Clinical trial results:
A randomized, double-blind, placebo-controlled trial of deferiprone in patients with pantothenate kinase-associated neurodegeneration (PKAN)

Summary

EudraCT number	2012-000845-11
Trial protocol	DE IT GB
Global end of trial date	21 October 2016

Results information

Result version number	v1 (current)
This version publication date	02 October 2020
First version publication date	02 October 2020

Trial information

Trial identification

Sponsor protocol code	TIRCON2012V1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01741532
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 104,880

Notes:

Sponsors

Sponsor organisation name	ApoPharma Inc.
Sponsor organisation address	200 Barmac Drive, Toronto, Ontario, Canada, M9L 2Z7
Public contact	Fernando Tricta, MD, ApoPharma Inc., +1 416-558-6342, f.tricta@chiesi.com
Scientific contact	Fernando Tricta, MD, ApoPharma Inc., +1 416-558-6342 , f.tricta@chiesi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 October 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 October 2016
Global end of trial reached?	Yes
Global end of trial date	21 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of the study were:

To evaluate the change in severity of dystonia in patients with PKAN treated with deferiprone vs. placebo for 18 months

To evaluate the global impression of improvement in patients with PKAN treated with deferiprone vs. placebo for 18 months

Protection of trial subjects:

An independent Data Safety Monitoring Board (DSMB) was established to monitor the safety of patients during the course of the trial. The DSMB was responsible for overseeing the conduct of the trial, and was empowered to recommend stopping the trial if in their judgement continuation was not ethically acceptable on the grounds of safety.

Background therapy:

Medications considered necessary for the patient’s welfare could be given at the discretion of the Investigator. Patients who were taking dystonia medications at baseline, whether on a regular schedule or as needed (PRN), were permitted to continue on these during the study provided that the dosage and regimen remained the same. For PRN medications, however, they had to observe a drug interruption period prior to each efficacy assessment visit, the duration of which depended on the particular drug.

The use of rescue medication, defined as the introduction or dosage change of a medication that has the potential to have an effect on dystonia symptoms, was limited to circumstances judged to be absolutely necessary by the Investigator. Such medications included but were not limited to baclofen, trihexyphenidyl, clonazepam, tizanidine, tetrabenazine, and Botox. If a patient was administered rescue medications for more than two events, the investigator was to notify the sponsor to discuss that patient’s continued participation in the study.

Evidence for comparator:

The study was placebo-controlled in order to detect the effect of deferiprone. Since PKAN is a progressive disorder, symptoms would be expected to worsen over time in the absence of effective treatment; thus, either an improvement, a stabilization, or a lesser decline in the deferiprone group compared to the placebo group would indicate some efficacy. The duration of 18 months was selected to allow enough time for the anticipated worsening in the placebo group to occur.

Actual start date of recruitment	13 December 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	18 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Germany: 37
Country: Number of subjects enrolled	Italy: 13
Country: Number of subjects enrolled	United States: 31
Worldwide total number of subjects	89
EEA total number of subjects	58

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)	24
Adolescents (12-17 years)	13
Adults (18-64 years)	52
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Starting in December 2012, patients were recruited in Germany, Italy, the United Kingdom, and the United States. Patients from neighbouring countries who were able to travel to one of the study sites were permitted to enroll as well. All appropriate regulatory and ethics committees standards were met.

Pre-assignment

Screening details:

A total of 100 prospective subjects were screened, of whom 89 were enrolled. The main criteria were a verified diagnosis of PKAN, a BAD score of at least 3, an expectation of stability in the use of concomitant medications and devices for the treatment of dystonia over the course of the trial, and no contraindications to the use of deferiprone.

Period 1

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

Blinding implementation details:

The placebo product matched the active product with respect to appearance, odor, and taste, and was provided in identical bottles. The patients, the staff at the study sites, employees of ApoPharma who were involved in the trial, and the neurologists who analyzed the videotapes for determination of BAD scores were all blinded as to which product was assigned.

Arms

Are arms mutually exclusive?	Yes
Arm title	Deferiprone

Arm description:

Patients in this arm received deferiprone oral solution (80 mg/mL) at a dosage of up to 15 mg/kg b.i.d., for a total daily dosage of up to 30 mg/kg, for up to 18 months.

Arm type	Experimental
Investigational medicinal product name	Deferiprone oral solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

The dosage was 15 mg/kg twice daily, for a total daily dosage of 30 mg/kg.

Arm title	Placebo

Arm description:

Patients in this arm received placebo solution twice daily, volume-matched to a 15 mg/kg b.i.d. dosage of deferiprone oral solution, for up to 18 months.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Volume-matched to a dosage of 15 mg/kg deferiprone oral solution

Number of subjects in period 1	Deferiprone	Placebo
Started	59	30
Completed	49	27
Not completed	10	3
Consent withdrawn by subject	1	1
Adverse event, non-fatal	4	-
Worsening of the disease	3	1
Sponsor decision	1	-
Medical event; withdrawn before dosing began	1	-
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Deferiprone
Reporting group description:	
Patients in this arm received deferiprone oral solution (80 mg/mL) at a dosage of up to 15 mg/kg b.i.d., for a total daily dosage of up to 30 mg/kg, for up to 18 months.	
Reporting group title	Placebo
Reporting group description:	
Patients in this arm received placebo solution twice daily, volume-matched to a 15 mg/kg b.i.d. dosage of deferiprone oral solution, for up to 18 months.	

Reporting group values	Deferiprone	Placebo	Total
Number of subjects	59	30	89
Age categorical			
Units: Subjects			
Age continuous			
Patients had to be at least 4 years of age at the time of enrollment. There was no maximum age.			
Units: years			
arithmetic mean	20.8	19.2	
standard deviation	± 10.7	± 12.5	-
Gender categorical			
Both male and female subjects were enrolled.			
Units: Subjects			
Female	25	17	42
Male	34	13	47
BAD score at baseline			
The Barry-Albright Dystonia (BAD) scale is an instrument for rating dystonia. It is scored on a scale from 0 (best) to 32 (worst).			
Units: points on a scale			
arithmetic mean	19.6	16.5	
standard deviation	± 8.4	± 8.1	-
UPDRS Part I score at baseline			
Part I of the Unified Parkinson's Disease Rating Scale (UPDRS) assesses mentation, behavior, and mood, and is scored from 0 (best) to 16 (worst)			
Units: Points on a scale			
arithmetic mean	2.0	2.0	
standard deviation	± 2.0	± 2.8	-
UPDRS Part II score at baseline			
Part II of the UPDRS score assesses activities of daily living. It is scored on a scale from 0 (best) to 52 (worst).			
Units: Points on a scale			
arithmetic mean	26.9	22.0	
standard deviation	± 8.5	± 11.4	-
UPDRS Part III score at baseline			
Part III of the UPDRS assesses motor performance. It is scored on a scale from 0 (best) to 108 (worst).			
Units: Points on a scale			
arithmetic mean	42.4	32.5	
standard deviation	± 22.4	± 20.3	-

UPDRS Part VI score at baseline			
Part VI of the UPDRS assesses the Schwab and England activities of daily living. It is scored on a scale from 0% (worst) to 100% (best).			
Units: Percentage			
arithmetic mean	43.2	51.1	
standard deviation	± 29.0	± 29.0	-
FIM score at baseline			
The FIM scale is used to measure a range of functional abilities in adults. A global score is generated that ranges from 18 (worst) to 126 (best).			
Units: Points on a scale			
arithmetic mean	81.6	84.9	
standard deviation	± 32.1	± 30.2	-
Global PedsQL score at baseline – child self-report			
The PedsQL questionnaire obtains information from patients and their parents on how the patient has felt over the previous month, and generates scores for physical health and psychosocial health as well as a total score. It is scored on a scale from 0 (worst) to 100 (best).			
Units: Points on a scale			
arithmetic mean	51.3	52.6	
standard deviation	± 19.1	± 16.2	-
Pittsburgh Sleep Quality Index (PSQI),			
The PSQI questionnaire obtains information on quality of sleep. Scores range from 0 (worst) to 100 (best).			
Units: Points on a scale			
arithmetic mean	6.4	6.5	
standard deviation	± 4.4	± 4.3	-
MRI R2*			
MRI R2* was used to measure iron levels in the globus pallidus			
Units: Hz			
arithmetic mean	96.6	93.5	
standard deviation	± 31.6	± 31.2	-
WeeFIM score at baseline			
The WeeFIM scale is used to measure a range of functional abilities in children. A global score is generated that ranges from 18 (worst) to 126 (best).			
Units: Points on a scale			
arithmetic mean	60.0	72.1	
standard deviation	± 25.9	± 33.3	-
Global PedsQL score at baseline - parent-proxy report			
The PedsQL questionnaire obtains information from patients and their parents on how the patient has felt over the previous month, and generates scores for physical health and psychosocial health as well as a total score. It is scored on a scale from 0 (worst) to 100 (best).			
Units: Points on a scale			
arithmetic mean	50.7	52.8	
standard deviation	± 14.4	± 15.7	-

End points

End points reporting groups

Reporting group title	Deferiprone
Reporting group description:	
Patients in this arm received deferiprone oral solution (80 mg/mL) at a dosage of up to 15 mg/kg b.i.d., for a total daily dosage of up to 30 mg/kg, for up to 18 months.	
Reporting group title	Placebo
Reporting group description:	
Patients in this arm received placebo solution twice daily, volume-matched to a 15 mg/kg b.i.d. dosage of deferiprone oral solution, for up to 18 months.	

Primary: Change from baseline to Month 18 in total score on the Barry Albright Dystonia (BAD) scale

End point title	Change from baseline to Month 18 in total score on the Barry Albright Dystonia (BAD) scale
End point description:	
The Barry-Albright Dystonia (BAD) scale is an instrument for rating dystonia (sustained muscle contractions causing twisting and repetitive movements or abnormal postures). It consists of a 5-point ordinal scale that rates severity of dystonia in 8 body regions. The individual scores are summed to provide a total score ranging from 0 to 32, with higher scores indicating greater severity.	
End point type	Primary
End point timeframe:	
Baseline to Month 18	

End point values	Deferiprone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	28		
Units: Points on the BAD scale				
least squares mean (standard error)	2.48 (± 0.63)	3.99 (± 0.82)		

Attachments (see zip file)	Change in BAD total score/Change in BAD total score.docx

Statistical analyses

Statistical analysis title	Mixed-Effect Model Repeated Measures model
Statistical analysis description:	
This model used the baseline value of the variable and age at onset of motor symptoms (before vs. at or after 6 years) as covariates and treatment group as the main factor. The least squares estimate of the mean (LSmean) change at Month 18 was used for determining the treatment effect in the primary analysis.	
Comparison groups	Deferiprone v Placebo

Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0761 [1]
Method	Mixed models analysis

Notes:

[1] - The difference between the groups in the change from baseline to Month 18 in total BAD score approached but did not reach significance.

Primary: Score on Patient Global Impression of Improvement (PGI-I) at Month 18

End point title	Score on Patient Global Impression of Improvement (PGI-I) at Month 18

End point description:

The Patient Global Impression of Improvement (PGI-I) is a global index that assesses the response of a condition to a therapy by asking patients to rate their current state relative to their state at baseline. It consists of a 7-point rating scale, where 1=very much improved, 2= much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse.

End point type	Primary

End point timeframe:

Month 18

End point values	Deferiprone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	28		
Units: Score on PGI-I				
least squares mean (standard error)	4.55 (± 0.30)	4.66 (± 0.38)		

Attachments (see zip file)	Change in PGI-I score.docx

Statistical analyses

Statistical analysis title	Mixed-Effect Model Repeated Measure model
Comparison groups	Deferiprone v Placebo
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7279 [2]
Method	Mixed models analysis

Notes:

[2] - There was no significant difference between the treatment groups in PGI-I score at Month 18, and neither group indicated subjective awareness of either improvement or worsening from baseline.

Secondary: Change from baseline to Month 18 in score on the Unified Parkinson's Disease Rating Scale (UPDRS) Part I

End point title	Change from baseline to Month 18 in score on the Unified Parkinson's Disease Rating Scale (UPDRS) Part I

End point description:

Part I of the UPDRS assesses mentation, behavior, and mood, and is scored from 0 (best) to 16 (worst).

Thus, an increase in score indicates worsening.

End point type	Secondary

End point timeframe:

Baseline to Month 18

End point values	Deferiprone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	28		
Units: Points on the UPDRS Part I scale				
least squares mean (standard error)	-0.25 (± 0.43)	-0.07 (± 0.55)		

Statistical analyses

Statistical analysis title	Mixed-Effect Model Repeated Measures (MMRM) model

Statistical analysis description:

The MMRM model used baseline value and age at onset of motor symptoms as covariates and treatment group as the main factor.

Comparison groups	Deferiprone v Placebo
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7228 [3]
Method	Mixed models analysis

Notes:

[3] - There was no significant difference between the treatment groups.

Secondary: Change from baseline to Month 18 in score on the Unified Parkinson's Disease Rating Scale (UPDRS) Part II

End point title	Change from baseline to Month 18 in score on the Unified Parkinson's Disease Rating Scale (UPDRS) Part II

End point description:

Part II of the UPDRS assesses activities of daily living, and is scored from 0 (best) to 52 (worst). Thus, an increase in score indicates worsening.

End point type	Secondary

End point timeframe:

Baseline to Month 18

End point values	Deferiprone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	28		
Units: Points on the UPDRS scale Part II				
least squares mean (standard error)	1.09 (± 1.19)	2.36 (± 1.52)		

Statistical analyses

Statistical analysis title	Mixed-Effect Model Repeated Measures (MMRM) model

Statistical analysis description:

The MMRM model used baseline value and age at onset of motor symptoms as covariates and treatment group as the main factor.

Comparison groups	Deferiprone v Placebo
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3677 [4]
Method	Mixed models analysis

Notes:

[4] - There was no significant difference between the treatment groups.

Secondary: Change from baseline to Month 18 in score on the Unified Parkinson's Disease Rating Scale (UPDRS) Part III

End point title	Change from baseline to Month 18 in score on the Unified Parkinson's Disease Rating Scale (UPDRS) Part III

End point description:

Part III of the UPDRS assesses motor performance, and is scored from 0 (best) to 108 (worst). Thus, an increase in score indicates worsening.

End point type	Secondary

End point timeframe:

Baseline to Month 18

End point values	Deferiprone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	28		
Units: Points on the UPDRS scale Part III				
least squares mean (standard error)	5.38 (± 2.20)	2.06 (± 2.79)		

Statistical analyses

Statistical analysis title	Mixed-Effect Model Repeated Measures (MMRM) model

Statistical analysis description:

The MMRM model used baseline value and age at onset of motor symptoms as covariates and treatment group as the main factor.

Comparison groups	Deferiprone v Placebo

Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2182 [5]
Method	Mixed models analysis

Notes:

[5] - There was no significant difference between the treatment groups.

Secondary: Change from baseline to Month 18 in score on the Unified Parkinson's Disease Rating Scale (UPDRS) Part VI

End point title	Change from baseline to Month 18 in score on the Unified Parkinson's Disease Rating Scale (UPDRS) Part VI

End point description:

Part VI of the UPDRS assesses the Schwab and England activities of daily living, and is scored from 0% (worst) to 100% (best). Thus, an decrease in score indicates worsening.

End point type	Secondary

End point timeframe:

Baseline to Month 18

End point values	Deferiprone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	28		
Units: Points on the UPDRS scale Part VI				
least squares mean (standard error)	-2.17 (± 2.94)	-7.66 (± 3.85)		

Statistical analyses

Statistical analysis title	Mixed-Effect Model Repeated Measures (MMRM) model

Statistical analysis description:

The MMRM model used baseline value and age at onset of motor symptoms as covariates and treatment group as the main factor.

Comparison groups	Deferiprone v Placebo
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1749 [6]
Method	Mixed models analysis

Notes:

[6] - There was no significant difference between the treatment groups.

Secondary: Change from baseline to Month 18 in global score on the Functional Independence Measure (FIM)

End point title	Change from baseline to Month 18 in global score on the Functional Independence Measure (FIM)

End point description:

The FIM scale is used to measure a range of functional abilities in adults. Items on this scale measure abilities across the domains of self-care (eating, grooming, bathing, dressing–upper body, dressing–

lower body, toileting, bladder management, bowel management), mobility (transfer: chair/wheelchair, transfer: toilet, transfer: tub/shower, walk/wheelchair, stairs; and cognition (comprehension, expression, social interaction, problem solving, memory). Each of the 18 items is scored from 1 (total assistance needed) to 7 (complete independence), and a global score is generated that ranges from 18 to 126. Thus, a decrease in score indicates worsening.

End point type	Secondary

End point timeframe:

Baseline to Month 18

End point values	Deferiprone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	14		
Units: Points on the FIM scale				
least squares mean (standard error)	5.40 (± 2.36)	0.69 (± 3.34)		

Statistical analyses

Statistical analysis title	Mixed-Effect Model Repeated Measures (MMRM) model

Statistical analysis description:

The MMRM model used baseline value and age at onset of motor symptoms as covariates and treatment group as the main factor.

Comparison groups	Deferiprone v Placebo
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1524 [7]
Method	Mixed models analysis

Notes:

[7] - There was no significant difference between the treatment groups.

Secondary: Change from baseline to Month 18 in global score on the pediatric Functional Independence Measure (WeeFIM) scale

End point title	Change from baseline to Month 18 in global score on the pediatric Functional Independence Measure (WeeFIM) scale

End point description:

The WeeFIM scale is used to measure a range of functional abilities in children. Items on this scale measure abilities across the domains of self-care (eating, grooming, bathing, dressing–upper body, dressing–lower body, toileting, bladder management, bowel management), mobility (transfer: chair/wheelchair, transfer: toilet, transfer: tub/shower, walk/wheelchair/crawl, stairs; and cognition (comprehension, expression, social interaction, problem solving, memory). Each of the 18 items is scored from 1 (total assistance needed) to 7 (complete independence), and a global score is generated that, and a global score is generated that ranges from 18 to 126. Thus, a decrease in score indicates worsening.

End point type	Secondary

End point timeframe:

Baseline to Month 18

End point values	Deferiprone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	14		
Units: Points on the WeeFIM scale				
least squares mean (standard error)	4.91 (± 5.30)	-2.40 (± 5.42)		

Statistical analyses

Statistical analysis title	Mixed-Effect Model Repeated Measures (MMRM) model

Statistical analysis description:

The MMRM model used baseline value and age at onset of motor symptoms as covariates and treatment group as the main factor.

Comparison groups	Deferiprone v Placebo
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2026 [8]
Method	Mixed models analysis

Notes:

[8] - There was no significant difference between the treatment groups.

Secondary: Change from baseline to Month 18 in total score on the Pediatric Quality of Life (PedsQL) scale, patient self-report version

End point title	Change from baseline to Month 18 in total score on the Pediatric Quality of Life (PedsQL) scale, patient self-report version

End point description:

The PedsQL questionnaire obtains information from patients and their parents on how the patient has felt over the previous month, and generates scores for physical health and psychosocial health as well as a total score. Each score ranges from 0 (worst) to 100 (best); i.e., a decrease in score indicates worsening.

End point type	Secondary

End point timeframe:

Baseline to Month 18

End point values	Deferiprone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	25		
Units: Points on the PedsQL scale				
least squares mean (standard error)	1.21 (± 3.68)	1.34 (± 4.49)		

Statistical analyses

Statistical analysis title	Mixed-Effect Model Repeated Measures (MMRM) model

Statistical analysis description:

The MMRM model used baseline value and age at onset of motor symptoms as covariates and treatment group as the main factor.

Comparison groups	Deferiprone v Placebo
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9759 [9]
Method	Mixed models analysis

Notes:

[9] - There was no significant difference between the treatment groups.

Secondary: Change from baseline to Month 18 in total score on the Pediatric Quality of Life (PedsQL) scale, parent proxy report version

End point title	Change from baseline to Month 18 in total score on the Pediatric Quality of Life (PedsQL) scale, parent proxy report version

End point description:

The PedsQL questionnaire obtains information from patients and their parents on how the patient has felt over the previous month, and generates scores for physical health and psychosocial health as well as a total score. Each score ranges from 0 (worst) to 100 (best); i.e., a decrease in score indicates worsening. This version was completed by the parent or guardian.

End point type	Secondary

End point timeframe:

Baseline to Month 18

End point values	Deferiprone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	19		
Units: Points on PedsQL scale, proxy version				
least squares mean (standard error)	-4.90 (± 3.99)	-2.37 (± 4.90)		

Statistical analyses

Statistical analysis title	Mixed-Effect Model Repeated Measures (MMRM) model

Statistical analysis description:

The MMRM model used baseline value and age at onset of motor symptoms as covariates and treatment

group as the main factor.

Comparison groups	Deferiprone v Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5781 [10]
Method	Mixed models analysis

Notes:

[10] - There was no significant difference between the treatment groups.

Secondary: Change from baseline to Month 18 in the Pittsburgh Sleep Quality Index (PSQI)

End point title	Change from baseline to Month 18 in the Pittsburgh Sleep Quality Index (PSQI)

End point description:

The PSQI is a self-rated questionnaire that assesses sleep quality and disturbances over a 1-month time interval. A total of 19 individual items are used to generate 7 "component" scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction, and a score
is generated that ranges from 0 (best) to 21 (worst).

End point type	Secondary

End point timeframe:

Baseline to Month 18

End point values	Deferiprone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	26		
Units: Points on the PSQI				
least squares mean (standard error)	0.48 (± 0.61)	0.14 (± 0.80)		

Statistical analyses

Statistical analysis title	Mixed-Effect Model Repeated Measures (MMRM) model

Statistical analysis description:

The MMRM model used baseline value and age at onset of motor symptoms as covariates and treatment group as the main factor.

Comparison groups	Deferiprone v Placebo
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6323 [11]
Method	Mixed models analysis

Notes:

[11] - There was no significant difference between the treatment groups.

Secondary: Change from baseline to Month 18 in level of brain iron

End point title	Change from baseline to Month 18 in level of brain iron

End point description:

Neurodegeneration in patients with PKAN appears to be related to intracellular mismanagement of iron, resulting in localized brain iron accumulation, toxicity, and eventual cell death. The region of the brain with the highest amount of iron accumulation is the globus pallidus, which is one of the main areas for motor control. Patients underwent MRI R2* for the measurement of iron levels in the globus pallidus.

End point type	Secondary

End point timeframe:

Baseline to Month 18

End point values	Deferiprone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	16		
Units: Hz as measured by MRI R2*				
least squares mean (standard error)	-36.1 (± 3.11)	-0.50 (± 3.97)		

Statistical analyses

Statistical analysis title	Mixed-Effect Model Repeated Measures (MMRM) model

Statistical analysis description:

The MMRM model used baseline value and age at onset of motor symptoms as covariates and treatment group as the main factor.

Comparison groups	Deferiprone v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [12]
Method	Mixed models analysis

Notes:

[12] - There was a highly significant difference between the treatment groups in the reduction of brain iron.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from the day of screening until the end of the study. For patients who did not continue in an extension study (TIRCON2012V1-EXT), adverse events continued to be collected for 4 weeks following the last dose administration

Adverse event reporting additional description:

Safety and tolerability of deferiprone oral solution were assessed through adverse events, clinical laboratory tests, physical examinations, vital signs, and ECG.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	Deferiprone

Reporting group description:

Patients in this arm received deferiprone oral solution (80 mg/mL) at a dosage of up to 15 mg/kg b.i.d., for a total daily dosage of up to 30 mg/kg, for /day, for up to 18 months.

Reporting group title	Placebo

Reporting group description:

Patients in this arm received placebo solution twice daily, volume-matched to a 15 mg/kg dosage of deferiprone oral solution

Serious adverse events	Deferiprone	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 58 (31.03%)	10 / 30 (33.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Thrombosis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 30 (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			
Colectomy			
subjects affected / exposed	1 / 58 (1.72%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal tube insertion			

subjects affected / exposed	1 / 58 (1.72%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal anastomosis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intrathecal pump insertion			
subjects affected / exposed	1 / 58 (1.72%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laparotomy			
subjects affected / exposed	1 / 58 (1.72%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device battery replacement			
subjects affected / exposed	2 / 58 (3.45%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal septal operation			
subjects affected / exposed	0 / 58 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheostomy			
subjects affected / exposed	1 / 58 (1.72%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheostomy tube removal			
subjects affected / exposed	1 / 58 (1.72%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound treatment			

subjects affected / exposed	1 / 58 (1.72%)	0 / 30 (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			
Condition aggravated			
subjects affected / exposed	0 / 58 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction			
subjects affected / exposed	1 / 58 (1.72%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 58 (1.72%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Choking			
subjects affected / exposed	1 / 58 (1.72%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	1 / 58 (1.72%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 58 (1.72%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory disorder			
subjects affected / exposed	1 / 58 (1.72%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory failure			
subjects affected / exposed	0 / 58 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Staring			
subjects affected / exposed	0 / 58 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device malfunction			
subjects affected / exposed	1 / 58 (1.72%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Medical observation			
subjects affected / exposed	0 / 58 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	0 / 58 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Chemical eye injury			
subjects affected / exposed	1 / 58 (1.72%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 58 (1.72%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Unintentional medical device removal			

subjects affected / exposed	1 / 58 (1.72%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative ileus			
subjects affected / exposed	1 / 58 (1.72%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dystonia			
subjects affected / exposed	3 / 58 (5.17%)	2 / 30 (6.67%)	
occurrences causally related to treatment / all	1 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotonia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	0 / 58 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oromandibular dystonia			
subjects affected / exposed	1 / 58 (1.72%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 58 (1.72%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	5 / 58 (8.62%)	2 / 30 (6.67%)	
occurrences causally related to treatment / all	6 / 7	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Intestinal dilatation			
subjects affected / exposed	1 / 58 (1.72%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 58 (1.72%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 58 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Volvulus			
subjects affected / exposed	1 / 58 (1.72%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 58 (1.72%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary bladder rupture			
subjects affected / exposed	1 / 58 (1.72%)	0 / 30 (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			
Bacterial disease carrier			
subjects affected / exposed	1 / 58 (1.72%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	2 / 58 (3.45%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cytomegalovirus infection			
subjects affected / exposed	0 / 58 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 58 (1.72%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 58 (3.45%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 58 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 58 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 58 (1.72%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 58 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Deferiprone	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 58 (96.55%)	30 / 30 (100.00%)	
General disorders and administration site conditions			
Abasia			
subjects affected / exposed	2 / 58 (3.45%)	2 / 30 (6.67%)	
occurrences (all)	2	2	
Condition aggravated			
subjects affected / exposed	10 / 58 (17.24%)	8 / 30 (26.67%)	
occurrences (all)	12	9	
Pain			
subjects affected / exposed	4 / 58 (6.90%)	0 / 30 (0.00%)	
occurrences (all)	4	0	
Pyrexia			
subjects affected / exposed	15 / 58 (25.86%)	13 / 30 (43.33%)	
occurrences (all)	33	28	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 58 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	8	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	9 / 58 (15.52%)	5 / 30 (16.67%)	
occurrences (all)	11	9	
Nasal congestion			
subjects affected / exposed	1 / 58 (1.72%)	2 / 30 (6.67%)	
occurrences (all)	1	3	
Oropharyngeal pain			
subjects affected / exposed	9 / 58 (15.52%)	3 / 30 (10.00%)	
occurrences (all)	10	3	
Rhinorrhoea			
subjects affected / exposed	4 / 58 (6.90%)	2 / 30 (6.67%)	
occurrences (all)	6	2	
Investigations			

Blood iron decreased			
subjects affected / exposed	3 / 58 (5.17%)	2 / 30 (6.67%)	
occurrences (all)	3	2	
Body temperature increased			
subjects affected / exposed	3 / 58 (5.17%)	0 / 30 (0.00%)	
occurrences (all)	3	0	
Neutrophil count decreased			
subjects affected / exposed	10 / 58 (17.24%)	3 / 30 (10.00%)	
occurrences (all)	18	20	
Serum ferritin decreased			
subjects affected / exposed	19 / 58 (32.76%)	5 / 30 (16.67%)	
occurrences (all)	23	5	
White blood cell count increased			
subjects affected / exposed	0 / 58 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 58 (1.72%)	2 / 30 (6.67%)	
occurrences (all)	1	4	
Contusion			
subjects affected / exposed	2 / 58 (3.45%)	2 / 30 (6.67%)	
occurrences (all)	2	2	
Fall			
subjects affected / exposed	2 / 58 (3.45%)	2 / 30 (6.67%)	
occurrences (all)	3	2	
Laceration			
subjects affected / exposed	6 / 58 (10.34%)	3 / 30 (10.00%)	
occurrences (all)	15	3	
Skin abrasion			
subjects affected / exposed	0 / 58 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	4	
Nervous system disorders			
Aphasia			
subjects affected / exposed	3 / 58 (5.17%)	2 / 30 (6.67%)	
occurrences (all)	3	2	
Drooling			

subjects affected / exposed	2 / 58 (3.45%)	2 / 30 (6.67%)	
occurrences (all)	2	2	
Dystonia			
subjects affected / exposed	24 / 58 (41.38%)	13 / 30 (43.33%)	
occurrences (all)	46	17	
Freezing phenomenon			
subjects affected / exposed	0 / 58 (0.00%)	3 / 30 (10.00%)	
occurrences (all)	0	3	
Headache			
subjects affected / exposed	13 / 58 (22.41%)	9 / 30 (30.00%)	
occurrences (all)	43	30	
Migraine			
subjects affected / exposed	3 / 58 (5.17%)	0 / 30 (0.00%)	
occurrences (all)	21	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 58 (17.24%)	0 / 30 (0.00%)	
occurrences (all)	15	0	
Leukocytosis			
subjects affected / exposed	2 / 58 (3.45%)	2 / 30 (6.67%)	
occurrences (all)	3	2	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 58 (1.72%)	3 / 30 (10.00%)	
occurrences (all)	1	3	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	4 / 58 (6.90%)	5 / 30 (16.67%)	
occurrences (all)	6	7	
Constipation			
subjects affected / exposed	2 / 58 (3.45%)	4 / 30 (13.33%)	
occurrences (all)	3	4	
Diarrhoea			
subjects affected / exposed	4 / 58 (6.90%)	3 / 30 (10.00%)	
occurrences (all)	7	8	
Toothache			

subjects affected / exposed	2 / 58 (3.45%)	2 / 30 (6.67%)	
occurrences (all)	2	3	
Vomiting			
subjects affected / exposed	9 / 58 (15.52%)	7 / 30 (23.33%)	
occurrences (all)	16	18	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	3 / 58 (5.17%)	1 / 30 (3.33%)	
occurrences (all)	3	1	
Rash			
subjects affected / exposed	4 / 58 (6.90%)	1 / 30 (3.33%)	
occurrences (all)	4	1	
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	3 / 58 (5.17%)	2 / 30 (6.67%)	
occurrences (all)	4	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 58 (13.79%)	1 / 30 (3.33%)	
occurrences (all)	8	1	
Back pain			
subjects affected / exposed	3 / 58 (5.17%)	2 / 30 (6.67%)	
occurrences (all)	3	8	
Muscle spasms			
subjects affected / exposed	3 / 58 (5.17%)	2 / 30 (6.67%)	
occurrences (all)	4	2	
Pain in extremity			
subjects affected / exposed	10 / 58 (17.24%)	4 / 30 (13.33%)	
occurrences (all)	13	7	
Infections and infestations			
Bronchitis			
subjects affected / exposed	5 / 58 (8.62%)	2 / 30 (6.67%)	
occurrences (all)	13	2	
Ear infection			
subjects affected / exposed	0 / 58 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	

Gastrointestinal infection			
subjects affected / exposed	3 / 58 (5.17%)	3 / 30 (10.00%)	
occurrences (all)	3	4	
Influenza			
subjects affected / exposed	3 / 58 (5.17%)	0 / 30 (0.00%)	
occurrences (all)	4	0	
Localised infection			
subjects affected / exposed	0 / 58 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Nasopharyngitis			
subjects affected / exposed	11 / 58 (18.97%)	6 / 30 (20.00%)	
occurrences (all)	20	10	
Rhinitis			
subjects affected / exposed	4 / 58 (6.90%)	1 / 30 (3.33%)	
occurrences (all)	6	1	
Upper respiratory tract infection			
subjects affected / exposed	8 / 58 (13.79%)	4 / 30 (13.33%)	
occurrences (all)	9	5	
Urinary tract infection			
subjects affected / exposed	2 / 58 (3.45%)	2 / 30 (6.67%)	
occurrences (all)	2	2	
Viral infection			
subjects affected / exposed	4 / 58 (6.90%)	1 / 30 (3.33%)	
occurrences (all)	5	1	
Metabolism and nutrition disorders			
Iron deficiency			
subjects affected / exposed	9 / 58 (15.52%)	3 / 30 (10.00%)	
occurrences (all)	9	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 August 2012	• As per FDA recommendation, a statement was added that the study would be considered positive if both primary endpoints reached statistical significance • Analytical methods were modified to comply with FDA recommendations • Return of medication and dose dispensing were added at Month 1.5 and Month 3, to accommodate the dose escalation • The visit window was increased to allow patients more flexibility
31 August 2012	• Addition of accountability of returned study medication at Month 1.5 and Month 3, in order to check patient compliance • Updated to refer to licensed versions of the FIM and WeeFIM questionnaires and removal of incorrect versions
06 December 2012	• Sponsorship of study switched from the TIRCON group to ApoPharma Inc. • Addition of Dr. Elliott Vichinsky as principal investigator • Clarification that MRI would be done only in patients where the investigator had no safety concerns • Likert scale for patient's assessment of PKAN symptoms added • Exclusion criteria #5 and #6 were modified/added to clarify and better define the illnesses for exclusion in the study. • List of rescue medications added in an appendix • Clarifications added for definition and management of neutropenia
18 January 2013	• Wording changes to ensure that the protocol was in line with the TIRCON FP7 Grant Agreement and Consortium Agreement
27 February 2013	• Clarification in exclusion criteria of the use of medications that may have an effect on dystonia symptoms • Addition of instructions and reminders for patients on the use of medications that might impact the study results due to the effect on dystonia symptoms
31 July 2013	• Exclusion criteria modified to permit a change in DBS parameters or baclofen pump settings in limited circumstances, to ensure that patients were appropriately treated and that patient safety took precedence over study protocol. • Reasons for discontinuation modified to permit use of rescue medication, limited to circumstances judged as absolutely necessary by the Investigator. At screening, patients currently taking a medication that might have an effect on dystonia could be enrolled provided they had been taking it for at least the period specified, to ensure that the baseline assessments were not associated with the use of a new medication. • Change in the name of the CRO used for the Bioanalytical/Pharmacokinetic analysis • Specification that AEs were to be collected for up to 14 days after the last dose of study medication

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

None

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31202468