the following domains: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/liability and aberrant motor behavior. The total score was a sum of the 10 domains, where the score of each domain was calculated as frequency (scale: 1=occasionally to 4=very frequently)*Severity(scale:1 = Mild to 3 = Severe). Each domain has a maximum score of 12 and all domains were equally weighted for total score, the range for total score is 0 to 120. Higher scores indicating a greater neuropsychiatric disturbance. FAS was included. Here number of subjects analysed are the subjects who were evaluable for the endpoint, "n" were evaluable for given time point.

End point type	Secondary

End point timeframe: Baseline and Week 12

End point values	Placebo	Irsenontrine 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	96		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline	13.5 (± 11.22)	14.9 (± 13.54)		
Change at Week 12 (n= 86,89)	0.6 (± 9.32)	-1.4 (± 12.53)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Irsenontrine 50 mg
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.409
Method	Mixed Models for Repeated Measures(MMRM)

Secondary: Change From Baseline in NPI-D (Caregiver Distress) Total Score at Week 12

End point title	Change From Baseline in NPI-D (Caregiver Distress) Total Score at Week 12

End point description:

The NPI scale assesses the frequency and severity of 12 neuropsychiatric symptoms commonly described in dementia
Subjects:delusions,hallucinations,agitation/aggression,depression/dysphoria,anxiety,elation/euphoria,apathy/indifference, disinhibition,irritability/lability,motor disturbance,nighttime behaviors,and appetite/eating changes. The scale assesses the degree of caregiver distress engendered by each of the symptoms. The NPI-D is rated by caregiver based on his or her own stress on a five point scale from 0 to 5,where: 0(no distress),1(minimal),2(mild),3(moderate),4(moderately severe),5(very severe or extreme). NPI-D total score is calculated by summing the scores of the 12 sub-scale distress scores. The NPI-D total scores ranges from 0 to 60 with higher scores indicating greater distress. The FAS was included. Here number of subjects analysed are the subjects who were evaluable for the endpoint, "n"

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	Irsenontrine 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	96		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline	8.8 (± 7.65)	9.4 (± 8.44)		
Change at Week12(n=86,89)	-0.2 (± 6.18)	-0.6 (± 7.28)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Irsenontrine 50 mg
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8736
Method	Mixed Models for Repeated Measures(MMRM)

Secondary: Number of Subjects With Treatment Emergent Adverse Events (TEAEs), Severe TEAEs, Serious TEAEs, Adverse Events (AEs) Resulting in Study Discontinuation

End point title	Number of Subjects With Treatment Emergent Adverse Events (TEAEs), Severe TEAEs, Serious TEAEs, Adverse Events (AEs) Resulting in Study Discontinuation

End point description:

TEAE was defined as an AE that emerged or worsened in severity relative to baseline during treatment or within 28 days after the last dose of study drug.); Severe TEAE was defined as inability to work or to perform normal daily activity; A Serious TEAE is any untoward medical occurrence that at any dose: results in death; is life threatening (that is, the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death) requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect or is medically important due to other reasons than the above mentioned criteria. An adverse event (AE) was defined as any untoward medical occurrence in a subject administered an investigational product. Safety analysis set.

End point type	Secondary

End point timeframe:

From first dose of study drug up to Week 16

End point values	Placebo	Irsenontrine 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	99		
Units: Subjects				
TEAEs	67	70		
Severe TEAEs	6	2		
Serious TEAEs	9	7		
AE Leading to Discontinuation from Study	7	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Orthostatic Hypotension

End point title	Number of Subjects With Orthostatic Hypotension

End point description:

Orthostatic hypotension was defined as drop in standing systolic blood pressure greater than or equal to (>=) 20 millimeter of mercury (mmHg) compared to supine, or drop in standing diastolic blood pressure >=10 mmHg compared to supine. The safety analysis set included the group of subjects who received at least 1 dose of study drug and had at least 1 post randomization safety assessment.

End point type	Secondary

End point timeframe:

Week 2, Week 4, Week 6, Week 9, Week 12, and Week 16

End point values	Placebo	Irsenontrine 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	99		
Units: Subjects				
Week 2	10	2		
Week 4	9	7		
Week 6	6	11		
Week 9	13	9		
Week 12	7	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Orthostatic Tachycardia

End point title	Number of Subjects With Orthostatic Tachycardia

End point description:

Orthostatic tachycardia by numerical criteria was defined by the following numerical criteria: Standing heart rate (HR) increased by >30 beats/min compared to supine and absolute standing HR was >100 beats/min. The safety analysis set included the group of subjects who received at least 1 dose of study drug and had at least 1 post randomization safety assessment.

End point type	Secondary

End point timeframe:

From first dose of study drug up to Week 16

End point values	Placebo	Irsenontrine 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	99		
Units: Subjects				
Number of Subjects With Orthostatic Tachycardia	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Markedly Abnormal Laboratory Values

End point title	Number of Subjects With Markedly Abnormal Laboratory Values

End point description:

A laboratory value was determined to be a markedly abnormal value if the postbaseline common toxicity criteria grade increased from baseline and the post-baseline grade was >= 2. The safety analysis set included the group of subjects who received at least 1 dose of study drug and had at least 1 post randomization safety assessment. Here "N" were the subjects who were evaluable for the endpoint. Number analysed "n" were the subjects who were evaluable for the endpoint for given categories.

End point type	Secondary

End point timeframe:

From first dose of study drug up to Week 16

End point values	Placebo	Irsenontrine 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	97		
Units: Subjects				
Albumin: Markedly Abnormal Low(n=94,96)	1	0		
Bilirubin: Markedly Abnormal High(n=94,96)	1	0		
Calcium:Markedly Abnormal Low(n=94,96)	1	0		
Creatinine:Markedly Abnormal High(n=94,96)	0	2		
GlutamylTransferase:MarkedlyAbnormal High(n=94,96)	2	0		
Hemoglobin:Markedly Abnormal Low(n=94,96)	0	1		
Leukocytes:Markedly Abnormal Low(n=94,96)	0	1		
Lymphocytes:Markedly Abnormal Low(n=94,96)	4	1		
Neutrophils:Markedly Abnormal Low(n=94,96)	1	0		

Phosphate:Markedly Abnormal Low(n=94,96)	0	1		
Potassium:Markedly Abnormal Low(n=94,97)	1	0		
Potassium:Markedly Abnormal High(n=94,97)	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Abnormal Electrocardiogram (ECG) Findings

End point title	Number of Subjects With Abnormal Electrocardiogram (ECG) Findings

End point description:

The safety analysis set included the group of subjects who received at least 1 dose of study drug and had at least 1 post randomization safety assessment. Here "N" were the subjects who were evaluable for the endpoint.

End point type	Secondary

End point timeframe:

From first dose of study drug up to Week 16

End point values	Placebo	Irsenontrine 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	98		
Units: Subjects				
QTcF prolongation by >60 milliseconds (ms)	2	0		
QTcF prolongation to >500 ms	2	0		
Change from baseline of PR >= 25 percent (%)	1	1		
Change from baseline of QRS >= 25%	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Suicidal Ideation or Suicidal Behavior as Measured Using Columbia Suicide Severity Rating Scale (C-SSRS)

End point title	Number of Subjects With Suicidal Ideation or Suicidal Behavior as Measured Using Columbia Suicide Severity Rating Scale (C-SSRS)

End point description:

The C-SSRS (mapped to C-CASA categories); is an interview-based instrument to systematically assess suicidal ideation and suicidal behavior. C-SSRS assess whether subject experience any of the following: completed suicide; suicide attempt; preparatory acts toward imminent suicidal behavior, suicidal ideation, wish to be dead, non-specific active suicidal thoughts, active suicidal ideation with methods without intent to act or some intent to act, without specific plan or with specific plan and intent, any

self-injurious behavior with no suicidal intent. Here, number of subjects with positive response (yes) to suicidal behavior or/and Ideation, any non-suicidal self-injurious behavior will be reported. The safety analysis set included the group of subjects who received at least 1 dose of study drug and had at least 1 post randomization safety assessment. Here number of subjects analysed were the subjects who were evaluable for the endpoint.

End point type	Secondary

End point timeframe:

From first dose of study drug up to Week 16

End point values	Placebo	Irsenontrine 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	98		
Units: Subjects				
Completed Suicide	0	0		
Suicide Attempt	0	0		
Imminent Suicidal Behavior	0	2		
Wish to Die	6	8		
Actual Suicidal Thoughts; Non-specific	1	1		
Actual Suicidal Thoughts with Method; No Intent	0	1		
Active Thoughts with Intent	0	0		
Active Thoughts with Plan and Intent	0	0		
Self-injurious Behavior; No Intent	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Total Score of Unified Parkinson’s Disease Rating Scale Part III: Motor Examination (UPDRS-III)

End point title	Change From Baseline in Total Score of Unified Parkinson’s Disease Rating Scale Part III: Motor Examination (UPDRS-III)

End point description:

The UPDRS scale evaluates extrapyramidal features in motor function in Parkinson’s disease. It contains 33 items in 18 categories:(1)speech,(2)facial expression,(3) rigidity,(4)finger tapping,(5)hand movements,(6)supinational and pronation movements of hands, (7)toe tapping,(8)leg agility,(9)arising from chair,(10) gait,(11)freezing of gait,(12)postural stability,(13) posture,(14)body bradykinesia,(15)postural tremor of hands, (16) kinetic tremor of hands, (17) rest tremor amplitude and (18) constancy of rest tremor. Each item is scored 0 to 4, giving a total score range 0 to 132. Higher scores indicating more severe symptoms. The safety analysis set included the group of subjects who received at least 1 dose of study drug and had at least 1 post randomization safety assessment. Here number analysed "n" were the subjects who were evaluable for the endpoint for given time points.

End point type	Secondary

End point timeframe:

Baseline up to Week 16

End point values	Placebo	Irsenontrine 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	99		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline	31.3 (± 18.51)	34.5 (± 18.12)		
Change at Week16(n=81,84)	-1.2 (± 10.97)	1.0 (± 9.22)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dose of study drug up to follow up (Week 16)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received Irsenontrine-matched placebo capsule, orally, once daily for 12 weeks.	
Reporting group title	Irsenontrine 50 mg
Reporting group description:	
Subjects received Irsenontrine 50 mg, capsule, once daily for 12 weeks.	

Serious adverse events	Placebo	Irsenontrine 50 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 97 (9.28%)	7 / 99 (7.07%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			

subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periprosthetic fracture			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dementia with Lewy bodies			
subjects affected / exposed	1 / 97 (1.03%)	2 / 99 (2.02%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal perforation			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Influenza			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Placebo	Irsenontrine 50 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	65 / 97 (67.01%)	68 / 99 (68.69%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lipoma			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Prostate cancer			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Haematoma			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Hypertension			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Orthostatic hypotension			
subjects affected / exposed	0 / 97 (0.00%)	3 / 99 (3.03%)	
occurrences (all)	0	4	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Fatigue			

subjects affected / exposed	2 / 97 (2.06%)	1 / 99 (1.01%)	
occurrences (all)	2	1	
Malaise			
subjects affected / exposed	1 / 97 (1.03%)	2 / 99 (2.02%)	
occurrences (all)	1	2	
Non-cardiac chest pain			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	2 / 97 (2.06%)	3 / 99 (3.03%)	
occurrences (all)	2	4	
Pyrexia			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 97 (1.03%)	1 / 99 (1.01%)	
occurrences (all)	1	1	
Atelectasis			
subjects affected / exposed	0 / 97 (0.00%)	2 / 99 (2.02%)	
occurrences (all)	0	2	
Alveolar lung disease			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Dyspnoea			
subjects affected / exposed	1 / 97 (1.03%)	1 / 99 (1.01%)	
occurrences (all)	1	1	
Oropharyngeal pain			
subjects affected / exposed	2 / 97 (2.06%)	0 / 99 (0.00%)	
occurrences (all)	2	0	
Orthopnoea			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Rales			

subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Pulmonary mass			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Psychiatric disorders			
Affective disorder			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Attention deficit/hyperactivity disorder			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Aggression			
subjects affected / exposed	0 / 97 (0.00%)	2 / 99 (2.02%)	
occurrences (all)	0	2	
Confusional state			
subjects affected / exposed	2 / 97 (2.06%)	3 / 99 (3.03%)	
occurrences (all)	2	3	
Behaviour disorder			
subjects affected / exposed	0 / 97 (0.00%)	2 / 99 (2.02%)	
occurrences (all)	0	3	
Delirium			
subjects affected / exposed	1 / 97 (1.03%)	1 / 99 (1.01%)	
occurrences (all)	1	1	
Delusion			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Depressed mood			
subjects affected / exposed	1 / 97 (1.03%)	1 / 99 (1.01%)	
occurrences (all)	1	1	
Depression			
subjects affected / exposed	2 / 97 (2.06%)	0 / 99 (0.00%)	
occurrences (all)	2	0	
Euphoric mood			

subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Hallucination, auditory			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Hallucination, visual			
subjects affected / exposed	9 / 97 (9.28%)	7 / 99 (7.07%)	
occurrences (all)	11	8	
Irritability			
subjects affected / exposed	2 / 97 (2.06%)	0 / 99 (0.00%)	
occurrences (all)	2	0	
Libido increased			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Neuropsychiatric symptoms			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Nightmare			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Panic attack			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Paranoia			
subjects affected / exposed	2 / 97 (2.06%)	0 / 99 (0.00%)	
occurrences (all)	2	0	
Sexually inappropriate behaviour			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Rapid eye movement sleep behaviour disorder			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Sleep disorder			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	

Suicidal ideation			
subjects affected / exposed	2 / 97 (2.06%)	2 / 99 (2.02%)	
occurrences (all)	2	2	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Blood triglycerides increased			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Blood pressure decreased			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Electrocardiogram T wave inversion			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Electrocardiogram QT prolonged			
subjects affected / exposed	2 / 97 (2.06%)	2 / 99 (2.02%)	
occurrences (all)	2	2	
Haemoglobin decreased			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Liver function test increased			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Lymphocyte count decreased			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	2	0	
Norovirus test positive			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Prostatic specific antigen increased			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Red blood cell count decreased			

subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Weight decreased			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	3 / 97 (3.09%)	1 / 99 (1.01%)	
occurrences (all)	4	1	
Facial bones fracture			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Fall			
subjects affected / exposed	15 / 97 (15.46%)	10 / 99 (10.10%)	
occurrences (all)	15	14	
Femur fracture			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	2	0	
Foot fracture			
subjects affected / exposed	2 / 97 (2.06%)	0 / 99 (0.00%)	
occurrences (all)	2	0	
Joint dislocation			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Ligament sprain			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Skin abrasion			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Rib fracture			
subjects affected / exposed	1 / 97 (1.03%)	1 / 99 (1.01%)	
occurrences (all)	1	1	
Skin laceration			

subjects affected / exposed	1 / 97 (1.03%)	1 / 99 (1.01%)	
occurrences (all)	1	1	
Spinal compression fracture			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Thermal burn			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Upper limb fracture			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Wound			
subjects affected / exposed	1 / 97 (1.03%)	1 / 99 (1.01%)	
occurrences (all)	2	1	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 97 (2.06%)	0 / 99 (0.00%)	
occurrences (all)	2	0	
Palpitations			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Nervous system disorders			
Disturbance in attention			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Dementia with Lewy bodies			
subjects affected / exposed	0 / 97 (0.00%)	4 / 99 (4.04%)	
occurrences (all)	0	4	
Cognitive disorder			
subjects affected / exposed	1 / 97 (1.03%)	1 / 99 (1.01%)	
occurrences (all)	1	1	
Dizziness			
subjects affected / exposed	1 / 97 (1.03%)	5 / 99 (5.05%)	
occurrences (all)	4	5	
Dizziness postural			

subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	1 / 97 (1.03%)	2 / 99 (2.02%)	
occurrences (all)	1	2	
Hypersomnia			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Loss of consciousness			
subjects affected / exposed	1 / 97 (1.03%)	1 / 99 (1.01%)	
occurrences (all)	1	2	
Hypoaesthesia			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Nystagmus			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Parkinsonism			
subjects affected / exposed	2 / 97 (2.06%)	1 / 99 (1.01%)	
occurrences (all)	2	1	
Paraesthesia			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Petit mal epilepsy			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Restless legs syndrome			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Somnolence			
subjects affected / exposed	1 / 97 (1.03%)	3 / 99 (3.03%)	
occurrences (all)	1	3	
Syncope			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Visuospatial deficit			

subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Tremor			
subjects affected / exposed	2 / 97 (2.06%)	1 / 99 (1.01%)	
occurrences (all)	2	1	
Blood and lymphatic system disorders			
Blood loss anaemia			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Lymphopenia			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Neutropenia			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Ear haemorrhage			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Dry eye			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Eye discharge			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Lacrimation increased			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			

Abdominal pain upper			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Anal incontinence			
subjects affected / exposed	2 / 97 (2.06%)	0 / 99 (0.00%)	
occurrences (all)	2	0	
Constipation			
subjects affected / exposed	4 / 97 (4.12%)	1 / 99 (1.01%)	
occurrences (all)	4	1	
Dental caries			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	3 / 97 (3.09%)	4 / 99 (4.04%)	
occurrences (all)	3	4	
Dry mouth			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	3 / 97 (3.09%)	1 / 99 (1.01%)	
occurrences (all)	3	1	
Stomatitis			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	2 / 97 (2.06%)	2 / 99 (2.02%)	
occurrences (all)	2	2	
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	0 / 97 (0.00%)	2 / 99 (2.02%)	
occurrences (all)	0	2	
Dermatitis bullous			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Eczema asteatotic			

subjects affected / exposed	2 / 97 (2.06%)	0 / 99 (0.00%)	
occurrences (all)	2	0	
Dermatitis allergic			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Papule			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	2 / 97 (2.06%)	0 / 99 (0.00%)	
occurrences (all)	2	0	
Rash macular			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Skin lesion			
subjects affected / exposed	0 / 97 (0.00%)	2 / 99 (2.02%)	
occurrences (all)	0	4	
Skin ulcer			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Xeroderma			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Dysuria			
subjects affected / exposed	1 / 97 (1.03%)	1 / 99 (1.01%)	
occurrences (all)	1	1	
Pollakiuria			
subjects affected / exposed	1 / 97 (1.03%)	1 / 99 (1.01%)	
occurrences (all)	1	1	
Urinary incontinence			
subjects affected / exposed	2 / 97 (2.06%)	2 / 99 (2.02%)	
occurrences (all)	2	2	

Urinary retention			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 97 (1.03%)	1 / 99 (1.01%)	
occurrences (all)	1	1	
Back pain			
subjects affected / exposed	2 / 97 (2.06%)	0 / 99 (0.00%)	
occurrences (all)	2	0	
Flank pain			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Joint range of motion decreased			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Lumbar spinal stenosis			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Mobility decreased			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Muscular weakness			
subjects affected / exposed	1 / 97 (1.03%)	1 / 99 (1.01%)	
occurrences (all)	1	1	
Musculoskeletal pain			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Neck pain			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Periarthritis			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Polymyalgia rheumatica			

subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Infections and infestations			
Cystitis			
subjects affected / exposed	2 / 97 (2.06%)	1 / 99 (1.01%)	
occurrences (all)	2	1	
Bronchitis			
subjects affected / exposed	2 / 97 (2.06%)	1 / 99 (1.01%)	
occurrences (all)	2	1	
Folliculitis			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Herpes zoster			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Oral herpes			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	3 / 97 (3.09%)	5 / 99 (5.05%)	
occurrences (all)	3	5	
Pharyngitis			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Pneumonia			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Tinea pedis			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Sinusitis			
subjects affected / exposed	1 / 97 (1.03%)	1 / 99 (1.01%)	
occurrences (all)	1	1	

Tooth abscess			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Tooth infection			
subjects affected / exposed	0 / 97 (0.00%)	2 / 99 (2.02%)	
occurrences (all)	0	3	
Upper respiratory tract infection			
subjects affected / exposed	1 / 97 (1.03%)	2 / 99 (2.02%)	
occurrences (all)	1	2	
Urinary tract infection			
subjects affected / exposed	5 / 97 (5.15%)	4 / 99 (4.04%)	
occurrences (all)	5	4	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Dehydration			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Folate deficiency			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Diabetes mellitus			
subjects affected / exposed	1 / 97 (1.03%)	1 / 99 (1.01%)	
occurrences (all)	1	1	
Hyperkalaemia			
subjects affected / exposed	1 / 97 (1.03%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Hyperglycaemia			
subjects affected / exposed	0 / 97 (0.00%)	2 / 99 (2.02%)	
occurrences (all)	0	2	
Hypophosphataemia			
subjects affected / exposed	0 / 97 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Vitamin D deficiency			

subjects affected / exposed occurrences (all)	1 / 97 (1.03%) 1	0 / 99 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 January 2018	Amendments 1: Addition inclusion criterion was added, Estimated blood volume collected during the study was updated, Description of the MDS-UPDRS was corrected, Instructions were added to recommend that subjects avoided prolonged exposure to the sun or exposure to artificial ultra-violet light, the criterion for pulse increase was removed from the definition of orthostatic hypotension.
15 June 2018	Amendment 2: Secondary endpoints for safety and tolerability were added, the information regarding breaking of blind was corrected, the "Capacity Rule" was added, CSF substudy criteria and description were added,
10 July 2019	Amendment 3: Restriction on the use of memantine prior to and during study participation was removed, The number of sites was increased from 60 to 70.
03 September 2019	Amendment 4: The percentage of randomized subjects who would be on memantine was specified.
03 January 2020	Amendment 5: Results of a nonclinical toxicology study were added, the requirement for male subjects to use highly effective contraception and the requirement to report pregnancy in female partners of male subjects were added, the order of the secondary efficacy endpoints was revised.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported