Clinical trial results:
A Phase II, Randomized, Placebo-Controlled, Double-Blind, Crossover, Study of the Pharmacodynamic Effects of CST-103 co-administered with CST-107 on the Central Nervous System in Subjects with Neurodegenerative Disorders

Summary

EudraCT number	2020-006067-28
Trial protocol	BE
Global end of trial date	31 August 2022

Results information

Result version number	v1 (current)
This version publication date	29 July 2023
First version publication date	29 July 2023

Trial information

Trial identification

Sponsor protocol code	CST103/CST107-CLIN-011

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04739423
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CuraSen Therapeutics, Inc.
Sponsor organisation address	930 Brittan Avenue, San Carlos, United States, CA 94070
Public contact	Clinical Trial Information Desk, CuraSen Therapeutics, Inc., +1 650 475 2842, clinicaltrials@curasen.com
Scientific contact	Clinical Trial Information Desk, CuraSen Therapeutics, Inc., +1 650 475 2842, clinicaltrials@curasen.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	24 April 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2022
Global end of trial reached?	Yes
Global end of trial date	31 August 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to identify a CNS signal in one of the planned pharmacodynamic measures (emotional facial processing, cognitive fluctuations) after multiple doses of CST-103 co-administered with CST-107 in subjects with neurodegenerative diseases.

The objective is to identify an improvement in cognition, for example in learning, thinking and remembering, a CNS signal in one of the planned pharmacodynamic measurements after multiple oral doses of CST-103 in the presence of CST-107 in four populations of subjects with neurodegenerative disorders. This includes patients with Parkinson's Disease (PD) , Mild Cognitive Impairment (MCI), Parkinson’s Disease Dementia (PDD) and Dementia with Lewy Bodies (DLB).

The primary objective for Cohort A population (PD or MCI) is a change in emotional facial recognition, a measure of mood. The primary objective for the Cohort B population (DLB or PDD) is to assess the change in cognitive fluctuations.

Protection of trial subjects:

Before each subject was screened, written informed consent was obtained from the subject. The consent forms were signed and dated and retained by the Investigator as part of the clinical trial records. The Investigator did not undertake any investigation specifically required for the clinical trial until valid consent had been obtained. The terms of the consent and when it was obtained were documented in the electronic case report form (eCRF). Each subject received a fully signed copy of each consent form that he/she signed for the clinical trial.
If the consent form was revised for a protocol amendment, it was reviewed and approved by the appropriate EC and signed by all subjects subsequently enrolled, as well as those currently enrolled in the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 April 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	Australia: 5
Country: Number of subjects enrolled	New Zealand: 15
Worldwide total number of subjects	41
EEA total number of subjects	10

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)	19
From 65 to 84 years	22
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

After informed consent, all subjects completed screening procedures and tests to establish eligibility during the Screening Period, which were performed between Day -28 and Day -8. If a subject fell outside the Screening Period window, screening could be extended with prior approval by the CuraSen Medical Monitor.

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

Arms

Are arms mutually exclusive?	No
Arm title	PD - Placebo

Arm description:

Subjects with Parkinson's Disease (PD) receiving placebo

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:

Taken daily in the morning after the first meal of the day during each Treatment Period (Day 1 - Day 14)

Arm title	PD - Active

Arm description:

Subjects with PD receiving active treatment.

Arm type	Experimental
Investigational medicinal product name	CST-103
Investigational medicinal product code	
Other name	Clenbuterol HCl
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Taken orally in the morning after the first meal of the day during each Treatment Period as 80 µg CST-103, administered as two 40 µg capsules once daily on Days 1 to 14

Investigational medicinal product name	CST-107
Investigational medicinal product code	
Other name	Nadolol
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Taken orally in the morning after the first meal of the day during each Treatment Period as 1 mg CST-107, administered as one 1 mg capsule once daily on Days 1 to 14.

Arm title	MCI - Placebo

Arm description:

Subjects with mild cognitive impairment (MCI) receiving placebo.

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:

Taken daily in the morning after the first meal of the day during each Treatment Period (Day 1 - Day 14)

Arm title	MCI - Active

Arm description:

Subjects with MCI receiving active treatment.

Arm type	Experimental
Investigational medicinal product name	CST-103
Investigational medicinal product code	
Other name	Clenbuterol HCl
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Taken orally in the morning after the first meal of the day during each Treatment Period as 80 µg CST-103, administered as two 40 µg capsules once daily on Days 1 to 14

Investigational medicinal product name	CST-107
Investigational medicinal product code	
Other name	Nadolol
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Taken orally in the morning after the first meal of the day during each Treatment Period as 1 mg CST-107, administered as one 1 mg capsule once daily on Days 1 to 14.

Arm title	PDD and DLB- Placebo

Arm description:

Subjects with Parkinson's Disease Dementia (PDD) or Dementia with Lewy Bodies (DLB) receiving placebo.

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:

Taken daily in the morning after the first meal of the day during each Treatment Period (Day 1 - Day 14)

Arm title	PDD and DLB - Active

Arm description:

Subjects with PDD or DLB receiving active treatment.

Arm type	Experimental

Investigational medicinal product name	CST-103
Investigational medicinal product code	
Other name	Clenbuterol HCl
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Taken orally in the morning after the first meal of the day during each Treatment Period as 80 µg CST-103, administered as two 40 µg capsules once daily on Days 1 to 14

Investigational medicinal product name	CST-107
Investigational medicinal product code	
Other name	Nadolol
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Taken orally in the morning after the first meal of the day during each Treatment Period as 1 mg CST-107, administered as one 1 mg capsule once daily on Days 1 to 14.

Number of subjects in period 1	PD - Placebo	PD - Active	MCI - Placebo
Started	25	24	12
Completed	24	24	12
Not completed	1	0	0
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	-	-	-
Protocol deviation	1	-	-

Number of subjects in period 1	MCI - Active	PDD and DLB-Placebo	PDD and DLB - Active
Started	13	3	2
Completed	12	1	2
Not completed	1	2	0
Consent withdrawn by subject	-	1	-
Adverse event, non-fatal	1	1	-
Protocol deviation	-	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall study

Reporting group description: -

Reporting group values	Overall study	Total	
Number of subjects	41	41	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 63.7 ± 7.40	 -	
Gender categorical Units: Subjects			
Female	13	13	
Male	28	28	

End points

End points reporting groups

Reporting group title	PD - Placebo
Reporting group description:	
Subjects with Parkinson's Disease (PD) receiving placebo	
Reporting group title	PD - Active
Reporting group description:	
Subjects with PD receiving active treatment.	
Reporting group title	MCI - Placebo
Reporting group description:	
Subjects with mild cognitive impairment (MCI) receiving placebo.	
Reporting group title	MCI - Active
Reporting group description:	
Subjects with MCI receiving active treatment.	
Reporting group title	PDD and DLB- Placebo
Reporting group description:	
Subjects with Parkinson's Disease Dementia (PDD) or Dementia with Lewy Bodies (DLB) receiving placebo.	
Reporting group title	PDD and DLB - Active
Reporting group description:	
Subjects with PDD or DLB receiving active treatment.	

Primary: Facial Expression Recognition Task (FERT) - Accuracy for happiness

End point title	Facial Expression Recognition Task (FERT) - Accuracy for happiness[1]
End point description:	
End point type	Primary
End point timeframe:	
Change from baseline to Day 14.	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Analysis performed on data from PD subjects only. It is noted that the sample size for all groups other than PD were too small for meaningful analysis.

End point values	PD - Placebo	PD - Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: Percentage				
least squares mean (standard error)	8.1316 (± 2.5783)	13.6138 (± 2.5462)		

Statistical analyses

Statistical analysis title	Between treatment analysis
Comparison groups	PD - Placebo v PD - Active
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.0479
Method	Mixed models analysis

Notes:

[2] - It is noted that the number of subjects in this analysis was 23 and not 47 as automatically imputed by EudraCT.

Primary: Facial Expression Recognition Task (FERT) - Accuracy for sadness

End point title	Facial Expression Recognition Task (FERT) - Accuracy for sadness[3]

End point description:

End point type	Primary

End point timeframe:

Change in baseline to Day 14.

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Analysis performed on data from PD subjects only. It is noted that the sample size for all groups other than PD were too small for meaningful analysis.

End point values	PD - Placebo	PD - Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: Percentage protective dose				
least squares mean (standard error)	-6.9002 (± 1.7950)	-2.1048 (± 1.7749)		

Statistical analyses

Statistical analysis title	Between treatment analysis
Comparison groups	PD - Active v PD - Placebo
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.0161
Method	Mixed models analysis

Notes:

[4] - It is noted that the number of subjects in this analysis was 23 and not 47 as automatically imputed by EudraCT.

Primary: Facial Expression Recognition Task (FERT) - Reaction time for anger

End point title	Facial Expression Recognition Task (FERT) - Reaction time for anger[5]

End point description:

End point type	Primary

End point timeframe:

Change from baseline to Day 7.

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Analysis performed on data from PD subjects only. It is noted that the sample size for all groups other than PD were too small for meaningful analysis.

End point values	PD - Placebo	PD - Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	23		
Units: ms				
least squares mean (standard error)	-150.77 (± 78.70)	16.52 (± 75.97)		

Statistical analyses

Statistical analysis title	Between treatment analysis
Comparison groups	PD - Placebo v PD - Active
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.0237
Method	Mixed models analysis

Notes:

[6] - It is noted that the number of subjects in this analysis was 21 and not 44 as automatically imputed by EudraCT.

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From first dose to end of study visit.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups	
Reporting group title	PD - Placebo
Reporting group description: Subjects with Parkinson's Disease (PD) receiving placebo	
Reporting group title	PD - Active
Reporting group description: Subjects with PD receiving active treatment.	
Reporting group title	MCI - Placebo
Reporting group description: Subjects with mild cognitive impairment (MCI) receiving placebo.	
Reporting group title	MCI - Active
Reporting group description: Subjects with MCI receiving active treatment.	
Reporting group title	PDD and DLB- Placebo
Reporting group description: Subjects with Parkinson's Disease Dementia (PDD) or Dementia with Lewy Bodies (DLB) receiving placebo.	
Reporting group title	PDD and DLB - Active
Reporting group description: Subjects with PDD or DLB receiving active treatment.	

Serious adverse events	PD - Placebo	PD - Active	MCI - Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 12 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Hypoglycaemic seizure			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	MCI - Active	PDD and DLB-Placebo	PDD and DLB - Active
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Hypoglycaemic seizure			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	PD - Placebo	PD - Active	MCI - Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 25 (68.00%)	21 / 24 (87.50%)	4 / 12 (33.33%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Hot flush			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Orthostatic hypotension			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Supine hypertension			

subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Oedema			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal pain			
subjects affected / exposed	1 / 25 (4.00%)	1 / 24 (4.17%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Psychiatric disorders			
Nervousness			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Anxiety			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Rapid eye movement sleep behaviour disorder			
subjects affected / exposed	2 / 25 (8.00%)	0 / 24 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Agitation			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Confusional state			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0

Depressed mood			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Hallucination, olfactory			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Initial insomnia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Irritability			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Mood altered			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Nightmare			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Restlessness			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Sleep disorder			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Lipase increased			
subjects affected / exposed	1 / 25 (4.00%)	1 / 24 (4.17%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Aspartate aminotransferase increased			

subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Hepatic enzyme increased			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 25 (8.00%)	0 / 24 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Contusion			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Head injury			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Skin laceration			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 25 (12.00%)	5 / 24 (20.83%)	0 / 12 (0.00%)
occurrences (all)	3	5	0
Tremor			
subjects affected / exposed	0 / 25 (0.00%)	6 / 24 (25.00%)	0 / 12 (0.00%)
occurrences (all)	0	6	0
Parkinson's disease			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Restless legs syndrome			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Somnolence			

subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Cognitive disorder			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Essential tremor			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Hypotonia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Lethargy			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Migraine			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Parkinsonian rest tremor			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Vertebral artery aneurysm			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Memory impairment			
subjects affected / exposed	1 / 25 (4.00%)	1 / 24 (4.17%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Eye oedema			

subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Vision blurred			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 25 (4.00%)	1 / 24 (4.17%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
Nausea			
subjects affected / exposed	0 / 25 (0.00%)	2 / 24 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Abdominal pain			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Flatulence			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Gastritis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	2 / 25 (8.00%)	4 / 24 (16.67%)	0 / 12 (0.00%)
occurrences (all)	2	4	0
Skin irritation			
subjects affected / exposed	0 / 25 (0.00%)	3 / 24 (12.50%)	0 / 12 (0.00%)
occurrences (all)	0	3	0
Dermatitis contact			

subjects affected / exposed	1 / 25 (4.00%)	1 / 24 (4.17%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Ecchymosis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Groin pain			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Joint swelling			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal discomfort			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Periarthritis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Infections and infestations			
Gastroenteritis viral			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Herpes zoster			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Tooth infection			

subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Viral infection			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 12 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	MCI - Active	PDD and DLB-Placebo	PDD and DLB - Active
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 13 (53.85%)	3 / 3 (100.00%)	2 / 2 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 13 (7.69%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Hot flush			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Orthostatic hypotension			
subjects affected / exposed	0 / 13 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Supine hypertension			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Malaise			
subjects affected / exposed	1 / 13 (7.69%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0

Oedema			
subjects affected / exposed	0 / 13 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 13 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Nervousness			
subjects affected / exposed	2 / 13 (15.38%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Anxiety			
subjects affected / exposed	2 / 13 (15.38%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Rapid eye movement sleep behaviour disorder			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Agitation			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Confusional state			
subjects affected / exposed	0 / 13 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Depressed mood			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Hallucination, olfactory			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Initial insomnia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Insomnia			

subjects affected / exposed	1 / 13 (7.69%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Irritability			
subjects affected / exposed	0 / 13 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Mood altered			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Nightmare			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Restlessness			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Sleep disorder			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Lipase increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Hepatic enzyme increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Contusion			

subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Head injury			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Skin laceration			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 13 (15.38%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Tremor			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Parkinson's disease			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Restless legs syndrome			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Somnolence			
subjects affected / exposed	1 / 13 (7.69%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Cognitive disorder			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Essential tremor			

subjects affected / exposed	1 / 13 (7.69%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Hypotonia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Lethargy			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Migraine			
subjects affected / exposed	1 / 13 (7.69%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Parkinsonian rest tremor			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Vertebral artery aneurysm			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Memory impairment			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Eye oedema			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Vision blurred			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 13 (7.69%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Nausea			

subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Abdominal pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Gastritis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Stomatitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Skin irritation			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Dermatitis contact			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Ecchymosis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			

Groin pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Joint swelling			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal discomfort			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Periarthritis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Gastroenteritis viral			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Herpes zoster			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Tooth infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Viral infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			

Hypoglycaemia subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 3 (0.00%) 0	0 / 2 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 January 2021	Version 1.1 added assessment of Freezing of Gait (FOG) using the FOG-Q for subjects with PD, PDD, and DLB.
18 March 2021	UK Version 2.0 added exclusion criterion #11 for known hypersentitivity to Spiropent (clenbuterol), Corgard (nadolol) or intolerance to lactose, and added the exclusion criterion for females who were breastfeeding. This amendment added the Columbia Suicide Severity Rating Scale (C-SSRS), including revising exclusion criterion #15 to specify suicidal ideation with actual intent or plan ("Yes" answer on the C-SSRS ideation items 4 or 5).
23 April 2021	UK Version 3.0 deleted use of the BioStamp digital device for activity tracking. A separate AUS/NZ version of the protocol was generated when Australian and New Zealand sites were initiated. The major difference was that AUS/NZ versions included the Sustained Attention Response Task (SART) and the BioStamp activity assessment whereas the UK/EU versions did not.
18 July 2021	UK Version 4.0 (Amendment 4) and AUS/NZ Version 3.0 (Amendment 3) added neuromelanin-sensitive MRI as an optional procedure based on imaging capabilities) for an added exploratory objective to characterize locus coeruleus volume and contrast ratio.
23 August 2021	UK Version 5.0 (Amendment 5) and AUS/NZ Version 4.0 (Amendment 4) added the verbal fluency test (alphabet and category) and added the Stop Signal Task to the CANTAB assessments. The UK version, but not the AUS/NZ version, deleted the SART.
19 October 2021	UK/EU Version 6.0 (Amendment 6) and AUS/NZ Version 5.0 (Amendment 5) included 3 main changes to the protocol. • HADS was deleted as an inclusion criterion but kept as an outcome measure. HADS led to a high screen failure rate. The criterion was intended to select subjects with a score cutoff of very mild depression but it was found that the FERT was sensitive even in subjects who did not have depressed mood so the criterion was not necessary. • APOE4 genotyping was added as an exploratory endpoint. The epsilon4 allele of the apolipoprotein E gene (APOE4) has been consistently associated with cognitive function in Alzheimer's disease and recently has also been found to be an important predictor of cognitive function in Parkinson's disease across multiple domains. Therefore, it would be important to ascertain whether the subjects in the study carry this allele as it is an important covariate to consider in the cognition data analysis. • The amendment allowed for the washout period between Treatment Periods 1 and 2 to be extended with Medical Monitor approval to accommodate holiday closure schedules at the clinical study centers as well as to accommodate subject availability.

18 February 2022	UK/EU Version 7.0 (Amendment 7) and AUS/NZ Version 6.0 (Amendment 6) were the final protocol versions and included 2 main changes: • Exclusion criterion #9 for subjects with a calculated creatinine clearance of ≤70 mL/min according to the Cockcroft-Gault equation was updated to ≤60 mL/min. A substantial number of potential patients in the study were older than 60 years of age and therefore were expected to have a GFR in the range of 60 to 70 mL/min so the criterion was modified to take that into account. This exclusion criterion was intended to ensure that patients who were medically ill with poor renal function were excluded from the trial. Subjects who were deemed to have normal to mildly impaired renal function based on either physical examination and/or laboratory values were eligible if their eGFR values were age-appropriate and not below 60 mL/min. • Wording was revised to clarify that the inclusion/exclusion criteria were to be evaluated only at Screening, Lead-In, and pre-dose on Day 1 of Treatment Period 1 (and not re-evaluated pre-dose on Day 1 of Treatment Period 2).

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.

Only the primary endpoint data with statistically significant treatment differences have been presented here. (PD only due to small sample size). The number of AE events has been assumed to equal the number of subjects experiencing the event term

Notes: