

RESEARCH ARTICLE

Intrapatamenal Cerebral Dopamine Neurotrophic Factor in Parkinson's Disease: A Randomized, Double-Blind, Multicenter Phase 1 Trial

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ABSTRACT: Background: Cerebral dopamine neurotrophic factor (CDNF) is an unconventional neurotrophic factor that protects dopamine neurons and improves motor function in animal models of Parkinson's disease (PD).

Objective: The primary objectives of this study were to assess the safety and tolerability of both CDFN and the drug delivery system (DDS) in patients with PD of moderate severity.

Methods: We assessed the safety and tolerability of monthly intrapatamenal CDFN infusions in patients with PD using an investigational DDS, a bone-anchored transcutaneous port connected to four catheters. This phase 1 trial was divided into a placebo-controlled, double-blind, 6-month main study followed by an active-treatment 6-month extension. Eligible patients, aged 35 to 75 years, had moderate idiopathic PD for 5 to 15 years and Hoehn

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and Yahr score ≤ 3 (off state). Seventeen patients were randomized to placebo ($n = 6$), 0.4 mg CDNF ($n = 6$), or 1.2 mg CDNF ($n = 5$). The primary endpoints were safety and tolerability of CDNF and DDS and catheter implantation accuracy. Secondary endpoints were measures of PD symptoms, including Unified Parkinson's Disease Rating Scale, and DDS patency and port stability. Exploratory endpoints included motor symptom assessment (PKG, Global Kinetics Pty Ltd, Melbourne, Australia) and positron emission tomography using dopamine transporter radioligand [^{18}F]FE-PE21.

Results: Drug-related adverse events were mild to moderate with no difference between placebo and treatment groups. No severe adverse events were associated with the drug, and device delivery accuracy met specification. The severe adverse events recorded were associated

with the infusion procedure and did not reoccur after procedural modification. There were no significant changes between placebo and CDNF treatment groups in secondary endpoints between baseline and the end of the main and extension studies.

Conclusions: Intraputamenally administered CDNF was safe and well tolerated, and possible signs of biological response to the drug were observed in individual patients. © 2023 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: clinical trial; neurotrophic factor; synucleinopathy; movement disorder; convection-enhanced delivery; transcutaneous port

The motor symptoms of Parkinson's disease (PD) reflect the degeneration and death of nigrostriatal dopamine neurons. Although the cause of the progressive cell death remains unknown, neuropathological hallmarks of PD include the accumulation of α -synuclein aggregates and neuroinflammation in the affected brain regions.^{1,2} Currently, there is no cure for PD, but medications, device-assisted therapies, and multidisciplinary management may provide symptomatic relief. Levodopa (L-dopa) remains the most effective and best-tolerated drug to treat motor symptoms in PD.¹ Because the available treatments do not retard or stop the underlying neurodegeneration,³ there remains an unmet need for neuroprotective and disease-modifying therapies in PD.⁴

Neurotrophic factors (NTFs) promote growth, survival, differentiation, and maintenance of neurons in the developing and adult vertebrate nervous system.^{5,6} Striatically delivered glial cell line-derived neurotrophic factor (GDNF) family NTFs GDNF (recombinant protein infusion) and neurturin (gene therapy) have been tested in phase 1 and 2 clinical trials in PD.⁷⁻¹¹ Continuous intracerebroventricular infusion of platelet-derived growth factor B has also been tested in patients with PD.¹² The previous clinical studies with growth factors have produced varying results potentially because of various technical challenges ranging from nonoptimal drug delivery and limited bioavailability of the growth factors to poor translation from preclinical models to patients, as well as clinical study design issues.¹³⁻¹⁶

Cerebral dopamine neurotrophic factor (CDNF) is a member of a novel family of unconventional NTFs that is structurally and mechanistically distinct from all other known NTFs.¹⁷ The lack of functional CDNF protein expression in mice leads to degeneration of enteric dopamine neurons and altered brain dopamine neuron function suggesting that CDNF has a physiological role in the maintenance and survival of dopamine

neurons.^{18,19} Intrastratially administered CDNF protein protects midbrain dopamine neurons and improves both motor and nonmotor functions in toxin-based rodent and primate models of PD^{17,20,21} via a multimodal mechanism that involves modulation of endoplasmic reticulum stress and neuroinflammation (reviewed by Lindholm and Saarma²² and Huttunen and Saarma²³). CDNF also interacts directly with α -synuclein; reduces its aggregation, neuronal entry, and toxicity; and improves motor function in α -synuclein-based rodent models.²⁴ The lack of heparan sulphate-binding motifs allows a broader volume of distribution after parenchymal infusion compared with many other NTFs.²¹ With these distinct and superior properties compared with growth factors previously tested in patients with PD, CDNF is well positioned to be tested as a disease-modifying drug candidate in PD.

As an 18-kDa protein, CDNF cannot pass the blood-brain barrier, and intracerebral administration is needed for bioavailability in the target brain regions. Several early-stage clinical studies have been conducted to evaluate this approach.^{15,25}

In rat brain, intrastratially infused CDNF has a half-life of 5.5 hours.²⁶ Despite the relatively short brain half-life, preclinical studies have shown a long-lasting effect of CDNF for up to several weeks,^{17,20} which makes intermittent drug infusion directly to the putamen, the target brain area of the nigrostriatal dopamine neurons, a feasible option. Dosing with monthly intervals reduces potential protein accumulation and potential desensitization of the target pathway, and it is supported by a nonhuman primate study using monthly intraputamenal administration of CDNF.²⁷ In this phase 1 study, we investigated intraputamenal administration of recombinant human CDNF protein using an intracerebral drug delivery system (DDS). The primary objectives of this study were to assess the safety and tolerability of both CDNF and the DDS in patients with

PD of moderate severity. Due to ethical reasons (first-in-human study for CDNF, risks of surgery and intracranial delivery), patients with PD of moderate severity were recruited to this phase 1 study. Although this clinical study was designed mainly for assessment of safety and tolerability of intraputamenal CDNF infusions and the assessment of device safety and accuracy performance, exploratory data were collected for evaluation of signs of biological response to the treatment.

Patients and Methods

The clinical study design and methods are described in full detail in the Supporting Information.

Study Design

This was a first-in-human, phase 1, randomized, double-blind, placebo-controlled, multicenter safety and tolerability study. The study was conducted at three clinical centers, two in Sweden (Karolinska and Skåne University Hospitals) and one in Finland (Helsinki University Hospital). Each site had their own surgical teams for implantation and explantation surgeries with a separate surgical and clinical support team at each site. Positron emission tomography (PET) investigations were performed at the Karolinska Institute PET Center, Sweden, and at the Turku PET Center, Finland. For Sweden, The Medical Products Agency of Sweden, the regional ethics committee in Stockholm, and the Stockholm Medicinal Biobank and radiation safety committee of Karolinska University Hospital approved the study. In Finland, approvals were granted from the Finnish Medicines Agency (drug) and National Supervisory Authority for Welfare and Health (device) and from the ethics committee of the Hospital District of Helsinki and Uusimaa.

The study was registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT03295786 and NCT03775538) and at EudraCT (2015-004175-73 and 2018-000346-19). The follow-up study was registered as NCT04228653 and 2017-005170-19, respectively.

Patients

Eligible patients were diagnosed with idiopathic PD according to the UK Brain Bank Criteria, were aged 35 to 75 years (inclusive), exhibited a Unified Parkinson's Disease Rating Scale (UPDRS) motor score (Part III)^{28,29} between 25 and 50 and Hoehn and Yahr score ≤ 3 in the practically defined *off* state, were responsive to L-dopa with at least five daily doses of L-dopa, and had motor fluctuations with, on average, at least 2.5 hours of daily *off* time. Exclusion criteria included atypical parkinsonism or any known secondary parkinsonism, tremor that could interfere with treatment and test infusions, significant neurological disorder other than PD, screening or

planning magnetic resonance imaging (MRI) demonstrating any abnormality that would suggest an alternative cause for parkinsonism or preclude neurosurgery, and any medical condition that might impair outcome measure or safety assessments or would put the patient at undue risk from surgical treatment or chronic implants. All patients provided written informed consent according to the Declaration of Helsinki.

A delay in the recruitment of eligible patients in the study led to the decision to end recruitment in June 2019 because the expiry date for the investigational medicinal product could not cover the entire treatment period in the extension phase of the study in patients recruited after June 2019.

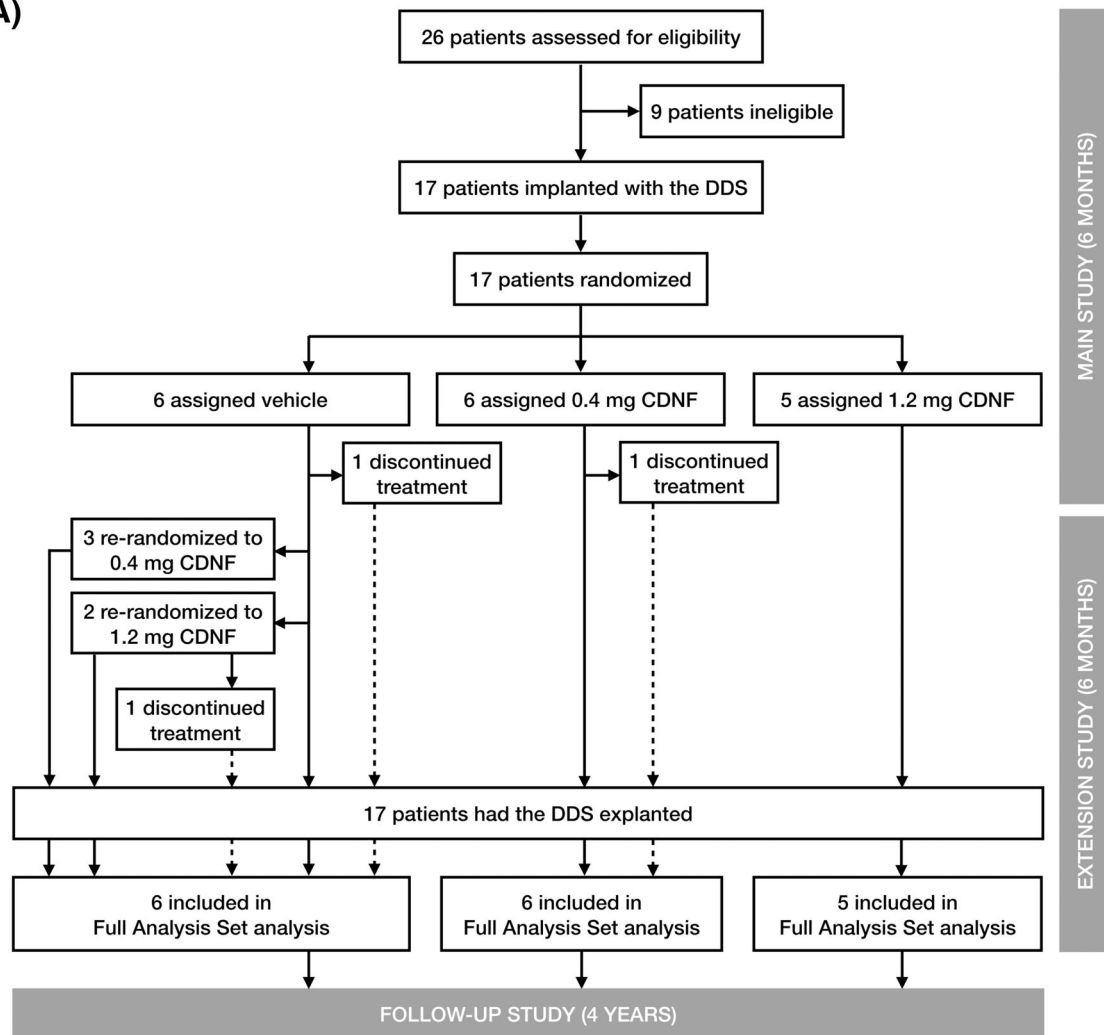
Randomization

Patients eligible for randomization were allocated a unique sequential randomization number. Each randomization number had an assigned treatment (placebo, 0.4 mg CDNF, or 1.2 mg CDNF) at a 1:1:1 ratio. The randomization structure ensured that the first two patients in the study were one with vehicle and one with 0.4 mg CDNF (starting with three first doses at the lowest dose level: 0.12 mg). Patients who received placebo in the first 6 months (main study) were rerandomized to either 0.4 or 1.2 mg CDNF at week 24 (start of extension study; Fig. 1A). Patients who were randomized to either the 0.4 mg or 1.2 mg CDNF group in the main study continued their treatment in the same treatment group in the extension study. Patients and investigators were blinded to treatment assignment for both the main and the extension study.

Procedures and Outcomes

Recombinant human CDNF was good manufacturing practice manufactured (Biovia Ltd, Turku, Finland), formulated at 1.0 mg/mL in artificial cerebrospinal fluid without glucose (aCSF), pH 7.2, and stored at less than -60°C until preparation for infusion. The aCSF solution was used as a vehicle in placebo infusions and diluent for the different CDNF dose concentrations. Surgery was performed approximately 8 weeks (week -8) before first treatment dose. The DDS was similar to that used in an earlier clinician-led study in PD¹⁰ and on humanitarian grounds in glioma treatment,³⁰ and it consisted of four catheters connected to an MRI-compatible transcatheter access port. The port kinematically locates to a novel four-needle giving set that is connected to an application set equipped with in-line air and bacterial filters to facilitate simultaneous, chronic intermittent infusions through each individual catheter (Fig. 2A; Supporting Information Fig. S2 in Data S1). Two catheters were implanted in each putamina in stereotactic neurosurgery assisted by the neuromate robotic system (Renishaw Mayfield SARL,

(A)



(B)

	All (n=17)	Placebo (n=6)	0.4 mg CDNF (n=6)	1.2 mg CDNF (n=5)
Age (y, mean ± SD)	61.8 (±7.5)	63.8 (±6.4)	63.2 (±8.9)	57.8 (±6.7)
Mean age range (y)	51–75	57–75	54–75	51–69
Sex (male / female)	12 / 5	5 / 1	3 / 3	4 / 1
Sex (M/F, %)	71% / 29%	83% / 17%	50% / 50%	80% / 20%
BMI (kg/m ² , mean ± SD)	25.5 (±3.9)	26.1 (±4.7)	25.1 (±3.1)	25.1 (±4.4)
Hoehn & Yahr stage	2.4 (±0.4)	2.3 (±0.4)	2.4 (±0.5)	2.4 (±0.4)
Disease duration (y, mean ± SD)	10.6 (±2.6)	10.5 (±2.7)	10.7 (±3.1)	10.8 (±2.3)
UPDRS-III (on, mean ± SD)	13.8 (±6.0)	14.8 (±6.9)	14.3 (±4.5)	11.8 (±7.1)
UPDRS-III (off, mean ± SD)	33.1 (±7.0)	33.3 (±7.6)	34.7 (±7.3)	31.0 (±6.8)
Levodopa response (% , mean ± SD)	59 (±15)	61 (±14)	58 (±12)	57 (±20)
Off time per day (h, mean ± SD)	5.1 (±1.4)	4.7 (±0.7)	6.1 (±1.5)	4.4 (±1.5)

FIG. 1. Study flow and demographic data at screening. (A) Cerebral dopamine neurotrophic factor (CDNF) phase 1 flowchart. Note that all patients started with the low (0.12 mg) dose of CDNF before receiving the indicated 0.4 or 1.2 mg doses of CDNF. (B) Patient demographic and Parkinson’s disease characteristics at screening. BMI, body mass index; DDS, drug delivery system; F, female; M, male; UPDRS, Unified Parkinson’s Disease Rating Scale.

Chassieu, France). The DDS and surgical planning software were designed and manufactured by Renishaw Neuro Solutions Ltd.

The patients were treated with either CDNF (1.0 mg/mL diluted to administer 0.12, 0.4, or 1.2 mg) or aCSF (placebo) on a monthly basis for 6 months (placebo-

controlled main study) and with 0.4 or 1.2 mg for another 6-month period (extension study). The main and extension studies consisted of a total of 26 visits over a period of 16 months.

At week -5, the first two patients had a test infusion with MRI to test the DDS functionality. Baseline safety

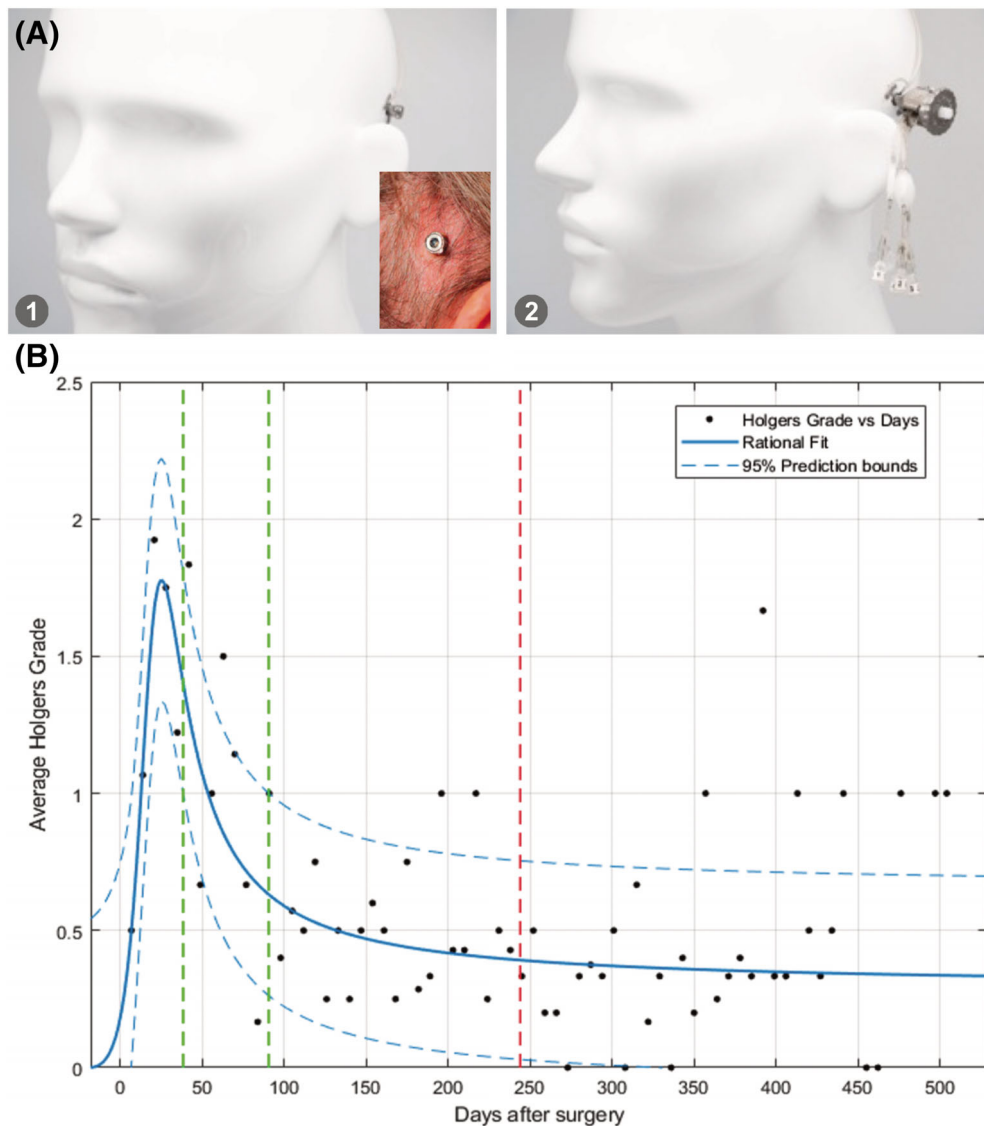


FIG. 2. Healing of the skin area around the titanium port of the drug delivery system (DDS). **(A)** Illustration of the DDS components: (1) three-dimensional printed titanium transcutaneous port, (2) port with four-channel application set attached. **(B)** Graph of average Holger's grade over time (days). Rational fit with 95% prediction bounds. Green dotted lines indicate time at which the predicated Holger's grade = 1. Red line indicates demarcation between main and extension studies. DDS, drug delivery system.

parameters and motor and non-motor scores were recorded at week -1 . PET imaging was performed at baseline (week -2), at 6 months (end of main study), at 12 months (end of extension study), and at 18 months (follow-up study) using the dopamine transporter (DAT) radioligand [^{18}F]FE-PE2I.³¹⁻³³ Parametric images of binding potential were generated and coregistered to the structural MRI. Regions of interest were nucleus caudate and putamen (the location of the catheter tips), using automated anatomical labeling, and substantia nigra using an in-house template.³²

The primary endpoints were the safety and tolerability of intraputamenally infused CDNF, the safety and tolerability of the DDS, and the accuracy of DDS implantation. Safety and tolerability were assessed by

the investigator at any time throughout the study at both scheduled and unscheduled visits. Safety assessments after first dosing included treatment-emergent adverse events (TEAEs), severe adverse events (SAEs), adverse device effects (ADEs), and severe ADEs (SADEs). Laboratory assessments of blood (including detection of anti-CDNF antibodies) and urine were performed at each visit. Physical examinations (including neurological examination), vital sign assessments, electrocardiogram, safety verification of DDS after surgery, assessments of DDS port (including wound healing time/skin-site reaction) and device deficiencies, patient-completed questionnaires on depression (Beck's Depression Inventory) and impulsive-compulsive disorders (Questionnaire for Impulsive-Compulsive Disorders in

Parkinson's Disease-Rating Scale), and patient cognition assessments (Montreal Cognitive Assessment) were performed. Healing of the port wound site was assessed using a modified Holger's grade (grades 0–4, where grade 1 was classed as “redness with slight swelling around the port” and grade 4 was classed as “overt signs of infection/purulent discharge”) and recorded across both studies. The system or catheter tip target accuracy was assessed by evaluating the Euclidean positional difference between the planned catheter, represented by a three-dimensional wireframe model within the planning MRI, and actual location of the radio-opaque catheter visualized via computed tomography.

Secondary outcomes included UPDRS Part III in practically defined *off* state; UPDRS total, Parkinson's Disease Questionnaire-39 (PDQ-39), clinical global impression, and timed up and go test in practically defined *off* state; and patient home diary recording of bad time and good time. Secondary device endpoints included the patency of individual catheter lines and the stability of the transcutaneous port. Exploratory outcomes were CDNF levels in serum and CSF after infusion (week 20), dyskinesia score (DKS) and bradykinesia score (BKS), with and without adjustment for L-dopa equivalent daily dose (LEDD) as measured by the wrist-worn PKG device (Global Kinetics Pty Ltd, Melbourne, Australia),³⁴ and change in DAT availability in putamen, nucleus caudate, and substantia nigra measured with PET imaging using [¹⁸F]FE-PE2I. Exploratory device endpoint was a T1 MRI assessment of the infusion coverage of the putamina target site before first active treatment infusion, via test infusion of aCSF/gadolinium contrast Magnevist® (Bayer AG, Leverkusen, Germany). LEDD was calculated based on conversion factors described by Tomlinson et al.³⁵

Statistical Analysis

Statistical analyses of clinical outcome measures were performed in SAS (version 9.4; SAS Institute, Cary, NC). All statistical tests are to be regarded as descriptive or exploratory. All randomized patients were included in the efficacy analyses according to the intention-to-treat principle. No power calculation was performed regarding the secondary efficacy outcomes in the main study.

Median BKS and median DKS, both adjusted to LEDD, were analyzed as change from baseline measurements by mixed-effect model for repeated measurements (ANOVA) with Dunnett post hoc test for multiple comparison.

Results

Patients were recruited between October 3, 2017, and February 27, 2019. A total of 26 patients were screened, of which 17 were randomized and implanted

with the DDS; 6 patients each were randomized to placebo or 0.4 mg CDNF, and 5 patients were randomized to 1.2 mg CDNF. In the main study, 17 patients were analyzed for safety and efficacy and 15 patients completed this phase of the study (1 patient each from the placebo and 0.4 mg CDNF groups discontinued). In the extension study, of the five remaining placebo-treated patients, three and two were randomized to 0.4 and 1.2 mg CDNF, respectively. Fifteen patients were analyzed for safety and efficacy in the extension study; 14 patients completed the extension study (one withdrew consent) (Fig. 1A). All 17 randomized patients had the DDS, either all parts ($n = 12$) or only the external parts of the DDS ($n = 5$) explanted at the end of the extension study. All explants were performed as expected with no ADEs. All except two patients enrolled in a separate 4-year follow-up study.

Mean (\pm SD) age at baseline was 61.8 ± 7.5 years; five (29%) patients were female. Mean disease duration since first motor symptoms was 10.6 ± 2.6 years. The mean Hoehn and Yahr score was 2.4 ± 0.4 , and the subjects had 5.1 ± 1.4 hours of *off* time per day (Fig. 1B). Mean UPDRS Part III score in *off* state was 33.1 ± 7.0 , with reduction of $58.5\% \pm 14.5\%$ after L-dopa challenge. Disease-related PD risk alleles were identified by next-generation sequencing in three patients: LRRK2 (G2019S), LRRK2 (R767C), and GBA (N409S). In addition, one patient had a VPS13A (D448H) variant (Supporting Information Table S1 in Data S1). All risk allele carriers were heterozygous.

After surgical implantation of the DDS, healing of the port wound site was graded by Holger's scale. Analysis of the average Holger's grade per week showed an average healing period of 80 days, as shown in Figure 2B.

The MRI-guided robot-assisted DDS implantation was accurate, 64 of 68 (94%) catheters were implanted within the 3-mm radial limit from the planned target location. Reasons for the target misalignment were an error in the placement of the skull in frame (surgery, 14/17) and an error in the DDS handling (surgery, 11/17). No clinical adverse reaction could be related to this. Retraining was delivered before the next surgery at each site following the case of DDS use error, after which no subsequent occurrences took place. All catheter lines were deemed to be in a safe and acceptable location within the putamen, and no reimplantations were required.

Only 1 of 68 infusion lines was found not patent, and this only at one single infusion visit of 201 infusion visits across the whole population. Although this was reported as occluded, this was subsequently attributed as user error (line misconnection) because the intracerebral catheter remained patent for the rest of the study. The assessment of port stability was calculated by either the number of cessations of infusions caused by an unstable port on line connection or the need for

TABLE 1 Treatment-emergent adverse effects

	Placebo (n = 6 NA)	0.4 mg CDNF (n = 6 n = 8)	1.2 mg CDNF (n = 5 n = 7)	Total (n = 17 n = 15)
Number of TEAEs, n	34 (34)	75 (36 39) ^a	127 (68 59) ^a	206 (108 98) ^a
Patients with at least one TEAE, n (%)	6 (100%)	6 8 (100% 100%)	5 7 (100% 100%)	17 15 (100% 100%)
SAEs, n	1	1 (1 0)	1 (0 1)	3 (2 1)
Patients with at least one SAE, n (%)	1 (17%)	1 0 (17% 0%)	0 1 (0% 14%)	2 1 (12% 7%)
AEs where action taken is study medication discontinued permanently, n	1	1 0	0 0	2 0
Patients with AEs where action taken is study medication discontinued permanently, n (%)	1 (17%)	1 0 (17% 0%)	0 0 (0% 0%)	2 0 (12% 0%)
TEAEs related to the study drug, n	11	25 (13 12)	32 (15 17)	68 (39 29)
Patients with at least one related AE to the study drug (CDNF or placebo), n (%)	2 (33%)	3 5 (50% 63%)	4 5 (80% 71%)	9 10 (53% 67%)
TEAEs related to the study device, n	6	22 (12 10)	27 (15 12)	55 (33 22)
TEAEs related to the surgical procedures, n	3	5 (5 NA)	9 (9 NA)	17 (17 NA)
TEAEs related to drug–device combination, n	6	12 (8 4)	19 (11 8)	37 (25 12)
TEAEs related to skin reaction around the port, n	2	4 (2 2)	12 (5 7)	18 (9 9)

Note: Numbers in parentheses show AEs and SAEs in the main study (black) and extension study (blue).

Abbreviations: CDNF, cerebral dopamine neurotrophic factor; SAE, serious adverse event; TEAE, treatment-emergent adverse event; AE, adverse event.

^aIncludes 8 AEs in the 0.4 mg CDNF group and 14 AEs in the 1.2 mg CDNF group (total 22 AEs) that were ongoing at the end of the main study.

TABLE 2 Summary of serious adverse events that occurred after first dosing

Treatment Group	Reported Event	Intensity	Relationship to Study Drug	Relationship to Drug–Device Combination	Relationship to Study Device or Surgical Procedures	Outcome	Other Actions Taken
Placebo	Brain abscess	Severe—grade 3	Unlikely	Probable	Probable	Recovered	Discontinued from the study
0.4 mg CDNF	Brain abscess	Moderate—grade 2	Unlikely	Possible	Probable	Recovered	Discontinued from the study
1.2 mg CDNF	Infection— not otherwise specified	Mild—grade 1	Unlikely	Unlikely	Unlikely	Recovered	None

Note: In the third serious adverse event case, a patient in the 1.2 mg CDNF dosing group was admitted to the hospital with general weakness and suspected mild infection (CTCAE grade 1). There were no clear and localizing symptoms or signs of infection. CRP was slightly elevated at admission and decreased spontaneously without any treatment over a few days. No X-rays or scans were performed. The patient was discharged 8 days later and recovered on the same day. A causal relationship between the study medication, study device, or treatment combination drug–device and the event of infection was considered to be unlikely, and no action was taken with study medication as a result of the event. The case was considered to be serious due to the required hospitalization.

Abbreviation: CRP, C-reactive protein; CDNF, cerebral dopamine neurotrophic factor; CTCAE, common terminology criteria for adverse events.

TABLE 3 Most common adverse events related to surgery

Adverse Events Related to Surgery	No. of Patients (n = 17)	No. of Events
Nervous system disorders		
Cerebral gas embolism ^a	6 (35.3%)	13
Headache	3 (17.6%)	4
Motor dysfunction	2 (11.8%)	2
General disorders and administration-site conditions		
Impaired healing	3 (17.6%)	3
Implant-site reaction	6 (35.3%)	12
Psychiatric disorders		
Confusional state	3 (17.6%)	4
Hallucination	4 (23.5%)	4
Insomnia	2 (11.8%)	2
Infection and infestations		
Implant-site infection	5 (29.4%)	5
Injury, poisoning, and procedural complications		
Postprocedural hemorrhage	5 (29.4%)	5

^aCerebral gas embolism is the closest MedDRA category for the imaging findings that may include small air bubbles or fluid pockets related to the infusion procedures.

TABLE 4 Most common adverse device events

Adverse Device Events	No. of Patients (n = 17 n = 15)	No. of Events
Nervous system disorders		
Cerebral gas embolism ^a	9 (9 5)	28 (21 7)
Headache	5 (3 3)	8 (4 5)
General disorders and administration-site conditions		
Chills	2 (2 1)	3 (2 1)
Impaired healing	4 (4 0)	4 (4 0)
Implant-site reaction	9 (8 4)	32 (16 6)
Infection and infestations		
Brain abscess	2 (2 0)	2 (2 0)
Implant-site infection	6 (4 2)	6 (4 2)
Injury, poisoning, and procedural complications		
Postprocedural hemorrhage	4 (4 0)	4 (4 0)
Cerebral microhemorrhage	2 (1 2)	3 (1 2)

Note: Numbers in parentheses show adverse events and severe adverse events in the main study (black) and extension study (blue).

^aCerebral gas embolism is the closest MedDRA category for the imaging findings that may include small air bubbles or fluid pockets related to the infusion procedures.

stabilization surgery. One hundred percent of ports were reported to be stable during the main and extension studies, based on 201 reaccess infusions.

As an exploratory DDS endpoint, volume of distribution in the putamen determined in two patients from the MRIs was 67% (left) and 61% (right) in patient P1 and 65% (left) and 75% (right) in patient P7. Due to general regulatory reasons,³⁶ Magnevist test infusion was not used in the remainder of the patients. Instead, vehicle test infusion was performed using the aCSF diluent only to verify DDS functionality.

A total of 206 TEAEs were recorded, of which 21 were counted in both the main and the extension study; all patients experienced at least one TEAE. Only one TEAE was classified as severe; all others were classified as mild or moderate. Sixty-eight TEAEs were considered related to CDNF (Tables 1–4; Supporting Information Table S2 in Data S1). There were 55 TEAEs related to the DDS, of which 17 were also related to the surgical procedure and 17 were skin-related TEAEs around the DDS port (1 TEAE was skin related around the DDS port only). Thirty-seven TEAEs were related to the drug-device combination, of which 20 were also related to the DDS. Infusion-related TEAEs experienced by at least two patients included asymptomatic microfluid sacs or micro-air bubbles (inappropriately termed cerebral gas embolism, as discussed later; three patients, five events) and nausea (two patients, three events) (Supporting Information Table S2 in Data S1). The most common adverse events related to surgery were asymptomatic microfluid sacs or micro-air bubbles (six patients, 13 events) and implant-site reaction (six patients, 12 events) (Tables 1–4). The most common ADEs were asymptomatic microfluid sacs or micro-air bubbles (nine patients, 28 events) and implant-site reaction (nine patients, 32 events) (Tables 1–4).

Two patients (one placebo, one 0.4 mg CDNF group) discontinued the main study because of an SAE (a brain abscess). Both patients had the DDS removed, were treated with prolonged antibiotic treatment based on microbiological findings, and have fully recovered. The incidents led to changes in the port-cleaning regimen and retraining at clinical sites before reaccess infusions, after which no further SAEs were observed.

There was one additional patient who had an SAE of infection without known location that was considered unrelated to CDNF or the DDS and did not require study discontinuation (Tables 1–4). Five postprocedural hemorrhages were reported during the study, of which four were also reported as ADEs. Four of the five were reported as “micro” (n = 3) or “small” (n = 1). The remaining case of postprocedural hemorrhage was reported as “recovered” before the first test infusion. One patient (P5) withdrew consent during the extension study (had received six placebo and three CDNF infusions at the time of discontinuation).

TABLE 5 Secondary outcome parameter functional scores

UPDRS Part III in <i>off</i> -medication state															
Visit	Placebo					0.4 mg CDFN					1.2 mg CDFN				
	n	Mean	SD	Min	Max	n	Mean	SD	Min	Max	n	Mean	SD	Min	Max
Baseline	6	29	6	24	39	5	29	12	17	48	5	32	7	25	39
6 months	5	29	10	21	46	5	28	7	22	39	5	29	10	19	40
12 months						5	30	15	15	49	5	34	21	21	51
Visit	Placebo → 0.4 mg CDFN					Placebo → 1.2 mg CDFN									
	n	Mean	SD	Min	Max	n	Mean	SD	Min	Max	n	Mean	SD	Min	Max
6 months	3	24	3	21	26	2	37	13	27	46					
12 months	3	18	12	11	32	2*	41	14	31	51					
UPDRS total in <i>off</i> -medication state															
Visit	Placebo					0.4 mg CDFN					1.2 mg CDFN				
	n	Mean	SD	Min	Max	n	Mean	SD	Min	Max	n	Mean	SD	Min	Max
Baseline	6	45	14	34	67	5	45	18	32	73	5	49	9	38	61
6 months	5	46	16	32	72	5	46	10	34	60	5	47	13	29	64
12 months						5	48	17	27	74	5	47	15	33	72
Visit	Placebo → 0.4 mg CDFN					Placebo → 1.2 mg CDFN									
	n	Mean	SD	Min	Max	n	Mean	SD	Min	Max	n	Mean	SD	Min	Max
6 months	3	37	5	32	41	2	59	19	45	72					
12 months	3	32	19	20	54	2*	62	21	47	76					
PDQ-39															
Visit	Placebo					0.4 mg CDFN					1.2 mg CDFN				
	n	Mean	SD	Min	Max	n	Mean	SD	Min	Max	n	Mean	SD	Min	Max
Baseline	6	26	12	12	41	5	24	13	10	40	5	21	11	10	38
6 months	5	24	5	17	28	5	26	16	10	43	5	28	12	9	39
12 months						5	24	16	11	45	5	23	15	13	48
Visit	Placebo → 0.4 mg CDFN					Placebo → 1.2 mg CDFN									
	n	Mean	SD	Min	Max	n	Mean	SD	Min	Max	n	Mean	SD	Min	Max
6 months	3	21	5	17	26	2	28	1	27	28					
12 months	3	22	11	12	34	2	24	0	24	24					
Home diary (good time, h)															
Visit	Placebo					0.4 mg CDFN					1.2 mg CDFN				
	n	Mean	SD	Min	Max	n	Mean	SD	Min	Max	n	Mean	SD	Min	Max
Baseline	6	11.7	2.0	9.5	15.3	5	12.5	3.6	6.7	15.6	5	10.8	2.0	9.0	13.0
6 months	5	11.2	2.6	7.0	13.2	5	11.2	2.1	9.0	14.5	5	11.4	2.1	9.5	14.8
12 months						5	11.9	2.9	9.8	15.3	5	11.3	3.6	6.5	13.8
Visit	Placebo → 0.4 mg CDFN					Placebo → 1.2 mg CDFN									
	n	Mean	SD	Min	Max	n	Mean	SD	Min	Max	n	Mean	SD	Min	Max
6 months	3	12.9	1.4	11.3	14.0	2	8.7	1.6	7.5	9.8					
12 months	3	12.8	1.2	11.5	13.8	2	9.4	4.5	6.2	12.5					

Note: UPDRS Part III evaluates motor dysfunction, and values are expressed from 0 to 108. The UPDRS total includes four sections, which evaluate the key areas of disability (mentation, behavior, and mood; activities of daily living; motor function; complications of therapy). Total score (Parts I–IV) can be maximum of 199 points. PDQ-39 is a self-administered questionnaire with eight dimensions each scaled 0 to 100, which assesses PD-specific frequency of experiencing difficulties in daily living over the past month. For home diary, the patients were requested to keep record of their motor state on a day-to-day basis for assessment of motor fluctuations and dyskinesias for a period of 3 days before the next scheduled study visit. The patient marked for each half-hour time period their functional status as asleep, *off*, or *on* without dyskinesias; *on* with nontroublesome dyskinesias; or *on* with troublesome dyskinesias. The total “bad time,” defined as *off* time and *on* time with troublesome dyskinesia, and “good time,” defined as *on* time without dyskinesia or with nontroublesome dyskinesia, were recorded. Good time in hours is shown.

Abbreviations: UPDRS, Unified Parkinson’s Disease Rating Scale; CDFN, cerebral dopamine neurotrophic factor; Min, minimum; Max, maximum; PDQ-39, Parkinson’s Disease Questionnaire-39.

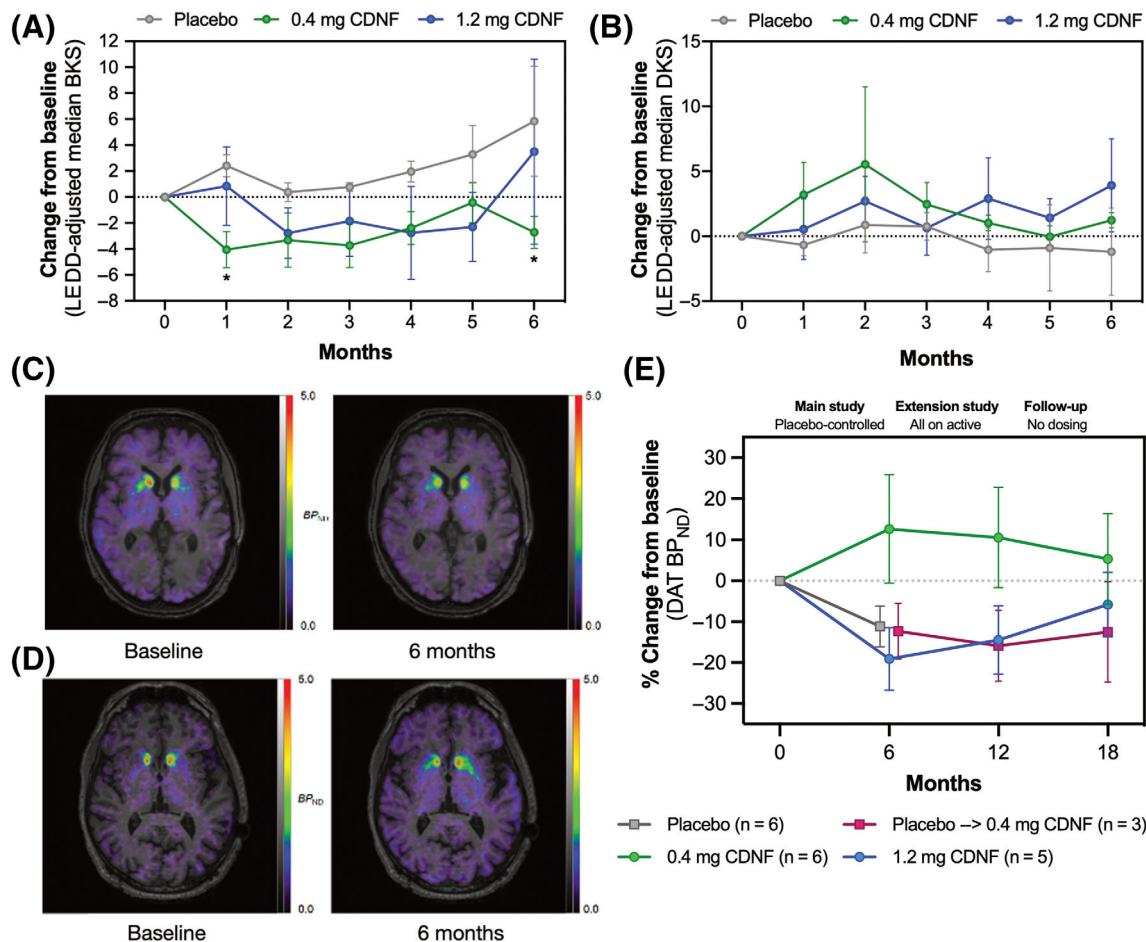


FIG. 3. Exploratory biomarker data. **(A, B)** PKG data from placebo-controlled main study. A wrist-worn PKG device recorded movement data every 2 minutes over a 6-day period at baseline and before each infusion visit. Levodopa equivalent daily dose (LEDD)-adjusted median bradykinesia score (BKS) **(A)** and dyskinesia score (DKS) **(B)** are shown. Statistical analysis was done by using mixed-effect model ANOVA with Dunnett post hoc test for multiple comparison across all patients in all measured time points. **(C–E)** Dopamine transporter binding by positron emission tomography (PET). Representative images show a placebo group patient **(C)** and a 0.4 mg cerebral dopamine neurotrophic factor (CDNF) group patient **(D)** at baseline and at 6 months (end of main study). **(E)** Dopamine transporter (DAT) binding potential (BP_{ND}) was determined from mean parametric [^{18}F]FE-PE2I images of the placebo ($n = 6$; gray), 0.4 mg CDNF ($n = 6$; green), and 1.2 mg CDNF group ($n = 5$; blue) at the level of the striatum and at the level of the substantia nigra. Placebo group patients who switched to 0.4 mg CDNF after 6 months are shown in purple ($n = 3$). The 12- and 18-month PET imaging data for two placebo group patients who switched to 1.2 mg CDNF were not available. The differences in DAT BP_{ND} between groups were not statistically significant at any time point. * $P < 0.05$ (mixed-effect model for repeated measurements [ANOVA] with Dunnett post hoc test for multiple comparison).

One patient in the 0.4 mg CDNF group presented positive for CDNF antibodies at week 49. Analysis of serum samples before this time point and later in the follow-up study from this patient were not positive for CDNF antibodies, suggesting that the week 49 finding was a false positive.

At the end of treatment (week 20; approximately 2 hours after end of the last infusion of the main study), CSF CDNF levels in patients in the placebo group were less than the lower limit of quantitation. In contrast, patients in the 0.4 mg CDNF group had a mean (\pm SD) CSF CDNF level of 82.2 ± 65.4 ng/mL (range: 14–185 ng/mL). For patients in the 1.2 mg CDNF group, the average CDNF level in CSF was 131.8 ± 129.5 ng/mL (range: 22–342 ng/mL). In general, there was a large variation between patient CSF CDNF levels after

infusion. At the same 2-hour postinfusion time point, serum CDNF levels were on average (\pm SD) 1.8 ± 0.2 ng/mL (range: 1.7–3.2 ng/mL) in the 0.4 mg CDNF group and 4.6 ± 2.1 ng/mL (range: 1.6–6.9 ng/mL) in the 1.2 mg CDNF group. All except one patient in the placebo group had serum CDNF levels less than the detection limit (this patient had either high endogenous CDNF levels or this was a false-positive result for this individual; close to the detection limit). These data suggest, as expected, that intraputamenally infused CDNF is cleared via the CSF to systemic circulation.

No group-level clinical improvements were observed in either CDNF treatment group compared with the placebo group, as measured by UPDRS (Part III in *off* state and total), PDQ-39, patient home diary (Table 5), clinical global impression, or timed up and go

(Supporting Information Fig. S3 in Data S1). Individual UPDRS Part III in *off*-state scores are shown in Supporting Information Table S3 in Data S1 and show individual cases with an apparent reduction in UPDRS III score possibly indicating a biological effect. Two patients (P3 and P11) who received 0.4 mg CDNF showed at least a 10-point improvement in UPDRS Part III (*off* state) from baseline to the 12-month time point. Patient P3 did not show a notable change in UPDRS during the 6-month placebo infusion period but improved by nine points after receiving 0.4 mg CDNF for the second 6-month period (Supporting Information Fig. S5; Table S3 in Data S1). Changes in LEDD levels are shown in Supporting Information Table S4 in Data S1 and show individual cases for whom a reduction of dopaminergic medication was necessary due to development of dyskinesias. There were no significant changes compared with baseline in Beck's Depression Inventory, Montreal Cognitive Assessment, or Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale at any time point during the main or extension study (Supporting Information Fig. S4 in Data S1).

In PKG data, when compared with placebo in the main study, patients treated with 0.4 mg CDNF showed a statistically significant reduction in median BKS (adjusted for LEDD) at months 1 and 6 (both $P < 0.05$); this effect was not observed with 1.2 mg CDNF (Fig. 3A). No statistically significant differences between groups were observed for LEDD-adjusted DKS (Fig. 3B). At 6 months, a representative patient treated with placebo exhibited reduction of putamen DAT availability compared with baseline, as assessed by [^{18}F]FE-PE2I PET (Fig. 3C). In contrast, one patient in the 0.4 mg CDNF group exhibited an increase of putamenal DAT availability at 6 months compared with baseline (Fig. 3D). Overall, the 0.4 mg CDNF group exhibited increased putamen DAT availability throughout the main and extension studies when compared with the placebo group (Fig. 3E), a finding observed particularly in two patients (P9 and P10; Supporting Information Table S5 in Data S1). Increased putamenal DAT availability was not observed in the 1.2 mg CDNF group (Fig. 3E); one patient showed a decrease of DAT availability, whereas the others remained stable. Change from baseline data were not available for the placebo-treated patients who were rerandomized to 1.2 mg CDNF because of one discontinued patient and practical visit restrictions related to the COVID-19 pandemic (Fig. 1A). Two patients (P9 and P10) treated with 0.4 mg CDNF exhibited an increase of DAT availability at 6 months, although this increase was not sustained in P10 at 12 months (Supporting Information Table S5 in Data S1).

Discussion

In this first-in-human study, we observed that 12 monthly doses of CDNF delivered intraputamenally via a DDS were safe and well tolerated because there were no clear differences in safety profile between treatment groups and no dose-limiting toxic effects of CDNF observed. Although infusion procedure-related SAEs were recorded, it can be concluded that the primary safety endpoint for the study drug CDNF was met. There were two infusion procedure-related SAEs, which were either related to surgery, the DDS, or the infusion procedure. Two patients dropped out of the study because of SAEs attributed to an insufficient adherence to the port cleaning and decontamination regimen. One instance experienced a single hair across the microneedle channel that was subsequently pushed into the fluid path. The other was attributed to insufficient quantities of decontamination fluid applied to the port surface as a result of uncontrolled internal site retraining of the method. We accordingly revised the surgical, infusion, and device port wound maintenance procedures and provided additional training to investigators and site personnel. This included the addition of a specialized sterile drape as a physical barrier to hair and the introduction of chlorohexidine in isopropyl alcohol solution as a more clinically accepted solution, as compared with isopropyl alcohol alone. Unlike the in-house feasibility device described by Whone and colleagues,¹⁰ the device described in this article did not feature in-line bacteria filters. The absence of very low dead volume filters was due to several important factors, the primary being unachievable technical challenges required to manufacture a scalable and validated implantable filter. Instead, this device mitigated against the risk of intralumen bacteria ingress using an alternative, validated, preinfusion cleaning and decontamination method. This cleaning and decontamination method is the same approach as that used on a humanitarian named-case basis within an 18-patient diffuse intrinsic pontine glioma study, where no instance of cerebral infections was reported.³⁷ Following these safety-mitigation actions, 87 further infusions were performed without any procedure-related infections or other procedure-related ADEs. All drug-related AEs were transient and of mild-to-moderate intensity, and most AEs have resolved (follow-up study is ongoing). All patients recovered from the SAEs observed in this study.

CDNF, similar to other NTFs, does not penetrate the blood-brain barrier, and intracranial delivery has been considered the best way to reach therapeutic levels in the basal ganglia in subjects with PD. Because intracranial delivery of therapeutics poses additional risks for the patient beyond any side effects associated with the

therapeutic,²³ the safety profile and performance of direct delivery must be considered when evaluating the benefit–risk ratio of the intervention. This can be informed by prior studies performing drug infusion via intraparenchymal catheters, along with the surgery necessary to place them to target. The delivery accuracy can be compared with stereotactic procedures targeting similar structures.³⁸ Performance in tissue of the novel transcatheter port can be compared with experiences with Bone-Anchored Hearing Aid abutments.³⁹

We observed that implantation of the DDS used in this study is safe, and that intermittent, targeted drug delivery to the brain is functionally feasible. ADEs and SADEs were assessed as clinically acceptable by an independent safety monitoring board, and following specific actions and process improvements allowed for completion of the study. Duration of port wound site healing was comparable with previous observations of an approximate 90-day port site wound healing duration in an earlier clinical study¹⁰ (Renishaw Neuro Solutions, unpublished data). With regard to the drug alone, intraputamenally administered CDNF was assessed as safe and well tolerated.

In routine safety MRI scans, there were several imaging findings that were inappropriately classified, for the lack of a more appropriate term, as “cerebral gas embolism” according to the MedDRA (Medical Dictionary for Regulatory Activities) classification system.⁴⁰ These findings were associated with infusions, appeared close to the catheter track, were asymptomatic, and resolved spontaneously over time. Analysis identified these anomalies predominantly as microfluidic pockets because air filters were present between the port and lines. Because gadolinium contrast was removed from the study, a visual assessment of all catheter infusion performance could not be undertaken. However, it is likely that infusion coverage performance was high and consistent, as seen in the first two patients, and unaffected by the presence of these transient events, similar to a previous report.⁴¹

PD-related outcomes were assessed by UPDRS, PDQ-39, and patient home diary as secondary endpoints. The study was not designed, or powered, to assess efficacy on any of the secondary outcome measures. Accordingly, it was not expected to find any signals related to efficacy different from placebo. Indeed, there were no statistically significant differences in UPDRS, PDQ-39, or home diary between placebo and the active dosing groups at 6 months and no difference between the dosing groups at 12 months of exposure to CDNF. The fact that only two patients showed a clinically meaningful improvement in secondary outcome measures or DAT PET may be related to a variety of factors, such as the advanced stage of disease, study duration, frequency of dosing, suboptimal drug delivery, or insufficient retention of CDNF in the putamina.

Exploratory endpoints included collection of digital and imaging biomarker data to support future development of CDNF and related compounds. PKG data (presented as BKS and DKS values) were retrieved for a period covering 6 days before baseline, each dosing, and at the end of study visits to explore the long-term effect of CDNF versus placebo on motor symptoms. PKG offers an objective means to assess PD motor symptoms outside the clinic (as compared with traditional clinician-assessed outcomes). For bradykinesia, PKG showed a statistically significant improvement in the 0.4 mg CDNF group compared with the placebo group at the 1- and 6-month time points. There were no significant differences in DKS scores between groups in the 6-month placebo-controlled part of the study. Although this explorative assessment should be interpreted with caution, and was significant only for the lower dose, the BKS difference at two time points appears biologically plausible and is an encouraging finding supporting the future use of the PKG, or similar digital biomarkers, in future trials. It remains to be established whether these findings are (1) due to increased sprouting of dopamine fibers in the putamen and (2) reflect a true U-shaped dose–response curve of CDNF that has been previously observed in preclinical studies.^{21,27} Although in animal models of PD a single striatal injection of CDNF has been sufficient for long-term improvement of motor function,^{17,20,27} it remains unknown whether a single intraputamenal infusion would be sufficient for a similar effect in human patients with PD.

Two patients (P9 and P10) treated with 0.4 mg CDNF exhibited increased putamen and substantia nigra DAT availability during the placebo-controlled 6-month stage. This effect was sustained at 12 months in P9, but not in P10. One may speculate whether this indicates partial recovery of dopaminergic phenotype in degenerating neuronal cell bodies in the substantia nigra and increased sprouting of dopamine terminals in the putamen. However, because this is a small, unpowered study and because the baseline DAT availability levels are low in patients with moderately advanced disease, these results should be interpreted with caution.

As previously referenced, a similar study design and system for intermittent intraputamenal drug delivery was recently used in a phase 2 clinical study with GDNF.^{10,42} In that study, a single dose level of GDNF (0.24 mg) was infused once monthly for 40 + 40 weeks (randomized, placebo-controlled phase + open-label extension) in patients with moderately advanced PD. Although there was no statistically significant difference between treatment groups in *off*-state UPDRS motor score at the end of the randomized phase, a post hoc analysis demonstrated that 9 of 21 patients in the GDNF group had at least a 10-point improvement in the *off* state. Moreover, ¹⁸F-DOPA PET imaging showed a significantly increased uptake throughout the

putamen only in the GDNF group. Although the present CDNF study had a smaller cohort of patients with PD and direct comparison of these studies may not be possible, the data from these two studies suggest that intraputamenal administration of neuroprotective/neurorestorative biological agents using this novel DDS is safe and feasible. Encouraging signals in individual patients may indicate a potential biological response to the treatment despite the advanced stage of disease in this study. Interestingly, in both studies, there were observations of individual responders. Further analyses may demonstrate patient features or biomarkers that could guide enrichment strategies for future trials. The good safety profile of CDNF warrants further clinical trials in less advanced patient populations. ■

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Data Availability Statement

Data are available at the EU Clinical Trials Register at: <https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-004175-73/results> and <https://www.clinicaltrialsregister.eu/ctr-search/trial/2018-000346-19/results>.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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