



## 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:

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**Results analysis stage**

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|  |                 |
|--|-----------------|
| 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:

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**General information about the trial**

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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

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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:

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**Population of trial subjects**

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**Subjects enrolled per country**

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|                                      |                   |
|--------------------------------------|-------------------|
| 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:

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**Subjects enrolled per age group**

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|   |    |
|---|----|
| 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         |
| <b>Arm title</b>             | 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.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | 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

| <b>Number of subjects in period 1</b>        | 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:<br>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:<br>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:<br>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:<br>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)   |  |  |

|                                   |  |
|-----------------------------------|--|
| <b>Attachments (see zip file)</b> | 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:<br>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 <sup>[1]</sup> |
| 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)   |  |  |

|                                   |                            |
|-----------------------------------|----------------------------|
| <b>Attachments (see zip file)</b> | Change in PGI-I score.docx |
|-----------------------------------|----------------------------|

### Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | 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 <sup>[2]</sup>                   |
| 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 ( $\pm$ 0.43) | -0.07 ( $\pm$ 0.55) |  |  |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | 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 <sup>[3]</sup>                           |
| 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 ( $\pm$ 1.19) | 2.36 ( $\pm$ 1.52) |  |  |

## Statistical analyses

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Mixed-Effect Model Repeated Measures (MMRM) model |
| Statistical analysis description:<br>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 <sup>[4]</sup>                           |
| 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:<br>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:<br>Baseline to Month 18  |  |

|   |                 |                 |  |  |
|---|-----------------|-----------------|--|--|
| <b>End point values</b>                   | 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

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Mixed-Effect Model Repeated Measures (MMRM) model |
| Statistical analysis description:<br>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 <sup>[5]</sup> |
| 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 ( $\pm$ 2.94) | -7.66 ( $\pm$ 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 <sup>[6]</sup> |
| 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 ( $\pm$ 2.36) | 0.69 ( $\pm$ 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 <sup>[7]</sup> |
| 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 ( $\pm$ 5.30) | -2.40 ( $\pm$ 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 <sup>[8]</sup> |
| 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 ( $\pm$ 3.68) | 1.34 ( $\pm$ 4.49) |  |  |

## Statistical analyses

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | 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 <sup>[9]</sup> |
| 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

|  |                 |                 |  |  |
|--|-----------------|-----------------|--|--|
| <b>End point values</b>                      | 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

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | 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 <sup>[10]</sup> |
| 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 <sup>[11]</sup> |
| 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 <sup>[12]</sup> |
| 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 %



| <b>Non-serious adverse events</b>                     | 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<br>subjects affected / exposed<br>occurrences (all)             | 3 / 58 (5.17%)<br>3    | 2 / 30 (6.67%)<br>2   |  |
| Body temperature increased<br>subjects affected / exposed<br>occurrences (all)       | 3 / 58 (5.17%)<br>3    | 0 / 30 (0.00%)<br>0   |  |
| Neutrophil count decreased<br>subjects affected / exposed<br>occurrences (all)       | 10 / 58 (17.24%)<br>18 | 3 / 30 (10.00%)<br>20 |  |
| Serum ferritin decreased<br>subjects affected / exposed<br>occurrences (all)         | 19 / 58 (32.76%)<br>23 | 5 / 30 (16.67%)<br>5  |  |
| White blood cell count increased<br>subjects affected / exposed<br>occurrences (all) | 0 / 58 (0.00%)<br>0    | 2 / 30 (6.67%)<br>2   |  |
| Injury, poisoning and procedural complications                                       |                        |                       |  |
| Arthropod bite<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 58 (1.72%)<br>1    | 2 / 30 (6.67%)<br>4   |  |
| Contusion<br>subjects affected / exposed<br>occurrences (all)                        | 2 / 58 (3.45%)<br>2    | 2 / 30 (6.67%)<br>2   |  |
| Fall<br>subjects affected / exposed<br>occurrences (all)                             | 2 / 58 (3.45%)<br>3    | 2 / 30 (6.67%)<br>2   |  |
| Laceration<br>subjects affected / exposed<br>occurrences (all)                       | 6 / 58 (10.34%)<br>15  | 3 / 30 (10.00%)<br>3  |  |
| Skin abrasion<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 58 (0.00%)<br>0    | 2 / 30 (6.67%)<br>4   |  |
| Nervous system disorders   |                        |                       |  |
| Aphasia<br>subjects affected / exposed<br>occurrences (all)                          | 3 / 58 (5.17%)<br>3    | 2 / 30 (6.67%)<br>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<br>occurrences (all)                         | 2 / 58 (3.45%)<br>2    | 2 / 30 (6.67%)<br>3   |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)             | 9 / 58 (15.52%)<br>16  | 7 / 30 (23.33%)<br>18 |  |
| Skin and subcutaneous tissue disorders                                   |                        |                       |  |
| Hyperhidrosis<br>subjects affected / exposed<br>occurrences (all)        | 3 / 58 (5.17%)<br>3    | 1 / 30 (3.33%)<br>1   |  |
| Rash<br>subjects affected / exposed<br>occurrences (all)                 | 4 / 58 (6.90%)<br>4    | 1 / 30 (3.33%)<br>1   |  |
| Renal and urinary disorders  |                        |                       |  |
| Urinary incontinence<br>subjects affected / exposed<br>occurrences (all) | 3 / 58 (5.17%)<br>4    | 2 / 30 (6.67%)<br>2   |  |
| Musculoskeletal and connective tissue disorders                          |                        |                       |  |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)           | 8 / 58 (13.79%)<br>8   | 1 / 30 (3.33%)<br>1   |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)            | 3 / 58 (5.17%)<br>3    | 2 / 30 (6.67%)<br>8   |  |
| Muscle spasms<br>subjects affected / exposed<br>occurrences (all)        | 3 / 58 (5.17%)<br>4    | 2 / 30 (6.67%)<br>2   |  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)    | 10 / 58 (17.24%)<br>13 | 4 / 30 (13.33%)<br>7  |  |
| Infections and infestations  |                        |                       |  |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)           | 5 / 58 (8.62%)<br>13   | 2 / 30 (6.67%)<br>2   |  |
| Ear infection<br>subjects affected / exposed<br>occurrences (all)        | 0 / 58 (0.00%)<br>0    | 2 / 30 (6.67%)<br>2   |  |

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

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 21 August 2012   | <ul style="list-style-type: none"><li>As per FDA recommendation, a statement was added that the study would be considered positive if both primary endpoints reached statistical significance</li><li>Analytical methods were modified to comply with FDA recommendations</li><li>Return of medication and dose dispensing were added at Month 1.5 and Month 3, to accommodate the dose escalation</li><li>The visit window was increased to allow patients more flexibility</li></ul>  |
| 31 August 2012   | <ul style="list-style-type: none"><li>Addition of accountability of returned study medication at Month 1.5 and Month 3, in order to check patient compliance</li><li>Updated to refer to licensed versions of the FIM and WeeFIM questionnaires and removal of incorrect versions</li></ul>   |
| 06 December 2012 | <ul style="list-style-type: none"><li>Sponsorship of study switched from the TIRCON group to ApoPharma Inc.</li><li>Addition of Dr. Elliott Vichinsky as principal investigator</li><li>Clarification that MRI would be done only in patients where the investigator had no safety concerns</li><li>Likert scale for patient's assessment of PKAN symptoms added</li><li>Exclusion criteria #5 and #6 were modified/added to clarify and better define the illnesses for exclusion in the study.</li><li>List of rescue medications added in an appendix</li><li>Clarifications added for definition and management of neutropenia</li></ul>  |
| 18 January 2013  | <ul style="list-style-type: none"><li>Wording changes to ensure that the protocol was in line with the TIRCON FP7 Grant Agreement and Consortium Agreement</li></ul>  |
| 27 February 2013 | <ul style="list-style-type: none"><li>Clarification in exclusion criteria of the use of medications that may have an effect on dystonia symptoms</li><li>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</li></ul>   |
| 31 July 2013     | <ul style="list-style-type: none"><li>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.</li><li>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.</li><li>Change in the name of the CRO used for the Bioanalytical/Pharmacokinetic analysis</li><li>Specification that AEs were to be collected for up to 14 days after the last dose of study medication</li></ul> |

Notes:

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## 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.

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| None |
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Notes:

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## Online references

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