



Clinical trial results:

A Long-Term Follow-up Safety Study for Patients with Idiopathic Parkinson's Disease (PD) Implanted with the DDS and/or Who Received Treatment in the Main Study and/or Extension Study

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2017-005170-19 |
| Trial protocol | SE FI |
| Global end of trial date | 27 August 2021 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 |
| This version publication date | 28 July 2022 |
| First version publication date | 28 July 2022 |

Trial information

Trial identification

| | |
|-----------------------|---------------|
| Sponsor protocol code | HP-CD-CL-2004 |
|-----------------------|---------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Renishaw Neuro Solutions Ltd. & Herantis Pharma Plc |
| Sponsor organisation address | Wotton Road, Gloucestershire, United Kingdom, |
| Public contact | Project Manager, Renishaw Neuro Solutions Ltd. , +44 7810 056247, paul.skinner@renishaw.com |
| Scientific contact | Project Manager, Renishaw Neuro Solutions Ltd. , +44 7810 056247, paul.skinner@renishaw.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 | 23 February 2022 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 27 August 2021 |
| Global end of trial reached? | Yes |
| Global end of trial date | 27 August 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the long-term safety and tolerability of

- The implanted IMD, and,
- The previous administered bilateral intraputamenal IMP infusions

Protection of trial subjects:

All patients received written and verbal information regarding the study. The given information emphasised that participation in the study was voluntary and that the patient could withdraw from the study at any time and for any reason. All patients 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 (ICF) was signed and personally dated by the patient (no patient needed a legally acceptable representative or witness) and by the person who conducted the informed consent discussion. The patients signed the consent form to indicate that the information had been explained and understood. The patients were allowed time to consider the information presented before signing and dating the ICF to indicate that they fully understood the information, and willingly volunteered to participate in the study. The patients were given a copy of the ICF for their information. The original copy of the informed consent was kept in a confidential file in the Investigator's site records.

Three Major protocol deviations were reported related to the ICF. In three cases, the ICF was not signed before the inclusion in the study: in one case, ICF version 8.0 was signed after study completion; in one case the ICF version 3.0 was signed before the explantation visit; and the last case, ICF was signed after visit 27.

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 General Data Protection Regulation (2016/679) (GDPR) and the data did not identify any persons taking part in the study.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 07 March 2019 |
| 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: 9 |
| Country: Number of subjects enrolled | Finland: 6 |
| 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 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) | 10 |
| From 65 to 84 years | 5 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Two Swedish and one Finnish sites were involved in this study. Fifteen patients were all eligible and enrolled in the Follow-up Study and all of them completed the 13 months follow-up. Five patients had only removal of port at the time to finalize this CSR. Follow-up of these 5 patients will be documented as an addendum to the CSR.

Pre-assignment

Screening details:

Patients who completed Visit 4 in the main study (HP-CD-CL-2002), or, completed the main study having received 6 doses of treatment, but did not continue in the extension study (HP-CD-CL-2003), or, patients that completed the extension study, receiving a total of 12 doses of treatment.

Pre-assignment period milestones

| | |
|------------------------------|----|
| Number of subjects started | 15 |
| Number of subjects completed | 15 |

Period 1

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

Blinding implementation details:

In this follow-up study, assignment of CDNF treatment group or placebo (vehicle) treatment in study HP-CD-CL-2002 and HP-CD-CL-2003 remained blinded only for the patient until follow-up for the drug-related efficacy parameters of the last patient was completed (Visit 34), i.e. until approximately thirteen months after treatment end in study HP-CD-CL-2002 and/or study HP-CD-CL-2003.

Arms

| | |
|------------------------------|---------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | CDNF mid-dose group |

Arm description:

CDNF formulated in artificial cerebrospinal fluid to administer a total dose of 400 µg.

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

Dosage and administration details:

The patients that were randomised in the Main Protocol Phase of the study to active treatment with either mid-dose or high-dose CDNF level, continued treatment in the Extension study at the same CDNF dose-level as the last dose received in the Main Protocol Phase.

Patients who were previously randomised to the placebo group in the Main Protocol Phase, started treatment with active CDNF in the Extension study in accordance with their re-randomisation schedule. CDNF was not administered during the Follow-up study.

All patients enrolled in the follow-up study were implanted with the DDS, the IMD, during the Main Protocol Phase of the study (HP-CD-CL-2002). The intended use of the DDS was to facilitate intermittent delivery of therapeutic from a set of extracorporeal sources (syringe pumps) to intraparenchymal targets within the brain.

| | |
|--|--|
| Arm title | CDNF high-dose group |
| Arm description: CDNF formulated in artificial cerebrospinal fluid to administer a total dose of 1200 µg. | |
| Arm type | Experimental |
| Investigational medicinal product name | Cerebral Dopamine Neurotrophic Factor (CDNF) |
| Investigational medicinal product code | CDNF |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intracerebral use |

Dosage and administration details:

The patients that were randomised in the Main Protocol Phase of the study to active treatment with either mid-dose or high-dose CDFN level, continued treatment in the Extension study at the same CDFN dose-level as the last dose received in the Main Protocol Phase.

Patients who were previously randomised to the placebo group in the Main Protocol Phase, started treatment with active CDFN in the Extension study in accordance with their re-randomisation schedule. CDFN was not administered during the Follow-up study.

All patients enrolled in the follow-up study were implanted with the DDS, the IMD, during the Main Protocol Phase of the study (HP-CD-CL-2002). The intended use of the DDS was to facilitate intermittent delivery of therapeutic from a set of extracorporeal sources (syringe pumps) to intraparenchymal targets within the brain.

| Number of subjects in period 1 | CDNF mid-dose group | CDNF high-dose group |
|---------------------------------------|---------------------|----------------------|
| Started | 8 | 7 |
| Completed | 8 | 7 |

Baseline characteristics

Reporting groups

| | |
|--|----------------------|
| Reporting group title | CDNF mid-dose group |
| Reporting group description: CDNF formulated in artificial cerebrospinal fluid to administer a total dose of 400 µg. | |
| Reporting group title | CDNF high-dose group |
| Reporting group description: CDNF formulated in artificial cerebrospinal fluid to administer a total dose of 1200 µg. | |

| Reporting group values | CDNF mid-dose group | CDNF high-dose group | 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 | 64.1 | 61.6 | |
| standard deviation | ± 7.9 | ± 8.3 | - |
| Gender categorical Units: Subjects | | | |
| Female | 4 | 1 | 5 |
| Male | 4 | 6 | 10 |
| Duration of PD motor symptoms Units: Subjects | | | |
| 6 Years | 1 | 0 | 1 |
| 8 Years | 0 | 1 | 1 |
| 9 Years | 1 | 0 | 1 |
| 10 Years | 2 | 2 | 4 |
| 11 Years | 1 | 0 | 1 |
| 12 Years | 0 | 2 | 2 |
| 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 | CDNF mid-dose group |
| Reporting group description: CDNF formulated in artificial cerebrospinal fluid to administer a total dose of 400 µg. | |
| Reporting group title | CDNF high-dose group |
| Reporting group description: CDNF formulated in artificial cerebrospinal fluid to administer a total dose of 1200 µg. | |

Primary: Occurrence of adverse device effects (ADE)

| | |
|--|---|
| End point title | Occurrence of adverse device effects (ADE) ^[1] |
| End point description: Occurrence of adverse device effects (ADE), for either the whole system or the individual sub-systems (guide tubes/catheters, subcutaneous components, port), evaluated separately for - the explantation procedure (Week 55), - the healing period (Weeks 55 to 57), - the subsequent safety visits during the entire study period outside of the explantation and healing period (Week 55 to Week 57), with serious ADE (SADE), including long term pathological changes seen by MRI, neurological deficit (seizures), infection (local to components, in CNS), severe skin breakdown or necrosis requiring component removal and life threatening or major (requiring intervention) intracerebral haemorrhage up to 5 years since the initial surgical implantation of the DDS. | |
| End point type | Primary |
| End point timeframe: Occurrence of adverse device effects (ADE) during the entire study period evaluated separately for the explantation procedure (Week 55), the healing period (Weeks 55 to 57), and the subsequent safety visits. | |

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 | CDNF mid-dose group | CDNF high-dose group | | |
|---|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 7 | | |
| Units: Adverse device effects | | | | |
| Number of related ADEs to study device | 4 | 5 | | |
| Number of related ADEs to surgical procedures | 1 | 1 | | |
| Number of ADEs with skin reaction around the port | 1 | 2 | | |
| Number of related ADEs to drug-device combination | 2 | 2 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Electrocardiogram (ECG) (Change from baseline (Week -1))

| | |
|-----------------|---|
| End point title | Electrocardiogram (ECG) (Change from baseline (Week -1)) ^[2] |
|-----------------|---|

End point description:

A standard 12-lead ECG was performed. The following parameters were recorded: ventricular rate, PR interval, QRS duration, QT and QTc, as well as ECG findings. ECG findings were recorded and assessed as normal, abnormal without clinical relevance (ANCL) or abnormal with clinical relevance (ACL). An asymptomatic abnormal ECG finding was reported as an AE only if it was assessed as: clinically significant, if it fulfilled the criteria for an SAE or if it caused the patient to discontinue the study.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

ECGs were recorded at inclusion (Visit 27, Week 49), after six months of follow-up (Visit 32, Week 71) and after 13 months of follow-up (Visit 34, Month 25), for screening of coronary heart disease.

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 | CDNF mid-dose group | CDNF high-dose group | | |
|--|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 ^[3] | 7 ^[4] | | |
| Units: unit(s) | | | | |
| arithmetic mean (standard deviation) | | | | |
| QRS duration (msec) - Visit 32 (Week 71) | 1.25 (± 6.58) | -3.60 (± 7.13) | | |
| QRS duration (msec) - Visit 34 (Month 25) | 0.00 (± 7.48) | 1.60 (± 13.59) | | |
| PR interval (msec) - Visit 32 (Week 71) | -9.25 (± 37.23) | -156.60 (± 305.92) | | |
| PR Interval (msec) - Visit 34 (Month 25) | -23.00 (± 45.48) | -161.80 (± 301.71) | | |
| QT (msec) - Visit 32 (Week 71) | 2.00 (± 14.42) | -9.20 (± 23.65) | | |
| QT (msec) - Visit 34 (Month 25) | -12.00 (± 14.31) | 1.20 (± 19.88) | | |
| QTc (msec) - Visit 32 (Week 71) | 1.25 (± 22.15) | -15.20 (± 13.94) | | |
| QTc (msec) - Visit 34 (Month 25) | -18.67 (± 24.70) | -0.20 (± 19.29) | | |
| Ventricular rate (bpm) - Visit 32 (Week 71) | 0.50 (± 9.83) | -1.20 (± 9.55) | | |
| Ventricular rate (bpm) - Visit 34 (Month 25) | -1.67 (± 11.64) | -1.00 (± 8.34) | | |

Notes:

[3] - Corresponds to the SAS population

[4] - Corresponds to the SAS population

Statistical analyses

No statistical analyses for this end point

Primary: Electrocardiogram (ECG) (Change from follow-up study baseline (Week 49))

| | |
|-----------------|---|
| End point title | Electrocardiogram (ECG) (Change from follow-up study baseline (Week 49)) ^[5] |
|-----------------|---|

End point description:

A standard 12-lead ECG was performed. The following parameters were recorded: ventricular rate, PR

interval, QRS duration, QT and QTc, as well as ECG findings. ECG findings were recorded and assessed as normal, abnormal without clinical relevance (ANCL) or abnormal with clinical relevance (ACL). An asymptomatic abnormal ECG finding was reported as an AE only if it was assessed as: clinically significant, if it fulfilled the criteria for an SAE or if it caused the patient to discontinue the study.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

ECGs were recorded at inclusion (Visit 27, Week 49), after six months of follow-up (Visit 32, Week 71) and after 13 months of follow-up (Visit 34, Month 25), for screening of coronary heart disease.

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 | CDNF mid-dose group | CDNF high-dose group | | |
|--|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 ^[6] | 7 ^[7] | | |
| Units: unit(s) | | | | |
| arithmetic mean (standard deviation) | | | | |
| QRS duration (msec) - Visit 32 (Week 71) | 1.50 (± 4.50) | -2.50 (± 3.79) | | |
| QRS duration (msec) - Visit 34 (Month 25) | 0.67 (± 5.75) | -0.50 (± 5.51) | | |
| PR interval (msec) - Visit 32 (Week 71) | -12.00 (± 39.68) | 2.50 (± 10.12) | | |
| PR Interval (msec) - Visit 34 (Month 25) | -22.67 (± 50.92) | 9.50 (± 17.39) | | |
| QT (msec) - Visit 32 (Week 71) | 2.75 (± 9.62) | -13.00 (± 16.21) | | |
| QT (msec) - Visit 34 (Month 25) | -12.33 (± 11.48) | -4.00 (± 18.11) | | |
| QTc (msec) - Visit 32 (Week 71) | 14.63 (± 16.65) | -18.00 (± 19.10) | | |
| QTc (msec) - Visit 34 (Month 25) | -0.17 (± 15.07) | -4.75 (± 24.13) | | |
| Ventricular rate (bpm) - Visit 32 (Week 71) | 4.13 (± 5.06) | -0.25 (± 11.62) | | |
| Ventricular rate (bpm) - Visit 34 (Month 25) | 4.00 (± 7.35) | -0.50 (± 10.66) | | |

Notes:

[6] - Corresponds to the SAS population

[7] - Corresponds to the SAS population

Statistical analyses

No statistical analyses for this end point

Primary: Beck Depression Inventory score (Change from baseline (Week -1))

| | |
|-----------------|---|
| End point title | Beck Depression Inventory score (Change from baseline (Week -1)) ^[8] |
|-----------------|---|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

The self-administered questionnaire was completed at inclusion (Visit 27, Week 49), after six months of follow-up (Visit 32, Week 71) and after 13 months of follow-up (Visit 34, Month 25).

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 | CDNF mid-dose group | CDNF high-dose group | | |
|--------------------------------------|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 ^[9] | 7 ^[10] | | |
| Units: unit(s) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Visit 32 (Week 71) Safety&Efficacy | 0.38 (± 3.34) | 3.60 (± 3.21) | | |
| Visit 34 (Month 25) Safety | 2.13 (± 4.05) | 4.86 (± 8.55) | | |

Notes:

[9] - Corresponds to the SAS population

[10] - Corresponds to the SAS population

Statistical analyses

No statistical analyses for this end point

Primary: Beck Depression Inventory score (Change from follow-up study baseline (Week 49))

| | |
|-----------------|--|
| End point title | Beck Depression Inventory score (Change from follow-up study baseline (Week 49)) ^[11] |
|-----------------|--|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

The self-administered questionnaire was completed at inclusion (Visit 27, Week 49), after six months of follow-up (Visit 32, Week 71) and after 13 months of follow-up (Visit 34, Month 25).

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: The primary endpoints were assessments of safety and no statistical testing was performed.

| End point values | CDNF mid-dose group | CDNF high-dose group | | |
|--------------------------------------|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 ^[12] | 7 ^[13] | | |
| Units: unit(s) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Visit 32 (Week 71) Safety&Efficacy | 0.13 (± 3.36) | 2.75 (± 1.71) | | |
| Visit 34 (Month 25) Safety | 1.88 (± 3.04) | 4.17 (± 4.96) | | |

Notes:

[12] - Corresponds to the SAS population

[13] - Corresponds to the SAS population

Statistical analyses

No statistical analyses for this end point

Primary: Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease

(QUIP-RS) (Change from baseline (Week -1))

| | |
|-----------------|---|
| End point title | Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP-RS) (Change from baseline (Week - |
|-----------------|---|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

The self-administered questionnaire was completed on three occasions during the follow-up study: at inclusion (Visit 27, Week 49), after six months of follow-up (Visit 32, Week 71) and after 13 months of follow-up (Visit 34, Month 25).

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: The primary endpoints were assessments of safety and no statistical testing was performed.

| End point values | CDNF mid-dose group | CDNF high-dose group | | |
|---|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 ^[15] | 7 ^[16] | | |
| Units: unit(s) | | | | |
| arithmetic mean (standard deviation) | | | | |
| ICD total score (A-D) - Visit 32 (Week 71) | -1.00 (± 0.00) | 0.25 (± 2.63) | | |
| ICD total score (A-D) - Visit 34 (Month 25) | 0.00 (± 0.00) | 2.25 (± 3.40) | | |
| Total score (A-G) - Visit 32 (Week 71) | 2.50 (± 4.95) | 2.00 (± 6.27) | | |
| Total score (A-G) - Visit 34 (Month 25) | -3.00 (± 11.53) | 3.20 (± 10.13) | | |

Notes:

[15] - Corresponds to the SAS population

[16] - Corresponds to the SAS population

Statistical analyses

No statistical analyses for this end point

Primary: Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP-RS) (Change from follow-up study baseline (Week 49))

| | |
|-----------------|--|
| End point title | Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP-RS) (Change from follow-up study baseline (Week 49)) ^[17] |
|-----------------|--|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

The self-administered questionnaire was completed on three occasions during the follow-up study: at inclusion (Visit 27, Week 49), after six months of follow-up (Visit 32, Week 71) and after 13 months of follow-up (Visit 34, Month 25).

Notes:

[17] - 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 | CDNF mid-dose group | CDNF high-dose group | | |
|---|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 ^[18] | 7 ^[19] | | |
| Units: unit(s) | | | | |
| arithmetic mean (standard deviation) | | | | |
| ICD total score (A-D) - Visit 32 (Week 71) | 1.00 (± 0.00) | 3.00 (± 5.20) | | |
| ICD total score (A-D) - Visit 34 (Month 25) | 1.00 (± 0.00) | 4.00 (± 2.71) | | |
| Total score (A-G) - Visit 32 (Week 71) | 3.00 (± 2.83) | 5.00 (± 8.66) | | |
| Total score (A-G) - Visit 34 (Month 25) | -4.00 (± 13.08) | 4.60 (± 4.72) | | |

Notes:

[18] - Corresponds to the SAS population

[19] - Corresponds to the SAS population

Statistical analyses

No statistical analyses for this end point

Primary: Montreal Cognitive Assessment (MoCA) (Change from baseline (Week -1))

| | |
|-----------------|---|
| End point title | Montreal Cognitive Assessment (MoCA) (Change from baseline (Week -1)) ^[20] |
|-----------------|---|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

The self-administered questionnaire was completed on three occasions during the follow-up study: at inclusion (Visit 27, Week 49), after six months of follow-up (Visit 32, Week 71) and after 13 months of follow-up (Visit 34, Month 25).

Notes:

[20] - 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 | CDNF mid-dose group | CDNF high-dose group | | |
|--------------------------------------|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 ^[21] | 7 ^[22] | | |
| Units: unit(s) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Visit 32 (Week 71) Safety&Efficacy | 0.63 (± 1.51) | 0.40 (± 3.13) | | |
| Visit 34 (Month 25) Safety | 0.38 (± 1.19) | -1.86 (± 3.63) | | |

Notes:

[21] - Corresponds to the SAS population

[22] - Corresponds to the SAS population

Statistical analyses

No statistical analyses for this end point

Primary: Montreal Cognitive Assessment (MoCA) (Change from follow-up study baseline (Week 49))

| | |
|-----------------|---|
| End point title | Montreal Cognitive Assessment (MoCA) (Change from follow-up |
|-----------------|---|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

The self-administered questionnaire was completed on three occasions during the follow-up study: at inclusion (Visit 27, Week 49), after six months of follow-up (Visit 32, Week 71) and after 13 months of follow-up (Visit 34, Month 25).

Notes:

[23] - 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 | CDNF mid-dose group | CDNF high-dose group | | |
|--------------------------------------|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 ^[24] | 7 ^[25] | | |
| Units: unit(s) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Visit 32 (Week 71) Safety&Efficacy | 0.00 (± 1.07) | 1.00 (± 2.16) | | |
| Visit 34 (Month 25) Safety | -0.25 (± 1.28) | -0.20 (± 2.59) | | |

Notes:

[24] - Corresponds to the SAS population

[25] - Corresponds to the SAS population

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 ^[26] |
|-----------------|---|

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; and lower extremities.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Physical examination was performed on 3 to 5 occasions during the follow-up study: at inclusion (Visit 27, Week 49), after six months of follow-up (Visit 32, Week 71), and after 13 months of follow-up (Visit 34, Month 25).

Notes:

[26] - 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 | CDNF mid-dose group | CDNF high-dose group | | |
|--|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 ^[27] | 7 ^[28] | | |
| Units: Subjects | | | | |
| Upper extremities - Baseline (Week -1) | 0 | 0 | | |
| Upper extremities - Visit 27 (Week 49) | 0 | 1 | | |
| Upper extremities - Visit 32 (Week 71) | 0 | 0 | | |

| | | | | |
|---|---|---|--|--|
| Upper extremities - Visit 34 (Month 25) | 0 | 0 | | |
| Head,eyes,ears,nose,throat,lymph nodes - Baseline | 0 | 0 | | |
| Head,eyes,ears,nose,throat,lymph nodes - Visit 27 | 1 | 0 | | |
| Head,eyes,ears,nose,throat,lymph nodes - Visit 32 | 0 | 0 | | |
| Head,eyes,ears,nose,throat,lymph nodes - Visit 34 | 0 | 0 | | |
| Neck, shoulders, back - Baseline (Week -1) | 1 | 0 | | |
| Neck, shoulders, back - Visit 27 (Week 49) | 1 | 1 | | |
| Neck, shoulders, back - Visit 32 (Week 71) | 2 | 1 | | |
| Neck, shoulders, back - Visit 34 (Month 25) | 0 | 0 | | |
| Chest and lungs - Baseline (Week -1) | 0 | 0 | | |
| Chest and lungs - Visit 27 (Week 49) | 0 | 0 | | |
| Chest and lungs - Visit 32 (Week 71) | 0 | 0 | | |
| Chest and lungs - Visit 34 (Month 25) | 0 | 0 | | |
| Cardiovascular - Baseline (Week -1) | 0 | 0 | | |
| Cardiovascular - Visit 27 (Week 49) | 0 | 0 | | |
| Cardiovascular - Visit 32 (Week 71) | 0 | 0 | | |
| Cardiovascular - Visit 34 (Month 25) | 0 | 0 | | |
| Abdomen - Baseline (Week -1) | 0 | 0 | | |
| Abdomen - Visit 27 (Week 49) | 0 | 0 | | |
| Abdomen - Visit 32 (Week 71) | 0 | 0 | | |
| Abdomen - Visit 34 (Month 25) | 0 | 0 | | |
| Lower extremities - Baseline (Week -1) | 1 | 0 | | |
| Lower extremities - Visit 27 (Week 49) | 0 | 0 | | |
| Lower extremities - Visit 32 (Week 71) | 0 | 0 | | |
| Lower extremities - Visit 34 (Month 25) | 0 | 1 | | |

Notes:

[27] - Corresponds to the SAS population

[28] - Corresponds to the SAS population

Statistical analyses

No statistical analyses for this end point

Primary: Neurological Examination - Abnormal with clinical relevance

| | |
|-----------------|---|
| End point title | Neurological Examination - Abnormal with clinical relevance ^[29] |
|-----------------|---|

End point description:

The following functions were included in the neurological examination: motor function; sensory function; cranial nerve function; cortical functions; and reflexes.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

A neurological examination was performed as part of the physical examination, during the follow-up study: at inclusion (Visit 27, Week 49), after 6 months of follow-up (Visit 32, Week 71), and after 13 months of follow-up (Visit 34, Month 25).

Notes:

[29] - 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 | CDNF mid-dose group | CDNF high-dose group | | |
|--|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 ^[30] | 7 ^[31] | | |
| Units: Subjects | | | | |
| Motor function - Baseline (Week -1) | 3 | 4 | | |
| Motor function - Visit 27 (Week 49) | 7 | 5 | | |
| Motor function - Visit 32 (Week 71) | 5 | 3 | | |
| Motor function - Visit 34 (Month 25) | 4 | 2 | | |
| Sensory function - Baseline (Week -1) | 1 | 0 | | |
| Sensory function - Visit 27 (Week 49) | 1 | 1 | | |
| Sensory function - Visit 32 (Week 71) | 1 | 0 | | |
| Sensory function - Visit 34 (Month 25) | 0 | 0 | | |
| Cranial nerve function - Baseline (Week -1) | 1 | 0 | | |
| Cranial nerve function - Visit 27 (Week 49) | 0 | 0 | | |
| Cranial nerve function - Visit 32 (Week 71) | 0 | 0 | | |
| Cranial nerve function - Visit 34 (Month 25) | 0 | 0 | | |
| Cortical functions - Baseline (Week -1) | 0 | 0 | | |
| Cortical functions - Visit 27 (Week 49) | 0 | 1 | | |
| Cortical functions - Visit 32 (Week 71) | 0 | 0 | | |
| Cortical functions - Visit 34 (Month 25) | 0 | 1 | | |
| Reflexes - Baseline (Week -1) | 0 | 0 | | |
| Reflexes - Visit 27 (Week 49) | 0 | 0 | | |
| Reflexes - Visit 32 (Week 71) | 0 | 1 | | |
| Reflexes - Visit 34 (Month 25) | 0 | 0 | | |

Notes:

[30] - Corresponds to the SAS population

[31] - Corresponds to the SAS population

Statistical analyses

No statistical analyses for this end point

Primary: Vital signs

| | |
|-----------------|-----------------------------|
| End point title | Vital signs ^[32] |
|-----------------|-----------------------------|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Vital signs were assessed at inclusion (Visit 27), after six months of follow-up (Visit 32) and after 13 months of follow-up (Visit 34, Month 25) as part of the physical examination.

Notes:

[32] - 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 | CDNF mid-dose group | CDNF high-dose group | | |
|--|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 ^[33] | 7 ^[34] | | |
| Units: unit(s) | | | | |
| arithmetic mean (standard deviation) | | | | |
| DBP (mmHg) - Visit 32 (Week 71) | 79.00 (± 9.01) | 81.60 (± 9.24) | | |
| DBP (mmHg) - Visit 34 (Month 25) | 76.29 (± 10.01) | 80.50 (± 15.86) | | |
| SBP (mmHg) - Visit 32 (Week 71) | 122.50 (± 14.65) | 132.60 (± 14.62) | | |
| SBP (mmHg) - Visit 34 (Month 25) | 117.57 (± 10.75) | 140.83 (± 35.66) | | |
| Pulse rate (bpm) - Visit 32 (Week 71) | 76.75 (± 8.56) | 77.40 (± 16.21) | | |
| Pulse rate (bpm) - Visit 34 (Month 25) | 72.43 (± 9.98) | 65.50 (± 17.60) | | |

Notes:

[33] - Corresponds to the SAS population

[34] - Corresponds to the SAS population

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) ^[35] |
|-----------------|---|

End point description:

There were no abnormal with clinical relevance laboratory values at baseline of the Main study (Week - 1) and at baseline of the inclusion in the Follow-up study (Week 49).

Clinical laboratory variables included:

- Clinical chemistry (Alanine transaminase, Alkaline phosphatase, Aspartate transaminase, Bilirubin, Calcium, Creatine kinase, Creatinine and eGFR, Potassium, Sodium, IgG, Albumin, and 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:

Blood and urine samples for determination of clinical laboratory variables were taken at the times given in the Schedule of Assessments and as clinically indicated.

Notes:

[35] - 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 | CDNF mid-dose group | CDNF high-dose group | | |
|---|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 ^[36] | 7 ^[37] | | |
| Units: Subjects | | | | |
| Laboratory Variable - Baseline (Week - 1) | 0 | 0 | | |
| Laboratory Variable - Visit 27 (Week 49) | 0 | 0 | | |
| Laboratory Variable - Visit 32 (Week 71) | 0 | 2 | | |

| | | | | |
|---|---|---|--|--|
| Laboratory variable - Visit 34 (Month 25) | 0 | 1 | | |
|---|---|---|--|--|

Notes:

[36] - Corresponds to the SAS population

[37] - V32 2 patients with ACL in 3 parameters

V34 1 patient with ACL in 2 parameters

Statistical analyses

No statistical analyses for this end point

Primary: anti-CDNF-antibodies in serum

| | |
|-----------------|---|
| End point title | anti-CDNF-antibodies in serum ^[38] |
|-----------------|---|

End point description:

Collected samples were analysed for anti-CDNF antibodies only if there had been positive antibody titres reported in either the main or the extension studies (HP-CD-CL-2002 or HP-CD-CL-2003, respectively). There was no risk of anti-CDNF antibody formation occurrence in the follow-up study, if the samples collected in the previous studies had been negative.

Only 1 patient (in the mid-dose CDFN treatment group) presented a positive result for CDFN antibodies at Week 49 (End of Extension study).

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Samples for anti-CDNF antibody were collected with each drug safety assessment visit, i.e. 31, 32 and 34. The sample for Visit 27 was collected on Visit 26 in the extension study, as the two visits preferably coincided.

Notes:

[38] - 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 | CDNF mid-dose group | CDNF high-dose group | | |
|--------------------------------|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1 | 0 ^[39] | | |
| Units: Subjects | | | | |
| Visit 32 (Week 71) - positive | 0 | | | |
| Visit 32 (Week 71) - negative | 1 | | | |
| Visit 34 (Month 25) - positive | 0 | | | |
| Visit 34 (Month 25) - negative | 1 | | | |

Notes:

[39] - Only 1 patient (in mid-dose CDFN treatment group) presented + CDFN antibodies at Visit 27 (Week 49)

Statistical analyses

No statistical analyses for this end point

Secondary: Severity of PD non-motor and motor symptoms by UPDRS Part I-IV total scores (Parts I, II and IV in ON-state; Part III in OFF-state) (Change from baseline (Week -1))

| | |
|-----------------|--|
| End point title | Severity of PD non-motor and motor symptoms by UPDRS Part I-IV total scores (Parts I, II and IV in ON-state; Part III in OFF-state) (Change from baseline (Week -1)) |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

The UPDRS assessment was performed by the Investigator on three occasions during the follow-up study: at inclusion (Visit 27, Week 49), after six months of follow-up (Visit 32, Week 71) and after 13 months of follow-up (Visit 34, Month 25).

| End point values | CDNF mid-dose group | CDNF high-dose group | | |
|-----------------------------------|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 ^[40] | 6 ^[41] | | |
| Units: score | | | | |
| arithmetic mean (standard error) | | | | |
| Part I - Visit 27 (Week 49) | -0.25 (± 1.28) | 0.33 (± 1.03) | | |
| Part I - Visit 32 (Week 71) | 0.00 (± 1.41) | -0.75 (± 2.22) | | |
| Part I - Visit 34 (Month 25) | 0.63 (± 1.41) | 1.17 (± 1.72) | | |
| Part II - Visit 27 (Week 49) | 0.50 (± 3.07) | 0.17 (± 5.08) | | |
| Part II - Visit 32 (Week 71) | 0.75 (± 4.17) | 4.25 (± 4.03) | | |
| Part II - Visit 34 (Month 25) | 4.88 (± 4.55) | 5.00 (± 7.56) | | |
| Part III - Visit 27 (Week 49) | -2.75 (± 9.41) | -1.20 (± 7.53) | | |
| Part III - Visit 32 (Week 71) | -3.43 (± 8.16) | 0.25 (± 7.14) | | |
| Part III - Visit 34 (Month 25) | 0.43 (± 4.58) | 2.80 (± 7.56) | | |
| Part IV - Visit 27 (Week 49) | 0.38 (± 2.20) | -0.67 (± 2.73) | | |
| Part IV - Visit 32 (Week 71) | 0.25 (± 2.49) | 2.00 (± 2.16) | | |
| Part IV - Visit 34 (Month 25) | -0.25 (± 1.58) | 0.33 (± 2.07) | | |
| UPDRS Total - Visit 27 (Week 49) | -2.13 (± 12.01) | -1.80 (± 8.70) | | |
| UPDRS Total - Visit 32 (Week 71) | -4.00 (± 9.18) | 5.75 (± 7.89) | | |
| UPDRS Total - Visit 34 (Month 25) | 4.71 (± 6.07) | 6.20 (± 12.72) | | |

Notes:

[40] - Corresponds to the FAS population

[41] - Corresponds to the FAS population

Statistical analyses

No statistical analyses for this end point

Secondary: Timed Up and Go (TUG) values (Change from baseline (Week -1))

| | |
|-----------------|---|
| End point title | Timed Up and Go (TUG) values (Change from baseline (Week -1)) |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

The TUG was performed in the OFF-state and was performed on three occasions during the follow-up study: at inclusion (Visit 27, Week 49), after six months of follow-up (Visit 32, Week 71) and after 13 months of follow-up (Visit 34, Month 25).

| End point values | CDNF mid-dose group | CDNF high-dose group | | |
|---------------------------------------|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 ^[42] | 6 ^[43] | | |
| Units: seconds | | | | |
| arithmetic mean (standard deviation) | | | | |
| Visit 27 (Week 49) Follow-up Baseline | 6.07 (± 22.78) | 0.82 (± 1.86) | | |
| Visit 32 (Week 71) Safety&Efficacy | 3.61 (± 11.66) | 0.73 (± 0.81) | | |
| Visit 34 (Month 25) Safety | 4.33 (± 8.45) | 2.30 (± 3.26) | | |

Notes:

[42] - Corresponds to the FAS population

[43] - Corresponds to the FAS population

Statistical analyses

No statistical analyses for this end point

Secondary: Functional status by home diary score - Bad time (Change from baseline (Week -1))

| | |
|-----------------|---|
| End point title | Functional status by home diary score - Bad time (Change from baseline (Week -1)) |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

The diary was completed on 4 occasions during the follow-up study: at inclusion (Visit 27, Week 49), after 3 months of follow-up (Visit 31, week 58), after 6 months of follow-up (Visit 32, Week 71) and after 13 months of follow-up (Visit 34, Month 25).

| End point values | CDNF mid-dose group | CDNF high-dose group | | |
|---------------------------------------|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 ^[44] | 6 ^[45] | | |
| Units: hours | | | | |
| arithmetic mean (standard deviation) | | | | |
| Visit 27 (Week 49) Follow-up Baseline | -1.22 (± 4.11) | -1.01 (± 2.74) | | |
| Visit 32 (Week 71) Safety&Efficacy | -1.33 (± 3.13) | 0.89 (± 1.99) | | |
| Visit 34 (Month 25) Safety | -1.96 (± 2.87) | 0.19 (± 5.02) | | |

Notes:

[44] - Corresponds to the FAS population

[45] - Corresponds to the FAS population

Statistical analyses

No statistical analyses for this end point

Secondary: Functional status by home diary score - Good time (Change from baseline (Week -1))

| | |
|-----------------|--|
| End point title | Functional status by home diary score - Good time (Change from baseline (Week -1)) |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

The diary was completed on 4 occasions during the follow-up study: at inclusion (Visit 27, Week 49), after 3 months of follow-up (Visit 31, week 58), after 6 months of follow-up (Visit 32, Week 71) and after 13 months of follow-up (Visit 34, Month 25).

| End point values | CDNF mid-dose group | CDNF high-dose group | | |
|---------------------------------------|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 ^[46] | 6 ^[47] | | |
| Units: hours | | | | |
| arithmetic mean (standard deviation) | | | | |
| Visit 27 (Week 49) Follow-up Baseline | 0.33 (± 4.26) | 0.64 (± 1.77) | | |
| Visit 32 (Week 71) Safety&Efficacy | -0.20 (± 2.93) | -1.33 (± 2.02) | | |
| Visit 34 (Month 25) Safety | 0.96 (± 2.85) | -0.26 (± 3.21) | | |

Notes:

[46] - Corresponds to the FAS population

[47] - Corresponds to the FAS population

Statistical analyses

No statistical analyses for this end point

Secondary: Functional status by home diary score - OFF time (Change from baseline (Week -1))

| | |
|-----------------|---|
| End point title | Functional status by home diary score - OFF time (Change from baseline (Week -1)) |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

The diary was completed on 4 occasions during the follow-up study: at inclusion (Visit 27, Week 49), after 3 months of follow-up (Visit 31, week 58), after 6 months of follow-up (Visit 32, Week 71) and after 13 months of follow-up (Visit 34, Month 25).

| End point values | CDNF mid-dose group | CDNF high-dose group | | |
|---------------------------------------|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 ^[48] | 6 ^[49] | | |
| Units: hour | | | | |
| arithmetic mean (standard deviation) | | | | |
| Visit 27 (Week 49) Follow-up Baseline | -1.35 (± 4.03) | -0.40 (± 2.23) | | |
| Visit 32 (Week 71) Safety&Efficacy | -1.02 (± 3.16) | 0.39 (± 3.77) | | |
| Visit 34 (Month 25) Safety | -2.09 (± 2.79) | -0.19 (± 3.32) | | |

Notes:

[48] - Corresponds to the FAS population

[49] - Corresponds to the FAS population

Statistical analyses

No statistical analyses for this end point

Secondary: Functional status by home diary score - ON-time with non-troublesome dyskinesia (Change from baseline (Week -1))

| | |
|-----------------|--|
| End point title | Functional status by home diary score - ON-time with non-troublesome dyskinesia (Change from baseline (Week -1)) |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

The diary was completed on 4 occasions during the follow-up study: at inclusion (Visit 27, Week 49), after 3 months of follow-up (Visit 31, week 58), after 6 months of follow-up (Visit 32, Week 71) and after 13 months of follow-up (Visit 34, Month 25).

| End point values | CDNF mid-dose group | CDNF high-dose group | | |
|---------------------------------------|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 ^[50] | 6 ^[51] | | |
| Units: hour | | | | |
| arithmetic mean (standard deviation) | | | | |
| Visit 27 (Week 49) Follow-up Baseline | 0.08 (± 3.59) | -1.83 (± 2.25) | | |
| Visit 32 (Week 71) Safety&Efficacy | -1.61 (± 2.17) | -1.33 (± 2.46) | | |
| Visit 34 (Month 25) Safety | 0.70 (± 2.02) | -0.96 (± 2.75) | | |

Notes:

[50] - Corresponds to the FAS population

[51] - Corresponds to the FAS population

Statistical analyses

No statistical analyses for this end point

Secondary: Functional status by home diary score - ON-time with troublesome dyskinesia (Change from baseline (Week -1))

| | |
|-----------------|--|
| End point title | Functional status by home diary score - ON-time with troublesome dyskinesia (Change from baseline (Week -1)) |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

The diary was completed on 4 occasions during the follow-up study: at inclusion (Visit 27, Week 49), after 3 months of follow-up (Visit 31, week 58), after 6 months of follow-up (Visit 32, Week 71) and after 13 months of follow-up (Visit 34, Month 25).

| End point values | CDNF mid-dose group | CDNF high-dose group | | |
|---------------------------------------|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 ^[52] | 6 ^[53] | | |
| Units: hour | | | | |
| arithmetic mean (standard deviation) | | | | |
| Visit 27 (Week 49) Follow-up Baseline | 0.13 (± 0.29) | -0.61 (± 1.04) | | |
| Visit 32 (Week 71) Safety&Efficacy | -0.31 (± 0.49) | 0.50 (± 1.96) | | |
| Visit 34 (Month 25) Safety | 0.13 (± 0.49) | 0.39 (± 2.01) | | |

Notes:

[52] - Corresponds to the FAS population

[53] - Corresponds to the FAS population

Statistical analyses

No statistical analyses for this end point

Secondary: Functional status by home diary score - ON-time without dyskinesia (Change from baseline (Week -1))

| | |
|-----------------|---|
| End point title | Functional status by home diary score - ON-time without dyskinesia (Change from baseline (Week -1)) |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

The diary was completed on 4 occasions during the follow-up study: at inclusion (Visit 27, Week 49), after 3 months of follow-up (Visit 31, week 58), after 6 months of follow-up (Visit 32, Week 71) and after 13 months of follow-up (Visit 34, Month 25).

| End point values | CDNF mid-dose group | CDNF high-dose group | | |
|---------------------------------------|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 ^[54] | 6 ^[55] | | |
| Units: hour | | | | |
| arithmetic mean (standard deviation) | | | | |
| Visit 27 (Week 49) Follow-up Baseline | 0.25 (± 4.51) | 2.47 (± 3.42) | | |
| Visit 32 (Week 71) Safety&Efficacy | 1.40 (± 3.30) | 0.00 (± 1.01) | | |
| Visit 34 (Month 25) Safety | 0.27 (± 2.69) | 0.69 (± 5.36) | | |

Notes:

[54] - Corresponds to the FAS population

[55] - Corresponds to the FAS population

Statistical analyses

No statistical analyses for this end point

Secondary: Parkinson disease questionnaire - PDQ-39 total score (Change from

baseline (Week -1))

| | |
|-----------------|---|
| End point title | Parkinson disease questionnaire - PDQ-39 total score (Change from baseline (Week -1)) |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

It was completed on three occasions during the follow-up study: at inclusion (Visit 27, Week 49), after six months of follow-up (Visit 32, Week 71) and after 13 months of follow-up (Visit 34, Month 25).

| End point values | CDNF mid-dose group | CDNF high-dose group | | |
|---------------------------------------|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 ^[56] | 6 ^[57] | | |
| Units: score | | | | |
| arithmetic mean (standard deviation) | | | | |
| Visit 27 (Week 49) Follow-up Baseline | -1.78 (± 8.08) | 1.96 (± 7.27) | | |
| Visit 32 (Week 71) Safety&Efficacy | 0.83 (± 10.92) | 10.63 (± 6.78) | | |
| Visit 34 (Month 25) Safety | 0.90 (± 11.47) | 10.38 (± 6.92) | | |

Notes:

[56] - Corresponds to the FAS population

[57] - Corresponds to the FAS population

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression (Change from baseline (Week -1))

| | |
|-----------------|---|
| End point title | Clinical Global Impression (Change from baseline (Week -1)) |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

The CGI was assessed on 4 occasions during the follow-up study: at inclusion (Visit 27, Week 49), after three months of follow-up (Visit 31, week 58), after six months of follow-up (Visit 32, Week 71) and after 13 months of follow-up (Visit 34, Month 25).

| End point values | CDNF mid-dose group | CDNF high-dose group | | |
|---------------------------------------|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 ^[58] | 6 ^[59] | | |
| Units: score | | | | |
| arithmetic mean (standard deviation) | | | | |
| Visit 27 (Week 49) Follow-up Baseline | 3.50 (± 0.93) | 4.33 (± 0.82) | | |
| Visit 32 (Week 71) Safety&Efficacy | 3.75 (± 0.89) | 4.75 (± 0.96) | | |
| Visit 34 (Month 25) Safety | 3.75 (± 0.46) | 5.00 (± 0.89) | | |

Notes:

[58] - Corresponds to the FAS population

[59] - Corresponds to the FAS population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events (AEs)/adverse device effects (ADEs) occurring during the course of the study were reported and collected in the eCRF, starting from obtained Informed Consent and until completed End of Study visit.

Adverse event reporting additional description:

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 | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 20.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------|
| Reporting group title | CDNF mid-dose group |
|-----------------------|---------------------|

Reporting group description: -

| | |
|-----------------------|----------------------|
| Reporting group title | CDNF high-dose group |
|-----------------------|----------------------|

Reporting group description: -

| Serious adverse events | CDNF mid-dose group | CDNF high-dose group | |
|---|---------------------|----------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 4 / 7 (57.14%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Dystonia | | | |
| 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 | |
| Headache | | | |
| 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 | |

| | | | |
|---|----------------|----------------|--|
| Parkinson's disease | | | |
| 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 | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| 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 | |
| Gastrointestinal disorders | | | |
| Duodenal ulcer | | | |
| 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 | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| 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 | |
| Musculoskeletal and connective tissue disorders | | | |
| Spinal column stenosis | | | |
| 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 | |
| Metabolism and nutrition disorders | | | |
| Acidosis | | | |
| 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 | CDNF mid-dose group | CDNF high-dose group | |
|---|---------------------|----------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 8 / 8 (100.00%) | 7 / 7 (100.00%) | |
| Injury, poisoning and procedural complications | | | |
| Procedural headache | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Procedural pain | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Nervous system disorders | | | |
| Cerebral gas embolism | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 2 / 7 (28.57%) | |
| occurrences (all) | 1 | 2 | |
| Headache | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 3 / 7 (42.86%) | |
| occurrences (all) | 0 | 4 | |
| Migraine with aura | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 7 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 7 (28.57%) | |
| occurrences (all) | 0 | 2 | |
| General disorders and administration site conditions | | | |
| Implant site reaction | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 7 (28.57%) | |
| occurrences (all) | 0 | 2 | |
| Ear and labyrinth disorders | | | |
| Hypoacusis | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Gastrointestinal disorders | | | |

| | | | |
|--|---------------------|---------------------|--|
| Diarrhoea subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 2 | 0 / 7 (0.00%) 0 | |
| Psychiatric disorders Depression subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 2 / 7 (28.57%) 2 | |
| Hallucination subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 2 / 7 (28.57%) 2 | |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 2 / 7 (28.57%) 3 | |
| Pain in extremity subjects affected / exposed occurrences (all) | 2 / 8 (25.00%) 2 | 1 / 7 (14.29%) 2 | |
| Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 1 / 7 (14.29%) 2 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 25 September 2018 | Protocol Amendment #1: -Updated short title; -Updated list of abbreviations; - Parallel compassionate use program – study Design: The removal of the port could be postponed until after the last treatment infusion in the CUP was administered. Efficacy assessment was done at 6 and 13 months of follow-up, allowing at least six months of follow-up after the last treatment infusion, in case the patient received further doses of CDNF in a separate CUP. Statistical methods were updated to reflect a longer period of follow-up for the efficacy assessment of the IMP; -Primary analysis at 13 months of follow-up: Patients were assessed for safety and efficacy at 6 months and 13 months from follow-up study start (18 and 25 months from treatment start, respectively); -Study flow-chart addition and update; -Timing of explantation surgery: If the patient received further treatment doses in a separate CUP, removal of the transcutaneous port could be postponed until after any additional treatment infusions had been completed. In case the investigator and patient decided to remove also other implanted parts of the DDS, explantation was scheduled as soon as possible in the beginning of the follow-up study; -Off-state not required during DAT-PET: As it was unclear if levodopa or dopamine agonists affected the final image, it was decided not to require the patients to be off medication for up to 24 hours, but to allow intake of their normal prescribed dose of medication; -Final safety and efficacy assessment at visit 34: The final safety and efficacy assessment was performed at thirteen months in the follow-up study, approximately seven months since the last treatment infusion under the CUP (Visit 34, Month 25 from baseline). The assessments were the same as during the six months follow-up assessment (Visit 32, Month 18); -Updated schedule of assessment: The Schedule of Assessment was updated to include the efficacy assessments to be performed. |
| 28 January 2019 | Protocol Amendment #2: -Removal of reference to Compassionate Use Program The protocol was amended to delete any references to the optional CUP, as this was not applicable or approvable in the country where the follow-up study (HP-CD-CL-2004) was conducted. The list of abbreviations was double checked, and unreferenced abbreviations deleted; -Administrative structure changes; - Correction of timepoint for explantation: The protocol was corrected to reflect the maximum time for scheduling the explantation surgery after study start. The explantation surgery of the transcutaneous port was to be explanted as soon as possible after the last treatment infusion through the DDS. If the original explantation surgery was scheduled around 6 weeks after follow-up study start and postponed with up to 22 weeks for patients who received infusions under compassionate use, this was approximately 28 weeks, or seven months, from study start; -Timepoint for central laboratory sample collection: For practical reasons, the serum sample for anti-CDNF antibodies was changed to be collected on the day of the visit to the clinic. This sample was stored at the clinic until shipment to the central laboratory for analysis of anti-CDNF antibodies; - Correction of local laboratory sample collection: The table 7 was updated to delete the sample collection at Visit 33 and to include the sample collection at Visit 35. Furthermore, no CSF collection would be performed routinely in the follow-up study, and the table title was updated to reflect this; -Clarification of statistical analysis on device safety and performance: Since the occurrence of ADEs related to explantation of the DDS was the primary endpoint of the study, analysis of this needed to consider the three scenarios for explantation described in the protocol. The protocol was amended to clarify that this was the case. |

| | |
|---------------|---|
| 03 June 2019 | Protocol Amendment #3: -Update of risk mitigation section: The section 9.2.2 of the CSP (Appendix 16.1.1), corresponding to the risk mitigation of the DDS, was updated in alignment with the latest applicable Clinical Evaluation Report (CER) for the IMD; -Explantation options: The description of options for port removal was clarified to also include the sub-cutaneous manifold; -Removal of compassionate use program aspects: The CUP aspects were removed from the study. Without the CUP, the port was surgically removed in the beginning of the study, and there was no further need for port assessment after removal of the port; -Change of contact information: The administrative structure was updated to reflect the new address of the bioanalytical laboratory for pharmacokinetics and antibody testing; -Update to collection of device deficiencies and analysis of the investigational device performance: The Device Deficiencies Form and associated process were introduced with the aim to better document device deficiencies and make verification of data possible. In addition, the description on how device performance would be analysed was clarified; -Update to visit and assessment schedules to include recording device deficiency as an assessment: There was a formal introduction of device deficiency assessments to ensure more reliable and accurate recording of device deficiencies. |
| 06 April 2020 | Protocol Amendment #4: -Sponsor, manufacturer, and legal representative update; -Contracted regulatory tasks: The contract research organization responsible for regulatory submissions and communications changed; -Explantation surgery and PET visit window widened: The device explantation surgery could be postponed by up to 6 months from study entry, to allow more flexibility in scheduling the surgery during special circumstances, such as the COVID-19 outbreak. Whilst the port remained implanted, the risk of infection continued so the patient continued to maintain the port until it was removed, in accordance with their port care instructions (wearing the port cap 12h on/12h off and daily cleaning). Scheduled port assessments could be organised as remote visits; -Cross-contamination safety precautions: During the COVID-19 outbreak, special precautions to reduce the risk of cross-contamination were considered; -Levodopa challenge test: To confirm the patient's responsiveness thirteen months after treatment end, a levodopa challenge test was added to the patient's UPDRS Part III assessment in off-medication state, where their improvement in UPDRS Part III motor score one hour after dosing was expressed as a percentage from the off-state; -Blinding procedures: Unblinding procedures and timepoints were clarified and specified, to indicate that patients had to remain blinded for their treatment group in studies until the last efficacy assessment was performed (Visit 34), approximately thirteen months after treatment end; Analysis of anti-drug antibody samples: There was no risk of anti-CDNF antibody formation occurrence in the follow-up study, if the samples collected in the previous studies had been negative. Samples for anti-CDNF antibody were collected with each drug safety assessment visit. The sample for Visit 27 was collected on Visit 26 in the extension study, as the two visits preferably coincided. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported.

Notes: