Clinical trial results:
Long-term Safety and Efficacy Study of Deferiprone in Patients with Pantothenate Kinase-Associated Neurodegeneration (PKAN)

Summary

EudraCT number	2014-001427-79
Trial protocol	DE GB IT
Global end of trial date	16 March 2018

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-EXT

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02174848
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	ApoPharma Inc.
Sponsor organisation address	200 Barmac Drive, Toronto, 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	16 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 March 2018
Global end of trial reached?	Yes
Global end of trial date	16 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long-term safety and tolerability of deferiprone in patients with PKAN.

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. During treatment with deferiprone, patients were not to receive any other investigational product or any drugs that are known to cause neutropenia or agranulocytosis.

Evidence for comparator:

This was a single-arm study in which all participants received deferiprone.

Actual start date of recruitment	01 July 2014
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 States: 27
Country: Number of subjects enrolled	Germany: 32
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Italy: 4
Worldwide total number of subjects	68
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)	14
Adolescents (12-17 years)	14
Adults (18-64 years)	40
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All patients who had completed the placebo-controlled study TIRCON2012V1 were invited to enroll in the extension study.

Pre-assignment

Screening details:

To be eligible, patients had to have completed TIRCON2012V1 and to have no current contraindications to being in the trial.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable. All participants in this trial received deferiprone.

Arms

Are arms mutually exclusive?	No
Arm title	DFP-DFP

Arm description:

Patients in this group had been randomized to deferiprone treatment in the TIRCON2012V1 study and continued on deferiprone in the extension study.

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

Dosage and administration details:

The dosage was up to 15 milligrams of deferiprone per kilogram of body weight (mg/kg) twice daily, for a total dosage of up to 30 mg/kg per day.

Arm title	Placebo-DFP

Arm description:

Patients in this group had been randomized to placebo treatment in the TIRCON2012V1 study and were then switched to deferiprone in the extension study.

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

Dosage and administration details:

The dosage was up to 15 milligrams of deferiprone per kilogram of body weight (mg/kg) twice daily, for a total dosage of up to 30 mg/kg per day.

Arm title	Placebo-DFP in initial study

Arm description:

These are the same patients as those included in the Placebo-DFP group. During the initial study, they received 18 months of placebo treatment.

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:

The volume of placebo was matched to the volume prescribed for deferiprone.

Arm title	DFP-DFP in initial study

Arm description:

These are the same patients as those included in the DFP-DFP group. During the initial study, they received 18 months of deferiprone treatment.

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

Dosage and administration details:

The dosage was up to 15 milligrams of deferiprone per kilogram of body weight (mg/kg) twice daily, for a total dosage of up to 30 mg/kg per day.

Number of subjects in period 1	DFP-DFP	Placebo-DFP	Placebo-DFP in initial study
Started	44	24	24
Completed	38	17	24
Not completed	6	7	0
Adverse event, serious fatal	1	1	-
Consent withdrawn by subject	3	3	-
Adverse event, non-fatal	-	1	-
Worsening of disease	1	1	-
Inability to comply with study requirements	-	1	-
Lost to follow-up	1	-	-

Number of subjects in period 1	DFP-DFP in initial study
Started	44
Completed	44
Not completed	0
Adverse event, serious fatal	-
Consent withdrawn by subject	-
Adverse event, non-fatal	-
Worsening of disease	-
Inability to comply with study requirements	-
Lost to follow-up	-

Baseline characteristics

Reporting groups	
Reporting group title	DFP-DFP
Reporting group description:	
Patients in this group had been randomized to deferiprone treatment in the TIRCON2012V1 study and continued on deferiprone in the extension study.	
Reporting group title	Placebo-DFP
Reporting group description:	
Patients in this group had been randomized to placebo treatment in the TIRCON2012V1 study and were then switched to deferiprone in the extension study.	
Reporting group title	Placebo-DFP in initial study
Reporting group description:	
These are the same patients as those included in the Placebo-DFP group. During the initial study, they received 18 months of placebo treatment.	
Reporting group title	DFP-DFP in initial study
Reporting group description:	
These are the same patients as those included in the DFP-DFP group. During the initial study, they received 18 months of deferiprone treatment.	

Reporting group values	DFP-DFP	Placebo-DFP	Placebo-DFP in initial study
Number of subjects	44	24	24
Age categorical Units: Subjects			
Age continuous			
For the main study, whose duration was 18 months, subjects had to be at least 4 years old. Therefore, in this extension study, the minimum age was 5.5 years.			
Units: years arithmetic mean standard deviation	 22.4 ± 9.6	 19.9 ± 13.0	 19.9 ± 13.0
Gender categorical Units: Subjects			
Female Male	16 28	14 10	14 10

Reporting group values	DFP-DFP in initial study	Total	
Number of subjects	44	68	
Age categorical Units: Subjects			
Age continuous			
For the main study, whose duration was 18 months, subjects had to be at least 4 years old. Therefore, in this extension study, the minimum age was 5.5 years.			
Units: years arithmetic mean standard deviation	 22.4 ± 9.6	 -	
Gender categorical Units: Subjects			
Female	16	30	

Male	28	38	

End points

End points reporting groups

Reporting group title	DFP-DFP
Reporting group description:	
Patients in this group had been randomized to deferiprone treatment in the TIRCON2012V1 study and continued on deferiprone in the extension study.	
Reporting group title	Placebo-DFP
Reporting group description:	
Patients in this group had been randomized to placebo treatment in the TIRCON2012V1 study and were then switched to deferiprone in the extension study.	
Reporting group title	Placebo-DFP in initial study
Reporting group description:	
These are the same patients as those included in the Placebo-DFP group. During the initial study, they received 18 months of placebo treatment.	
Reporting group title	DFP-DFP in initial study
Reporting group description:	
These are the same patients as those included in the DFP-DFP group. During the initial study, they received 18 months of deferiprone treatment.	

Primary: Number of participants with adverse events

End point title	Number of participants with adverse events[1][2]
End point description:	
Safety and tolerability were assessed based on changes in frequency of adverse events (AEs), frequency of serious adverse events (SAEs), and discontinuation due to AEs. No statistical comparison between the groups was conducted as all participants received the same study product.	
End point type	Primary
End point timeframe:	
Baseline to end of study	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This was a single-arm study in which all patients received the same product. Unlike the efficacy analyses, which were based on which product patients had been taking in an earlier randomized study, in the case of safety, the data were consolidated into a single reporting group. Hence, despite this being a primary endpoint, no statistical analyses were possible.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The safety analyses were concerned only with data obtained in the current study, so only the groups "DFP-DFP" and "Placebo-DFP" were applicable. The arms "Placebo-DFP in initial study" and "DFP-DFP in initial study", which applied to data that had been obtained in the initial study, were used for the efficacy analyses but were not part of the safety analyses.

End point values	DFP-DFP	Placebo-DFP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	24		
Units: Participants				
Number of patients with at least one AE	42	22		
Number of patients with at least one serious AE	14	12		
Number of patients who withdrew due to an AE	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Score on the BAD Scale -- Comparison of Treatment Groups Over Each Study

End point title	Change in Score on the BAD Scale -- Comparison of Treatment Groups Over Each Study[3]

End point description:

The Barry-Albright Dystonia (BAD) scale is an instrument for rating the severity of dystonia in eight body regions. The individual scores are summed to provide a total score that ranges from 0 to 32; the higher the score, the more severe the dystonia. Patients were assessed for the change in total BAD score over the course of both the initial study (during which one group received placebo and the other received deferiprone) and the extension study (during which both groups received deferiprone).

End point type	Secondary

End point timeframe:

Baseline and Month 18 of each study

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This between-groups analysis is comparing the results of the DFP-DFP patients vs. those of the Placebo-DFP patients, so uses only the arms "DFP-DFP" and "Placebo-DFP". The arms "DFP-DFP in initial study" and "Placebo-DFP in initial study" are used only for the within-group analyses, and are not applicable here.

End point values	DFP-DFP	Placebo-DFP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	19		
Units: Points on the BAD scale				
arithmetic mean (standard deviation)				
Change in BAD score over initial study	1.9 (± 3.2)	4.4 (± 4.8)		
Change in BAD score over extension study	1.4 (± 2.4)	1.4 (± 3.7)		

Statistical analyses

Statistical analysis title	T-test

Statistical analysis description:

Comparison between the treatment groups in the change from baseline to Month 18 in total BAD score during the placebo-controlled study

Comparison groups	DFP-DFP v Placebo-DFP

Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05 [4]
Method	t-test, 2-sided

Notes:

[4] - During the controlled trial, in which the two groups received different treatments, the difference between them fell just short of statistical significance (defined as $p < 0.05$)

Statistical analysis title	T-test

Statistical analysis description:

Comparison between the treatment groups in the change from baseline to Month 18 in total BAD score during the extension study

Comparison groups	DFP-DFP v Placebo-DFP
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9781 [5]
Method	t-test, 2-sided

Notes:

[5] - During the extension study, in which both groups received deferiprone, there was no difference in progression of dystonia, based on change in BAD score.

Secondary: Change in Score on the BAD Scale -- Comparison of Placebo-DFP Patients Across Studies

End point title	Change in Score on the BAD Scale -- Comparison of Placebo-DFP Patients Across Studies[6]

End point description:

The Barry-Albright Dystonia (BAD) scale is an instrument for rating the severity of dystonia in eight body regions. The individual scores are summed to provide a total score that ranges from 0 to 32; the higher the score, the more severe the dystonia. Patients were assessed for the change in total BAD score over the course of each study.

End point type	Secondary

End point timeframe:

Baseline to Visit 4, where Visit 4 is Month 18 in the initial study and the final visit (Month 18 or earlier) in the extension study.

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was concerned with comparing the results of the 24 Placebo-DFP patients across studies: i.e., the change in BAD score during placebo treatment in the initial study vs. the change in BAD score during deferiprone treatment in the current study. The results of the 44 patients who received deferiprone in both studies were not part of this analysis, so the arms "DFP-DFP in initial study" and "DFP-DFP" are not applicable here.

End point values	Placebo-DFP	Placebo-DFP in initial study		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: Points on the BAD scale				
arithmetic mean (standard deviation)	1.4 (± 3.7)	4.4 (± 4.8)		

Statistical analyses

Statistical analysis title	Paired t-test

Statistical analysis description:

Comparison between the change in total BAD score during the controlled study and during the extension study, for the placebo-DFP group

Comparison groups	Placebo-DFP v Placebo-DFP in initial study
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0206 [7]
Method	t-test, 2-sided

Notes:

[7] - Patients showed significantly slower progress in dystonia during deferiprone treatment than during placebo treatment

Secondary: Change in score on the BAD scale - Comparison of DFP-DFP Patients Across Studies

End point title	Change in score on the BAD scale - Comparison of DFP-DFP Patients Across Studies[8]

End point description:

The Barry-Albright Dystonia (BAD) scale is an instrument for rating the severity of dystonia in eight body regions. The individual scores are summed to provide a total score that ranges from 0 to 32; the higher the score, the more severe the dystonia. Patients were assessed for the change in total BAD score over the course of each study.

End point type	Secondary

End point timeframe:

Baseline to Visit 4, where Visit 4 is Month 18 in the initial study and the final visit (Month 18 or earlier) in the extension study.

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was concerned with comparing the results of the 44 DFP-DFP patients across studies: i.e., the change in BAD score during deferiprone treatment in the initial study vs. the change in BAD score during deferiprone treatment in the current study. The results of the 24 patients who received placebo in the first study and deferiprone in the second were not part of this analysis, so the arms "Placebo-DFP in initial study" and "Placebo-DFP" are not applicable here.

End point values	DFP-DFP	DFP-DFP in initial study		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	43		
Units: Points on the BAD scale				
arithmetic mean (standard deviation)	1.4 (± 2.4)	1.9 (± 3.2)		

Statistical analyses

Statistical analysis title	Paired t-test

Statistical analysis description:

Comparison between the change in total BAD score during the controlled study and during the extension study, for the DFP-DFP group

Comparison groups	DFP-DFP v DFP-DFP in initial study

Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2684 [9]
Method	t-test, 2-sided

Notes:

[9] - For patients who received deferiprone in both studies, was no difference between the progression in dystonia seen during the two studies.

Secondary: Patient Global Impression of Improvement (PGI-I) Comparison of Placebo-DFP Patients Across Studies

End point title	Patient Global Impression of Improvement (PGI-I) Comparison of Placebo-DFP Patients Across Studies[10]

End point description:

The Patient Global Impression of Improvement (PGI-I) is a global index used to rate the response of a condition to a therapy. Patients were asked at each post-baseline visit to rate their overall condition since the start of the extension study on a 7-point rating scale: 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	Secondary

End point timeframe:

End of each study

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was concerned with comparing the results of the Placebo-DFP patients across studies: i.e., the PGI-I score following placebo treatment in the initial study vs. the PGI-I score following deferiprone treatment in the current study. The results of the patients who received deferiprone in both studies were not part of this analysis, so the arms "DFP-DFP in initial study" and "DFP-DFP" are not applicable here.

End point values	Placebo-DFP	Placebo-DFP in initial study		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: Points on the PGI-I scale				
arithmetic mean (standard deviation)	4.7 (± 1.4)	4.4 (± 1.5)		

Statistical analyses

Statistical analysis title	Paired t-test

Statistical analysis description:

Comparison of the PGI-I score following 12 months of placebo treatment vs. the PGI-I score vs. 12 months of deferiprone treatment

Comparison groups	Placebo-DFP v Placebo-DFP in initial study
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3306 [11]
Method	t-test, 2-sided

Notes:

[11] - Patients did not report a difference in this measure between studies.

Secondary: Patient Global Impression of Improvement (PGI-I) Comparison of DFP-DFP Patients Across Studies

End point title	Patient Global Impression of Improvement (PGI-I) Comparison of DFP-DFP Patients Across Studies[12]

End point description:

The Patient Global Impression of Improvement (PGI-I) is a global index used to rate the response of a condition to a therapy. Patients were asked at each post-baseline visit to rate their overall condition since the start of the extension study on a 7-point rating scale: 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	Secondary

End point timeframe:

End of each study

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was concerned with comparing the results of the 44 DFP-DFP patients across studies: i.e., the PGI-I score following deferiprone treatment in the initial study vs. the PGI-I score following deferiprone treatment in the current study. The results of the 24 patients who received placebo in the first study and deferiprone in the second were not part of this analysis, so the arms "Placebo-DFP in initial study" and "Placebo-DFP" are not applicable here.

End point values	DFP-DFP	DFP-DFP in initial study		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	43		
Units: Points on the PGI-I scale				
arithmetic mean (standard deviation)	4.1 (± 1.4)	4.4 (± 1.3)		

Statistical analyses

Statistical analysis title	Paired t-test
Comparison groups	DFP-DFP v DFP-DFP in initial study
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3079 [13]
Method	t-test, 2-sided

Notes:

[13] - Patients did not report a difference in this measure between studies.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Start of deferiprone treatment to end of TIRCON-EXT study. For DFP-DFP patients, this included any AEs that occurred during the 18 months of the initial study, while for placebo-DFP patients, it included only AEs that occurred during the TIRCON-EXT study.

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	21.0

Reporting groups

Reporting group title	Safety population

Reporting group description:

The safety population included all patients who took at least one dose of study drug in the extension study.

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 68 (48.53%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	2		
Vascular disorders			
Thrombosis			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Colostomy closure			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dental operation			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal tube insertion			

subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrostomy				
subjects affected / exposed	4 / 68 (5.88%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hip surgery				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intrathecal pump insertion				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Jejunostomy				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Medical device battery replacemen				
subjects affected / exposed	2 / 68 (2.94%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Medical device change				
subjects affected / exposed	2 / 68 (2.94%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Medical device implantation				
subjects affected / exposed	3 / 68 (4.41%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Medical device removal				

subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tracheostomy				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Tracheostomy tube removal				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wound treatment				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Condition aggravated				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Medical device site inflammation				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Multiple organ dysfunction syndrome				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Obstruction				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				

subjects affected / exposed	3 / 68 (4.41%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Choking			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cough			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia aspiration			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory disorder			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			

Agitation				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Product issues				
Device dislocation				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Device malfunction				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Device stimulation issue				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Device function test				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Physical examination				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Weight decreased				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Chemical eye injury				

subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Clavicle fracture				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Toxicity to various agents				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Unintentional medical device removal				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wound				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Cyanosis				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tachycardia				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Dystonia				
subjects affected / exposed	8 / 68 (11.76%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 0			
Headache				

subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyporesponsive to stimuli			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Loss of consciousness			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oromandibular dystonia			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Somnolence			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	4 / 68 (5.88%)		
occurrences causally related to treatment / all	5 / 7		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis			

subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal dilatatio				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oesophagitis				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Salivary hypersecretion				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Urinary bladder rupture				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Bursitis				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Infections and infestations			
Bacterial disease carrier			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infective glossitis			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peritonitis			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Respiratory tract infection			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral infection			

subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound infection			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	66 / 68 (97.06%)		
Investigations			
Body temperature increased			
subjects affected / exposed	4 / 68 (5.88%)		
occurrences (all)	4		
Neutrophil count decreased			
subjects affected / exposed	10 / 68 (14.71%)		
occurrences (all)	26		
Serum ferritin decreased			
subjects affected / exposed	18 / 68 (26.47%)		
occurrences (all)	25		
Iron deficiency			
subjects affected / exposed	11 / 68 (16.18%)		
occurrences (all)	11		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	5 / 68 (7.35%)		
occurrences (all)	5		
Laceration			
subjects affected / exposed	8 / 68 (11.76%)		
occurrences (all)	20		
Nervous system disorders			

Aphasia subjects affected / exposed occurrences (all)	5 / 68 (7.35%) 6		
Ataxia subjects affected / exposed occurrences (all)	4 / 68 (5.88%) 4		
Balance disorder subjects affected / exposed occurrences (all)	5 / 68 (7.35%) 5		
Dystonia subjects affected / exposed occurrences (all)	32 / 68 (47.06%) 74		
Headache subjects affected / exposed occurrences (all)	19 / 68 (27.94%) 64		
Somnolence subjects affected / exposed occurrences (all)	6 / 68 (8.82%) 8		
Tremor subjects affected / exposed occurrences (all)	4 / 68 (5.88%) 7		
Blood and lymphatic system disorders Anemias subjects affected / exposed occurrences (all)	12 / 68 (17.65%) 27		
General disorders and administration site conditions Condition aggravated subjects affected / exposed occurrences (all)	17 / 68 (25.00%) 25		
Pain subjects affected / exposed occurrences (all)	5 / 68 (7.35%) 5		
Pyrexia subjects affected / exposed occurrences (all)	20 / 68 (29.41%) 64		
Gastrointestinal disorders			

Abdominal pain upper subjects affected / exposed occurrences (all)	8 / 68 (11.76%) 16		
Diarrhoea subjects affected / exposed occurrences (all)	4 / 68 (5.88%) 6		
Dysphagia subjects affected / exposed occurrences (all)	8 / 68 (11.76%) 8		
Nausea subjects affected / exposed occurrences (all)	5 / 68 (7.35%) 5		
Vomiting subjects affected / exposed occurrences (all)	10 / 68 (14.71%) 13		
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	12 / 68 (17.65%) 19		
Oropharyngeal pain subjects affected / exposed occurrences (all)	10 / 68 (14.71%) 11		
Rhinorrhoea subjects affected / exposed occurrences (all)	6 / 68 (8.82%) 8		
Skin and subcutaneous tissue disorders			
Rash subjects affected / exposed occurrences (all)	5 / 68 (7.35%) 5		
Psychiatric disorders			
Agitation subjects affected / exposed occurrences (all)	5 / 68 (7.35%) 13		
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	11 / 68 (16.18%)		
occurrences (all)	12		
Back pain			
subjects affected / exposed	4 / 68 (5.88%)		
occurrences (all)	4		
Muscle spasms			
subjects affected / exposed	8 / 68 (11.76%)		
occurrences (all)	11		
Infections and infestations			
Bronchitis			
subjects affected / exposed	6 / 68 (8.82%)		
occurrences (all)	30		
Influenza			
subjects affected / exposed	4 / 68 (5.88%)		
occurrences (all)	4		
Nasopharyngitis			
subjects affected / exposed	11 / 68 (16.18%)		
occurrences (all)	22		
Upper respiratory tract infection			
subjects affected / exposed	13 / 68 (19.12%)		
occurrences (all)	19		
Urinary tract infection			
subjects affected / exposed	6 / 68 (8.82%)		
occurrences (all)	8		
Metabolism and nutrition disorders			
Pain in extremity			
subjects affected / exposed	14 / 68 (20.59%)		
occurrences (all)	26		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 August 2014	• The EudraCT number was corrected • An Extension Study Scientific Steering Committee was formed to clarify ownership of data and publication • The vendor for centralized evaluation of. BAD scores was changed • Paracetamol/acetaminophen was removed from the list of prohibited drugs

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/31202468