Clinical trial results:
A Randomised, Double-Blind, Multi-centre, Active Treatment, Extension and Safety Study for Patients with Idiopathic Parkinson's Disease (PD) Who Previously Completed the CDNF/DDS Main Study HP-CD-CL-2002.

Summary

EudraCT number	2018-000346-19
Trial protocol	SE FI
Global end of trial date	31 August 2020

Results information

Result version number	v1 (current)
This version publication date	22 May 2021
First version publication date	22 May 2021

Trial information

Trial identification

Sponsor protocol code	HP-CD-CL-2003

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Herantis Pharma Plc
Sponsor organisation address	Bertel Jungin Aukio 1, FI-02600 , Espoo, Finland,
Public contact	Project Manager, Herantis Pharma Plc, dpo@herantis.com
Scientific contact	Project Manager, Herantis Pharma Plc, dpo@herantis.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	31 August 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2020
Global end of trial reached?	Yes
Global end of trial date	31 August 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the safety and tolerability of
– the IMP administered as long-term monthly intermittent bilateral intraputamenal CDNF infusions, and,
– the investigational medical device for the intended long-term use and within the intended patient population during infusions.

Protection of trial subjects:

All subjects received written and verbal information regarding the study. The given information emphasised that participation in the study was voluntary and that the subject could withdraw from the study at any time and for any reason. All subjects were given the opportunity to ask questions about the study and were given sufficient time to decide whether to participate in the study.
Before any study-related procedures, the informed consent form was signed and personally dated by the subject (no patient needed a legally acceptable representative or witness) and by the person who conducted the informed consent discussion.
The consent included information that data was recorded, collected, processed and could be transferred to European Economic Area (EEA) or non-EEA countries. In accordance with the European Union Data Protection Directive (95/46/EC), the data did not identify any persons taking part in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 July 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	10 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 8
Country: Number of subjects enrolled	Finland: 7
Worldwide total number of subjects	15
EEA total number of subjects	15

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	10
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients who underwent surgery in the Main Protocol Phase study (CDNF/DDS Main Study HP-CD-CL-2002) for implantation of the four catheters of the Drug Delivery System (DDS) into each putamen (i.e., 2 catheters in each putamen).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	400 µg (mid dose, 200 µg/putamen)

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Cerebral Dopamine Neurotrophic Factor (CDNF)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intracerebral use

Dosage and administration details:

4x 400 microlitres of CDNF solution for infusion was infused via an implanted drug delivery system. The IMP was flushed out by infusing 4x 80 microlitres of artificial cerebrospinal fluid at the end of each infusion

Arm title	1200 µg (high dose, 600 µg/putamen)

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Cerebral Dopamine Neurotrophic Factor (CDNF)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intracerebral use

Dosage and administration details:

4x 400 microlitres of CDNF solution for infusion was infused via an implanted drug delivery system. The IMP was flushed out by infusing 4x 80 microlitres of artificial cerebrospinal fluid at the end of each infusion.

Number of subjects in period 1	400 µg (mid dose, 200 µg/putamen)	1200 µg (high dose, 600 µg/putamen)
Started	8	7
Completed	8	6
Not completed	0	1
Consent withdrawn by subject	-	1

Baseline characteristics

Reporting groups	
Reporting group title	400 µg (mid dose, 200 µg/putamen)
Reporting group description: -	
Reporting group title	1200 µg (high dose, 600 µg/putamen)
Reporting group description: -	

Reporting group values	400 µg (mid dose, 200 µg/putamen)	1200 µg (high dose, 600 µg/putamen)	Total
Number of subjects	8	7	15
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)	5	5	10
From 65-84 years	3	2	5
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	63.6	61.9	
standard deviation	± 7.8	± 8.4	-
Gender categorical Units: Subjects			
Female	4	1	5
Male	4	6	10
Duration of disease (PD motor symptoms) Units: Subjects			
6 years	1	0	1
8 years	0	1	1
9 years	1	1	2
10 years	2	2	4
11 years	1	0	1
12 years	0	1	1
13 years	1	1	2
14 years	2	1	3
Hoehn and Yahr staging Units: Subjects			
staging 2	4	3	7
staging 2.5	2	2	4
staging 3	2	2	4

End points

End points reporting groups

Reporting group title	400 µg (mid dose, 200 µg/putamen)
Reporting group description: -	
Reporting group title	1200 µg (high dose, 600 µg/putamen)
Reporting group description: -	

Primary: ECG

End point title	ECG[1]
End point description:	
End point type	Primary
End point timeframe:	

ECGs were recorded at Screening (Visit 18, Week 24; i.e., Visit 17 in the Main Protocol Phase), at interim visit (Visit 22, Week 37), and at End of Extension Phase (Visit 26, Week 49), for screening of coronary heart disease.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The primary endpoints were assessments of safety and no statistical testing was performed.

End point values	400 µg (mid dose, 200 µg/putamen)	1200 µg (high dose, 600 µg/putamen)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: unit(s)				
arithmetic mean (standard deviation)				
PR interval (msec) - Visit 17 (Week 24) Baseline	175.25 (± 31.33)	156.29 (± 14.30)		
PR interval (msec) - Visit 26 (Week 49)	170.00 (± 35.89)	150.80 (± 13.46)		
QRS duration (msec) - Visit 17 (Week 24) Baseline	96.50 (± 24.79)	90.57 (± 9.36)		
QRS duration (msec) - Visit 26 (Week 49)	96.25 (± 25.24)	86.80 (± 11.19)		
QT (msec) - Visit 17 (Week 24) Baseline	384.75 (± 48.01)	407.14 (± 16.85)		
QT (msec) - Visit 26 (Week 49)	390.00 (± 42.24)	394.80 (± 17.12)		
QTc (msec) - Visit 17 (Week 24) Baseline	419.75 (± 24.82)	419.00 (± 21.31)		
QTc (msec) - Visit 26 (Week 49)	416.63 (± 34.18)	426.60 (± 20.22)		
Ventricular rate (bpm) - Visit 17 (Week 24)	73.00 (± 11.92)	64.29 (± 9.34)		
Ventricular rate (bpm) - Visit 26 (Week 49)	69.63 (± 12.47)	70.80 (± 10.64)		

Statistical analyses

No statistical analyses for this end point

Primary: Beck Depression Inventory II (BDI-II)

End point title	Beck Depression Inventory II (BDI-II)[2]

End point description:

End point type	Primary

End point timeframe:

The self-administered questionnaire BDI was completed by the patients at screening (Visit 17, Week 24), at interim visit (Visit 22, Week 37), and at the End of Extension Phase (Visit 26, Week 49).

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The primary endpoints were assessments of safety and no statistical testing was performed.

End point values	400 µg (mid dose, 200 µg/putamen)	1200 µg (high dose, 600 µg/putamen)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: unit(s)				
arithmetic mean (standard deviation)				
Visit 17 (Week 24) - baseline	8.63 (± 3.93)	9.00 (± 7.66)		
Visit 26 (Week 49)	9.13 (± 4.76)	8.17 (± 6.31)		

Statistical analyses

No statistical analyses for this end point

Primary: Questionnaire for Impulsive-Compulsive Disorders in Parkinson’s Disease Rating Scale (QUIP-RS)

End point title	Questionnaire for Impulsive-Compulsive Disorders in Parkinson’s Disease Rating Scale (QUIP-RS)[3]

End point description:

End point type	Primary

End point timeframe:

The self-administered questionnaire QUIP-RS was completed by the patients at screening (Visit 17, Week 24), at interim visit (Visit 22, Week 37), and at the End of Extension Phase (Visit 26, Week 49).

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The primary endpoints were assessments of safety and no statistical testing was performed.

End point values	400 µg (mid dose, 200 µg/putamen)	1200 µg (high dose, 600 µg/putamen)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: unit(s)				
arithmetic mean (standard deviation)				
Total ICD Score (A-D) - Visit 17 (Week 24)	1.88 (± 2.47)	3.00 (± 5.92)		
Total ICD Score (A-D) - Visit 26 (Week 49)	1.88 (± 3.72)	1.50 (± 2.07)		
Total QUIP-RS Score (A-G) - Visit 17 (Week 24)	3.88 (± 4.64)	3.71 (± 6.95)		
Total QUIP-RS Score (A-G) - Visit 26 (Week 49)	3.75 (± 7.03)	3.00 (± 4.00)		

Statistical analyses

No statistical analyses for this end point

Primary: Montreal Cognitive Assessment (MoCA)

End point title	Montreal Cognitive Assessment (MoCA)[4]

End point description:

End point type	Primary

End point timeframe:

The MoCA was completed by the patients at screening (Visit 17, Week 24), at interim visit (Visit 22, Week 37), and at the End of Extension Phase (Visit 26, Week 49).

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The primary endpoints were assessments of safety and no statistical testing was performed.

End point values	400 µg (mid dose, 200 µg/putamen)	1200 µg (high dose, 600 µg/putamen)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: unit(s)				
arithmetic mean (standard deviation)				
Visit 17 (Week 24) - baseline	28.88 (± 0.64)	28.00 (± 2.83)		
Visit 26 (Week 49)	29.25 (± 0.89)	26.80 (± 5.54)		

Statistical analyses

No statistical analyses for this end point

Primary: Physical Examination - abnormal with clinical relevance

End point title	Physical Examination - abnormal with clinical relevance[5]

End point description:

Physical examination is the process of evaluating objective anatomic findings through the use of observation, palpation, percussion, and auscultation. The following body systems were examined: General Inspection/Upper extremities; head, eyes, ears, nose, throat, and superficial cervical lymph nodes; neck, shoulders, back; chest and lungs; cardiovascular; abdomen; lower extremities

Baseline is defined as the Visit 17 (Week 24) assessment from the HP-CD-CL-2002 Study

End point type	Primary

End point timeframe:

A physical examination was performed at Screening (Visit 18, Week 24; i.e., Visit 17 in the Main Protocol Phase), and at End of Extension Phase (Visit 26, Week 49).

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The primary endpoints were assessments of safety and no statistical testing was performed.

End point values	400 µg (mid dose, 200 µg/putamen)	1200 µg (high dose, 600 µg/putamen)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: unit(s)				
number (not applicable)				
Abdomen- baseline	0	0		
Abdomen - Visit 26 (Week 49)	0	0		
Cardiovascular - baseline	0	0		
Cardiovascular - Visit 26 (Week 49)	0	0		
Chest and lungs - baseline	0	0		
Chest and lungs - Visit 26 (Week 49)	0	0		
General inspection / Upper extremities - baseline	1	1		
General inspection / Upper extremities - Visit 26	0	1		
Head,eyes,ears,nose,throat,lymph nodes - baseline	0	0		
Head,eyes,ears,nose,throat,lymph nodes - Visit 26	1	0		
Lower extremities - baseline	0	1		
Lower extremities - Visit 26 (Week 49)	0	0		
Neck, shoulders and back - baseline	1	1		
Neck, shoulders and back - Visit 26 (Week 49)	1	1		
Motor function - baseline	4	5		
Motor function - Visit 26 (Week 49)	7	5		
Sensory function - baseline	1	0		
Sensory function - Visit 26 (Week 49)	1	1		
Cranial nerve function - baseline	0	1		
Cranial nerve function - Visit 26 (Week 49)	0	0		
Cortical functions - baseline	0	0		
Cortical functions - Visit 26 (Week 49)	0	1		

Statistical analyses

No statistical analyses for this end point

Primary: Vital signs

End point title	Vital signs[6]

End point description:

End point type	Primary

End point timeframe:

Vital signs were assessed at Screening (Visit 18, Week 24; i.e., Visit 17 in the Main Protocol Phase), and at End of Extension Phase (Visit 26, Week 49).

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The primary endpoints were assessments of safety and no statistical testing was performed.

End point values	400 µg (mid dose, 200 µg/putamen)	1200 µg (high dose, 600 µg/putamen)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: unit(s)				
arithmetic mean (standard deviation)				
BMI (kg/m2)- Visit 17 (Week 24) baseline	24.23 (± 3.86)	24.29 (± 3.77)		
BMI (kg/m2) - Visit 26 (Week 49)	24.22 (± 3.64)	23.86 (± 4.05)		
Diastolic blood pressure (mmHg) - Visit 17	80.13 (± 7.75)	76.00 (± 8.23)		
Diastolic blood pressure (mmHg) - Visit 26	81.50 (± 7.50)	70.20 (± 13.46)		
Height (cm) - Visit 17 (Week 24) baseline	168.38 (± 8.11)	179.57 (± 7.18)		
Height (cm) - Visit 26 (Week 49)	168.13 (± 8.31)	181.20 (± 7.85)		
Pulse rate (bpm) - Visit 19 (Week 25)	70.13 (± 14.72)	64.29 (± 5.94)		
Pulse rate (bpm) - Visit 26 (Week 49)	73.00 (± 10.80)	76.00 (± 8.57)		
Systolic blood pressure (mmHg) - Visit 17	129.75 (± 16.54)	137.86 (± 27.87)		
Systolic blood pressure (mmHg) - Visit 26	126.25 (± 12.15)	127.80 (± 21.81)		
Temperature (C) - Visit 17 (Week 24) baseline	36.56 (± 0.44)	36.54 (± 0.37)		
Temperature (C) - Visit 26 (Week 49)	36.75 (± 0.23)	36.64 (± 0.55)		
Weight (kg) - Visit 17 (Week 24) baseline	68.39 (± 9.11)	77.94 (± 10.28)		
Weight (kg) - Visit 26 (Week 49)	68.14 (± 8.55)	77.98 (± 11.73)		

Statistical analyses

No statistical analyses for this end point

Primary: Laboratory Variables - Abnormal with clinical relevance

End point title	Laboratory Variables - Abnormal with clinical relevance[7]

End point description:

There were no abnormal with clinical relevance laboratory values at baseline (i.e., at start of the Extension Phase at Week 24) nor at Visit 26 (Week 49, End of study).

Clinical laboratory variables included:
- Clinical chemistry (Alanine transaminase, Alkaline phosphatase, Aspartate transaminase, Bilirubin, Calcium, Creatine kinase, Creatinine and eGFR, Potassium, Sodium, IgG, Albumin, Urea)
- Hematology analysis (Activated partial thromboplastin time (aPTT), International Normalized Ratio (INR), Hematocrit, Hemoglobin
Leukocyte differential count, Mean cell hemoglobin of RBC (MCH), Mean cell volume of RBC (MCV), Platelet count, Red blood cell count (RBC), White blood cell count (WBC)
- Urinalysis (Blood (alternative: erythrocytes), Glucose, Ketones, Leukocytes, Nitrites, pH, Protein)

End point type	Primary

End point timeframe:

Laboratory variables were evaluated from the Extension Phase start (Visit 18, Week 24) to the end of treatment evaluation (Visit 26, Week 49).

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The primary endpoints were assessments of safety and no statistical testing was performed.

End point values	400 µg (mid dose, 200 µg/putamen)	1200 µg (high dose, 600 µg/putamen)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: number				
Laboratory Variable - Visit 17 (Week 24) baseline	0	0		
Laboratory Variable - Visit 26 (Week 49)	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Anti-CDNF Antibodies - Abnormal

End point title	Anti-CDNF Antibodies - Abnormal[8]

End point description:

The samples from Visit 26 (Week 49) were analysed for anti-CDNF antibody titre and CDNF levels in serum, unless Visit 26 samples were not collected and further samples were analysed in case of a positive finding.

End point type	Primary

End point timeframe:

Serum samples for CDNF were collected at Screening, prior to infusion of the 8th through to the 12th treatment dosing and at End of Extension Phase (Visit 26, Week 49).

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The primary endpoints were assessments of safety and no statistical testing was performed.

End point values	400 µg (mid dose, 200 µg/putamen)	1200 µg (high dose, 600 µg/putamen)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: number				
Visit 21 (Week 33) - negative	0	1		
Visit 21 (Week 33) - positive	0	0		
Visit 22 (Week 37) - negative	1	0		
Visit 22 (Week 37) - positive	0	0		
Visit 23 (Week 41) - negative	1	0		
Visit 23 (Week 41) - positive	0	0		
Visit 24 (Week 45) - negative	1	1		
Visit 24 (Week 45) - positive	0	0		
Visit 26 (Week 49) - negative	7	5		
Visit 26 (Week 49) - positive	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Parkinson disease motor and non-motor symptoms by UPDRS part I-IV total scores and overall total scores

End point title	Parkinson disease motor and non-motor symptoms by UPDRS part I-IV total scores and overall total scores

End point description:

Placebo patients included at visit 9 (Week -1) were re-randomized for active treatment after the end of the main study.

End point type	Secondary

End point timeframe:

From baseline in the Main Protocol Phase (Week -1), at Extension Phase start (Week 24), after three months (Week 37), and at end of treatment evaluation (Week 49).

End point values	400 µg (mid dose, 200 µg/putamen)	1200 µg (high dose, 600 µg/putamen)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: score				
arithmetic mean (standard deviation)				
part I - Visit 9 (Week 1)	1.00 (± 1.41)	2.00 (± 2.08)		
part I - Visit 17 (Week 24)	0.88 (± 0.99)	1.86 (± 1.77)		
part I - Visit 26 (Week 49)	0.75 (± 0.71)	2.67 (± 1.97)		
part II - Visit 9 (Week 1)	8.13 (± 6.31)	10.00 (± 4.16)		
part II - Visit 17 (Week 24)	8.38 (± 3.74)	12.14 (± 4.45)		
part II - Visit 26 (Week 49)	8.63 (± 5.66)	10.50 (± 5.68)		
part III - Visit 9 (Week 1)	28.75 (± 9.50)	32.43 (± 6.53)		
part III - Visit 17 (Week 24)	26.50 (± 5.76)	31.00 (± 10.23)		

part III - Visit 26 (Week 49)	26.00 (± 12.85)	31.00 (± 13.06)		
part IV - Visit 9 (Week 1)	6.25 (± 3.15)	5.86 (± 2.34)		
part IV - Visit 17 (Week 24)	6.88 (± 2.90)	5.14 (± 1.95)		
part IV - Visit 26 (Week 49)	6.63 (± 2.33)	5.50 (± 1.38)		
UPDRS Total - Visit 9 (Week 1)	44.13 (± 15.57)	50.29 (± 11.10)		
UPDRS Total - Visit 17 (Week 24)	42.63 (± 9.02)	50.14 (± 14.35)		
UPDRS Total - Visit 26 (Week 49)	42.00 (± 18.17)	47.40 (± 15.36)		

Statistical analyses

No statistical analyses for this end point

Secondary: Timed Up and Go (TUG) values

End point title	Timed Up and Go (TUG) values

End point description:

Placebo patients included at visit 9 (Week -1) were re-randomized for active treatment after the end of the main study.

End point type	Secondary

End point timeframe:

From baseline in the Main Protocol Phase (Week -1), at Extension Phase start (Week 24), after three months (Week 37), and at end of treatment evaluation (Week 49).

End point values	400 µg (mid dose, 200 µg/putamen)	1200 µg (high dose, 600 µg/putamen)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: seconds				
arithmetic mean (standard deviation)				
Visit 9 (Week -1) Baseline	12.96 (± 5.73)	9.74 (± 2.87)		
Visit 17 (Week 24)	16.72 (± 19.63)	10.95 (± 5.20)		
Visit 26 (Week 49)	19.03 (± 27.16)	9.15 (± 2.96)		

Statistical analyses

No statistical analyses for this end point

Secondary: Functional status by home diary score - OFF time

End point title	Functional status by home diary score - OFF time

End point description:

End point type	Secondary

End point timeframe:

From first dosing (Week 0), at Extension Phase start (Week 24), and at end of treatment evaluation (Week 49).

End point values	400 µg (mid dose, 200 µg/putamen)	1200 µg (high dose, 600 µg/putamen)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: hours				
arithmetic mean (standard deviation)				
Visit 10 (Week 0) First Dosing	5.58 (± 2.48)	4.20 (± 2.47)		
Visit 17 (Week 24)	5.23 (± 2.03)	4.54 (± 1.38)		
Visit 26 (Week 49)	4.24 (± 3.30)	3.54 (± 2.42)		

Statistical analyses

No statistical analyses for this end point

Secondary: Functional status by home diary score - ON without dyskinesias

End point title	Functional status by home diary score - ON without dyskinesias

End point description:

End point type	Secondary

End point timeframe:

From first dosing (Week 0), at Extension Phase start (Week 24/Visit 18), and at end of treatment evaluation (Week 49).

End point values	400 µg (mid dose, 200 µg/putamen)	1200 µg (high dose, 600 µg/putamen)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: hours				
arithmetic mean (standard deviation)				
Visit 10 (Week 0) First Dosing	9.11 (± 4.68)	9.20 (± 1.93)		
Visit 17 (Week 24)	8.48 (± 1.93)	9.89 (± 2.51)		
Visit 26 (Week 49)	9.35 (± 1.59)	11.53 (± 3.25)		

Statistical analyses

No statistical analyses for this end point

Secondary: Functional status by home diary score - ON with non-troublesome dyskinesias

End point title	Functional status by home diary score - ON with non-troublesome dyskinesias

End point description:

End point type	Secondary

End point timeframe:

From first dosing (Week 0), at Extension Phase start (Week 24), and at end of treatment evaluation (Week 49).

End point values	400 µg (mid dose, 200 µg/putamen)	1200 µg (high dose, 600 µg/putamen)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: hours				
arithmetic mean (standard deviation)				
Visit 10 (Week 0) First Dosing	2.82 (± 3.60)	1.60 (± 2.15)		
Visit 17 (Week 24)	3.36 (± 3.05)	0.74 (± 1.12)		
Visit 26 (Week 49)	2.91 (± 2.28)	0.00 (± 0.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Functional status by home diary score - ON with troublesome dyskinesias

End point title	Functional status by home diary score - ON with troublesome dyskinesias

End point description:

End point type	Secondary

End point timeframe:

From first dosing (Week 0), at Extension Phase start (Week 24), and at end of treatment evaluation (Week 49).

End point values	400 µg (mid dose, 200 µg/putamen)	1200 µg (high dose, 600 µg/putamen)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: hours				
arithmetic mean (standard deviation)				
Visit 10 (Week 0) First Dosing	0.31 (± 0.58)	0.52 (± 0.97)		
Visit 17 (Week 24)	0.25 (± 0.42)	0.07 (± 0.19)		
Visit 26 (Week 49)	0.44 (± 0.62)	0.00 (± 0.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Functional status by home diary score - Bad time

End point title	Functional status by home diary score - Bad time

End point description:

End point type	Secondary

End point timeframe:

From first dosing (Week 0), at Extension Phase start (Week 24), and at end of treatment evaluation (Week 49).

End point values	400 µg (mid dose, 200 µg/putamen)	1200 µg (high dose, 600 µg/putamen)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: hours				
arithmetic mean (standard deviation)				
Visit 10 (Week 0) First Dosing	5.90 (± 2.15)	4.72 (± 2.20)		
Visit 17 (Week 24)	5.48 (± 1.90)	4.61 (± 1.35)		
Visit 26 (Week 49)	4.68 (± 3.20)	3.54 (± 2.42)		

Statistical analyses

No statistical analyses for this end point

Secondary: Functional status by home diary score - Good time

End point title	Functional status by home diary score - Good time

End point description:

End point type	Secondary

End point timeframe:

From first dosing (Week 0), at Extension Phase start (Week 24), and at end of treatment evaluation (Week 49).

End point values	400 µg (mid dose, 200 µg/putamen)	1200 µg (high dose, 600 µg/putamen)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: hours				
arithmetic mean (standard deviation)				
Visit 10 (Week 0) First Dosing	11.93 (± 2.92)	10.80 (± 1.63)		
Visit 17 (Week 24)	11.83 (± 1.95)	10.63 (± 2.27)		
Visit 26 (Week 49)	12.26 (± 2.32)	11.53 (± 3.25)		

Statistical analyses

No statistical analyses for this end point

Secondary: Parkinson disease questionnaire - PDQ-39 total score

End point title	Parkinson disease questionnaire - PDQ-39 total score

End point description:

End point type	Secondary

End point timeframe:

From baseline in the Main Protocol Phase (Week -1), at Extension Phase start (Week 24), after three months (Week 37), and at end of treatment evaluation (Week 49).

End point values	400 µg (mid dose, 200 µg/putamen)	1200 µg (high dose, 600 µg/putamen)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: score				
arithmetic mean (standard deviation)				
Visit 9 (Week -1) Baseline	25.05 (± 12.30)	19.82 (± 9.80)		
Visit 17 (Week 24)	24.25 (± 12.41)	27.68 (± 9.92)		
Visit 22 (Week 37)	23.44 (± 13.18)	20.92 (± 14.86)		
Visit 26 (Week 49)	23.26 (± 13.42)	22.97 (± 12.99)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression

End point title	Clinical Global Impression

End point description:

End point type	Secondary

End point timeframe:

From baseline in the Main Protocol Phase (Week -1), at Extension Phase start (Week 24), and at end of treatment evaluation (Week 49).

End point values	400 µg (mid dose, 200 µg/putamen)	1200 µg (high dose, 600 µg/putamen)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: score				
arithmetic mean (standard deviation)				
Visit 9 (Week -1) Baseline	1.00 (± 0.00)	2.00 (± 1.73)		
Visit 17 (Week 24)	3.50 (± 0.76)	4.57 (± 0.53)		
Visit 26 (Week 49)	3.50 (± 0.93)	4.33 (± 0.82)		

Statistical analyses

No statistical analyses for this end point

Secondary: Patency of drug delivery system

End point title	Patency of drug delivery system

End point description:

End point type	Secondary

End point timeframe:

From first dosing in the Extension Phase (Week 25) until final treatment infusion (Week 45).

End point values	400 µg (mid dose, 200 µg/putamen)	1200 µg (high dose, 600 µg/putamen)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: number of lines				
All infusions constantly <590 mmHg	192	156		

Statistical analyses

No statistical analyses for this end point

Secondary: Port Stability

End point title	Port Stability

End point description:

Number of cessation of infusions the inability to secure an external system due to looseness of port (Looseness of port) and the need for surgical removal of the transcutaneous port or surgical intervention to stabilise the port (Surgical intervention to stabilise the port).

End point type	Secondary

End point timeframe:

Assessed at every treatment dosing visit during the Extension Phase of the study, i.e., Visit 19 (Week 25) through Visit 24 (Week 45).

End point values	400 µg (mid dose, 200 µg/putamen)	1200 µg (high dose, 600 µg/putamen)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: number of events				
Looseness of port	0	0		
Surgical intervention to stabilise port	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Entire observation period (i.e., from Week 24 to Week 49) and on the days of infusion on Weeks 25, 29, 33, 37, 41, and 45, and during the entire study period outside of infusion.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	400 µg (mid dose, 200 µg/putamen)
Reporting group description: -	
Reporting group title	1200 µg (high dose, 600 µg/putamen)

Reporting group description: -

Serious adverse events	400 µg (mid dose, 200 µg/putamen)	1200 µg (high dose, 600 µg/putamen)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
Infection	Additional description: Infection without known location, unspecified		
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	400 µg (mid dose, 200 µg/putamen)	1200 µg (high dose, 600 µg/putamen)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)	7 / 7 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Elastofibroma			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			

Hypertension			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Implant site pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Implant site reaction			
subjects affected / exposed	1 / 8 (12.50%)	3 / 7 (42.86%)	
occurrences (all)	1	5	
Pyrexia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Chest pain			
subjects affected / exposed	1 / 8 (12.50%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Fatigue			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Hyperthermia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Dysphonia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Psychiatric disorders			
Adjustment disorder			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Depression			
subjects affected / exposed	1 / 8 (12.50%)	2 / 7 (28.57%)	
occurrences (all)	1	2	

Hallucination			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Nightmare			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Blood bilirubin increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Blood urea increased			
subjects affected / exposed	1 / 8 (12.50%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Nitrite urine present			
subjects affected / exposed	1 / 8 (12.50%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Weight decreased			
subjects affected / exposed	1 / 8 (12.50%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Injury, poisoning and procedural complications			
Tendon rupture			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Tooth fracture			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Wound			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	

Nervous system disorders			
Cerebral gas embolism			
subjects affected / exposed	2 / 8 (25.00%)	2 / 7 (28.57%)	
occurrences (all)	3	3	
Cerebral microhaemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	3 / 8 (37.50%)	5 / 7 (71.43%)	
occurrences (all)	4	9	
Somnolence			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Carpal tunnel syndrome			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Parkinson's disease			
subjects affected / exposed	1 / 8 (12.50%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Pleurothotonus			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Sensory disturbance			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Tremor			
subjects affected / exposed	0 / 8 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	0	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	2	
Ear and labyrinth disorders			

Hypoacusis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Photokeratitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Vision blurred			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Dry mouth			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Haemorrhoids			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Skin reaction			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Blister			

subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Livedo reticularis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Leukocyturia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Muscle spasms			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	2 / 8 (25.00%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Pain in jaw			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Genital herpes			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Implant site infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Upper respiratory tract infection			

subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 2	1 / 7 (14.29%) 1	
Urinary tract infection subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	1 / 7 (14.29%) 1	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 7 (14.29%) 1	
Folate deficiency subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 7 (14.29%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 September 2019	Protocol Amendment #1: - Additional exploratory analyses were added for already collected CSF samples in order to analyse changes in the aggregation propensity of α-synuclein in CSF, measure level of distribution of CDNF, and screen for proteomic biomarker. A saliva sample was collected for genome sequence testing for correlations with other endpoints; - Study period: The study period was prolonged to approximately 9 months;- PD medication prior to DAT-PET scanning: recommendation not to be off levodopa medication for 10 hours, and not off dopamine agonist or MAO-B inhibitors for 24 hours. - Deletion of procedures at Visit 19 (Week 25): At Visit 19, the following assessments to be originally performed prior to the seventh (7th) treatment infusion, were deleted: serum sample for anti-CDNF antibody, patient PD diary and PKG data collection. - Change in time window for MRI scan after infusion: The original MRI post-infusion protocol was updated to commence the MRI post-infusion within 60 minutes after the end of treatment infusion. - Silicon cap wearing regime: The new regimen instructed patients to wear the port cap immediately after surgery and, after dressings are removed, on a 12-hours on 12-hours off basis, wearing it overnight. - Explantation procedures after study discontinuation; - Change of forbidden concomitant medications; - Clarification of the explantation options; - Update of risk mitigation section; -Port assessment: Infusion should be postponed if there is purulent exudate when pressure is applied to the area around the port or the application set does not easily attach to the port; - Reporting of device deficiencies; - UPDRS off-score rating: The CSP was modified to clarify that the UPDRS OFF-score (part III motor part) rating for each individual patient should be performed by the same Investigator to reduce the effects of interrater variability.
07 April 2020	Protocol Amendment #2: - Visit window widened: Due to the COVID-19 outbreak, the hospital or the national authorities could lay upon restriction for patients travelling to or visiting the clinical sites (both the neurology clinics and PET centres). To allow some flexibility in scheduling the visits according to the protocol, the visit window for the last three infusion visits (Visits 22, 23, and 24) was widened from originally ±5 days to ±14 days. Based on the duration of the pharmacological effect observed in preclinical studies, the change in the visit window was deemed to not affect the outcome of the treatment. For the safety of the patient and to allow flexibility in the protocol, the DAT-PET visit (Visit 25) could be postponed until it was safe for the patient to visit the PET centre. Regardless of when the visit could be performed, the End of Study visit in the Extension Phase (Visit 26) was to be scheduled after Visit 25. Under these special circumstances, additional unscheduled visits could be arranged as remote (phone) visits if the postponement of Visit 25 and Visit 26 would take more than two months. - Cross-contamination safety precautions: During the COVID-19 outbreak, special precautions to reduce the risk of cross-contamination were to be considered. For that reason, and as the PKG devices and wrist bands could be used by several patients, the wristbands had to be sanitized at the clinical study site every time the device was collected and before it was sent out to the next patient.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported