Clinical trial results:
A Placebo-Controlled, Randomised, Double-Blind Trial 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	2011-003866-34
Trial protocol	GB
Global end of trial date	29 April 2016

Results information

Result version number	v1 (current)
This version publication date	04 December 2020
First version publication date	04 December 2020

Trial information

Trial identification

Sponsor protocol code	2553

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03652363
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	North Bristol NHS Trust
Sponsor organisation address	Level 3, Learning & Research building, Bristol, United Kingdom, BS10 5NB
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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	06 July 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 April 2016
Global end of trial reached?	Yes
Global end of trial date	29 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Assessing the benefit and safety of administering intermittent glial cell line derived neurotrophic factor (GDNF) infusions in PD.
At present only drugs which improve the symptoms of Parkinson’s disease (PD) are available. What is needed is a treatment which slows or reverses disease progression. The aim of this research is to test such a treatment. We have now developed an in-house device which animal model studies suggest will allow GDNF to be given much more reliably to the putamen area of the brain. We feel that this now allows for definitive testing of GDNFs effects in humans. We propose conducting a placebo controlled trial of intermittent GDNF infusions in 42 patients at our centre. We anticipate that the information gained from this study, if successful, will rapidly lead to a large multinational trial with the prospect of a new disease slowing therapy being available to PD patients within 5 years.

Protection of trial subjects:

Ahead of enrolling "Primary Study Participants (n=36)", six "Pilot Study Participants" will be enrolled (4 active GDNF; 2 placebo). The pilot study cohort safety data was submitted for the MHRA evaluation after the last of the pilot patients had received three months of infusions. Only after the MHRA reported their evaluation satisfactory were we permitted to begin enrolling Primary Study Stage patients, during this evaluation period, however, the pilot patients continued to receive infusions.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 October 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	0

months)	
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:

Between October 2012 and April 2015, 196 subjects from throughout the UK were pre-screened, of whom 64 patients underwent full study screening , 43 were enrolled and implanted with the device, and 41 were randomized and treated with study medication (6 in the Pilot Stage, 35 in the Primary Stage).

Pre-assignment

Screening details:

Eligibility criteria and informed consent followed by a series of questions relating to having Parkinson's disease, their health and medications. Participants underwent a physical examination, measuring; blood pressure, memory, ECG and submitting a blood sample. If eligible participants completed a 3 day motor diary, and additional screening visits

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	GDNF

Arm description:

Intermittent Bilateral intraputamenal convection enhanced delivery of GDNF for Parkinson's Disease

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

Dosage and administration details:

Post-randomization the n=35 patients that made up the primary stage population, from which the primary and secondary outcome measures were determined, received a total of 10 study treatments at 4-week intervals (Weeks 0 to 36). At each treatment, 400 ml of infusate (300 ml GDNF or placebo, followed by 100 ml artificial CSF) were delivered per catheter. The infusate GDNF concentration was 0.2 mg/ml, and the total GDNF dose given every 4 weeks was 240 mg (120 mg/putamen). The pilot stage patients received infusions every 2 weeks at 0.1 µg/µL.

Arm title	Placebo

Arm description:

Intermittent Bilateral intraputamenal convection enhanced delivery of artificial CSF, aCSF

Arm type	Placebo
Investigational medicinal product name	Artificial Cerebral Spinal Fluid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion in administration system
Routes of administration	Intracerebral use

Dosage and administration details:

Initially received every 2 weeks, this was adjusted during the Pilot phase to every 4 weeks

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

Baseline characteristics

Reporting groups	
Reporting group title	GDNF
Reporting group description:	
Intermittent Bilateral intraputamenal convection enhanced delivery of GDNF for Parkinson's Disease	
Reporting group title	Placebo
Reporting group description:	
Intermittent Bilateral intraputamenal convection enhanced delivery of artificial CSF, aCSF	

Reporting group values	GDNF	Placebo	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
Age continuous Units: years			
arithmetic mean	55.9	54.3	
standard deviation	± 8.75	± 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 (kg)			
Units: kilogram(s)			
arithmetic mean	76.15	79.34	

standard deviation	± 14.201	± 21.216	-
Height			
Height at baseline (m)			
Units: meter			
arithmetic mean	1.707	1.714	
standard deviation	± 0.08	± 0.099	-
BMI			
BMI at baseline (kg/m^2)			
Units: kilogram(s)/square meter			
arithmetic mean	26.096	26.758	
standard deviation	± 4.22	± 5.55	-
NARTerror score			
National Adult Reading Test (NART) error score is the number of words pronounced incorrectly out of 50 total words.			
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: percent			
arithmetic mean	56.86	54.17	
standard deviation	± 11.303	± 9.977	-

End points

End points reporting groups	
Reporting group title	GDNF
Reporting group description:	
Intermittent Bilateral intraputamenal convection enhanced delivery of GDNF for Parkinson's Disease	
Reporting group title	Placebo
Reporting group description:	
Intermittent Bilateral intraputamenal convection enhanced delivery of artificial CSF, aCSF	

Primary: Percentage change in the practically defined OFF state UPDRS motor score	
End point title	Percentage change in the practically defined OFF state UPDRS motor score
End point description:	
End point type	Primary
End point timeframe:	
From baseline assessment at Week 0 (post surgical implantation and test infusion but prior to first treatment infusion) to Week 40	

End point values	GDNF	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: Percentage				
arithmetic mean (standard deviation)	-17.3 (± 17.6)	-11.8 (± 15.76)		

Statistical analyses

Statistical analysis title	Treatment Comparison
Statistical analysis description:	
LS mean difference vs placebo	
Comparison groups	GDNF v Placebo
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4123
Method	Mixed models analysis
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.9
upper limit	7.1

Variability estimate	Standard deviation

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 assessment at Week 0 (post surgical implantation and test infusion but prior to first treatment infusion) to Week 40

End point values	GDNF	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	20		
Units: Percentage				
arithmetic mean (standard deviation)	-8.2 (± 32.36)	6.1 (± 22.26)		

Statistical analyses

Statistical analysis title	Treatment Comparison

Statistical analysis description:

LS mean difference vs placebo

Comparison groups	GDNF v Placebo
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1108
Method	Mixed models analysis
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.1
upper limit	3.4

Secondary: Percentage change in UPDRS mentation, behavior, and mood score (part I)

End point title	Percentage change in UPDRS mentation, behavior, and mood score (part I)

End point description:

End point type	Secondary

End point timeframe:

From baseline assessment at Week 0 (post surgical implantation and test infusion but prior to first treatment infusion) to Week 40

End point values	GDNF	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: Percentage				
arithmetic mean (standard deviation)	48.3 (± 164.51)	-18.6 (± 58.03)		

Statistical analyses

Statistical analysis title	Treatment Comparison
Statistical analysis description:	
LS mean difference vs placebo	
Comparison groups	GDNF v Placebo
Number of subjects included in analysis	35
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.1331
Method	Mixed models analysis
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23
upper limit	163.4

Secondary: Percentage change in UPDRS complications of therapy score (part IV)

End point title	Percentage change in UPDRS complications of therapy score (part IV)
End point description:	
End point type	Secondary
End point timeframe:	
From baseline assessment at Week 0 (post surgical implantation and test infusion but prior to first treatment infusion) to Week 40	

End point values	GDNF	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: Percentage				
arithmetic mean (standard deviation)	6.9 (± 34.32)	15 (± 43.37)		

Statistical analyses

Statistical analysis title	Treatment Comparison
Statistical analysis description: LS mean difference vs placebo	
Comparison groups	GDNF v Placebo
Number of subjects included in analysis	35
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.4197
Method	Mixed models analysis

Secondary: Percentage change in UPDRS ADL score (part II) in the OFF and in the ON state

End point title	Percentage change in UPDRS ADL score (part II) in the OFF and in the ON state
End point description:	
End point type	Secondary
End point timeframe: From baseline assessment at Week 0 (post surgical implantation and test infusion but prior to first treatment infusion) to Week 40	

End point values	GDNF	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	20		
Units: percent				
arithmetic mean (standard deviation)				
OFF	-14.6 (± 25.94)	-2.9 (± 26)		
ON	13.1 (± 109.56)	-9.8 (± 53.14)		

Statistical analyses

Statistical analysis title	OFF state treatment comparison
Statistical analysis description: LS mean difference vs placebo	
Comparison groups	GDNF v Placebo
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2329
Method	Mixed models analysis
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.6
upper limit	6.7

Statistical analysis title	ON state treatment comparison
Statistical analysis description: LS mean difference vs placebo	
Comparison groups	GDNF v Placebo
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4371
Method	Mixed models analysis
Confidence interval	
level	95 %
sides	2-sided
lower limit	-34.4
upper limit	78

Secondary: Percentage change in UPDRS total score (sum of motor + ADL scores) in the OFF and the ON state

End point title	Percentage change in UPDRS total score (sum of motor + ADL scores) in the OFF and the ON state
End point description:	
End point type	Secondary
End point timeframe: From baseline assessment at Week 0 (post surgical implantation and test infusion but prior to first treatment infusion) to Week 40	

End point values	GDNF	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	20		
Units: percent				
arithmetic mean (standard deviation)				
OFF	-18.4 (± 17.19)	-10.3 (± 10.42)		
ON	-6.1 (± 40.16)	2.4 (± 21.25)		

Statistical analyses

Statistical analysis title	OFF state treatment comparison
Statistical analysis description: LS mean difference vs placebo	
Comparison groups	GDNF v Placebo
Number of subjects included in analysis	41
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0696
Method	Mixed models analysis
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.7
upper limit	0.7

Statistical analysis title	ON state treatment comparison
Statistical analysis description: LS mean difference vs placebo	
Comparison groups	GDNF v Placebo
Number of subjects included in analysis	41
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.4084
Method	Mixed models analysis
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.2
upper limit	12.1

Secondary: Change in PD diary ratings

End point title	Change in PD diary ratings

End point description:

End point type	Secondary

End point timeframe:

From baseline assessment at Week 0 (post surgical implantation and test infusion but prior to first treatment infusion) to Week 40

End point values	GDNF	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: hour				
arithmetic mean (standard deviation)				
Total OFF time per day	-1.01 (± 1.902)	0.42 (± 2.052)		
Total good-quality ON time per day	1.3 (± 1.886)	-0.43 (± 1.858)		
ON time per day with troublesome dyskinesias	-0.12 (± 1.190)	-0.11 (± 0.549)		

Statistical analyses

Statistical analysis title	Total OFF time per day treatment comparison
Statistical analysis description:	
LS mean difference vs placebo	
Comparison groups	GDNF v Placebo
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.165
Method	Mixed models analysis
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.41
upper limit	0.429

Statistical analysis title	Good-Quality ON Time treatment comparison
Statistical analysis description:	
LS mean difference vs placebo	
Comparison groups	GDNF v Placebo

Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.125
Method	Mixed models analysis
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.339
upper limit	2.651

Statistical analysis title	ON time per day (with troublesome dyskinesias)
Statistical analysis description: LS mean difference vs placebo	
Comparison groups	GDNF v Placebo
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9174
Method	Mixed models analysis
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.63
upper limit	0.698

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were reported from the point of consent to end of treatment

Adverse event reporting additional description:

AEs marked as 'Occurrences causally related to treatment number' could be related to the trial treatment or the trial device.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	GDNF

Reporting group description: -

Reporting group title	Placebo

Reporting group description: -

Serious adverse events	GDNF	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 21 (47.62%)	7 / 20 (35.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Pelvic pain / Muscular weakness / Deep vein thrombosis / Spinal	Additional description: Car accident		
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	
Cardiac disorders			
Atrial flutter			
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	
General disorders and administration site conditions			
Oral disorder			
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	

Subdural hygroma			
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	
Skin and subcutaneous tissue disorders			
Application site scar	Additional description: Skin overgrowth.		
subjects affected / exposed	1 / 21 (4.76%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Application site reaction			
subjects affected / exposed	4 / 21 (19.05%)	3 / 20 (15.00%)	
occurrences causally related to treatment / all	4 / 4	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Application site erythema			
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	
Application site infection			
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	
Skin exfoliation			
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	
Site inflammation			
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	
Psychiatric disorders			
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	

Infections and infestations			
Infection	Additional description: Port site infection, antibiotics required.		
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection	Additional description: Diagnosed with E.coli pyelonephritis.		
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	
Ear infection			
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	
Urinary tract infection			
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	
Product issues			
Complication associated with device			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	GDNF	Placebo	
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	4 / 21 (19.05%)	6 / 20 (30.00%)	
occurrences (all)	8	16	
Joint injury			
subjects affected / exposed	2 / 21 (9.52%)	4 / 20 (20.00%)	
occurrences (all)	2	5	

Head injury			
subjects affected / exposed	2 / 21 (9.52%)	4 / 20 (20.00%)	
occurrences (all)	5	7	
Nervous system disorders			
Lhermitte's sign			
subjects affected / exposed	8 / 21 (38.10%)	0 / 20 (0.00%)	
occurrences (all)	9	0	
Paraesthesia			
subjects affected / exposed	8 / 21 (38.10%)	2 / 20 (10.00%)	
occurrences (all)	17	2	
Freezing phenomenon			
subjects affected / exposed	4 / 21 (19.05%)	3 / 20 (15.00%)	
occurrences (all)	5	3	
General disorders and administration site conditions			
Headache			
subjects affected / exposed	6 / 21 (28.57%)	7 / 20 (35.00%)	
occurrences (all)	10	14	
Cough			
subjects affected / exposed	3 / 21 (14.29%)	4 / 20 (20.00%)	
occurrences (all)	5	4	
Dizziness			
subjects affected / exposed	4 / 21 (19.05%)	1 / 20 (5.00%)	
occurrences (all)	5	1	
Pain in extremity			
subjects affected / exposed	4 / 21 (19.05%)	1 / 20 (5.00%)	
occurrences (all)	5	1	
Drug effect decreased			
subjects affected / exposed	2 / 21 (9.52%)	4 / 20 (20.00%)	
occurrences (all)	2	4	
Application site pain			
subjects affected / exposed	1 / 21 (4.76%)	4 / 20 (20.00%)	
occurrences (all)	1	5	
Nausea			
subjects affected / exposed	3 / 21 (14.29%)	1 / 20 (5.00%)	
occurrences (all)	4	1	
Arthralgia			

subjects affected / exposed	1 / 21 (4.76%)	3 / 20 (15.00%)	
occurrences (all)	0	0	
Depressed mood			
subjects affected / exposed	2 / 21 (9.52%)	2 / 20 (10.00%)	
occurrences (all)	2	0	
Fatigue			
subjects affected / exposed	3 / 21 (14.29%)	2 / 20 (10.00%)	
occurrences (all)	5	4	
Burning sensation			
subjects affected / exposed	0 / 21 (0.00%)	3 / 20 (15.00%)	
occurrences (all)	0	0	
Confusion			
subjects affected / exposed	1 / 21 (4.76%)	2 / 20 (10.00%)	
occurrences (all)	0	0	
Lethargy			
subjects affected / exposed	3 / 21 (14.29%)	1 / 20 (5.00%)	
occurrences (all)	4	1	
Insomnia			
subjects affected / exposed	1 / 21 (4.76%)	3 / 20 (15.00%)	
occurrences (all)	1	3	
Eye disorders			
Diplopia			
subjects affected / exposed	3 / 21 (14.29%)	0 / 20 (0.00%)	
occurrences (all)	3	0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	4 / 21 (19.05%)	1 / 20 (5.00%)	
occurrences (all)	4	1	
Diarrhoea			
subjects affected / exposed	3 / 21 (14.29%)	0 / 20 (0.00%)	
occurrences (all)	8	0	
Skin and subcutaneous tissue disorders			
Application site erythema			
subjects affected / exposed	3 / 21 (14.29%)	3 / 20 (15.00%)	
occurrences (all)	3	5	
Application site reaction			

subjects affected / exposed	3 / 21 (14.29%)	3 / 20 (15.00%)	
occurrences (all)	3	3	
Application site swelling			
subjects affected / exposed	1 / 21 (4.76%)	4 / 20 (20.00%)	
occurrences (all)	1	4	
Psychiatric disorders			
Impulsive behaviour			
subjects affected / exposed	0 / 21 (0.00%)	3 / 20 (15.00%)	
occurrences (all)	0	3	
Anxiety			
subjects affected / exposed	1 / 21 (4.76%)	4 / 20 (20.00%)	
occurrences (all)	0	0	
Paranoia			
subjects affected / exposed	2 / 21 (9.52%)	1 / 20 (5.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Dyskinesia			
subjects affected / exposed	9 / 21 (42.86%)	5 / 20 (25.00%)	
occurrences (all)	12	5	
Muscle spasms			
subjects affected / exposed	4 / 21 (19.05%)	3 / 20 (15.00%)	
occurrences (all)	5	4	
On and off phenomenon			
subjects affected / exposed	7 / 21 (33.33%)	2 / 20 (10.00%)	
occurrences (all)	12	2	
Back pain			
subjects affected / exposed	2 / 21 (9.52%)	5 / 20 (25.00%)	
occurrences (all)	3	5	
Dystonia			
subjects affected / exposed	3 / 21 (14.29%)	3 / 20 (15.00%)	
occurrences (all)	0	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 21 (28.57%)	8 / 20 (40.00%)	
occurrences (all)	8	10	
Application site infection			

subjects affected / exposed	5 / 21 (23.81%)	2 / 20 (10.00%)	
occurrences (all)	6	2	
Urinary tract infection			
subjects affected / exposed	3 / 21 (14.29%)	2 / 20 (10.00%)	
occurrences (all)	4	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 August 2012	To allow intraputamenal GDNF and placebo infusions to be delivered using a linear ramping regime, rather than a stepped infusion profile.
17 October 2012	Switching to a fully programmable linear ramping scheme is thought to minimize the risk of infusion errors, while providing for a desirable distribution profile in tissue.
25 April 2013	This amendment covers a switch from 2 weekly infusion intervals to 4 weekly infusion intervals, along with a compensatory increase in the concentration of GDNF to maintain the original total dose delivered per 4 week period (240 micrograms).
26 June 2013	Minor alterations in screening assessments and outcome data collected.
02 June 2014	Part 1: To change the protocol to include that Gadolinium contrast will be infused into the putamen at the time of the first test infusion and this is explained in the amendment and Participant Information Sheet. Part 2: To agree to repeat certain screening tests or baseline efficacy measures if they fall beyond certain substantial time intervals.
01 August 2014	The study has been suspended by the sponsor following monitoring which revealed a number of minor breaches of GCP, collectively constituting a major breach of GCP. As this is what we submitted to the MHRA, and they check things like this.
24 September 2014	To restart the trial.
02 December 2014	Amendment to Patient Information Sheet and to Patient Consent form.
26 March 2015	This amendment to simplify the magnetic resonance imaging (MRI) schedule and delete the previously planned functional MRI sub-study.
02 July 2015	Change to the patient consent form to allow access to blinded trial subject data by monitoring and auditing groups such as Pfizer, external contract research organizations, and UBC.
05 November 2015	To further revise the study protocol, the alterations are of a minor nature to address or clarify areas of potential misinterpretation or administrative type alterations to the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

01 August 2014	The study was halted by the sponsor following monitoring which revealed a number of minor breaches of GCP, collectively constituting a major breach of GCP. Recruitment was stopped but treatment was not stopped, 14 patients were still receiving treatment at this time.	24 September 2014

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30808022