Clinical trial results:
A Phase I-II, Randomised, Double-Blind, Placebo Controlled, Safety and Tolerability Study of Intermittent Bilateral Intraputamenal Cerebral Dopamine Neurotrophic Factor (CDNF) Infusions Administered via an Investigational Drug Delivery System to Patients with Idiopathic Parkinson's Disease (PD) of Moderate Severity.

Summary

EudraCT number	2015-004175-73
Trial protocol	FI
Global end of trial date	19 December 2019

Results information

Result version number	v1 (current)
This version publication date	05 May 2021
First version publication date	05 May 2021

Trial information

Trial identification

Sponsor protocol code	HP-CD-CL-2002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03295786
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Herantis Pharma Plc
Sponsor organisation address	Bertel Jungin Aukio 1, Espoo, Finland, 02600
Public contact	Project Director, Herantis Pharma Plc, 358 401585669, sigrid.booms@herantis.com
Scientific contact	Project Director, Herantis Pharma Plc, 358 401585669, sigrid.booms@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	18 November 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 December 2019
Global end of trial reached?	Yes
Global end of trial date	19 December 2019
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 investigational medicinal product administered as monthly intermittent bilateral intraputamenal CDNF infusions, and,
- the investigational medical device for the intended use and within the intended patient population during device implantation and follow-up, including the test infusion procedure.

To demonstrate the accuracy of investigational device as implantation accuracy to the target site during implantation surgery.

Protection of trial subjects:

The evening before any off-medication assessments, patients were to stay overnight at the clinic or patient-hotel for safety reasons. In some cases the patient was allowed to stay overnight at home without medication, if their caregiver could bring the patient to the clinic the next morning.
Patients were allowed to take their normal anti-Parkinson medication prior to DAT-PET imaging, to prevent them from having painful cramps while in the scanner.
After the first and second treatment dosing, patients were monitored for safety for 24 hours. After any subsequent treatment dosing, patients were advised not to drive or operate machines for 24 hours.

Background therapy:

Patients were allowed to continue to use their anti-Parkinson's medication as prescribed.

Evidence for comparator: -

Actual start date of recruitment	01 September 2017
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	Sweden: 10
Country: Number of subjects enrolled	Finland: 7
Worldwide total number of subjects	17
EEA total number of subjects	17

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)	11
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient first visit of the study was in Sweden on 03 October 2017.
The first patient first visit in Finland was on 20 February 2018, after the DSMB recommended to open two more sites for recruitment and surgery in Finland and Sweden.
The last patient recruited in Sweden was on 19 November 2018 and in Finland on 27 February 2019.

Pre-assignment

Screening details:

Altogether 26 patients were screened of which 19 patients were eligible, but two patients withdrew their consent prior to surgery and randomisation. Three patients met some of the psychiatric exclusion criteria, and three other patients had medical conditions making them unsuitable for inclusion. One patient's motor state was not advanced enough.

Period 1

Period 1 title	Screening
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

patients would be randomised after surgery, meeting the post-surgery inclusion criteria and none of the exclusion criteria.

Arms

Arm title	Eligibility screening

Arm description:

Screening for eligibility to undergo surgery for implantation of drug delivery system.

Arm type	Eligibility screening

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Eligibility screening
Started	17
Completed	17

Period 2

Period 2 title	Surgery, Baseline and Treatment period
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject, Monitor, Data analyst, Carer, Assessor

Arms	
Are arms mutually exclusive?	Yes
Arm title	Vehicle

Arm description:

artificial cerebrospinal fluid is used as the vehicle.

Arm type	Placebo
Investigational medicinal product name	artificial cerebrospinal fluid
Investigational medicinal product code	
Other name	vehicle
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intracerebral use

Dosage and administration details:

4x 480 micro litre was infused intracerebrally via an implanted drug delivery system.

Arm title	CDNF mid-dose

Arm description:

CDNF formulated in artificial cerebrospinal fluid to a final concentration of 0.25 mg/mL

Arm type	Experimental
Investigational medicinal product name	CDNF
Investigational medicinal product code	CDNF
Other name	rhCDNF
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 infusion via an implanted drug delivery system. The IMP was flushed out by infusing 4x 80 micrometers of artificial cerebrospinal fluid at the end of each infusion.

Arm title	CDNF high-dose

Arm description:

CDNF formulated in artificial cerebrospinal fluid to a final concentration of 0.75 mg/mL.

Arm type	Experimental
Investigational medicinal product name	CDNF
Investigational medicinal product code	CDNF
Other name	rhCDNF
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 infusion via an implanted drug delivery system. The IMP was flushed out by infusing 4x 80 micrometers of artificial cerebrospinal fluid at the end of each infusion.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 is the screening and surgery period. Baseline assessments for the drug are done 1 week before first dosing, ie. approximately 7 weeks after surgical implantation of the drug delivery system.

Number of subjects in period 2	Vehicle	CDNF mid-dose	CDNF high-dose
Started	6	6	5
Completed	5	5	5
Not completed	1	1	0
Adverse event, non-fatal	1	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Vehicle
Reporting group description:	
artificial cerebrospinal fluid is used as the vehicle.	
Reporting group title	CDNF mid-dose
Reporting group description:	
CDNF formulated in artificial cerebrospinal fluid to a final concentration of 0.25 mg/mL	
Reporting group title	CDNF high-dose
Reporting group description:	
CDNF formulated in artificial cerebrospinal fluid to a final concentration of 0.75 mg/mL.	

Reporting group values	Vehicle	CDNF mid-dose	CDNF high-dose
Number of subjects	6	6	5
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			
Mean age of the patients who underwent surgery and thereafter randomised to the treatment group.			
Units: years			
arithmetic mean	63.8	63.2	57.8
standard deviation	± 6.4	± 8.9	± 6.7
Gender categorical Units: Subjects			
Female	1	3	1
Male	5	3	4

Reporting group values	Total		
Number of subjects	17		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Mean age of the patients who underwent surgery and thereafter randomised to the treatment group.			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	5		
Male	12		

Subject analysis sets

Subject analysis set title	Vehicle screening
Subject analysis set type	Full analysis
Subject analysis set description:	
Full Surgical Analysis Set (FSAS) for analysis of device objectives from the day of surgery onwards.	
Subject analysis set title	CDNF mid-dose
Subject analysis set type	Full analysis
Subject analysis set description:	
Full Surgical Analysis Set (FSAS) for analysis of device objectives from the day of surgery onwards.	
Subject analysis set title	CDNF high-dose
Subject analysis set type	Full analysis
Subject analysis set description:	
Full Surgical Analysis Set (FSAS) for analysis of device objectives from the day of surgery onwards.	

Reporting group values	Vehicle screening	CDNF mid-dose	CDNF high-dose
Number of subjects	6	6	5
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			
Mean age of the patients who underwent surgery and thereafter randomised to the treatment group.			
Units: years			
arithmetic mean	63.8	63.2	57.8
standard deviation	± 6.4	± 8.9	± 6.7
Gender categorical			
Units: Subjects			
Female	1	3	1
Male	5	3	4

End points

End points reporting groups

Reporting group title	Eligibility screening
Reporting group description:	
Screening for eligibility to undergo surgery for implantation of drug delivery system.	
Reporting group title	Vehicle
Reporting group description:	
artificial cerebrospinal fluid is used as the vehicle.	
Reporting group title	CDNF mid-dose
Reporting group description:	
CDNF formulated in artificial cerebrospinal fluid to a final concentration of 0.25 mg/mL	
Reporting group title	CDNF high-dose
Reporting group description:	
CDNF formulated in artificial cerebrospinal fluid to a final concentration of 0.75 mg/mL.	
Subject analysis set title	Vehicle screening
Subject analysis set type	Full analysis
Subject analysis set description:	
Full Surgical Analysis Set (FSAS) for analysis of device objectives from the day of surgery onwards.	
Subject analysis set title	CDNF mid-dose
Subject analysis set type	Full analysis
Subject analysis set description:	
Full Surgical Analysis Set (FSAS) for analysis of device objectives from the day of surgery onwards.	
Subject analysis set title	CDNF high-dose
Subject analysis set type	Full analysis
Subject analysis set description:	
Full Surgical Analysis Set (FSAS) for analysis of device objectives from the day of surgery onwards.	

Primary: Beck Depression Inventory II (BDI-II)

End point title	Beck Depression Inventory II (BDI-II)[1]
End point description:	
Mean change; as part of the overall safety assessment	
End point type	Primary
End point timeframe:	
Baseline (Week -1) to End-of-Study (Week 24)	

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: safety endpoint, descriptive statistics.

End point values	Vehicle	CDNF mid-dose	CDNF high-dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	5	5	
Units: score				
arithmetic mean (standard deviation)	0.0 (± 2.12)	-0.20 (± 2.68)	4.60 (± 5.18)	

Statistical analyses

No statistical analyses for this end point

Primary: questionnaire for impulsive-compulsive disorder in Parkinson's disease rating scale (QUIP_RS)

End point title	questionnaire for impulsive-compulsive disorder in Parkinson's disease rating scale (QUIP_RS)[2]

End point description:

Mean change; as part of the overall safety assessment

End point type	Primary

End point timeframe:

Baseline (Week -1) to End-of-Study (Week 24)

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: safety endpoint, descriptive statistics.

End point values	Vehicle	CDNF mid-dose	CDNF high-dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	5	5	
Units: total score				
arithmetic mean (standard deviation)	2.75 (± 4.19)	-2.50 (± 4.95)	5.00 (± 5.66)	

Statistical analyses

No statistical analyses for this end point

Primary: Montreal Cognitive Assessment (MoCA)

End point title	Montreal Cognitive Assessment (MoCA)[3]

End point description:

Mean change; as part of the overall safety assessment

End point type	Primary

End point timeframe:

Baseline (Week -1) to End-of- Study (Week 24)

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: safety endpoint, descriptive statistics.

End point values	Vehicle	CDNF mid-dose	CDNF high-dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	5	5	
Units: score				
least squares mean (standard deviation)	0.00 (± 1.87)	0.60 (± 1.52)	0.40 (± 2.61)	

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[4]

End point description:

Shift number of patients with abnormal measurements with clinical relevance; as part of the overall safety assessment

End point type	Primary

End point timeframe:

Baseline (Week -1) to End-of-Study (Week 24)

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: safety endpoint, descriptive statistics

End point values	Vehicle	CDNF mid-dose	CDNF high-dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5[5]	5[6]	5	
Units: normal - abnormal no CR - abnormal CR				
number (not applicable)				
Abdomen – Baseline	0	0	0	
Abdomen – Week 24	0	0	0	
Cardiovascular – Baseline	0	0	0	
Cardiovascular – Week 24	0	0	0	
Chest and lungs – Baseline	0	0	0	
Chest and lungs – Week 24	0	0	0	
General inspection / Upper extremitis – Baseline	0	0	0	
General inspection / Upper extremitis – Week 24	0	1	1	
Head,eyes,ears,nose,throat,lymph nodes – Baseline	0	0	0	
Head,eyes,ears,nose,throat,lymph nodes – Week 24	0	0	0	
Lower extremities – Baseline	0	1	0	
Lower extremities – Week 24	1	0	0	
Neck, shoulders and back – Baseline	0	1	0	
Neck, shoulders and back – Week 24	0	1	1	

Notes:

[5] - Only patients with a baseline value and End of Study (Week 24) value are represented in this table.
[6] - Only patients with a baseline value and End of Study (Week 24) value are represented in this table.

Statistical analyses

No statistical analyses for this end point

Primary: Vital Signs - diastolic/systolic blood pressure, pulse rate, temperature, weight

End point title	Vital Signs - diastolic/systolic blood pressure, pulse rate, temperature, weight[7]

End point description:

as part of the overall safety assessment

End point type	Primary

End point timeframe:

at End-of-Study (Week 24)

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: safety endpoint, descriptive statistics.

End point values	Vehicle	CDNF mid-dose	CDNF high-dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	5	5	
Units: mmHg, bpm, degrees Celsius, kg				
least squares mean (standard deviation)				
Diastolic blood pressure	77.40 (± 7.50)	79.80 (± 8.29)	77.40 (± 9.63)	
Systolic blood pressure	149.40 (± 143.00)	123.80 (± 123.00)	127.40 (± 124.00)	
Pulse rate	66.20 (± 11.50)	75.20 (± 9.78)	73.00 (± 11.68)	
Body Temperature	36.26 (± 0.24)	36.78 (± 0.41)	36.62 (± 0.38)	
Body Weight	70.08 (± 7.45)	70.16 (± 11.15)	78.30 (± 12.39)	

Statistical analyses

No statistical analyses for this end point

Primary: Clinical Laboratory Variables - Clinical Chemistry

End point title	Clinical Laboratory Variables - Clinical Chemistry[8]

End point description:

Clinical Chemistry; as part of the overall safety assessment

End point type	Primary

End point timeframe:

at End-of-Study (Week 24)

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: safety endpoint, descriptive statistics.

End point values	Vehicle	CDNF mid-dose	CDNF high-dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	5	5	
Units: ukat/L,umol/L,ml/min/1.73,mmol/ml,g/				
number (not applicable)				
ALP	1.34	1.36	1.42	
ALT	0.14	0.21	0.19	
AST	0.36	0.37	0.33	
Albumin	40.60	42.00	39.40	

Bilirubin	8.00	8.80	9.60	
Calcium	2.31	2.34	2.37	
Creatinine kinase	1.69	1.70	1.27	
Creatinine	63.20	68.60	64.80	
IgG	9.30	11.12	9.99	
Potassium	3.78	3.90	4.06	
Sodium	139.20	139.80	140.80	
Urea	5.56	7.22	7.06	
eGFR	73.50	86.67	111.00	

Statistical analyses

No statistical analyses for this end point

Primary: Clinical Laboratory Variables - Hematology

End point title	Clinical Laboratory Variables - Hematology[9]
End point description:	
as part of the overall safety assessment	
End point type	Primary
End point timeframe:	
at End-of-Study (Week 24)	

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: safety endpoint, descriptive statistics.

End point values	Vehicle	CDNF mid-dose	CDNF high-dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	5	5	
Units: 10E9/L, g/L, pg, fL, 10E12/L, s				
number (not applicable)				
Basophils	0.09	0.08	0.07	
Eosinophils	0.17	0.15	0.11	
Hematocrit	16.45	16.05	24.58	
Hemoglobin	137.40	135.40	142.60	
INR	1.06	1.00	1.03	
Lymphocytes	1.72	1.91	1.27	
MCH	30.80	30.00	30.00	
MCV	92.00	89.60	88.80	
Monocytes	0.45	0.40	0.51	
Neutrophils	3.67	3.23	5.04	
Platelet count	267.40	247.20	281.40	
RBC	4.46	4.52	4.76	
WBC	6.04	5.76	6.98	
aPTT	26.20	27.40	30.50	

Statistical analyses

No statistical analyses for this end point

Primary: Clinical Laboratory Variables - Urinalysis (dipstick)

End point title	Clinical Laboratory Variables - Urinalysis (dipstick)[10]

End point description:

as part of the overall safety assessment

End point type	Primary

End point timeframe:

at End-of-Study (Week 24)

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: safety endpoint, descriptive statistics.

End point values	Vehicle	CDNF mid-dose	CDNF high-dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	5	5	
Units: present/absent				
number (not applicable)				
Blood	3.00	2.00	1.00	
Glucose	0.00	0.00	0.00	
Ketones	1.00	1.00	1.00	
Leukocytes	1.50	1.00	0.00	
Protein	1.00	1.00	0.00	
pH	6.74	5.10	5.20	

Statistical analyses

No statistical analyses for this end point

Primary: ECG

End point title	ECG[11]

End point description:

Difference in mean value from baseline; as part of the overall safety assessment

End point type	Primary

End point timeframe:

Baseline (Week -1) until End-of-Study (Week 24)

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: safety endpoint, descriptive statistics.

End point values	Vehicle	CDNF mid-dose	CDNF high-dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	5	5	
Units: msec, bpm				
least squares mean (standard deviation)				
PR Interval	12.80 (± 13.46)	3.60 (± 9.53)	-154.60 (± 302.83)	
QRS duration	-3.20 (± 6.42)	0.40 (± 4.10)	-1.20 (± 3.03)	
QT	-2.80 (± 18.14)	-10.80 (± 18.36)	4.40 (± 7.92)	
QTc	-5.20 (± 16.32)	-11.20 (± 10.71)	-5.00 (± 13.69)	
Ventricular rate	0.20 (± 8.64)	0.40 (± 9.02)	-3.60 (± 6.11)	

Statistical analyses

No statistical analyses for this end point

Primary: Adverse Events

End point title	Adverse Events[12]

End point description:

Two periods are reported, to distinguish between the Adverse Events related to the surgery, procedures, and device, and, the Adverse Events reported after IMP treatment start.

End point type	Primary

End point timeframe:

From Surgery (Week -8) to Treatment Start (Week 0), and, from Treatment Start (Week 0) to End-of-Study (Week 24)

Notes:

[12] - 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: safety endpoint, descriptive statistics.

End point values	Vehicle	CDNF mid-dose	CDNF high-dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	5	
Units: 200				
Surgery until Treatment Start	34	28	30	
Treatment Start until End-of-Study	34	36	38	

Statistical analyses

No statistical analyses for this end point

Primary: Anti-CDNF Antibody (ADA)

End point title	Anti-CDNF Antibody (ADA)[13]

End point description:

As part of the overall safety analysis.

End point type	Primary

End point timeframe:

At Baseline (Week -1) and prior to the last dosing (Week 20).

Notes:

[13] - 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: safety endpoint, descriptive statistics.

End point values	Vehicle	CDNF mid-dose	CDNF high-dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	5	5	
Units: positive/negative units				
positive	0	0	0	
negative	5	5	5	

Statistical analyses

No statistical analyses for this end point

Primary: Positional accuracy of Implantation

End point title	Positional accuracy of Implantation[14]

End point description:

The positional accuracy measured by comparing the tip of each individual catheter defined in the plan of the surgical procedure (target) with the position of each catheter measured by the post-operative CT scan (actual) given as the resultant of the X, Y and Z axes error between the target and actual tip position.

End point type	Primary

End point timeframe:

Surgery - Visit 4 (Week -8)

Notes:

[14] - 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: safety endpoint, descriptive statistics.

End point values	Vehicle	CDNF mid-dose	CDNF high-dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	5	
Units: mm				
arithmetic mean (standard deviation)	1.93 (± 0.83)	0.97 (± 0.77)	1.62 (± 0.98)	

Statistical analyses

No statistical analyses for this end point

Primary: Anatomical accuracy of implantation

End point title	Anatomical accuracy of implantation[15]

End point description:

Number of patients with both catheter tips within each putamen and the number of patients the surgeon answered 'yes' to the question “Satisfied with the location of the catheter position from a safety perspective?” (with one answer for all catheters altogether).

End point type	Primary

End point timeframe:

Surgery - Visit 4 (Week -8)

Notes:

[15] - 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: safety endpoint, descriptive statistics.

End point values	Vehicle	CDNF mid-dose	CDNF high-dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	5	
Units: Number of patients				
Both catheters left putamen	6	6	5	
Both catheters right putamen	6	6	5	
Surgeon satisfied with location	6	6	5	

Statistical analyses

No statistical analyses for this end point

Secondary: Unified Parkinson's Disease Rating Scale - Part III (UPDRS III)

End point title	Unified Parkinson's Disease Rating Scale - Part III (UPDRS III)

End point description:

Estimated difference vs. placebo

End point type	Secondary

End point timeframe:

Baseline (Week -1) until End-of-Study (Week 24)

End point values	Vehicle	CDNF mid-dose	CDNF high-dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	5	5	
Units: score				
least squares mean (confidence interval 95%)	0 (0 to 0)	-1.1 (-10.6 to 8.3)	-2.0 (-11.6 to 7.5)	

Statistical analyses

Statistical analysis title	ANCOVA (FAS) - mid-dose

Statistical analysis description:	
Analysis of change from Baseline to Week 24 in UPDRS Part III, OFF stage (Full Analysis Set)	
Comparison groups	CDNF mid-dose v Vehicle
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	ANCOVA (FAS) - high-dose
Statistical analysis description:	
Analysis of change from Baseline to Week 24 in UPDRS Part III, OFF stage (Full Analysis Set)	
Comparison groups	Vehicle v CDNF high-dose
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.65
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	ANCOVA (FAS) - all CDNF
Statistical analysis description:	
Analysis of change from Baseline to Week 24 in UPDRS Part III, OFF stage (Full Analysis Set)	
Comparison groups	Vehicle v CDNF high-dose v CDNF mid-dose
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.68
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Secondary: Unified Parkinson's Disease Rating Scale - Parts I-IV (UPDRS Total)	
End point title	Unified Parkinson's Disease Rating Scale - Parts I-IV (UPDRS Total)

End point description:	
Estimated difference vs. placebo	
End point type	Secondary
End point timeframe:	
Baseline (Week -1) until End-of-Study (Week 24)	

End point values	Vehicle	CDNF mid-dose	CDNF high-dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	5	5	
Units: score				
least squares mean (confidence interval 95%)				
UPDRS Part I	0 (0 to 0)	0.2 (-1.9 to 2.2)	1.3 (-0.7 to 3.2)	
UPDRS Part II	0 (0 to 0)	-0.4 (-5.3 to 4.5)	-0.1 (-5.0 to 4.7)	
UPDRS Part III	0 (0 to 0)	-1.1 (-10.6 to 8.3)	-2.0 (-11.6 to 7.5)	
UPDRS Part IV	0 (0 to 0)	2.7 (1.0 to 4.4)	0.7 (-1.0 to 2.3)	
UPDRS Total	0 (0 to 0)	1.9 (-10.3 to 14.1)	-0.3 (-12.5 to 11.9)	

Statistical analyses

Statistical analysis title	ANCOVA for Total UPDRS Score - mid-dose
Statistical analysis description:	
Analysis of change from Baseline to Week 24 in Total UPDRS Score (Full Analysis Set) vs. Vehicle	
Comparison groups	CDNF mid-dose v Vehicle
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.74
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	ANCOVA for Total UPDRS Score - high-dose
Statistical analysis description:	
Analysis of change from Baseline to Week 24 in Total UPDRS Score (Full Analysis Set) vs. Vehicle	
Comparison groups	Vehicle v CDNF high-dose

Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.96
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	ANCOVA for Total UPDRS Score - all CDNF
Statistical analysis description:	
Analysis of change from Baseline to Week 24 in Total UPDRS Score (Full Analysis Set) vs. Vehicle	
Comparison groups	Vehicle v CDNF high-dose v CDNF mid-dose
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.87
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Secondary: Timed Up-and-Go test (TUG)	
End point title	Timed Up-and-Go test (TUG)
End point description:	
Change from Baseline until End-of-Study vs. Vehicle	
End point type	Secondary
End point timeframe:	
Baseline (Week -1) until End-of-Study (Week 24)	

End point values	Vehicle	CDNF mid-dose	CDNF high-dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	5	5	
Units: seconds				
least squares mean (confidence interval 95%)	0 (0 to 0)	-3.6 (-17.0 to 9.8)	3.9 (-8.6 to 16.4)	

Statistical analyses

Statistical analysis title	ANCOVA (FAS) - mid-dose
Comparison groups	Vehicle v CDNF mid-dose
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.56
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	ANCOVA (FAS) - high-dose
Comparison groups	Vehicle v CDNF high-dose
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.51
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	ANCOVA (FAS) - all CDNF
Comparison groups	Vehicle v CDNF high-dose v CDNF mid-dose
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.92
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided

Secondary: Unified Parkinson's Disease Rating Scale Part I (UPDRS I)	
End point title	Unified Parkinson's Disease Rating Scale Part I (UPDRS I)
End point description: Mean change from baseline to end-of-study vs. Vehicle	
End point type	Secondary
End point timeframe: Baseline (Week -1) until End-of-Study (Week 24)	

End point values	Vehicle	CDNF mid-dose	CDNF high-dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	5	5	
Units: score				
least squares mean (confidence interval 95%)	0 (0 to 0)	0.2 (-1.9 to 2.2)	1.3 (-0.7 to 3.2)	

Statistical analyses

Statistical analysis title	ANCOVA (FAS) - mid-dose
Comparison groups	Vehicle v CDNF mid-dose
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.87
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	ANCOVA (FAS) - high-dose
Comparison groups	Vehicle v CDNF high-dose
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.18
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	ANCOVA (FAS) - all CDNF
Comparison groups	Vehicle v CDNF high-dose v CDNF mid-dose

Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.35
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Secondary: Unified Parkinson's Disease Rating Scale Part II (UPDRS II)

End point title	Unified Parkinson's Disease Rating Scale Part II (UPDRS II)
End point description:	
Change from baseline until end-of-study vs. Vehicle	
End point type	Secondary
End point timeframe:	
Baseline (Week -1) until End-of-Study (Week 24)	

End point values	Vehicle	CDNF mid-dose	CDNF high-dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	5	5	
Units: score				
least squares mean (confidence interval 95%)	0 (0 to 0)	-0.4 (-5.3 to 4.5)	-0.1 (-5.0 to 4.7)	

Statistical analyses

Statistical analysis title	ANCOVA (FAS) - mid-dose
Comparison groups	Vehicle v CDNF mid-dose
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.86
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	ANCOVA (FAS) - high-dose
Comparison groups	Vehicle v CDNF high-dose

Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.95
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	ANCOVA (FAS) - all CDNF
Comparison groups	Vehicle v CDNF high-dose v CDNF mid-dose
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.88
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Secondary: Unified Parkinson's Disease Rating Scale Part IV (UPDRS IV)	
End point title	Unified Parkinson's Disease Rating Scale Part IV (UPDRS IV)
End point description:	
Change from baseline until end-of-study vs. Vehicle	
End point type	Secondary
End point timeframe:	
Baseline (Week -1) until End-of-Study (Week 24)	

End point values	Vehicle	CDNF mid-dose	CDNF high-dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	5	5	
Units: score				
least squares mean (confidence interval 95%)	0 (0 to 0)	2.7 (1.0 to 4.4)	0.7 (-1.0 to 2.3)	

Statistical analyses

Statistical analysis title	ANCOVA (FAS) - mid-dose
Comparison groups	Vehicle v CDNF mid-dose

Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0042
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	ANCOVA (FAS) - high-dose
Comparison groups	Vehicle v CDNF high-dose
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	ANCOVA (FAS) - all CDNF
Comparison groups	Vehicle v CDNF high-dose v CDNF mid-dose
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.059
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Secondary: Parkinson's Home Diary

End point title	Parkinson's Home Diary

End point description:

Mean change from baseline to end-of-study vs. Vehicle in OFF, ON with troublesome dyskinesias, ON with non-troublesome dyskinesias, ON. In addition the derived average Bad time (OFF + ON with troublesome dyskinesias) and derived average Good time (ON without troublesome dyskinesias + ON) are assessed in the analysis.

End point type	Secondary

End point timeframe:

Baseline (Week 0) until End-of-Study (Week 24)

End point values	Vehicle	CDNF mid-dose	CDNF high-dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	5	5	
Units: hours				
least squares mean (confidence interval 95%)				
Derived average Bad time	0 (0 to 0)	2.6 (0.9 to 4.3)	0.8 (-0.9 to 2.5)	
Derived average Good time	0 (0 to 0)	-0.7 (-3.7 to 2.3)	0.3 (-2.6 to 3.2)	
OFF	0 (0 to 0)	2.4 (0.5 to 4.3)	0.7 (-1.1 to 2.6)	
ON with troublesome dyskinesias	0 (0 to 0)	0.1 (-0.5 to 0.7)	0.0 (-0.6 to 0.5)	
ON without troublesome dyskinesias	0 (0 to 0)	0.4 (-4.0 to 4.9)	-1.3 (-5.7 to 3.2)	
ON	0 (0 to 0)	-0.5 (-4.4 to 3.4)	1.6 (-2.0 to 5.1)	

Statistical analyses

Statistical analysis title	ANCOVA (FAS) - Bad time all CDNF vs. Vehicle
Comparison groups	Vehicle v CDNF mid-dose v CDNF high-dose
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.039
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	ANCOVA (FAS) - Good time all CDNF vs. Ve...
Comparison groups	Vehicle v CDNF mid-dose v CDNF high-dose
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.89
Method	ANCOVA
Parameter estimate	Mean difference (final values)

Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	ANCOVA (FAS) - OFF time all CDNF vs. V...
Comparison groups	Vehicle v CDNF mid-dose v CDNF high-dose
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.079
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	ANCOVA (FAS) - ON with dyskinesias, all CDNF
Comparison groups	Vehicle v CDNF mid-dose v CDNF high-dose
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.89
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	ANCOVA (FAS) - ON without dyskinesias, all...
Comparison groups	Vehicle v CDNF mid-dose v CDNF high-dose
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.83
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	ANCOVA (FAS) - ON time all CDNF

Comparison groups	Vehicle v CDNF mid-dose v CDNF high-dose
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.62
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Secondary: Parkinson's Disease Questionnaire - 39 point (PDQ-39)

End point title	Parkinson's Disease Questionnaire - 39 point (PDQ-39)
End point description: Mean change in score from baseline until end-of-study vs. Vehicle	
End point type	Secondary
End point timeframe: from Baseline (Week -1) until End-of-Study (Week 24)	

End point values	Vehicle	CDNF mid-dose	CDNF high-dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	5	5	
Units: score				
least squares mean (confidence interval 95%)	0 (0 to 0)	1.8 (-13.2 to 16.9)	5.1 (-9.9 to 20.2)	

Statistical analyses

Statistical analysis title	ANCOVA (FAS) - mid-dose vs. vehicle
Comparison groups	Vehicle v CDNF mid-dose
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.79
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	ANCOVA (FAS) - high-dose vs. vehicle

Comparison groups	Vehicle v CDNF high-dose
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.47
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Copy of ANCOVA (FAS) - all CDNF vs. vehicle
Comparison groups	Vehicle v CDNF high-dose v CDNF mid-dose
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.55
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Secondary: Clinical Global Impression (CGI)

End point title	Clinical Global Impression (CGI)

End point description:

Mean change in scale from baseline to end-of-study vs. Vehicle.
7 point scale to indicate if in the opinion of the investigator is doing better or worse than the previous assessment (1=very much better, 4=no change, 7= very much worse).

End point type	Secondary

End point timeframe:

Baseline (Week -1) until End-of-Study (Week 24)

End point values	Vehicle	CDNF mid-dose	CDNF high-dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	5	5	
Units: scale				
least squares mean (confidence interval 95%)	0 (0 to 0)	0.1 (-1.1 to 1.4)	0.6 (-0.6 to 1.8)	

Statistical analyses

Statistical analysis title	ANCOVA (FAS) - mid-dose vs. Vehicle
Comparison groups	Vehicle v CDNF mid-dose
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	ANCOVA (FAS) - high-dose vs. Vehicle
Comparison groups	Vehicle v CDNF high-dose
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.27
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Copy of ANCOVA (FAS) - all CDNF vs. Vehicle
Comparison groups	Vehicle v CDNF high-dose v CDNF mid-dose
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.41
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

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:

Visit 6 vehicle infusion (Week -5) to Visit 15 (Week 20)

End point values	Vehicle	CDNF mid-dose	CDNF high-dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	5	
Units: Number of events				
Looseness of port	0	0	0	
Surgical intervention to stabilise port	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Patency

End point title	Patency

End point description:

The patency of the drug delivery system measured as occurrence of blockage of an individual implanted catheter preventing or limiting infusion as measured by pressure rise above 590 mmHg.

End point type	Secondary

End point timeframe:

Post-implantation (Week -5) until end of treatment evaluation (Week 24)

End point values	Vehicle	CDNF mid-dose	CDNF high-dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	5	
Units: Pressure rises above 590 mmHg				
Catheters >590 mmHg at individual infusion	0	1	0	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Dopamine Transporter Positron Emission Tomography (DAT-PET)

End point title	Dopamine Transporter Positron Emission Tomography (DAT-PET)

End point description:

Mean change analysed for six predefined brain areas.

End point type	Other pre-specified

End point timeframe:
From pre-treatment (Week -2) until post-treatment (Week 22)

End point values	Vehicle	CDNF mid-dose	CDNF high-dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	5	5	
Units: BPnd				
least squares mean (standard deviation)				
Total Nucleus caudate	-0.28 (± 0.13)	-0.05 (± 0.25)	-0.28 (± 0.30)	
Total Putamen	-0.10 (± 0.09)	0.08 (± 0.19)	-0.13 (± 0.12)	
Total Striatum	-0.17 (± 0.07)	0.03 (± 0.18)	-0.19 (± 0.19)	
Total Substantia nigra	-0.04 (± 0.08)	0.07 (± 0.26)	-0.10 (± 0.08)	
Total Ventral striatum	-0.26 (± 0.15)	0.09 (± 0.33)	-0.37 (± 0.36)	
Total infused putamen	-0.09 (± 0.09)	0.10 (± 0.21)	-0.15 (± 0.13)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Pharmacokinetics - CDNF concentration

End point title	Pharmacokinetics - CDNF concentration

End point description:
CDNF concentration in blood serum and cerebrospinal fluid (CSF) before and after the sixth dosing

End point type	Other pre-specified

End point timeframe:
at Baseline (Week -1; CSF only) and after the sixth dosing (Week 20)

End point values	Vehicle	CDNF mid-dose	CDNF high-dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	5	5	
Units: ng/mL				
arithmetic mean (standard deviation)				
CSF prior to infusion	5.0 (± 0)	5.0 (± 0)	5.0 (± 0)	
CSF 2h post end of infusion	5.0 (± 0)	82.2 (± 65.4)	131.8 (± 129.5)	
Serum prior to infusion	1.0 (± 1.2)	0.8 (± 0.4)	1.9 (± 1.9)	
Serum 2h post end of infusion	1.0 (± 1.2)	1.0 (± 0.7)	4.6 (± 2.1)	
Serum 4h post end of infusion	0.9 (± 1.0)	1.2 (± 0.9)	4.2 (± 1.8)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Parkinson's Kinetigraph (PKG)

End point title	Parkinson's Kinetigraph (PKG)

End point description:

Mean change estimated different of the two treatment groups vs. vehicle.

End point type	Other pre-specified

End point timeframe:

Baseline (Week 0) End-of-Study (Week 24)

End point values	Vehicle	CDNF mid-dose	CDNF high-dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	5	5	
Units: score				
least squares mean (confidence interval 95%)				
Mean Daily BK>=III	0 (0 to 0)	-12.5 (-33.8 to 8.7)	-5.6 (-26.9 to 15.7)	
Mean Daily DK>=III	0 (0 to 0)	3.4 (-13.6 to 20.3)	5.0 (-11.7 to 21.8)	
Median BKS	0 (0 to 0)	-5.2 (-13.5 to 3.1)	-3.1 (-11.5 to 5.2)	
Median BKS (LED corrected)	0 (0 to 0)	-8.5 (-23.1 to 6.2)	-3.2 (-18.9 to 12.4)	
Median DKS	0 (0 to 0)	0.9 (-7.4 to 9.3)	2.9 (-5.4 to 11.2)	
Median DKS (LED corrected)	0 (0 to 0)	1.1 (-8.0 to 10.2)	3.1 (-6.4 to 12.7)	

Statistical analyses

Statistical analysis title	ANCOVA (FAS) - BK>=III all CDNF vs. Vehicle

Statistical analysis description:

Full Analysis Set

Comparison groups	CDNF mid-dose v CDNF high-dose v Vehicle
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	ANCOVA (FAS) - DK>=III all CDNF vs. Veh...
Statistical analysis description: Full Analysis Set	
Comparison groups	CDNF mid-dose v CDNF high-dose v Vehicle
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.52
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	ANCOVA (FAS) - BKS all CDNF vs. Vehicle
Statistical analysis description: Full Analysis Set	
Comparison groups	CDNF mid-dose v CDNF high-dose v Vehicle
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.22
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	ANCOVA (FAS) -BKS LED adjusted all CDNF vs Vehicle
Comparison groups	CDNF mid-dose v CDNF high-dose v Vehicle
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.31
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	ANCOVA (FAS) -DKS all CDNF vs. Vehicle
Comparison groups	CDNF mid-dose v CDNF high-dose v Vehicle
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.56
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	ANCOVA (FAS) -DKS LED adjusted all CDNF vs Vehicle
Comparison groups	CDNF mid-dose v CDNF high-dose v Vehicle
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.58
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Other pre-specified: Coverage of the infusate in target anatomy

End point title	Coverage of the infusate in target anatomy[16]

End point description:

Coverage of the infusate in putamen, as assessed by MRI, as a percentage of infusate volume over putamen volume.

End point type	Other pre-specified

End point timeframe:

first vehicle infusion (Week -5)

Notes:

[16] - 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: Descriptive statistics.

End point values	Vehicle	CDNF mid-dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1[17]	1[18]		
Units: percent volume/volume				
number (not applicable)				
Percentage coverage left putamen	67.00	65.45		
Percentage coverage right putamen	60.64	74.68		

Notes:
[17] - Gadolinium removed from the market during trial, only first two patients analysed (first infusion)
[18] - Gadolinium removed from the market during trial, only first two patients analysed (first infusion)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From surgery (Week -8) to end of study (Week 24).
In addition, a separate analysis was done from surgery (Week -8) to first dosing (Week 0), and from first dosing (Week 0) to end of study (Week 24).

Adverse event reporting additional description:

All adverse events occurring during the study were reported and collected in the eCRF, starting from obtained Informed Consent and until End of Study visit in the study. AEs/ADEs were collected with non-leading questions at each clinic visit, by direct observation of the patient, or by spontaneous reports by the patient.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Vehicle

Reporting group description:

all patients who underwent surgery and were later randomised to the vehicle treatment group.

Reporting group title	CDNF mid-dose

Reporting group description:

all patients who underwent surgery and were later randomised to the mid-dose CDNF treatment group.

Reporting group title	CDNF high-dose

Reporting group description:

all patients who underwent surgery and were later randomised to the high-dose CDNF treatment group.

Serious adverse events	Vehicle	CDNF mid-dose	CDNF high-dose
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	2 / 5 (40.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Radius fracture	Additional description: A month after surgery, prior to treatment start, the patient fell and fractured their radius. The patient underwent surgery to set the fracture. The patient recovered.		
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Implant site necrosis	Additional description: Necrosis of the skin around the port site four weeks after surgery, prior to treatment start. The patient underwent skin graft plastic surgery and fully recovered.		

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional State / disorientation	Additional description: Post-surgery, prior to treatment start, the patients were hospitalised due to disorientation or confusional state. The patients recovered.		
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Implant site infection	Additional description: Two weeks after surgery, prior to treatment start, the patient was hospitalised due to suspected infection of the skin around the port site. The patient was treated with antibiotics and fully recovered.		
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain abscess	Additional description: The patient was diagnosed with a brain abscess by MRI after receiving several treatment infusions. The infection likely happened during an infusion.		
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Vehicle	CDNF mid-dose	CDNF high-dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	6 / 6 (100.00%)	5 / 5 (100.00%)
Vascular disorders			
Aortic dilatation			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Hypertension			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Surgical and medical procedures			

Carpal tunnel decompression			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Dental operation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Gait disturbance			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Impaired healing			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	2 / 5 (40.00%)
occurrences (all)	1	2	2
Implant site necrosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	1 / 6 (16.67%)	3 / 6 (50.00%)	1 / 5 (20.00%)
occurrences (all)	1	3	1
Implant site reaction			
subjects affected / exposed	2 / 6 (33.33%)	4 / 6 (66.67%)	4 / 5 (80.00%)
occurrences (all)	3	4	11
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Dyspnoea			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 5 (20.00%)
occurrences (all)	0	1	1

Confusional state			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	1 / 5 (20.00%)
occurrences (all)	1	2	2
Delusion			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Depression			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	2 / 5 (40.00%)
occurrences (all)	1	0	3
Hallucination			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	1 / 5 (20.00%)
occurrences (all)	2	1	1
Impulse-control disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 5 (40.00%)
occurrences (all)	0	0	3
Insomnia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Irritability			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Product issues			
Device leakage			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Investigations			
Blood pressure systolic increased			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Electrocardiogram T wave inversion			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Hepatic enzyme increased			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Nitrite urine present			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Weight decreased			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	1 / 5 (20.00%)
occurrences (all)	1	1	1
Foot fracture			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Head injury			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 5 (40.00%)
occurrences (all)	0	0	2
Post procedural haemorrhage			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	2 / 5 (40.00%)
occurrences (all)	2	1	2
Procedural pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Radius fracture			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Tendon rupture			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Tooth fracture			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0

Wound			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Cardiac disorders			
Bradycardia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Palpitations			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Cerebral microhaemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Dizziness			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Dyskinesia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	1	2	0
Headache			
subjects affected / exposed	3 / 6 (50.00%)	4 / 6 (66.67%)	1 / 5 (20.00%)
occurrences (all)	3	5	2
Neuralgia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Pleurothotonus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Presyncope			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Sensory disturbance			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	1	1	0

Balance disorder			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Carpal tunnel syndrome			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Cranial nerve disorder			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Disturbance in attention			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Epilepsy			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Memory impairment			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Migraine			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Motor dysfunction			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	2	1	0
Parkinson's disease			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 5 (20.00%)
occurrences (all)	0	2	1
Tremor			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Cerebral gas embolism	Additional description: Non-symptomatic, based on imaging findings showing air or fluid pockets.		
subjects affected / exposed	3 / 6 (50.00%)	2 / 6 (33.33%)	4 / 5 (80.00%)
occurrences (all)	7	5	9
Visual field defect			

subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Lymphopenia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Eye disorders			
Corneal erosion			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Strabismus			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Fatigue			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	1 / 5 (20.00%)
occurrences (all)	1	1	1
Abdominal pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Constipation			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Diarrhoea			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	2	0	1
Dry mouth			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 5 (40.00%)
occurrences (all)	0	0	3
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Ecchymosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Hyperhidrosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Skin dystrophy			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Urticaria			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Leukocyturia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Micturition urgency			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	2	0	1

Back pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Muscle rigidity			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Muscle spasms			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Spinal column stenosis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Brain abscess			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Clostridium difficile infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Implant site infection			
subjects affected / exposed	0 / 6 (0.00%)	3 / 6 (50.00%)	2 / 5 (40.00%)
occurrences (all)	0	3	2
Infected bite			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Infusion site infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Skin infection			

subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Hyponatraemia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 September 2017	Eligibility criteria modified to more clearly define inclusion and discontinuation criteria. Plans for treatment after completion of the study - extension study. Recording of infusion pump pressures. Clarification of the timeframe to conduct the post-infusion MRI. Review timepoints of safety lab and imaging scans for safety clarified.
16 February 2018	Deletion of gadolinium test-infusions. Introduction of an optional CT(A) scan.
16 February 2018	Timepoint correction for PET. Neurological examination. Discontinuation criterion clarifying missing of an infusion. Clarification of follow-up data for the DSMB. Clarification of medication recording during surgery. Instructions for LED calculation. Deletion of thrombin time testing.
18 April 2019	Update of risk mitigation section. Port assessment and instructions when an infusion should be postponed. Silicon cap wearing regime changed. Allowance of anti-Parkinson medication prior to PET scanning.
28 August 2019	Additional exploratory analysis - proteomics biomarkers and alpha-synuclein. Study period was extended by 9 months. MRI scans before and after an infusion. Concomitant medication and use of selegiline. UPDRS off-score rating by same rater. Safety laboratory variables. Reporting of device deficiencies.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported