



Clinical trial results:

An Extension Study to Assess the Safety and Efficacy of Intermittent Bilateral Intraputamenal Glial Cell Line-Derived Neurotrophic Factor (GDNF) Infusions Administered via Convection Enhanced Delivery (CED) in Subjects with Parkinson's Disease

Summary

EudraCT number	2013-001881-40
Trial protocol	GB
Global end of trial date	15 February 2017

Results information

Result version number	v1 (current)
This version publication date	09 April 2022
First version publication date	09 April 2022
Summary attachment (see zip file)	tudy 2797 CSR_171018_FINAL_REPORT (Study 2797 CSR_171018_FINAL_Complete_without Appendices.pdf)

Trial information

Trial identification

Sponsor protocol code	2797
-----------------------	------

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	North Bristol NHS Trust
Sponsor organisation address	Level 3, Learning and Research building , Bristol, United Kingdom, BS10 5NB
Public contact	Clinical Trials Manager Helen Lewis, North Bristol NHS Trust (NBT) , +44 1173238602, research@nbt.nhs.uk
Scientific contact	Clinical Trials Manager Helen Lewis, North Bristol NHS Trust (NBT) , +44 1173238602, research@nbt.nhs.uk

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	25 July 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	15 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effects of intermittent bilateral intraputamenal GDNF infusions on OFF-state motor function after 18 months of treatment with the effects after 9 months of treatment in subjects who completed in Study 2553.

Protection of trial subjects:

Local institutional approval was obtained including protocol approval, the study was executed in accord with the Helsinki Declaration of 1975 and all patients provided written informed consent. The Trial Steering Committee and an independent Data Monitoring Committee provided clinical oversight.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 September 2012
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	United Kingdom: 41
Worldwide total number of subjects	41
EEA total number of subjects	41

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)	35
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All 41 patients randomised and treated in the parent study were enrolled and completed the extension study.

Pre-assignment

Screening details:

All parent study completers had the option to enrol in the extension investigation. Exclusion criteria were early discontinuation of treatment or significant protocol deviation in the parent study, presence of clinically significant depression, cognitive decline or any new medical condition that might impair outcome measure assessments or safety.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	GDNF - GDNF

Arm description:

Patients randomised to receive GDNF in the Parent study and continuing these GDNF infusions in this extension study

Arm type	Experimental
Investigational medicinal product name	Glial Cell Line-Derived Neutrophic Factor
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion in administration system
Routes of administration	Intracerebral use

Dosage and administration details:

GDNF concentration was 0.2 mg/ml every 4 weeks

Arm title	Placebo - GDNF
------------------	----------------

Arm description:

Participants randomised to placebo in Parent study and then received GDNF infusions for this extension study

Arm type	Experimental
Investigational medicinal product name	Glial Cell Line-Derived Neutrophic Factor
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion in administration system
Routes of administration	Intracerebral use

Dosage and administration details:

GDNF concentration was 0.2 mg/ml every 4 weeks

Number of subjects in period 1	GDNF - GDNF	Placebo - GDNF
Started	21	20
Completed	21	20

Baseline characteristics

Reporting groups

Reporting group title	GDNF - GDNF
Reporting group description: Patients randomised to receive GDNF in the Parent study and continuing these GDNF infusions in this extension study	
Reporting group title	Placebo - GDNF
Reporting group description: Participants randomised to placebo in Parent study and then received GDNF infusions for this extension study	

Reporting group values	GDNF - GDNF	Placebo - GDNF	Total
Number of subjects	21	20	41
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)	17	18	35
From 65-84 years	4	2	6
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	55.9	54.3	-
standard deviation	± 8.8	± 7.6	-
Gender categorical			
Units: Subjects			
Female	12	7	19
Male	9	13	22
Race			
Units: Subjects			
White	21	19	40
Asian	0	1	1
Hoehn and Yahr stage in OFF state			
Hoehn and Yahr stage in OFF state (n%)			
Units: Subjects			
Stage 0	0	0	0
Stage 1	0	0	0
Stage 1.5	0	0	0
Stage 2	11	5	16
Stage 2.5	4	9	13
Stage 3	6	6	12

Weight			
Weight at baseline week 0 of parent study			
Units: kilogram(s)			
arithmetic mean	76.15	79.34	-
standard deviation	± 14.201	± 21.216	-
Height			
Height at baseline (week 0 of parent study)			
Units: meter			
arithmetic mean	1.707	1.714	-
standard deviation	± 0.08	± 0.099	-
BMI			
BMI at baseline (week 0 of parent study)			
Units: kilogram(s)/square meter			
arithmetic mean	26.096	26.758	-
standard deviation	± 4.22	± 5.55	-
NART error score			
National Adult Reading Test (NART) error score is the number of words pronounced incorrectly out of 50 total words. Score from week 0 of parent study.			
Units: Points			
arithmetic mean	11.8	13.3	-
standard deviation	± 5.36	± 6.91	-
Duration since first PD symptoms			
Units: Years			
arithmetic mean	10.6	10.6	-
standard deviation	± 5.01	± 5.54	-
Duration since PD diagnosis			
Units: Years			
arithmetic mean	8.6	7.9	-
standard deviation	± 4.39	± 3.5	-
Responsiveness to levodopa			
Units: Years			
arithmetic mean	56.86	54.17	-
standard deviation	± 11.303	± 9.977	-

End points

End points reporting groups

Reporting group title	GDNF - GDNF
Reporting group description: Patients randomised to receive GDNF in the Parent study and continuing these GDNF infusions in this extension study	
Reporting group title	Placebo - GDNF
Reporting group description: Participants randomised to placebo in Parent study and then received GDNF infusions for this extension study	

Primary: Percentage change in defined OFF state UPDRS motor score (part III)

End point title	Percentage change in defined OFF state UPDRS motor score (part III)
End point description:	
End point type	Primary
End point timeframe: From baseline (1 week post parent study) to week 80/e40.	

End point values	GDNF - GDNF	Placebo - GDNF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	20		
Units: percent				
arithmetic mean (standard deviation)	-26.7 (± 20.7)	27.6 (± 23.6)		

Statistical analyses

Statistical analysis title	Treatment Comparison
Statistical analysis description: Least Squares Mean Difference vs Placebo	
Comparison groups	GDNF - GDNF v Placebo - GDNF
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.96
Method	Mixed models analysis
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.9
upper limit	14.6

Secondary: Percentage change in UPDRS motor score (part III) in the ON-state

End point title	Percentage change in UPDRS motor score (part III) in the ON-state
-----------------	---

End point description:

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

End point timeframe:

From baseline (1 week post Parent study) to end of treatment (week 80/e40).

End point values	GDNF - GDNF	Placebo - GDNF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	20		
Units: Percentage change				
arithmetic mean (standard deviation)	-7 (\pm 32.3)	5.1 (\pm 22.7)		

Statistical analyses

Statistical analysis title	Treatment Comparison
-----------------------------------	----------------------

Statistical analysis description:

Least Squares Mean Difference vs Placebo

Comparison groups	GDNF - GDNF v Placebo - GDNF
-------------------	------------------------------

Number of subjects included in analysis	41
---	----

Analysis specification	Pre-specified
------------------------	---------------

Analysis type	superiority
---------------	-------------

P-value	= 0.67
---------	--------

Method	Mixed models analysis
--------	-----------------------

Confidence interval

level	95 %
-------	------

sides	2-sided
-------	---------

lower limit	-21.7
-------------	-------

upper limit	14.2
-------------	------

Secondary: Percentage change in UPDRS ADL (part II)

End point title	Percentage change in UPDRS ADL (part II)
-----------------	--

End point description:

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

End point timeframe:

From baseline (1 week post parent study) to end of treatment (week 40)

End point values	GDNF - GDNF	Placebo - GDNF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	20		
Units: Percentage change				
arithmetic mean (standard deviation)				
OFF	-34.3 (± 22.3)	28.2 (± 26.2)		
ON	-33.9 (± 62.6)	32.3 (± 52)		

Statistical analyses

Statistical analysis title	Treatment Comparison in the OFF state
Statistical analysis description: Least Squares Mean Difference vs. Placebo in the OFF state	
Comparison groups	GDNF - GDNF v Placebo - GDNF
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.58
Method	Mixed models analysis
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.2
upper limit	11.4

Statistical analysis title	Treatment Comparison in the ON state
Statistical analysis description: Least Squares Mean Difference vs. Placebo	
Comparison groups	GDNF - GDNF v Placebo - GDNF
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.86
Method	Mixed models analysis
Confidence interval	
level	95 %
sides	2-sided
lower limit	-40.1
upper limit	33.5

Secondary: Percentage change in UPDRS total score (sum of motor and ADL)

End point title	Percentage change in UPDRS total score (sum of motor and ADL)
-----------------	---

End point description:

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

End point timeframe:

From baseline to week 80/e40

End point values	GDNF - GDNF	Placebo - GDNF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	20		
Units: percent				
arithmetic mean (standard deviation)				
ON	-17.5 (± 31.9)	-11.3 (± 23.1)		
OFF	-31.3 (± 14.8)	-28.3 (± 19.8)		

Statistical analyses

Statistical analysis title	Treatment Comparison in the OFF state
-----------------------------------	---------------------------------------

Statistical analysis description:

Least Squares Mean Difference vs Placebo

Comparison groups	Placebo - GDNF v GDNF - GDNF
-------------------	------------------------------

Number of subjects included in analysis	41
---	----

Analysis specification	Pre-specified
------------------------	---------------

Analysis type	superiority
---------------	-------------

P-value	= 0.56
---------	--------

Method	Mixed models analysis
--------	-----------------------

Confidence interval

level	95 %
-------	------

sides	2-sided
-------	---------

lower limit	-14.6
-------------	-------

upper limit	8
-------------	---

Statistical analysis title	Treatment Comparison in the ON state
-----------------------------------	--------------------------------------

Statistical analysis description:

Least Squares Mean Difference vs Placebo

Comparison groups	GDNF - GDNF v Placebo - GDNF
-------------------	------------------------------

Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.37
Method	Mixed models analysis
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.7
upper limit	9.9

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were reported for all patients between week 40 (start of extension) and until 28 days after the last dose of study medication.

Adverse event reporting additional description:

AEs were reported when experienced by at least 5 patients overall

Assessment type	Systematic
-----------------	------------

Dictionary used

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

Dictionary version	19
--------------------	----

Reporting groups

Reporting group title	GDNF - GDNF
-----------------------	-------------

Reporting group description:

Patients randomised to receive GDNF in the Primary study and continuing these infusions in this extension study

Reporting group title	Placebo - GDNF
-----------------------	----------------

Reporting group description:

Participants randomised to placebo in primary study and now receiving GDNF infusions for this extension study

Serious adverse events	GDNF - GDNF	Placebo - GDNF	
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 21 (85.71%)	10 / 20 (50.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Traumatic muscle rupture			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
menorrhagia requiring hysterectomy	Additional description: menorrhagia requiring hysterectomy and post- operative infection		
subjects affected / exposed	2 / 21 (9.52%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Osteoarthritis			

subjects affected / exposed	2 / 21 (9.52%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
multifactorial confusion and fluctuating cognition			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
depression and paranoia	Additional description: recurrence of pre-study depression and paranoia		
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device related events			
subjects affected / exposed	9 / 21 (42.86%)	10 / 20 (50.00%)	
occurrences causally related to treatment / all	0 / 9	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	GDNF - GDNF	Placebo - GDNF	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 21 (100.00%)	20 / 20 (100.00%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	5 / 21 (23.81%)	7 / 20 (35.00%)	
occurrences (all)	5	7	
Contusion			
subjects affected / exposed	4 / 21 (19.05%)	3 / 20 (15.00%)	
occurrences (all)	4	3	
Nervous system disorders			
Dyskinesia			
subjects affected / exposed	10 / 21 (47.62%)	9 / 20 (45.00%)	
occurrences (all)	8	9	
Lhermitte's sign			

subjects affected / exposed occurrences (all)	9 / 21 (42.86%) 9	4 / 20 (20.00%) 4	
Paresthesia subjects affected / exposed occurrences (all)	6 / 21 (28.57%) 6	7 / 20 (35.00%) 7	
On and off phenomenon subjects affected / exposed occurrences (all)	4 / 21 (19.05%) 4	7 / 20 (35.00%) 7	
Freezing phenomenon subjects affected / exposed occurrences (all)	7 / 21 (33.33%) 7	3 / 20 (15.00%) 3	
Dystonia subjects affected / exposed occurrences (all)	5 / 21 (23.81%) 5	4 / 20 (20.00%) 4	
Dizziness subjects affected / exposed occurrences (all)	3 / 21 (14.29%) 3	3 / 20 (15.00%) 3	
General disorders and administration site conditions Application site erythema subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2	4 / 20 (20.00%) 4	
Drug effect decreased subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2	3 / 20 (15.00%) 3	
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2	3 / 20 (15.00%) 3	
Respiratory, thoracic and mediastinal disorders Nasopharyngitis subjects affected / exposed occurrences (all)	7 / 21 (33.33%) 7	6 / 20 (30.00%) 6	
Musculoskeletal and connective tissue disorders Back pain			

subjects affected / exposed occurrences (all)	3 / 21 (14.29%) 3	5 / 20 (25.00%) 5	
Pain in extremity subjects affected / exposed occurrences (all)	5 / 21 (23.81%) 5	2 / 20 (10.00%) 2	
Joint injury subjects affected / exposed occurrences (all)	4 / 21 (19.05%) 4	2 / 20 (10.00%) 2	
Infections and infestations			
Application site infection subjects affected / exposed occurrences (all)	5 / 21 (23.81%) 5	4 / 20 (20.00%) 4	
Urinary tract infection subjects affected / exposed occurrences (all)	3 / 21 (14.29%) 3	4 / 20 (20.00%) 4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 June 2014	Amendment to protocol, PIS and Patient consent form.
19 September 2014	Modification of the magnetic resonance imaging (MRI) schedule.
16 December 2015	Amendment to protocol, informed consent form and patient information sheet.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/30829619>