Title: Safety and efficacy of deferiprone for pantothenate kinase-associated neurodegeneration (PKAN): a randomised, double-blind, controlled trial and open-label extension study

Article Type: Article (Randomised Controlled Trial)

Keywords: Pantothenate kinase-associated neurodegeneration (PKAN), Neurodegeneration with brain iron accumulation (NBIA), iron chelation, deferiprone, randomised trial

Corresponding Author: Professor Thomas Klopstock, Corresponding Author's Institution:

First Author: Thomas Klopstock

Order of Authors: Thomas Klopstock; Fernando Tricta, MD; Lynne Neumayr, MD; Ivan Karin, MD; Giovanna Zorzi, MD; Caroline Fradette, PhD; Tomasz Kmiec, MD; Boriana Büchner, MD; Hannah E Steele, MBBS; Rita Horvath, MD; Patrick F Chinnery, MBBS; Anna Basu, BMBCh; Clemens Küpper, MD; Christiane Neuhofer, MD; Bernadette Kálmán, MD; Petr Dušek, MD; Zuhal Yapici, MD; Ian Wilson, BSc(Hons); Peng Zhao, MSc; Federica Zibordi, MD; Nardo Nardocci, MD; Christine Aguilar, MD; Susan J Hayflick, MD; Michael Spino, PharmD; Andrew M Blamire, PhD; Penelope Hogarth, MD; Elliott Vichinsky, MD

Manuscript Region of Origin: GERMANY

Abstract: Background. Pantothenate kinase-associated neurodegeneration (PKAN) is a rare genetic disorder characterized by progressive generalized dystonia and brain iron accumulation. We assessed whether the iron chelator deferiprone (DFP) can reduce brain iron and slow disease progression.

Methods. An 18-month, randomized, double-blind, placebo-controlled trial, followed by a pre-planned 18-month open-label extension study in patients with PKAN, was conducted in 4 hospitals in Germany, Italy, England and the USA. Patients aged ≥4 years with a genetically confirmed diagnosis of PKAN, a total score ≥3 on the Barry-Albright Dystonia (BAD) scale, and no evidence of iron deficiency, neutropenia, or abnormal liver or renal function, were randomly allocated (2:1) to receive DFP oral solution (30 mg/kg/day) or placebo for 18 months. Randomization was done using a centralized computer random number generator with stratification based on age group at onset of symptoms, and patients were allocated to groups by a non-blinded randomization team that was independent of the study. Patients, caregivers, and investigators were masked to treatment allocation. Patients who completed the randomized trial were eligible to enroll in a single-arm extension study of another 18 months in which all participants received DFP. Co-primary endpoints were the change from baseline to Month 18 in the total score on the BAD scale and the score at Month 18 on the Patient Global Impression of Improvement (PGI-I).

Efficacy analyses were done on the modified Intent to Treat (mITT)
population, which included all patients who received at least one dose of study drug and who provided a baseline and at least one post-baseline efficacy assessment; safety analyses were done on all patients who received at least one dose of study drug. The trial was registered on ClinicalTrials.gov (NCT01741532) and EudraCT (2012-000845-11).

Findings. Between December 2012 and April 2015, 88 patients were randomly assigned to DFP (N=58) or placebo (N=30). Of these, 76 patients completed the study: 49 in the DFP group and 27 in the placebo group. After 18 months, the BAD score worsened by 2.48±0.63 points (DFP), versus 3.99±0.82 points (placebo; difference -1.51 points, 95% CI [-3.19,0.16], p=0.0761). In the predefined subgroup with atypical (disease onset ≥ age 6) PKAN, the BAD score worsened by 2.33±0.73 points (DFP) versus 4.52±0.91 points (placebo; difference -2.19 points, 95% CI [ 4.00,-0.38], p=0.0187). No subjective change was detected as assessed by the PGI-I: mean scores at Month 18 were 4.7±0.4 for placebo and 4.6±0.3 for DFP (p=0.7279). In the extension study, patients continuing DFP retained a similar rate of disease progression (1.9±0.5 points in the first 18 months vs 1.4±0.4 points in the second 18 months, p=0.2684), while progression in patients switching from placebo to DFP seemed to slow (4.4±1.1 points when they were receiving placebo vs 1.4±0.9 points when they were receiving DFP, p=0.0206). Patients did not detect a change in their condition after the additional 18 months of treatment, with mean scores of 4.1±0.2 in the DFP-DFP group and of 4.7±0.3 in the placebo-DFP group. DFP was well tolerated and rates of adverse events were similar between the treatment groups except for anemia, which was seen in 20.7% of DFP-treated patients vs. no placebo patients. No patient discontinued therapy due to anemia. There were two deaths, both secondary to aspiration. Neither of these events was considered related to DFP use.

Interpretation. Deferiprone was well tolerated and seemed to show slower, although not statistically significant, disease progression at 18 months. Patients in neither group perceived an improvement or worsening of disease progression by deferiprone, although patients continued to not perceive a change in their condition. This study will help shape the design of future trials in this ultraorphan disease.

Funding. European Commission; FDA; ApoPharma Inc., Canada.
Safety and efficacy of deferiprone for pantothenate kinase-associated neurodegeneration (PKAN): a randomised, double-blind, controlled trial and open-label extension study

Thomas Klopstock, Fernando Tricta, Lynne Neumayr, Ivan Karin, Giovanna Zorzi, Caroline Fradette, Tomasz Kmieć, Boriana Büchner, Hannah E Steele, Rita Horvath, Patrick F Chinnery, Anna Basu, Clemens Küpper, Christiane Neuhofer, Bernadette Kálmán, Petr Dušek, Zuhal Yapici, Ian Wilson, Feng Zhao, Federica Zibordi, Nardo Nardocci, Christine Aguilar, Susan J. Hayflick, Michael Spino, Andrew M Blamire, Penelope Hogarth, Elliott Vichinsky

Department of Neurology, Friedrich-Baur-Institute, Ludwig-Maximilians-University of Munich, Munich, Germany (Prof T Klopstock MD, I Karin MD, B Büchner MD, C Küpper MD, C Neuhofer MD); German Center for Neurodegenerative Diseases (DZNE), Munich, Germany (Prof T Klopstock MD); Munich Cluster for Systems Neurology (SyNergy), Munich, Germany (Prof T Klopstock MD); ApoPharma Inc, Toronto, Ontario, Canada (F Tricta MD, Caroline Fradette PhD, Feng Zhao MSc, Michael Spino PharmD); Department of Hematology/Oncology, UCSF Benioff Children’s Hospital and Research Center Oakland, Oakland, California, USA (Prof E Vichinsky MD, L Neumayr MD); Pediatric Rehabilitation Department, UCSF Benioff Children’s Hospital and Research Center Oakland (C Aguilar MD); Department of Pediatric Neuroscience, Neurological Institute Carlo Besta, Milan, Italy (Prof N Nardocci MD, G Zorzi MD, F Zibordi MD); Department of Neurology and Epileptology, Children’s Memorial Health Institute, Warsaw, Poland (T Kmieć MD); Institute of Genetic Medicine, Newcastle University, Newcastle Upon Tyne, UK (Prof R Horvath MD, H Steele MBBS); Institute of Neuroscience, Newcastle University. Newcastle Upon Tyne, UK (A Basu PhD); Department of Clinical Neurosciences, Cambridge University, Cambridge, UK (Prof R Horvath MD, Prof P Chinnery MBBS); Charles University, Prague, Czechia (Dr. P Dušek MD); Institute of Laboratory Medicine, Szentagothai Research Center, University of Pécs, Pécs, Hungary (Prof B Kálmán MD); Department of Child Neurology, Istanbul Faculty of Medicine, Turkey (Prof Z Yapici MD); Department of Molecular & Medical Genetics, Oregon Health & Science University, Portland, Oregon, USA (Prof S Hayflick MD, P Hogarth MD); Institute of Cellular Medicine & Newcastle Magnetic Resonance Centre, Newcastle University, Newcastle Upon Tyne, UK (I Wilson Bsc(Hons), A Blamire PhD)

Correspondence to:
Prof Thomas Klopstock, Department of Neurology, Friedrich-Baur-Institute, Ludwig-Maximilians-University of Munich, Munich 80336, Germany
Thomas.Klopstock@med.LMU.de
Summary

Background Pantothenate kinase-associated neurodegeneration (PKAN) is a rare genetic disorder characterized by progressive generalized dystonia and brain iron accumulation. We assessed whether the iron chelator deferiprone (DFP) can reduce brain iron and slow disease progression.

Methods An 18-month, randomized, double-blind, placebo-controlled trial, followed by a pre-planned 18-month open-label extension study in patients with PKAN, was conducted in 4 hospitals in Germany, Italy, England and the USA. Patients aged ≥4 years with a genetically confirmed diagnosis of PKAN, a total score ≥3 on the Barry-Albright Dystonia (BAD) scale, and no evidence of iron deficiency, neutropenia, or abnormal liver or renal function, were randomly allocated (2:1) to receive DFP oral solution (30 mg/kg/day) or placebo for 18 months. Randomization was done using a centralized computer random number generator with stratification based on age group at onset of symptoms, and patients were allocated to groups by a non-blinded randomization team that was independent of the study. Patients, caregivers, and investigators were masked to treatment allocation. Patients who completed the randomized trial were eligible to enroll in a single-arm extension study of another 18 months in which all participants received DFP. Co-primary endpoints were the change from baseline to Month 18 in the total score on the BAD scale and the score at Month 18 on the Patient Global Impression of Improvement (PGI-I). Efficacy analyses were done on the modified Intent to Treat (mITT) population, which included all patients who received at least one dose of study drug and who provided a baseline and at least one post-baseline efficacy assessment; safety analyses were done on all patients who received at least one dose of study drug. The trial was registered on ClinicalTrials.gov (NCT01741532) and EudraCT (2012-000845-11).

Findings Between December 2012 and April 2015, 88 patients were randomly assigned to DFP (N=58) or placebo (N=30). Of these, 76 patients completed the study: 49 in the DFP group and 27 in the placebo group. After 18 months, the BAD score worsened by 2.48±0.63 points (DFP), versus 3.99±0.82 points (placebo; difference -1.51 points, 95% CI [-3.19,0.16], p=0.0761). In the predefined subgroup with atypical (disease onset ≥ age 6) PKAN, the BAD score worsened by 2.33±0.73 points (DFP) versus 4.52±0.91 points (placebo; difference -2.19 points, 95% CI [-4.00,-0.38], p=0.0187). No subjective change was detected as assessed by the PGI-I: mean scores at Month 18 were 4.7±0.4 for placebo and 4.6±0.3 for DFP (p=0.7279). In the extension study, patients continuing DFP retained a similar rate of disease progression (1.9±0.5 points in the first 18 months vs 1.4±0.4 points in the second 18 months, p=0.2684), while progression in patients switching from placebo to DFP seemed to slow (4.4±1.1 points when they were receiving placebo vs 1.4±0.9 points when they were receiving DFP, p=0.0206). Patients did not detect a change in their condition after the additional 18 months of treatment, with mean scores of 4.1±0.2 in the DFP-DFP group and of 4.7±0.3 in the placebo-DFP group. DFP was well tolerated and rates of adverse events were similar between the treatment groups except for anemia, which was seen in 20.7% of DFP-treated patients vs. no placebo patients. No patient discontinued therapy due to anemia. There were two deaths, both secondary to aspiration. Neither of these events was considered related to DFP use.
Interpretation  Deferiprone was well tolerated and seemed to show slower, although not statistically significant, disease progression at 18 months. Patients in neither group perceived an improvement or worsening at 18 months based on PGI-I assessments. After an additional 18 months of treatment in the extension trial, there was further evidence of slowing of disease progression by deferiprone, although patients continued to not perceive a change in their condition. This study will help shape the design of future trials in this ultraorphan disease.

Funding  European Commission; FDA; ApoPharma Inc., Canada.
Introduction

Neurodegeneration with brain iron accumulation (NBIA) is a clinically and genetically heterogeneous group of rare hereditary neurodegenerative disorders characterized by high levels of brain iron.\(^1\) Around 50% of cases are due to pantothenate kinase-associated neurodegeneration (PKAN), caused by mutations in the pantothenate kinase 2 (\(PANK2\)) gene.\(^2\) The PANK2 enzyme localizes to mitochondria and is essential for the biosynthesis of coenzyme A (CoA), which in turn is vital for adenosine triphosphate synthesis and fatty acid and neurotransmitter metabolism. Absence or abnormal function of PANK2 may contribute to iron accumulation in specific brain regions.\(^3\) Onset of clinical signs ranges from infancy to adulthood; progression ranges from rapid to slow; and symptoms may vary greatly. Disease characteristics include progressive dystonia, parkinsonism, rigidity and spasticity. The factors that influence disease severity and progression rate of PKAN remain unknown. No disease-modifying therapies are yet available in PKAN or any form of NBIA.\(^4,5,6\)

Historically, PKAN has been described as either classic or atypical. In classic PKAN, symptoms usually develop before 6 years of age, and most patients require a wheelchair by their mid-teens. Atypical PKAN usually becomes evident after 10 years of age, is less severe, and progresses more slowly.\(^3,7\) It is hypothesized that classic PKAN results from complete absence of the PANK2 enzyme, whereas atypical disease results from severe deficiency.\(^3\)

While iron is essential for normal physiological function, an excessive amount or dysregulated iron metabolism is potentially toxic. Increased “free” iron in tissues leads to the formation of highly reactive oxygen species, causing localized toxicity.\(^8,9\) Although proof that iron causes neurodegeneration in PKAN and most other NBIA is lacking, preferential iron accumulation in the basal ganglia likely explains the predominant movement disorder phenotype.\(^10\) Accordingly, iron chelation holds promise to decrease brain iron levels in NBIA, which may retard disease progression.

Deferiprone (DFP, 3-hydroxy-1,2-dimethylpyridin-4-one) is an oral iron chelator approved for the treatment of transfusional iron overload in patients with thalassemia. DFP crosses the blood brain barrier, chelates excess iron from intracellular organelles, and may transfer it to biologic receptors.\(^11\) Limited safety and efficacy data are available on patients with brain iron accumulation. Based on the available data in patients with PKAN or other neurodegenerative disorders who received DFP,\(^6,12-20\) it was hypothesized that DFP could reduce brain iron, which might lead to clinical benefit. This article describes the results of the TIRCON2012V1 study - the first randomized clinical trial of a putative therapeutic agent in patients with PKAN, and of its single-arm extension study, TIRCON2012V1-EXT.
Methods

Key information on study methods is provided here, and further details are available in the Supplement.

Study design

TIRCON2012V1 was an 18-month randomized, double-blind, placebo-controlled trial that evaluated the safety and efficacy of DFP in patients with PKAN. Patients who completed the randomized trial were eligible to enroll in a single-arm extension study of another 18 months, TIRCON2012V1-EXT, in which all participants received DFP.

An independent Data and Safety Monitoring Board regularly reviewed the safety data of both trials, and each study was registered on ClinicalTrials.gov prior to enrollment of the first patient (trial registration numbers NCT01741532 and NCT02174848, respectively).

Patients

Patients were eligible for enrollment in TIRCON2012V1 if they had a diagnosis of PKAN confirmed by genetic testing and a total score ≥ 3 on the Barry-Albright Dystonia (BAD) scale, which ranges from 0 (best) to 32 (worst). Exclusion criteria included treatment with any iron chelator in the past 12 months and the presence of medical conditions or other indicators that might increase safety concerns. The full list of inclusion/exclusion criteria is provided in the Supplement. The use of symptomatic treatments was permitted; however, to reduce confounds, individuals were excluded if they had recent (< 2 months) or anticipated changes in any regimen being used to treat dystonia, whether medication or a Deep Brain Stimulation (DBS) device. Written informed consent was obtained from each participant or the parent/legal guardian before any procedures were carried out.

Randomization and masking

In TIRCON2012V1, patients were assigned in a 2:1 ratio to receive either DFP at a dose of up to 30 mg/kg/day divided b.i.d or matching placebo (identical packaging, appearance, and taste), using block randomization. The randomization list was generated using a computer random number generator. A centralized randomization was used for all study sites, and patients were allocated to groups by a non-blinded randomization team that was independent of the study. Allocation concealment was through a centralized randomization process with computer generated randomization list. Randomization was stratified based on the patient’s age at diagnosis, with one list generated for individuals who had been younger than 6 years at the onset of motor symptoms and one for those who had been 6 years or older. Patients, caregivers, study staff, and the neurologists who analyzed videotapes for determination of BAD scores were blinded as to treatment assignment, as were the radiologists who analyzed the MRI images for determination of iron levels in the globus pallidus.

In the extension trial, all patients received DFP. However, since the randomized study was still in progress when this study began, both patients and staff remained blinded as to which product had been taken for the previous 18 months until both studies had been completed and their data
Procedures

Participants took the assigned study product twice daily for 18 months. Compliance was evaluated at each post-baseline visit by calculating the volume of medication dispensed and the amount of unused drug supply remaining in the bottle. Efficacy was assessed every 6 months, using the following measures: 1) the BAD scale, which measures the severity of dystonia in 8 body regions (eyes, mouth, neck, trunk, and each upper and lower extremity) and generates individual scores and a total score; 2) the Patient Global Impression of Improvement (PGI-I), a subjective instrument which consists of a single question asking patients to rate their condition on a scale from 1 (very much better) to 7 (very much worse) in comparison to how they had felt at baseline; 3) the Unified Parkinson’s Disease Rating Scale (UPDRS) Parts I, II, III, and VI, for assessment of motor symptoms that resemble those in Parkinson’s disease as well as quality of life aspects; 4) the Functional Independence Measure (FIM) or WeeFIM (pediatric version) for assessment of various measures of functional independence; 5) the Pediatric Quality of Life (PedsQL) scale for measurement of quality of life; and 6) the Pittsburgh Sleep Quality Index (PSQI) for measurement of quality of sleep. For the BAD scale, the required tests were administered and videotaped at the site, and the videotapes were sent to a central site for blinded assessment by movement disorders experts. Iron levels in the globus pallidus were measured by MRI-R2* in a subset of patients at baseline and Month 18. Safety assessments were done at each visit, and involved collecting adverse events and conducting clinical laboratory tests, physical examination, vital signs, and electrocardiogram (screening and Month 18 only).

In the extension study, patients who had been randomized to DFP continued to receive it and those who had been randomized to placebo were switched to DFP. Again, assessments were conducted every 6 months. Safety evaluations were the same as before, but efficacy measures were limited to BAD scale and PGI-I.

Outcomes

In the randomized trial, the co-primary efficacy endpoints were change from baseline to Month 18 in the BAD total score and the score at Month 18 on the PGI-I. The outcome was to be considered positive if the group differences in both primary endpoints reached statistical significance (p<0.05). Secondary efficacy endpoints were change from baseline to Month 18 in the BAD score for each body region, iron levels in the globus pallidus (as assessed by MRI-R2*), and scores on the FIM/ WeeFIM, UPDRS, PedsQL, and PSQI; and the proportions of patients at Month 18 with improved or unchanged BAD total scores and PGI-I scores. For the safety endpoints, the groups were compared for the frequency of adverse events, frequency of serious adverse events, and number of discontinuations due to adverse events.

In the extension study, the primary endpoint was safety, and the efficacy endpoints were change in BAD score and score on the PGI-I.
Statistical analysis

Determination of Sample Size: At the time of planning the randomized trial, there were no published studies with data sufficient to estimate sample size based on either the natural history of the disease or the expected impact from an agent that interfered with iron-related neurodegeneration. An estimate of the effect size was based on a retrospective study of 23 patients with NBIA, 22 of whom had most probably PKAN (14 genetically confirmed, the others with eye-of-the-tiger sign), and 21 of whom had been assessed for dystonia using the BAD scale. It was assumed that with similar disease progression, after 18 months there could be a substantial worsening of the BAD total score in the control group, with a possible difference from the DFP group of ≥5 points. Assuming a standard deviation of 6.3 points, 2:1 randomization, and 30% drop-out rate, 87 patients would be needed to detect a difference of at least 5 points at a two-sided 0.05 level of significance with 80% power. For the extension study, there was no formal sample size and power calculation; all patients completing TIRCON2012V1 were invited to enroll.

Analyses: All statistical analyses were performed using SAS (Windows version 9.3). Safety analyses were based on all randomized patients who received at least one dose of study drug. Efficacy analyses were based on the modified Intent-to-Treat (mITT) population, defined as all randomized patients who 1) received at least one dose of study drug, and 2) provided a baseline and at least one post-baseline efficacy assessment. A Mixed Model for Repeated Measures (MMRM) model was used as the primary analysis method to assess the primary and secondary endpoints of changes from baseline to the specified time points (Months 6, 12, and 18), with baseline value and age of onset of motor symptoms (before 6 years versus at or after 6 years) as covariates, and treatment group as the main factor in the model. The marginal mean change (least squares estimate) at Month 18 was used to determine the treatment effect in the primary analysis. Over the 18-month course of the trial, some participants required changes in their DBS settings or in the use or frequency of rescue or as-needed medications, and these variables were also included in the MMRM model as visit-dependent covariates.

A similar MMRM model was used for the analysis of the PGI-I. As the PGI-I score is a measurement of change from baseline, it was treated directly as the outcome variable. A logistic regression model with similar covariates was used for analysis of the proportion of responders. Finally, a subgroup analysis using a similar MMRM model was performed on the co-primary efficacy endpoints based on age at onset of motor symptoms (≥6 years vs. <6 years). The safety data for continuous variables were summarized using descriptive statistics, and the safety data for discrete variables were tabulated with frequency tables.

In the extension study, changes in the BAD scale and PGI-I scores were summarized using descriptive statistics. Last Observation Carried Forward (LOCF) was used for the scores of patients who did not complete treatment. A paired t-test was used to compare the change in BAD total score and PGI-I score between the randomized and the extension studies, while a student t-test was used for within-study comparison of treatment groups.
Role of the funding source

Funding for the study was provided by the European Commission, the US FDA, and ApoPharma Inc., Canada. The US FDA had input into the design and selection of endpoints. ApoPharma participated in study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Randomized trial

Following screening of 100 prospective subjects, 89 of a planned 90 patients were enrolled between December 13, 2012 and April 21, 2015, with 59 randomized to receive DFP and 30 to receive placebo (Figure 1). One patient assigned to the DFP group withdrew prior to receiving the first dose, and two assigned to placebo withdrew after receiving study drug but before providing any post-baseline efficacy data; accordingly, there were 58 DFP patients and 30 placebo patients evaluable for safety, and 58 and 28, respectively, for efficacy. 76 patients (85.4%) completed the trial, and 12 (in addition to the one patient who was never dosed) withdrew: 3 (10.0%) in the placebo group and 9 (15.3%) in the DFP group. Reasons for withdrawal in the placebo group were 1 case each of worsening of the disease, protocol violation, and voluntary withdrawal, while those in the DFP group were 4 cases of an adverse event, 3 of worsening of the disease, and 1 each of investigator’s decision and voluntary withdrawal. Of the withdrawals due to adverse events, 3 were for neutropenia (for which withdrawal was mandated by the study protocol), and 1 was for fever and pneumonia.

At baseline, there were no major differences between the treatment groups with respect to age at enrolment, duration of disease, sex, and race (Table 1), baseline BAD score, or amount of iron in the relevant brain areas. Stratification was used to ensure that each treatment group had approximately equal percentages of patients with classic or atypical PKAN, as determined by age at onset of motor symptoms: among the 86 patients who were evaluable for efficacy, there were 12 classic and 16 atypical patients in the placebo arm, and 29 of each type in the DFP arm. Mean age at randomization differed considerably between the subgroups (13.7 and 26.5 years for patients with classic and atypical PKAN, respectively), but disease duration was similar for both, approximately 13 years. As expected, the disease had progressed further in those with classic PKAN, as indicated by baseline BAD scores (20.3 vs. 17.0), but the difference did not reach statistical significance (p=0.0753).

Concomitant treatments for dystonia symptoms were an important consideration because of their possible confounding effect on the BAD score. Most participants, 18 placebo patients (60.0%)
and 42 DFP patients (72.4%), were taking at least one dystonia medication at baseline; 25 patients, 6 (20%) and 19 (32%), respectively, had a DBS system in place; and 3 patients (1 and 2 respectively), had a baclofen pump in place. There were no statistically significant differences between treatment groups regarding the use of any medication or device for the treatment of dystonia at baseline. During the study, additional dystonia medications administered on an as-needed basis were taken by a higher percentage of placebo patients (21.4%) than DFP patients (10.9%), with the difference reaching significance (p=0.0345) for botulinum toxin type A.

Compliance was very high at all time points, ranging from 95.1% to 99.4% in the placebo group and from 96.6% to 99.5% in the DFP group.

BAD scores at baseline are shown in Table 1. One patient in the placebo group had a score of 31 and one in the DFP group had the maximum score of 32, meaning that little or no further worsening could be detected in those individuals through this instrument. Further analyses showed that results were not confounded by a ceiling effect (cf. Discussion, Supplementary material and Suppl. Tables 1a and 1b). Patients in both treatment groups showed a worsening over time (Figures 2a, 2b, and 2c). In the main analysis using the marginal means from the MMRM model, there was a mean ±SE worsening of 2.48±0.63 points in the DFP group vs. 3.99±0.82 points in the placebo group: i.e., the DFP group overall worsened by 1.51 points less, a difference that approached the protocol-defined criterion of p=0.05 for statistical significance (95% CI [-3.19, 0.16], p=0.0761) (Table 2). A predefined subgroup analysis that looked separately at patients with classic or atypical PKAN showed that DFP use was associated with slower progression in clinical symptoms (2.33±0.73 points) than patients on placebo (4.52±0.91 points) in atypical PKAN, a difference of 2.19 points, that reached statistical significance (95% CI [-4.00,-0.38], p=0.0187).

Within the classic subgroup, the difference of 0.81 points in favor of DFP did not reach significance (p=0.5701). In the responder analysis, 36% of DFP-treated patients responded to therapy compared to 14% of placebo-treated patients (p=0.0893).

In contrast to the objective signs of disease progression, as assessed by the BAD score, no subjective change was detected as assessed by the PGI-I. At Month 18, mean PGI-I scores were 4.7±0.4 for placebo and 4.6±0.3 for DFP (p=0.7279), indicating that patients in both groups did not perceive either improvement or worsening since baseline. There was only a weak correlation (r = 0.29) between the PGI-I and the change in BAD score at month 18 (cf. Supplementary material and Suppl. Figure 1).

MRI-R2* imaging for the measurement of iron levels in the globus pallidus was conducted in a subset of patients at the start (16 placebo, 24 DFP) and end of the study (13 placebo, 19 DFP). In the placebo group, there was virtually no change (an R2* decrease of 0.5±4.0 Hz), while in the DFP group there was a decrease of 36.1±3.1 Hz, for a significant treatment group difference of -35.6 Hz (95%CI, [-44.8,-26.3], p <0.0001) (Figure 3).

Figure 4 presents a summary of all secondary efficacy endpoints as a Forest plot. Each point represents the marginal mean difference between DFP and placebo. The line indicates the 95% confidence interval for the difference, both standardized by the standard error of the marginal
mean difference. For each endpoint, this graph indicates whether the results were in favor of DFP (point to the left of 0.00) or placebo (point to the right of 0.00). Of the 21 measures examined, 13 were in favor of DFP, 4 showed no treatment difference and 4 were in favor of placebo.

Differences between the treatment groups that reached statistical significance in favor of DFP were seen for the WeeFIM, and for certain BAD body region scores (neck: -0.43; p=0.0465; left lower extremity: -0.28; p=0.0391; and right lower extremity: -0.25; p=0.0435). No significant differences were seen in other endpoints. More detailed results on the WeeFIM assessments are provided in the Supplement, including Suppl. Figure 2.

Overall, DFP was well tolerated, and rates of adverse events (AEs) seen in >10% of patients is provided in Table 3. Rates were similar between the treatment groups except for AEs related to study treatment such as anemia, which was seen in 20.7% of DFP-treated patients vs. no placebo patients; however, the hemoglobin value was <10 g/dL in only three patients with anemia. Non-significant differences were seen between the DFP and placebo groups in rates of decreased serum ferritin (32.8% vs. 16.7%; p=0.1341) and iron deficiency (15.5% vs. 10.0%; p=0.7442). Iron supplementation was permitted, based on the investigator’s assessment of need, and was taken by 39% of patients in the DFP group and by 27% of patients in the placebo group. There were no deaths or episodes of agranulocytosis or severe neutropenia, and there was no significant difference between the study groups in the rates of less severe neutropenia (8.6% in DFP vs. 6.7% in placebo).

Extension study

Of the 76 patients who completed the randomized trial, 68 enrolled in the extension study. Those who had received DFP continued to receive it (DFP-DFP group, N=44), while those who had received placebo were switched to DFP (placebo-DFP group, N=24). All 68 patients were evaluable for safety, and 62 (43 DFP-DFP, 19 placebo-DFP) were evaluable for efficacy. BAD scores at the start of the extension study are shown in Table 1 (at this time point, one placebo-DFP patient had a score of 30 and one DFP-DFP patient had the maximum score of 32). Figure 2d displays the change in BAD total score for the 62 patients who provided evaluable efficacy data in both studies. In both groups, scores continued to increase (worsen) over time, but the DFP-DFP patients showed a similar rate of progression in both studies, while the placebo-DFP patients progressed more rapidly in the first study and slowed when they were switched to DFP. Over the 18 months of the extension study, there was no significant difference in the change in BAD score for patients who had been on DFP from the start (1.9±0.5 points in the first 18 months vs 1.4±0.4 points in the second 18 months, p=0.2684) while there was significantly less worsening in the placebo-DFP group (4.4±1.1 points when they were receiving placebo vs 1.4±0.9 points when they were receiving DFP, p=0.0206) (Suppl. Table 2).

With respect to the PGI-I, as in the randomized study, patients did not detect a change in their condition after the additional 18 months of treatment, with mean scores of 4.1±0.2 in the DFP-DFP group and of 4.7±0.3 in the placebo-DFP group.
For evaluation of safety, data were combined for all 68 patients. Overall, DFP continued to be well tolerated for the 36-month period. There were two deaths, both secondary to aspiration (one pneumonia and multi-organ failure, the other to aspiration following the patient vomiting in his sleep). Neither of these patients had experienced neutropenia while in the study. The most common adverse event was dystonia, reported in 40 (58.8%) patients, followed by pyrexia in 23 (33.8%), headache in 20 (29.4%), and condition aggravated and decreased serum ferritin in 18 each (26.5%).

**Discussion**

The present study is the largest randomized trial to date and provides the longest prospective follow-up of any NBIA population. It yields valuable information on the impact of iron chelation but also on the natural history of PKAN through the detailed assessment of placebo recipients, indicating that the rate of disease progression is slower than previously estimated. In the current trial, the power calculation for the divergence in the change in BAD total score between the treatment groups had assumed that a clinically relevant difference of 5 points could be achieved; however, over 18 months, the placebo group worsened by less than anticipated. Accordingly, the only way a significant group difference could have been achieved would have been for DFP to reverse rather than slow the progression of the disease. It is noteworthy that even the difference of 1.51 points approached the protocol-defined criterion for statistical significance (p=0.0761), and it is possible that a study duration longer than 18 months with the same number of patients would have allowed the detection of a difference large enough to establish statistical significance.

For patient enrollment, there was no exclusion of patients with high BAD scores. This may lead to a ceiling effect where patients with high BAD scores (close to the maximum score of 32) at baseline cannot worsen as much as patients with lower BAD scores. Randomization resulted in proportionally more patients with high baseline BAD scores being assigned to the deferiprone treatment group. To investigate whether a ceiling effect confounds the results of our study, we repeated the MMRM analysis excluding all patients with a baseline BAD score > 27 who would potentially be subject to a ceiling effect. In this analysis, deferiprone-treated patients still exhibited a numerically lesser progression in BAD score than placebo-treated patients, with the marginal mean difference being very similar to that from the analysis of the mITT population (Suppl. Table 1a). The p value worsened from 0.0761 to 0.1114 as a function of the lower number of subjects. Additional analysis was conducted to compare response according to the tertiles of baseline BAD (Suppl. Table 1b), demonstrating a benefit of DFP versus placebo, although p values were not significant due to the low number of subjects. In conclusion, these analyses showed that PKAN progression as measured by the BAD score is slower with higher baseline values and that this results in a ceiling effect at very high baseline scores. While this is important information for the design of future trials, it did not affect the principal outcome of our
current study. The potential benefit of DFP is also supported by the lower use of dystonia medications during the trial by patients on DFP than patients on placebo, and by the results of the extension study. Among patients who received DFP in both studies, disease progression continued at the same rate, while among those who switched from placebo to DFP, it slowed to match the rate seen in those who had received DFP in the first study. The fact that the rate of deterioration in the placebo-DFP group was less (p=0.0206) during the 18 months of DFP treatment than it was during the 18 months of placebo treatment supports the effect of this drug in patients acting as their own controls.

Another factor for consideration is the stage of the disease, since in any neurodegenerative process, the later the intervention with an agent that might have the ability to slow progression, the less the expected benefit. Participants in this study had been experiencing PKAN symptoms for approximately 13 years at the time of enrollment, and it is likely that for many, the disease progression was too advanced for a preventative drug to provide significant benefit. If brain iron contributes to the pathology seen in PKAN, then early initiation of DFP, where there has been less extensive iron-induced neurodegeneration, would be expected to maximize its benefit in slowing disease progression. Support for the view of a greater impact of DFP when the disease is less advanced was provided by the predefined subgroup analysis looking separately at patients with classic vs. atypical PKAN. In atypical PKAN, in addition to symptoms appearing later, the disease progresses more slowly; hence, even though the patients with atypical PKAN had the disease for about the same duration as those with classic PKAN, the extent of irreversible neurodegeneration would have been less. This difference may explain why patients with atypical PKAN had a better response than patients on placebo in the randomized portion of the study (p=0.0187).

The low prevalence of PKAN (1 to 3 cases per million population) was responsible for a paucity of patients, and, in light of the slower than predicted rate of disease progression, a larger number of patients could have compensated for inadequate power to reach the preset level of significance of p<0.05 in the 18-month study. As the conduct of larger studies is improbable, any attempt at future clinical trials will likely require patient enrichment for targeted questions.

With respect to the PGI-I endpoint, most participants reported neither worsening nor improvement from baseline despite the indications seen on more objective measures; and the same was true in the extension study. The correlation between the PGI-I and the change in BAD score at Month-18 is weak (r = 0.29), in which < 10% of the PGI-I variation can be explained by the change in BAD (r² < 0.1), indicating that the PGI-I is not an adequate tool for assessment in PKAN over an 18-month period. The PGI-I is, by definition, subjective, and was likely inappropriate for this study. It may be a good tool for assessing the short-term effect of drugs that induce improvement or reversal of disease, but it was likely difficult for patients to judge whether their condition had worsened or improved over an 18-month period, explaining why no net worsening was detected, even by those on placebo.

The most notable change observed was the profound reduction of iron in the globus pallidus: a mean decrease of 36.1 Hz in the DFP-treated group compared to 0.50 Hz in the placebo group.
(p <0.0001). This finding is consistent with reports of DFP-induced reductions in the levels of brain iron seen in Friedreich’s ataxia, Parkinson’s disease, and other NBIA disorders. Importantly, the reduction in brain iron load induced by DFP was not associated with systemic iron depletion.

Freezing phenomenon, an event commonly observed in PKAN patients, was seen in 10% of patients on placebo versus in none of those on DFP (p=0.0370), even though there were twice as many patients on DFP. Freezing has been linked to pathology in the basal ganglia and brainstem, both of which are areas affected in PKAN and in which iron was decreased by treatment with DFP. Further exploration of the mechanism is warranted.

With respect to the secondary efficacy endpoints of the randomized study, although many of the group differences did not reach significance, patients who received DFP exhibited less worsening over 18 months of treatment than patients on placebo in most outcome measures. Responder analysis (the percentage of patients showing either improvement or stabilization on the total BAD score) found that the responder rate for patients on DFP was 2.6 times that for patients on placebo: 36% vs. 14% (p=0.0893). DFP patients showed less worsening on the individual BAD scores for nearly all body regions, with group differences reaching statistical significance (albeit marginal, as they would not reach significance if multiplicity were considered) for neck (p=0.0465), left lower extremity (p=0.0391), and right lower extremity (p=0.0435).

Next to the reduction of brain iron levels, the most substantial difference between treatments was seen on the WeeFIM measure, where actual improvement—not merely less worsening—was seen in DFP patients in the domain of cognition, with the treatment group difference reaching statistical significance (p=0.0324). No statistically significant group differences were seen on the other secondary measures. However, examination of all the secondary endpoints revealed a pattern suggesting a beneficial effect of DFP across a broad range of functions.

The tolerability of DFP was evidenced by the near-total compliance and low dropout rate in both studies. The two deaths were unrelated to study treatment, and rates of adverse events, which were mainly of mild intensity, were similar between the treatment groups on most measures (Table 3 and Suppl. Table 3). In general, the safety findings were consistent with those of other studies of DFP in patients with both brain iron overload and systemic iron overload. There were no occurrences of agranulocytosis, the most serious adverse event associated with DFP, and there was no significant group difference in the frequency of patients experiencing milder episodes of neutropenia, all of which resolved rapidly. There was a concern that non-iron-overloaded patients being treated with an iron chelator might experience hematological events linked to a lowering of iron body stores, such as decreased serum ferritin, anemia, and iron deficiency. However, while these events were seen in a higher percentage of DFP patients in the randomized trial, the rates were low, the group difference reached significance only for anemia, none of the events were serious, and all could be managed by iron supplementation.

A major strength of the study related to the ability to actually enroll close to 10% of all estimated
PKAN patients in the US and Europe. The major limitation in the study was the lack of adequate pre-existing natural history data in PKAN patients to enable an informed power calculation for the primary outcome related to a change in BAD. Consequently, the slower than expected rate of worsening in the placebo-treated patients impacted the ability to achieve a significant difference in the overall ITT population.

In summary, this study, together with previous findings, shows that the membrane permeable iron chelator deferiprone achieved target engagement (lowering of iron in the basal ganglia) in patients with PKAN. While the clinical endpoints were not met for the mITT population in the randomized trial, planned subgroup analysis provided some evidence of slowing of disease progression in the atypical patients and the results of the extension trial indicate potential slowing of progression by deferiprone in the overall population as well. This study will help shape the design of future trials in this ultraorphan disease.

**Contributors**

TK and EV conceived the study and were the Coordinating Investigators. TK, FT, CF, MS, SJH, PH and EV designed the study protocol. LN, BK and BB managed the trial. TK, RH, PFC, NN and EV were the site principal investigators, responsible for participant recruitment and data collection. IK, LN, GZ, HES, AB, CK, CN, FZ and CA were site investigators, contributing largely to participant recruitment and data collection. TKm, PD and ZY contributed largely to participant recruitment and local care in Poland, Czechia and Turkey, respectively. SH and PH were the central raters of videotapes for the BAD score examination of all patients from baseline and Month 18. BB was the central rater of BAD videotapes for the extension trial. IW and AMB defined the MRI protocol, oversaw image quality assurance, and analyzed all available MRI data from baseline and Month 18. FZh did the statistical analysis. TK wrote the first draft of the article. TK, FT, LN, MS and EV built a writing committee to work on the further drafts of the article which was reviewed by all authors.

**Declaration of interests**

Dr. Klopstock reports grants from European Commission, grants, personal fees, non-financial support and other from ApoPharma Inc., during the conduct of the study; grants from Retrophin Pharmaceuticals, outside the submitted work.

Drs. Fradette, Spino and Tricta, and F. Zhao are employees of ApoPharma Inc., the manufacturer of Deferiprone. Dr. Spino reports grants from European Commission, FP7, during the conduct of the study; In addition, Dr. Spino has a patent PCT WO 2009/129592 Al issued.

Dr. Neumayr reports grants from FDA, grants from ApoPharma Inc, grants from European Commission, grants from NIH, grants from NBIA Foundation, during the conduct of the study; other from Retrophrin, Inc, personal fees from ApoPharma Inc, outside the submitted work.
Dr. Zorzi reports grants from ApoPharma Inc, during the conduct of the study; grants from Retrophin, other from Biomarin, personal fees from Medtronic, outside the submitted work.

Dr. Büchner reports grants and other from ApoPharma Inc., grants from European Commission, during the conduct of the study.

Dr. Steele reports non-financial support from Apopharma Inc., during the conduct of the study; grants from GlaxoSmithKline, outside the submitted work.

Dr. Horvath was supported by the Medical Research Council (UK) [MR/N025431/1], the Wellcome Investigator fund [109915/Z/15/Z], the Newton Fund [UK/Turkey, MR/N027302/1], the European Research Council [309548] and the Wellcome Trust Pathfinder Scheme [201064/Z/16/Z].

Dr. Chinnery is a Wellcome Trust Principal Research Fellow (212219/Z/18/Z), and a UK NIHR Senior Investigator, who receives support from the Medical Research Council Mitochondrial Biology Unit (MC_UP_1501/2), the Evelyn Trust, and the National Institute for Health Research (NIHR) Biomedical Research Centre based at Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge.

Dr. Basu reports grants from European Commission, grants from Apopharma, during the conduct of the study; other from National Institute of Health Research, outside the submitted work.

Dr. Kuepper reports grants from European Commission, grants from ApoPharma Inc during the conduct of the study.

Dr. Dusek reports other from 024PKAN15004, outside the submitted work.

Dr. Zibordi reports grants from ApoPharma Inc, during the conduct of the study.

Dr. Nardocci reports grants from Apopharma, during the conduct of the study; personal fees from Medtronic, other from Biomarin, outside the submitted work.

Dr. Hogarth reports grants from European Union Seventh Framework Programme (FP7), during the conduct of the study; in addition, Dr. Hogarth has a pending patent “Methods and Models used in predicting pantothenate kinase-associated neurodegeneration and the amelioration thereof”. Dr. Hogarth serves as a non-compensated executive for the Spoonbill Foundation, a not-for-profit organization that may benefit from the results of this research and technology. This potential conflict of interest has been reviewed and managed by OHSU.

Dr. Vichinsky reports grants from FDA, grants from European Commission, grants and non-financial support from ApoPharma, Inc., grants from NIH, during the conduct of the study; other from Retrophin, Inc, outside the submitted work.

All other authors declare no competing interests.

Data sharing statement
The TIRCON Group and ApoPharma are committed to sharing with qualified external researchers, the study’s patient-level data and supporting clinical documents according to the criteria and process described on www.clinicalstudydatarequest.com.

Acknowledgments

This study was funded by the European Commission 7th Framework Programme (FP7/2007-2013, HEALTH-F2-2011, grant agreement No. 277984, TIRCON), the FDA 4 R01 FD004103-04 (Phase I/II randomized, blinded safety trial of deferiprone in NBIA/PKAN), and ApoPharma Inc.

Non-financial support was also provided through the European Reference Network (ERN) for Rare Neurological Diseases (ERN-RND), one of 24 ERNs funded by the European Commission (ERNRND: 3HP 767231).

We thank all the patients and their families who participated in this study. The great support of NBIA patient advocacies world-wide is very much appreciated, and we want to emphasize the help of Ms. Patricia Wood, President of the US NBIA Disorders Association, and Angelika Klucken, President of the German Hoffnungsbau e.V. We also thank the primary physicians taking care of these patients for being very supportive of this study. We are grateful to Dr. Eva Coppenrath for performing MRIs at the Munich site, and to Dr. Nihan Hande Akçakaya for excellent care of Turkish study participants. We also thank Ms. Anne Stilman, from ApoPharma Inc., for editorial assistance.
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Effect of the iron chelator Safety and efficacy of deferiprone on for pantothenate kinase-associated neurodegeneration (PKAN): Findings of a randomized, double-blind, controlled trial and an open-label extension study

Thomas Klopstock, Fernando Tricta, Lynne Neumayr, Ivan Karin, Giovanna Zorzi, Caroline Fradette, Tomasz Kmiec, Boriana Buchner, Hannah E Steele, Rita Horvath, Patrick F Chinnery, Anna Basu, Clemens Kupper, Christiane Neuhofer, Bernadette Kalmán, Petr Dusek, Zuhal Yapici, Ian Wilson, Feng Zhao, Federica Zibordi, Nardo Nardocci, Christine Aguilar, Susan J. Hayflick, Michael Spino, Andrew M Blamire, Penelope Hogarth, Elliott Vichinsky

Department of Neurology, Friedrich-Baur-Institute, Ludwig-Maximilians-University of Munich, Munich, Germany (Prof T Klopstock MD, I Karin MD, B Buchner MD, C Kupper MD, C Neuhofer MD); German Center for Neurodegenerative Diseases (DZNE), Munich, Germany (Prof T Klopstock MD); Munich Cluster for Systems Neurology (SyNergy), Munich, Germany (Prof T Klopstock MD); ApoPharma Inc, Toronto, Ontario, Canada (F Tricta MD, Caroline Fradette PhD, Feng Zhao MSc, Michael Spino PharmD); Department of Hematology/Oncology, UCSF Benioff Children's Hospital and Research Center Oakland, Oakland, California, USA (Prof E Vichinsky MD, L Neumayr MD); Pediatric Rehabilitation Department, UCSF Benioff Children's Hospital and Research Center Oakland (C Aguilar MD); Department of Pediatric Neuroscience, Neurological Institute Carlo Besta, Milan, Italy (Prof N Nardocci MD, G Zorzi MD, F Zibordi MD); Department of Neurology and Epileptology, Children's Memorial Health Institute, Warsaw, Poland (T Kmiec MD); Institute of Genetic Medicine, Newcastle University, Newcastle Upon Tyne, UK (Prof R Horvath MD, H Steele MBBS); Institute of Neuroscience, Newcastle University. Newcastle Upon Tyne, UK (A Basu PhD); Department of Clinical Neurosciences, Cambridge University, Cambridge, UK (Prof R Horvath MD, Prof P Chinnery MBBS); Charles University, Prague, Czechia (Dr. P Dusek MD); Institute of Laboratory Medicine, Szentagothai Research Center, University of Pécs, Pécs, Hungary (Prof B Kalmán MD); Department of Child Neurology, Istanbul Faculty of Medicine, Turkey (Prof Z Yapici MD); Department of Molecular & Medical Genetics, Oregon Health & Science University, Portland, Oregon, USA (Prof S Hayflick MD, P Hogarth MD); Institute of Cellular Medicine & Newcastle Magnetic Resonance Centre, Newcastle University, Newcastle Upon Tyne, UK (I Wilson Bsc(Hons), A Blamire PhD)

Correspondence to:
Prof Thomas Klopstock, Department of Neurology, Friedrich-Baur-Institute, Ludwig-Maximilians-University of Munich, Munich 80336, Germany
Thomas.Klopstock@med.LMU.de
Summary

Background Pantothenate kinase-associated neurodegeneration (PKAN) is a rare genetic disorder characterized by progressive generalized dystonia and brain iron accumulation. We assessed whether the iron chelator deferiprone (DFP) can reduce brain iron and slow disease progression.

Methods An 18-month, randomized, double-blind, placebo-controlled trial, followed by a pre-planned 18-month open-label extension study [A: was the extension study pre-planned? There are no details in the protocol provided] in patients with PKAN, was conducted in 4 hospitals in Germany, Italy, England and the USA. Key eligibility criteria included Patients aged ≥4 years with a genetically confirmed diagnosis of PKAN, a total score ≥3 on the Barry-Albright Dystonia (BAD) scale, and no evidence of iron deficiency, neutropenia, or abnormal liver or renal function. Eligible patients (N=88) were randomly allocated (2:1) to receive DFP oral solution (30 mg/kg/day) or placebo for 18 months. Randomization was done using a centralized computer random number generator with stratification based on age group at onset of symptoms, and patients were allocated to groups by a non-blinded randomization team that was independent of the study. Patients, caregivers, and investigators were masked to treatment allocation. Patients who completed the randomized trial were eligible to enroll in a single-arm extension study of another 18 months in which all participants received DFP. Co-primary endpoints were the change from baseline to Month 18 in the total score on the BAD scale and the score at Month 18 on the Patient Global Impression of Improvement (PGI-I). Efficacy analyses were done on the modified Intent to Treat (mITT) population, which included all patients who received at least one dose of study drug and who provided a baseline and at least one post-baseline efficacy assessment; safety analyses were done on all patients who received at least one dose of study drug. The trial was registered on ClinicalTrials.gov (NCT01741532) and EudraCT (2012-000845-11).

Findings Between December 2012 and April 2015, 88 patients were randomly assigned to DFP (N=58) or placebo (N=30). Of these, 76 patients completed the study: 49 in the DFP group and 27 in the placebo group. Participants in both groups had an average disease duration of 13 years before enrollment. After 18 months, the BAD score worsened by 2.33±0.73 points (DFP) versus 4.52±0.91 points (placebo; difference -2.19 points, 95% CI [-3.19, 0.16], p=0.0761). [A: subgroup analysis has been removed as reporting should not be selective in the abstract.] In the predefined subgroup with atypical (disease onset ≥ age 6) PKAN, the BAD score worsened by 2.33±0.73 points (DFP) versus 4.52±0.91 points (placebo; difference -2.19 points, 95% CI [-4.00, -0.38], p=0.0187). In the extension study, patients continuing on DFP retained the slower rate of disease progression while progression in patients switching from placebo to DFP slowed significantly. No subjective change was detected as assessed by the PGI-I: mean scores at Month 18 were 4.7±0.4 for placebo and 4.6±0.3 for DFP (p=0.7279), indicating that patients in both groups did not perceive either improvement or worsening since baseline. In the extension study, patients continuing on DFP retained the slower similar rate of disease progression (1.9±0.5 points in the first 18 months vs 1.4±0.4 points in the second 18 months, p=0.2684), while progression in patients switching from placebo to DFP seemed to slowed significantly (4.4±1.1 points when they were receiving placebo vs 1.4±0.9 points when they were receiving DFP).
Patients also did not detect a change in their condition after the additional 18 months of treatment, with mean scores of 4.1±0.2 in the DFP-DFP group and of 4.7±0.3 in the placebo-DFP group. Regarding safety, DFP was well tolerated, and rates of adverse events were similar between the treatment groups except for anemia, which was seen in 20.7% of DFP-treated patients vs. no placebo patients. No patient discontinued therapy due to anemia. There were two deaths, both secondary to aspiration. Neither of these events was considered related to DFP use.

Interpretation This trial is the largest randomized trial to date and provides the longest prospective follow-up of any NBIA population. Deferiprone was well tolerated but did not seem to show slower, although not statistically significant, disease progression at 18 months. Patients in neither group perceived an improvement or worsening at 18 months based on PGI-I assessments. After an additional 18 months of treatment in While the primary endpoints were not met for the Intent-to-Treat population in the randomized trial, subgroup analysis and the results of the extension trial, there was some further evidence of slowing of disease progression by deferiprone, although patients did not perceive a change in their condition. This study will help shape the design of future trials in this ultraorphan disease.

Funding European Commission; FDA; ApoPharma Inc., Canada.
Introduction

Neurodegeneration with brain iron accumulation (NBIA) is a clinically and genetically heterogeneous group of rare hereditary neurodegenerative disorders characterized by high levels of brain iron. Around 50% of cases are due to pantothenate kinase-associated neurodegeneration (PKAN), caused by mutations in the pantothenate kinase 2 (PANK2) gene. The PANK2 enzyme localizes to mitochondria and is essential for the biosynthesis of coenzyme A (CoA), which in turn is vital for adenosine triphosphate synthesis and fatty acid and neurotransmitter metabolism. Absence or abnormal function of PANK2 may contribute to iron accumulation in specific brain regions. Onset of clinical signs ranges from infancy to adulthood; progression ranges from rapid to slow; and symptoms may vary greatly. Disease characteristics include progressive dystonia, parkinsonism, rigidity and spasticity. The factors that influence disease severity and progression rate of PKAN remain unknown. No disease-modifying therapies are yet available in PKAN or any form of NBIA.

Historically, PKAN has been described as either classic or atypical. In classic PKAN, symptoms usually develop before 6 years of age, and most patients require a wheelchair by their mid-teens. Atypical PKAN usually becomes evident after 10 years of age, is less severe, and progresses more slowly. It is hypothesized that classic PKAN results from complete absence of the PANK2 enzyme, whereas atypical disease results from severe deficiency.

While iron is essential for normal physiological function, an excessive amount or dysregulated iron metabolism is potentially toxic. Increased “free” iron in tissues leads to the formation of highly reactive oxygen species, causing localized toxicity. Although proof that iron causes neurodegeneration in PKAN and most other NBIA is lacking, preferential iron accumulation in the basal ganglia likely explains the predominant movement disorder phenotype. Accordingly, iron chelation holds promise to decrease brain iron levels in NBIA, which may retard disease progression.

Deferiprone (DFP, 3-hydroxy-1,2-dimethylpyridin-4-one) is an oral iron chelator approved for the treatment of transfusional iron overload in patients with thalassemia. DFP crosses the blood brain barrier, chelates excess iron from intracellular organelles, and may transfer it to biologic receptors. Limited safety and efficacy data are available on patients with brain iron accumulation. Based on the available data in patients with PKAN or other neurodegenerative disorders who received DFP, it was hypothesized that DFP could reduce brain iron, which might lead to clinical benefit. This article describes the results of the TIRCON2012V1 study - the first randomized clinical trial of a putative therapeutic agent in patients with PKAN, and of its single-arm extension study, TIRCON2012V1-EXT.
Methods

Key information on study methods is provided here, and further details are available in the Supplement.

Study design

TIRCON2012V1 was an 18-month randomized, double-blind, placebo-controlled trial that evaluated the safety and efficacy of DFP in patients with PKAN. Patients who completed the randomized trial were eligible to enroll in a single-arm extension study of another 18 months, TIRCON2012V1-EXT, in which all participants received DFP.

An independent Data and Safety Monitoring Board regularly reviewed the safety data of both trials, and each study was registered on ClinicalTrials.gov prior to enrollment of the first patient (trial registration numbers NCT01741532 and NCT02174848, respectively).

Patients

Patients were eligible for enrollment in TIRCON2012V1 if they had a diagnosis of PKAN confirmed by genetic testing and a total score ≥3 on the Barry-Albright Dystonia (BAD) scale, which ranges from 0 (best) to 32 (worst). Exclusion criteria included treatment with any iron chelator in the past 12 months and the presence of medical conditions or other indicators that might increase safety concerns. The full list of inclusion/exclusion criteria is provided in the Supplement. The use of symptomatic treatments was permitted; however, to reduce confounds, individuals were excluded if they had recent (< 2 months) or anticipated changes in any regimen being used to treat dystonia, whether medication or a Deep Brain Stimulation (DBS) device. Written informed consent was obtained from each participant or the parent/legal guardian before any procedures were carried out.

Randomization and masking

In TIRCON2012V1, patients were assigned in a 2:1 ratio to receive either DFP at a dose of up to 30 mg/kg/day divided b.i.d or matching placebo (identical packaging, appearance, and taste), using block randomization. The randomization list was generated using a computer random number generator. A centralized randomization was used for all study sites, and patients were allocated to groups by a non-blinded randomization team that was independent of the study. Allocation concealment was through a centralized randomization process with computer generated randomization list. Randomization was stratified based on the patient’s age at diagnosis, with one list generated for individuals who had been younger than 6 years at the onset of motor symptoms and one for those who had been 6 years or older. Patients, caregivers, study staff, and the neurologists who analyzed videotapes for determination of BAD scores were blinded as to treatment assignment, as were the radiologists who analyzed the MRI images for determination of iron levels in the globus pallidus.

In the extension trial, all patients received DFP. However, since the randomized study was still in progress when this study began, both patients and staff remained blinded as to which product had been taken for the previous 18 months until both studies had been completed and their data
locked.

**Procedures**

Participants took the assigned study product twice daily for 18 months. Compliance was evaluated at each post-baseline visit by calculating the volume of medication dispensed and the amount of unused drug supply remaining in the bottle. Efficacy was assessed every 6 months, using the following measures: 1) the BAD scale, which measures the severity of dystonia in 8 body regions (eyes, mouth, neck, trunk, and each upper and lower extremity) and generates individual scores and a total score; 2) the Patient Global Impression of Improvement (PGI-I), a subjective instrument which consists of a single question asking patients to rate their condition on a scale from 1 (very much better) to 7 (very much worse) in comparison to how they had felt at baseline; 3) the Unified Parkinson’s Disease Rating Scale (UPDRS) Parts I, II, III, and VI, for assessment of motor symptoms that resemble those in Parkinson’s disease as well as quality of life aspects; 4) the Functional Independence Measure (FIM) or WeeFIM (pediatric version) for assessment of various measures of functional independence; 5) the Pediatric Quality of Life (PedsQL) scale for measurement of quality of life; and 6) the Pittsburgh Sleep Quality Index (PSQI) for measurement of quality of sleep. For the BAD scale, the required tests were administered and videotaped at the site, and the videotapes were sent to a central site for blinded assessment by movement disorders experts. Iron levels in the globus pallidus were measured by MRI-R2* in a subset of patients at baseline and Month 18. Safety assessments were done at each visit, and involved collecting adverse events and conducting clinical laboratory tests, physical examination, vital signs, and electrocardiogram (screening and Month 18 only).

In the extension study, patients who had been randomized to DFP continued to receive it and those who had been randomized to placebo were switched to DFP. Again, assessments were conducted every 6 months. Safety evaluations were the same as before, but efficacy measures were limited to BAD scale and PGI-I.

**Outcomes**

In the randomized trial, the co-primary efficacy endpoints were change from baseline to Month 18 in the BAD total score and the score at Month 18 on the PGI-I. The outcome was to be considered positive if the group differences in both primary endpoints reached statistical significance (p<0.05). Secondary efficacy endpoints were change from baseline to Month 18 in the BAD score for each body region, iron levels in the globus pallidus (as assessed by MRI-R2*), and scores on the FIM/ WeeFIM, UPDRS, PedsQL, and PSQI; and the proportions of patients at Month 18 with improved or unchanged BAD total scores and PGI-I scores. For the safety endpoints, the groups were compared for the frequency of adverse events, frequency of serious adverse events, and number of discontinuations due to adverse events.

In the extension study, the primary endpoint was safety, and the efficacy endpoints were change in BAD score and score on the PGI-I.
Statistical analysis

**Determination of Sample Size:** At the time of planning the randomized trial, there were no published studies with data sufficient to estimate sample size based on either the natural history of the disease or the expected impact from an agent that interfered with iron-related neurodegeneration. An estimate of the effect size was based on a retrospective study of 23 patients with NBIA, 22 of whom had most probably PKAN (14 genetically confirmed, the others with eye-of-the-tiger sign), and 21 of whom had been assessed for dystonia using the BAD scale. It was assumed that with similar disease progression, after 18 months there could be a substantial worsening of the BAD total score in the control group, with a possible difference from the DFP group of ≥5 points. Assuming a standard deviation of 6.3 points, 2:1 randomization, and 30% drop-out rate, 87 patients would be needed to detect a difference of at least 5 points at a two-sided 0.05 level of significance with 80% power. For the extension study, there was no formal sample size and power calculation; all patients completing TIRCON2012V1 were invited to enroll.

**Analyses:** All statistical analyses were performed using SAS (Windows version 9.3). Safety analyses were based on all randomized patients who received at least one dose of study drug. Efficacy analyses were based on the modified Intent-to-Treat (mITT) population, defined as all randomized patients who 1) received at least one dose of study drug, and 2) provided a baseline and at least one post-baseline efficacy assessment. A Mixed Model for Repeated Measures (MMRM) model was used as the primary analysis method to assess the primary and secondary endpoints of changes from baseline to the specified time points (Months 6, 12, and 18), with baseline value and age of onset of motor symptoms (before 6 years versus at or after 6 years) as covariates, and treatment group as the main factor in the model. The marginal mean change (least squares estimate) at Month 18 was used to determine the treatment effect in the primary analysis. Over the 18-month course of the trial, some participants required changes in their DBS settings or in the use or frequency of rescue or as-needed medications, and these variables were also included in the MMRM model as visit-dependent covariates.

A similar MMRM model was used for the analysis of the PGI-I. As the PGI-I score is a measurement of change from baseline, it was treated directly as the outcome variable. A logistic regression model with similar covariates was used for analysis of the proportion of responders. Finally, a subgroup analysis using a similar MMRM model was performed on the co-primary efficacy endpoints based on age at onset of motor symptoms (≥6 years vs. <6 years). The safety data for continuous variables were summarized using descriptive statistics, and the safety data for discrete variables were tabulated with frequency tables.

In the extension study, changes in the BAD scale and PGI-I scores were summarized using descriptive statistics. Last Observation Carried Forward (LOCF) was used for the scores of patients who did not complete treatment. A paired t-test was used to compare the change in BAD total score and PGI-I score between the randomized and the extension studies, while a student t-test was used for within-study comparison of treatment groups.
Role of the funding source

Funding for the study was provided by the European Commission, the US FDA, and ApoPharma Inc., Canada. The US FDA had input into the design and selection of endpoints. ApoPharma participated in study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Randomized trial

Following screening of 100 prospective subjects, 89 of a planned 90 patients were enrolled between December 13, 2012 and April 21, 2015, with 59 randomized to receive DFP and 30 to receive placebo (Figure 1). One patient assigned to the DFP group withdrew prior to receiving the first dose, and two assigned to placebo withdrew after receiving study drug but before providing any post-baseline efficacy data; accordingly, there were 58 DFP patients and 30 placebo patients evaluable for safety, and 58 and 28, respectively, for efficacy. 76 patients (85.4%) completed the trial, and 12 (in addition to the one patient who was never dosed) withdrew: 3 (10.0%) in the placebo group and 9 (15.3%) in the DFP group. Reasons for withdrawal in the placebo group were 1 case each of worsening of the disease, protocol violation, and voluntary withdrawal, while those in the DFP group were 4 cases of an adverse event, 3 of worsening of the disease, and 1 each of investigator’s decision and voluntary withdrawal. Of the withdrawals due to adverse events, 3 were for neutropenia (for which withdrawal was mandated by the study protocol), and 1 was for fever and pneumonia.

At baseline, there were no major differences between the treatment groups with respect to age at enrolment, duration of disease, sex, and race (Table 1), baseline BAD score, or amount of iron in the relevant brain areas. Stratification was used to ensure that each treatment group had approximately equal percentages of patients with classic or atypical PKAN, as determined by age at onset of motor symptoms: among the 86 patients who were evaluable for efficacy, there were 12 classic and 16 atypical patients in the placebo arm, and 29 of each type in the DFP arm. Mean age at randomization differed considerably between the subgroups (13.7 and 26.5 years for patients with classic and atypical PKAN, respectively), but disease duration was similar for both, approximately 13 years. As expected, the disease had progressed further in those with classic PKAN, as indicated by baseline BAD scores (20.3 vs. 17.0), but the difference did not reach statistical significance (p=0.0753).

Concomitant treatments for dystonia symptoms were an important consideration because of their possible confounding effect on the BAD score. Most participants, 18 placebo patients (60.0%)
and 42 DFP patients (72.4%), were taking at least one dystonia medication at baseline; 25 patients, 6 (20%) and 19 (32%), respectively, had a DBS system in place; and 3 patients (1 and 2 respectively), had a baclofen pump in place. There were no statistically significant differences between treatment groups regarding the use of any medication or device for the treatment of dystonia at baseline. During the study, additional dystonia medications administered on an as-needed basis were taken by a higher percentage of placebo patients (21.4%) than DFP patients (10.9%), with the difference reaching significance (p=0.0345) for botulinum toxin type A. Compliance was very high at all time points, ranging from 95.1% to 99.4% in the placebo group and from 96.6% to 99.5% in the DFP group.

BAD scores at baseline are shown in Table 1. One patient in the placebo group had a score of 31 and one in the DFP group had the maximum score of 32, meaning that little or no further worsening could be detected in those individuals through this instrument. Further analyses showed that results were not confounded by a ceiling effect (cf. Discussion, Supplementary material and Suppl. Tables 1a and 1b). Patients in both treatment groups showed a worsening over time (Figures 2a, 2b, and 2c). In the main analysis using the marginal means from the MMRM model, there was a mean ±SE worsening of 2.48±0.63 points in the DFP group vs. 3.99±0.82 points in the placebo group: i.e., the DFP group overall worsened by 1.51 points less, a difference that approached the protocol-defined criterion of p=0.05 for statistical significance (95% CI [-3.19, 0.16], p=0.0761) (Table 2). A predefined subgroup analysis that looked separately at patients with classic or atypical PKAN showed that DFP use was associated with slower progression in clinical symptoms (2.33±0.73 points) than patients on placebo (4.52±0.91 points) in atypical PKAN, a difference of 2.19 points, that reached statistical significance (95% CI [-4.00,-0.38], p=0.0187). Within the classic subgroup, the difference of 0.81 points in favor of DFP did not reach significance (p=0.5701). In the responder analysis, 36% of DFP-treated patients responded to therapy compared to 14% of placebo-treated patients (p=0.0893).

In contrast to the objective signs of disease progression, as assessed by the BAD score, no subjective change was detected as assessed by the PGI-I. At Month 18, mean PGI-I scores were 4.7±0.4 for placebo and 4.6±0.3 for DFP (p=0.7279), indicating that patients in both groups did not perceive either improvement or worsening since baseline. There was only a weak correlation (r = 0.29) between the PGI-I and the change in BAD score at month 18 (cf. Supplementary material and Suppl. Figure 1).

MRI-R2* imaging for the measurement of iron levels in the globus pallidus was conducted in a subset of patients at the start (16 placebo, 24 DFP) and end of the study (13 placebo, 19 DFP). In the placebo group, there was virtually no change (an R2* decrease of 0.5±4.0 Hz), while in the DFP group there was a decrease of 36.1±3.1 Hz, for a significant treatment group difference of -35.6 Hz (95%CI, [-44.8,-26.3], p <0.0001) (Figure 3). [A: could this figure be moved to the appendix]

Figure 4 presents a summary of all secondary efficacy endpoints as a Forest plot. Each point represents the marginal mean difference between DFP and placebo. The line indicates the 95%
confidence interval for the difference, both standardized by the standard error of the marginal mean difference. For each endpoint, this graph indicates whether the results were in favor of DFP (point to the left of 0.00) or placebo (point to the right of 0.00). Of the 21 measures examined, 13 were in favor of DFP, 4 showed no treatment difference and 4 were in favor of placebo.

Differences between the treatment groups that reached statistical significance in favor of DFP were seen for the WeeFIM, and for certain BAD body region scores (neck: -0.43; p=0.0465; left lower extremity: -0.28; p=0.0391; and right lower extremity: -0.25; p=0.0435). No significant differences were seen in other endpoints. More detailed results on the WeeFIM assessments are provided in the Supplement, including Suppl. Figure 42.

An overview of the different categories of safety findings during the randomized phase of the studies is shown in Suppl. Table 4, and a listing of individual AEs seen in >10% of patients in Suppl. Table 5. [A: ideally a table of AEs should be included in the main manuscript]

Overall, DFP was well tolerated, and rates of adverse events (AEs) seen in >10% of patients is provided in Table 3. Rates were similar between the treatment groups except for AEs related to study treatment such as anemia, which was seen in 20.7% of DFP-treated patients vs. no placebo patients; however, the hemoglobin value was <10 g/dL in only three patients with anemia. Non-significant differences were seen between the DFP and placebo groups in rates of decreased serum ferritin (32.8% vs. 16.7%; p=0.1341) and iron deficiency (15.5% vs. 10.0%; p=0.7442). Iron supplementation was permitted, based on the investigator’s assessment of need, and was taken by 39% of patients in the DFP group and by 27% of patients in the placebo group. There were no deaths or episodes of agranulocytosis or severe neutropenia, and there was no significant difference between the study groups in the rates of less severe neutropenia (8.6% in DFP vs. 6.7% in placebo).

**Extension study**

Of the 76 patients who completed the randomized trial, 68 enrolled in the extension study. Those who had received DFP continued to receive it (DFP-DFP group, N=44), while those who had received placebo were switched to DFP (placebo-DFP group, N=24). All 68 patients were evaluable for safety, and 62 (43 DFP-DFP, 19 placebo-DFP) were evaluable for efficacy.

BAD scores at the start of the extension study are shown in Table 1 (at this time point, one placebo-DFP patient had a score of 30 and one DFP-DFP patient had the maximum score of 32). Figure 2d displays the change in BAD total score for the 62 patients who provided evaluable efficacy data in both studies. In both groups, scores continued to increase (worsen) over time, but the DFP-DFP patients showed a similar rate of progression in both studies, while the placebo-DFP patients progressed more rapidly in the first study and slowed when they were switched to DFP. Over the 18 months of the extension study, there was no significant difference in the change in BAD score for patients who had been on DFP from the start (1.9±0.5 points in the first 18 months vs 1.4±0.4 points in the second 18 months, p=0.2684) while there was significantly less worsening in the placebo-DFP group (4.4±1.1 points when they were receiving placebo vs 1.4±0.9 points when they were receiving DFP, p=0.0206) (Suppl. Table 2).

Comment [KTPD6]: Done; The table of AEs was removed from the supplementary material and is now included in the main manuscript as Table 3.
With respect to the PGI-I, as in the randomized study, patients did not detect a change in their condition after the additional 18 months of treatment, with mean scores of 4.1±0.2 in the DFP-DFP group and of 4.7±0.3 in the placebo-DFP group.

For evaluation of safety, data were combined for all 68 patients. Overall, DFP continued to be well tolerated for the 36-month period. There were two deaths, both secondary to aspiration (one pneumonia and multi-organ failure, the other to aspiration following the patient vomiting in his sleep). Neither of these patients had experienced neutropenia while in the study. The most common adverse event was dystonia, reported in 40 (58.8%) patients, followed by pyrexia in 23 (33.8%), headache in 20 (29.4%), and condition aggravated and decreased serum ferritin in 18 each (26.5%).

**Discussion**

No disease-modifying therapies are yet available in PKAN or any form of NBIA. Excess brain iron is seen in various types of neurodegenerative conditions, including PKAN and Parkinson’s disease, as well as in normal aging. Excess iron is believed to catalyze the formation of reactive oxygen species from the by-products of oxygen consumption, which could affect neuronal functions either by directly damaging cell components or by chemically affecting signal mediators such as dopamine. Hence, chelators that remove brain iron may serve as therapy for those conditions. [As this section should be incorporated into the introduction or deleted if info is duplicated. Please start your discussion with a summary of your findings]}

The present study is the largest randomized trial to date and provides the longest prospective follow-up of any NBIA population. It yields valuable information on the impact of iron chelation but also on the natural history of PKAN through the detailed assessment of placebo recipients, indicating that the rate of disease progression is slower than previously estimated. In the current trial, the power calculation for the divergence in the change in BAD total score between the treatment groups had assumed that a clinically relevant difference of 5 points could be achieved; however, over 18 months, the placebo group worsened by less than anticipated. Accordingly, the only way a significant group difference could have been achieved would have been for DFP to reverse rather than slow the progression of the disease. It is noteworthy that even the difference of 1.51 points approached the protocol-defined criterion for statistical significance (p=0.0761), and it is possible that a study duration longer than 18 months with the same number of patients would have allowed the detection of a difference large enough to establish statistical significance.

For patient enrollment, there was no exclusion of patients with high BAD scores. This may lead to a ceiling effect where patients with high BAD scores (close to the maximum score of 32) at baseline cannot worsen as much as patients with lower BAD scores. Randomization resulted in proportionally more patients with high baseline BAD scores being assigned to the deferiprone treatment group. To investigate whether a ceiling effect confounds the results of our study, we repeated the MMRM analysis excluding all patients with a baseline BAD score > 27 who would...
potentially be subject to a ceiling effect. In this analysis, deferiprone-treated patients still exhibited a numerically lesser progression in BAD score than placebo-treated patients, with the marginal mean difference being very similar to that from the analysis of the mITT population (Suppl. Table 1a). The p value worsened from 0.0761 to 0.1114 as a function of the lower number of subjects. Additional analysis was conducted to compare response according to the tertiles of baseline BAD (Suppl. Table 1b), demonstrating a benefit of DFP versus placebo, although p values were not significant due to the low number of subjects. In conclusion, these analyses showed that PKAN progression as measured by the BAD score is slower with higher baseline values and that this results in a ceiling effect at very high baseline scores. While this is important information for the design of future trials, it did not affect the principal outcome of our current study.

The potential benefit of DFP is also supported by the lower use of dystonia medications during the trial by patients on DFP than patients on placebo, and by the results of the extension study. Among patients who received DFP in both studies, disease progression continued at the same rate, while among those who switched from placebo to DFP, it slowed to match the rate seen in those who had received DFP in the first study. The fact that the rate of deterioration in the placebo-DFP group was significantly lower than that in the DFP group during the 18 months of DFP treatment than it was during the 18 months of placebo treatment supports the effect of this drug in patients acting as their own controls.

Another factor for consideration is the stage of the disease, since in any neurodegenerative process, the later the intervention with an agent that might have the ability to slow progression, the less the expected benefit. Participants in this study had been experiencing PKAN symptoms for approximately 13 years at the time of enrollment, and it is likely that for many, the disease progression was too advanced for a preventative drug to provide significant benefit. If brain iron contributes to the pathology seen in PKAN, then early initiation of DFP, where there has been less extensive iron-induced neurodegeneration, would be expected to maximize its benefit in slowing disease progression. Support for the view of a greater impact of DFP when the disease is less advanced was provided by the predefined subgroup analysis looking separately at patients with classic vs. atypical PKAN. In atypical PKAN, in addition to symptoms appearing later, the disease progresses more slowly; hence, even though the patients with atypical PKAN had the disease for about the same duration as those with classic PKAN, the extent of irreversible neurodegeneration would have been less. This difference may explain why patients with atypical PKAN had a significantly better response than patients on placebo in the randomized portion of the study (p=0.0187). A similar finding of interest came from a post-hoc subgroup analysis (data not shown) to see if patients who had been diagnosed with PKAN more recently would respond better than those with a longer disease duration. Five years was selected as the threshold as there were not enough patients to allow for a lower one. Nine patients in the placebo group and 6 in the DFP group had a disease duration of less than 5 years. Among patients with a duration greater than 5 years, the treatment group difference on change in BAD score was just 0.86 points, while among those in whom it was less than 5 years, it was 3.14
points, although there was inadequate power to demonstrate statistical significance (p=0.3436). [A discussion on post-hoc analysis has been removed as these data are not presented here]

The low prevalence of PKAN (1 to 3 cases per million population\(^ {21}\)) was responsible for a paucity of patients, and, in light of the slower than predicted rate of disease progression, a larger number of patients could have compensated for inadequate power to reach the preset level of significance of p<0.05 in the 18-month study. As the conduct of larger studies is improbable, any attempt at future clinical trials will likely require patient enrichment for targeted questions.

With respect to the PGI-I endpoint, most participants reported neither worsening nor improvement from baseline despite the indications seen on more objective measures; and the same was true in the extension study. The correlation between the PGI-I and the change in BAD score at Month-18 is weak (r = 0.29), in which < 10% of the PGI-I variation can be explained by the change in BAD (r\(^2\) < 0.1), indicating that the PGI-I is not an adequate tool for assessment in PKAN over an 18-month period. The PGI-I is, by definition, subjective, and was likely inappropriate for this study. It may be a good tool for assessing the short-term effect of drugs that induce improvement or reversal of disease, but it was likely difficult for patients to judge whether their condition had worsened or improved over an 18-month period, explaining why no net worsening was detected, even by those on placebo.

The most notable change observed was the profound reduction of iron in the globus pallidus: a mean decrease of 36.1 Hz in the DFP-treated group compared to 0.50 Hz in the placebo group (p <0.0001). This finding is consistent with reports of DFP-induced reductions in the levels of brain iron seen in Friedreich’s ataxia,\(^ {17}\) Parkinson’s disease,\(^ {18}\) and other NBIA disorders.\(^ {22}\)

Importantly, the reduction in brain iron load induced by DFP was not associated with systemic iron depletion.

Freezing phenomenon, an event commonly observed in PKAN patients, was seen in 10% of patients on placebo versus in none of those on DFP (p=0.0370), even though there were twice as many patients on DFP. Freezing has been linked to pathology in the basal ganglia and brainstem, both of which are areas affected in PKAN and in which iron was decreased by treatment with DFP. Further exploration of the mechanism is warranted.\(^ {24}\)

With respect to other secondary efficacy endpoints of the randomized study, although many of the group differences did not reach significance, patients who received DFP exhibited less worsening over 18 months of treatment than patients on placebo in most outcome measures. Responder analysis (the percentage of patients showing either improvement or stabilization on the total BAD score) found that the responder rate for patients on DFP was 2.6 times that for patients on placebo: 36% vs. 14% (p=0.0893). DFP patients showed less worsening on the individual BAD scores for nearly all body regions, with group differences reaching statistical significance (albeit marginal, as they would not reach significance if multiplicity were considered) for neck (p=0.0465), left lower extremity (p=0.0391), and right lower extremity (p=0.0435).
Next to the reduction of brain iron levels, the most substantial difference between treatments was seen on the WeeFIM measure, where actual improvement—not merely less worsening—was seen in DFP patients in the domain of cognition, with the treatment group difference reaching statistical significance (p=0.0324). No statistically significant group differences were seen on the other secondary measures. However, examination of all the secondary endpoints revealed a pattern suggesting a beneficial effect of DFP across a broad range of functions.

The tolerability of DFP was evidenced by the near-total compliance and low dropout rate in both studies. The two deaths were unrelated to study treatment, and rates of adverse events, which were mainly of mild intensity, were similar between the treatment groups on most measures (Table 3 and Suppl. Table 3). In general, the safety findings were consistent with those of other studies of DFP in patients with both brain iron overload and systemic iron overload. There were no occurrences of agranulocytosis, the most serious adverse event associated with DFP, and there was no significant group difference in the frequency of patients experiencing milder episodes of neutropenia, all of which resolved rapidly. There was a concern that non-iron-overloaded patients being treated with an iron chelator might experience hematological events linked to a lowering of iron body stores, such as decreased serum ferritin, anemia, and iron deficiency. However, while these events were seen in a higher percentage of DFP patients in the randomized trial, the rates were low, the group difference reached significance only for anemia, none of the events were serious, and all could be managed by iron supplementation.

A major strength of the study related to the ability to actually enroll close to 10% of all estimated PKAN patients in the US and Europe. The major limitation in the study was the lack of adequate pre-existing natural history data in PKAN patients to enable an informed power calculation for the primary outcome related to a change in BAD. Consequently, the slower than expected rate of worsening in the placebo-treated patients impacted the ability to achieve a significant difference in the overall ITT population.

In summary, this study, together with previous findings, shows that the membrane permeable iron chelator deferiprone achieved target engagement (lowering of iron in the basal ganglia) in patients with PKAN. While the clinical endpoints were not met for the mITT population in the randomized trial, planned subgroup analysis revealed a statistically significant slowing of disease progression in the atypical patients (p=0.0187) and the results of the extension trial indicate potential slowing of progression by deferiprone in the overall population as well. This study will help shape the design of future trials in this ultraorphan disease.

Contributors

TK and EV conceived the study and were the Coordinating Investigators. TK, FT, CF, MS, SJH, PH and EV designed the study protocol. LN, BK and BB managed the trial. TK, RH, PFC, NN and EV were the site principal investigators, responsible for participant recruitment and data collection. IK, LN, GZ, HES, AB, CK, CN, FZ and CA were site investigators, contributing largely to participant recruitment and data collection. TKm, PD and ZY contributed largely to
participant recruitment and local care in Poland, Czechia and Turkey, respectively. SH and PH were the central raters of videotapes for the BAD score examination of all patients from baseline and Month 18. BB was the central rater of BAD videotapes for the extension trial. IW and AMB defined the MRI protocol, oversaw image quality assurance, and analyzed all available MRI data from baseline and Month 18. FZh did the statistical analysis. TK wrote the first draft of the article. TK, FT, LN, MS and EV built a writing committee to work on the further drafts of the article which was reviewed by all authors.

Declaration of interests

Dr. Klopstock reports grants from European Commission, grants, personal fees, non-financial support and other from ApoPharma Inc., during the conduct of the study; grants from Retrophin Pharmaceuticals, outside the submitted work.

Drs. Fradette, Spino and Tricta, and F. Zhao are employees of ApoPharma Inc., the manufacturer of Deferiprone. Dr. Spino reports grants from European Commission, FP7, during the conduct of the study; In addition, Dr. Spino has a patent PCT WO 2009/129592 Al issued.

Dr. Neumayr reports grants from FDA, grants from ApoPharma Inc., grants from European Commission, grants from NIH, grants from NBIA Foundation, during the conduct of the study; other from Retrophin, Inc, personal fees from ApoPharma Inc, outside the submitted work.

Dr. Zorzi reports grants from ApoPharma Inc, during the conduct of the study; grants from Retrophin, other from Biomarin, personal fees from Medtronic, outside the submitted work.

Dr. Büchner reports grants and other from ApoPharma Inc., grants from European Commission, during the conduct of the study.

Dr. Steele reports non-financial support from Apopharma Inc., during the conduct of the study; grants from GlaxoSmithKline, outside the submitted work.

Dr. Horvath was supported by the Medical Research Council (UK) [MR/N025431/1], the Wellcome Investigator fund [109915/Z/15/Z], the Newton Fund [UK/Turkey, MR/N027302/1], the European Research Council [309548] and the Wellcome Trust Pathfinder Scheme [201064/Z/16/Z].

Dr. Chinnery is a Wellcome Trust Principal Research Fellow (212219/Z/18/Z), and a UK NIHR Senior Investigator, who receives support from the Medical Research Council Mitochondrial Biology Unit (MC_UP_1501/2), the Evelyn Trust, and the National Institute for Health Research (NIHR) Biomedical Research Centre based at Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge.

Dr. Basu reports grants from European Commission, grants from Apopharma, during the conduct of the study; other from National Institute of Health Research, outside the submitted work.

Dr. Kuepper reports grants from European Commission, grants from ApoPharma Inc during the conduct of the study.
Dr. Dusek reports other from 024PKAN15004, outside the submitted work.

Dr. Zibordi reports grants from ApoPharma Inc, during the conduct of the study.

Dr. Nardocci reports grants from ApoPharma, during the conduct of the study; personal fees from Medtronic, other from Biomarin, outside the submitted work.

Dr. Hogarth reports grants from European Union Seventh Framework Programme (FP7), during the conduct of the study; in addition, Dr. Hogarth has a pending patent “Methods and Models used in predicting pantothenate kinase-associated neurodegeneration and the amelioration thereof”. Dr. Hogarth serves as a non-compensated executive for the Spoonbill Foundation, a not-for-profit organization that may benefit from the results of this research and technology. This potential conflict of interest has been reviewed and managed by OHSU.

Dr. Vichinsky reports grants from FDA, grants from European Commission, grants and non-financial support from ApoPharma, Inc., grants from NIH, during the conduct of the study; other from Retrophin, Inc, outside the submitted work.

All other authors declare no competing interests.

Data sharing statement
The TIRCON Group and ApoPharma are committed to sharing with qualified external researchers, the study’s patient-level data and supporting clinical documents according to the criteria and process described on www.clinicalstudydatarequest.com.

Acknowledgments
This study was funded by the European Commission 7th Framework Programme (FP7/2007-2013, HEALTH-F2-2011, grant agreement No. 277984, TIRCON), the FDA 4 R01 FD004103-04 (Phase I/II randomized, blinded safety trial of deferiprone in NBIA/PKAN), and ApoPharma Inc.

Non-financial support was also provided through the European Reference Network (ERN) for Rare Neurological Diseases (ERN-RND), one of 24 ERNs funded by the European Commission (ERNRND: 3HP 767231).

We thank all the patients and their families who participated in this study. The great support of NBIA patient advocacys world-wide is very much appreciated, and we want to emphasize the help of Ms. Patricia Wood, President of the US NBIA Disorders Association, and Angelika Klucken, President of the German Hoffnungbaurn e.V. We also thank the primary physicians taking care of these patients for being very supportive of this study. We are grateful to Dr. Eva Coppenrath for performing MRIs at the Munich site, and to Dr. Nihan Hande Akçakaya for excellent care of Turkish study participants. We also thank Ms. Anne Stilman, from ApoPharma Inc., for editorial assistance.
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Response to Reviewer #2 with particular focus on assessment of “Ceiling Effect”

Verbatim Comment from Reviewer #2:
The authors have addressed many of my points, but not fully addressed my main criticism of the study. As discussed below, I think the study is limited and possibly confounded by the inclusion of people with high baseline scores of BAD. While this is problematic, I don't think it is "fatal" to publishing the study, since there were no prior studies for this disease to refer to, and it is a significant challenge to recruit so many subjects of this rare disease.

Looking at the spaghetti diagram, I think quite clearly those with higher baseline BAD values (>27) have slower decline than the rest of the group. This is potentially problematic because the DFP group appear to have proportionally more subjects above this value at baseline compared to placebo. This difference in rates was confirmed with the analysis of slope in subjects stratified by baseline BAD - while this was on the cusp of significance, I am sure that significance would be observed if the parameters were changed (e.g. one group only had five subjects, so it lacked power). There is a real possibility that the apparent trend toward significance on the primary outcome was due to proportionally more ‘slow decliners’ (‘slow’ because of high baseline BAD) in the DFP group. Accordingly, in Supp Table 1, the trend on the primary outcome was further diminished when subjects with higher baseline BAD were removed.

The authors argue that it is appropriate to include subjects with high, even maximum BAD score because there is a chance that DFP will lower the score. However, the power analysis was predicated on average decline of subjects - which would be impossible (or only limited) in people with high (>27) BAD. While only a few subjects were on maximum BAD score at the beginning and conclusion of the study, the slope analysis performed by the authors demonstrated that those with high (>27) BAD did not decline over the study period (P=0.4738). So a limitation of the study is not just the maximum score of 32 reached, but a ceiling effect that begins at ~27. Not all subjects are therefore assessed equally in this study. Many subjects can show decline on the BAD instrument, but those with high baseline BAD cannot. It is not sufficient to say that the possibility that DFP could improve BAD justified the inclusion of a patient with maximum or very high BAD (because they are different to other subjects in the study whose symptoms could potentially change in either direction). I highlighted this limitation in my previous review, and I think the authors should mention this potential confound in the discussion. They talk about the staging of the disease in regard to neurodegeneration, but not the limitation of the instrument, the variable rates of decline according to BAD score, and the flaw in the study that allowed inclusion of patients with high, especially maximum BAD. This is an important limitation to highlight in order to aid interpretation of the result, but also to inform future studies that use the BAD scale (so that they can be aware of the limitations of this instrument).

Related to this last point, can I please request that the authors calculate and state in the manuscript the rates of decline in subjects according to strata of baseline BAD (e.g. <8, 9-16, 17-24, 25-32; or whatever the authors judge appropriate). The reason for this request is again for planning future studies involving this patient group. In the current manuscript, the authors calculate that the rate of decline for the whole group is less than they anticipated, but, as discussed above, this may be in part due to the fact that high baseline BAD patients do not materially decline over 18 months, therefore their inclusion likely attenuated the calculation of the average rate.

Supplementary table 1 & 3 are not referred to in the text, and supplementary info is presented out of order (e.g. Supp Table 4&5 is referred to before Supp Table
Response:

We want to thank Reviewer #2 for a most thoughtful review of the manuscript and we believe that our responses to the matters he raised has enhanced the quality of manuscript. Most particularly, we welcome his/her detailed query pertaining to the possibility that a “ceiling effect” in the BAD score may be responsible for the observed differences between placebo and deferiprone-treated patients. In fact, this question was one that we grappled with upon initial review of the data, and it was not until we were confident that a ceiling effect did not explain the difference, that we submitted the manuscript. We did not, at the time of submission, present all the analyses that were conducted to provide us with that assurance, but since this matter has been emphasized, we will present it now, as well as include the further analyses requested by the reviewer. This is in addition to the previous comments we provided.

We concur with Reviewer #2 that, on paper, a ceiling effect exists in the context that if a patient is already at BAD score 29, 30 or higher, there is little room for them to worsen, and if they do not worsen in the score, it might be categorized as a slower rate of deterioration in that patient. In this study, there were more patients with a higher score in the group that was randomized to deferiprone, thus raising the possibility that the observed results might have been an artefact of the randomization process.

To address the ceiling effect theory, we conducted a number of analyses, including those suggested by the reviewer, all of which led us to our conclusion that the observed reduction in patient worsening was a direct result of deferiprone administration and not an artefact due to a ceiling effect. The following analyses support this conclusion, albeit the lower number of subjects led to weaker p values, due to segmenting the population.

Note: In our previous responses, we called the estimated mean from the MMRM analysis as LSmean in all the tables. In this document, we changed the term LSmean to Marginal Mean, as requested by Reviewer #3, to be consistent with what was used in the manuscript.

1. Reanalysis using a cut-off of 27 in BAD:

By excluding all patients that would have had the potential to experience a ceiling effect, and using the cut-off of 27, as suggested by the reviewer, it is evident that the difference in response to treatment is not lessened whatsoever by the dropping of patients with a cut-off of 27, even though, as would be expected, fewer subjects lessens the level of statistical significance, as shown now in **Suppl. Table 1a**:

**Suppl. Table 1a**: Main MMRM analysis excluding baseline BAD > 27 in the TIRCON study

<table>
<thead>
<tr>
<th>Subpopulation</th>
<th>Placebo</th>
<th>DFP</th>
<th>DFP-Placebo Marginal Mean Difference (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Marginal Mean Change (SE)</td>
<td>n</td>
<td>Marginal Mean Change (SE)</td>
</tr>
<tr>
<td>All patients</td>
<td>28</td>
<td>3.99 (0.82)</td>
<td>58</td>
<td>2.48 (0.63)</td>
</tr>
<tr>
<td>Baseline BAD &lt;=27</td>
<td>26</td>
<td>4.62 (0.96)</td>
<td>42</td>
<td>3.07 (0.81)</td>
</tr>
</tbody>
</table>
This analysis demonstrates that removal of patients with a high baseline BAD did not adversely affect the outcome, arguing against the supposition that a ceiling effect may have been responsible for the observed decreased progression of disease.

2. **Reanalysis using different strata of baseline BAD score:**

As requested, the analysis was repeated using different strata of baseline. To avoid the risk of bias in selection of what might constitute suitable cut-off points, we let the data select the points by choosing tertiles of baseline BAD. The MMRM modelling performed for the primary analysis was repeated for each subgroup defined by the tertile of the baseline BAD score: ≤13, 13-24, >24. The results are summarized now in **Suppl. Table 1b**. The analysis reveals that the treatment effect as measured by the Marginal mean difference between DFP and placebo was observed for each subgroup, indicating benefit of deferiprone over placebo regardless of the baseline BAD level, and, numerically, the largest observed difference is in those with no potential for a ceiling effect.

**Suppl. Table 1b**: Main MMRM analysis by subgroups based on the tertiles of baseline BAD

<table>
<thead>
<tr>
<th>Subpopulation</th>
<th>Placebo</th>
<th>DFP</th>
<th>DFP-Placebo Marginal Mean Difference (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td></td>
<td>Marginal Mean Change(SE)</td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>28</td>
<td>58</td>
<td>3.99 (0.82)</td>
<td>-1.51 (-3.19, 0.16)</td>
</tr>
<tr>
<td>Baseline BAD: &lt;= 13</td>
<td>12</td>
<td>17</td>
<td>7.65 (1.57)</td>
<td>-1.59 (-5.46, 2.27)</td>
</tr>
<tr>
<td>Baseline BAD: 13-24</td>
<td>10</td>
<td>21</td>
<td>3.60 (1.29)</td>
<td>-1.27 (-3.65, 1.10)</td>
</tr>
<tr>
<td>Baseline BAD: &gt; 24</td>
<td>6</td>
<td>20</td>
<td>1.55 (0.76)</td>
<td>-0.78 (-2.42, 0.87)</td>
</tr>
</tbody>
</table>
3. Reanalysis by examination of the slopes for worsening of BAD over time according to strata:

As requested, the slopes of the change in BAD score (per month) in the 2 treatment groups were estimated for different strata of baseline. To avoid bias in the selection of strata, each subgroup was defined by the tertile of baseline BAD score. Results are given in Table 3 (not included in manuscript nor supplement). The analysis shows that as one approaches the upper range of BAD scores, the slopes tend to flatten, but in each case the slope for the placebo-treated patients is steeper than the slope for the deferiprone-treated patients, in support of the conclusion that the protective effect of deferiprone was not a function of the ceiling effect.

Table 3: Slope of change in BAD by strata based on tertile of baseline BAD and by treatment group

<table>
<thead>
<tr>
<th>Subpopulation</th>
<th>Treatment Group</th>
<th>Slope (SE)‡</th>
<th>DFP vs Placebo p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline BAD: &lt;= 13</td>
<td>DFP (N=17)</td>
<td>0.20 (0.05)</td>
<td>0.0003</td>
</tr>
<tr>
<td></td>
<td>Placebo (N=12)</td>
<td>0.26 (0.06)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline BAD: 13-24</td>
<td>DFP (N=21)</td>
<td>0.12 (0.05)</td>
<td>0.0108</td>
</tr>
<tr>
<td></td>
<td>Placebo (N=10)</td>
<td>0.17 (0.06)</td>
<td>0.0099</td>
</tr>
<tr>
<td>Baseline BAD: &gt; 24</td>
<td>DFP (N=20)</td>
<td>0.04 (0.05)</td>
<td>0.3772</td>
</tr>
<tr>
<td></td>
<td>Placebo (N=6)</td>
<td>0.11 (0.08)</td>
<td>0.2041</td>
</tr>
</tbody>
</table>

‡ Change in BAD score per month
4. Reanalysis by examination of the slopes for worsening of BAD in TIRCON + TIRCON EXT:

Using the suggestion of the reviewer to analyze the slopes for the change in BAD score (per month) in the 2 treatment groups for the randomized study, we thought there would be value in a similar analysis in which we compared the slopes in the randomized (TIRCON) study vs the open label (EXT) study. Here we examined the slopes for change in BAD over time for both deferiprone and placebo-treated patients in each arm for BAD ≤27. Analysis of the data showed the slope for the placebo patients was steeper in the randomized study than the slope for the deferiprone-treated patients, but when they transitioned to deferiprone in the EXT study, the rates were comparable (Table 4, not included in manuscript nor supplement).

Table 4. Slope of change in BAD (per month) for TIRCON and TIRCON-EXT study for those with baseline BAD ≤27

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Group</th>
<th>Slope (SE)† p-value</th>
<th>DFP vs Placebo p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIRCON (N=68)</td>
<td>DFP (N=42)</td>
<td>0.14 (0.04) 0.0002</td>
<td>0.2971</td>
</tr>
<tr>
<td></td>
<td>Placebo (N=26)</td>
<td>0.20 (0.04) &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>TIRCON-EXT (N=46)</td>
<td>DFP-DFP (N=32)</td>
<td>0.09 (0.03) 0.0122</td>
<td>0.8785</td>
</tr>
<tr>
<td></td>
<td>Placebo-DFP (N=14)</td>
<td>0.08 (0.05) 0.1305</td>
<td></td>
</tr>
</tbody>
</table>

† Change in BAD score per month

In summary, several different statistical approaches were used to assess whether a ceiling effect might explain the beneficial effect of deferiprone. Regardless of the method used, analysis of the data failed to support the supposition of a ceiling effect as the determinant of the observed results. More specifically, numerically, the greatest treatment difference was seen in those with less advanced disease, even though the analyses, employing the smaller “N” in each case, could not confer statistical significance. This greater response to deferiprone in those with less severe disease is consistent with other observations (e.g., atypical versus classical PKAN patients) in the manuscript and supplementary information.

We have inserted a paragraph in the Discussion to succinctly summarize the fact that we have addressed the question of a potential ceiling effect, but that analysis indicated that a ceiling effect did not explain the favourable response to deferiprone. Information has been added to the Supplement in support of the conclusion, as well.

We also thank the Reviewer for having noted the omission of the reference to the Supplementary table and the need to rearrange the order.
Supplement

Methods

Study design

TIRCON2012V1 was conducted at 4 treatment centers located in Germany, Italy, the United Kingdom and United States, and was approved by the respective Ethics Committees (Ludwig Maximilians University, Munich; Istituto Neurologico Carlo Besta, Milan; Yorkshire & The Humber, Leeds East Research; and Children’s Hospital & Research Center Oakland). The sites and Ethics Committees were the same for the single-arm extension study, TIRCON2012V1-EXT. An independent Data and Safety Monitoring Board regularly reviewed the safety data of both trials, and each study was registered on ClinicalTrials.gov prior to enrollment of the first patient (trial registration numbers NCT01741532 and NCT02174848, respectively).

Patients

Recruitment was via the centers’ own patients, referral from other neurologists and by posting information on the NBIA Disorders Association website.

Full list of inclusion and exclusion criteria:

Inclusion Criteria

1. Males or females 4 years of age and older at screening visit
2. Have PKAN, confirmed by genetic testing
3. BAD total score ≥ 3 at the screening visit
4. Patients who have Deep Brain Stimulation (DBS) systems or baclofen pumps in place will be eligible for the study, but they must have had a stable setting for at least two months prior to the screening visit; Enrollment of non-DBS patients will be given priority in order to ensure the majority can undergo imaging
5. Informed consent/assent obtained before any study-related activities
6. Ability and willingness to adhere to the protocol including appointments and evaluation schedule
7. Sexually active female patients of childbearing potential must have a negative pregnancy test result at Screening Visit. In addition, if applicable, females of childbearing potential must use an effective method of contraception according to local requirements, OR have had a tubal ligation, OR have had a hysterectomy, OR participates in a non-heterosexual lifestyle, OR have a male sexual partner has been sterilized
8. If the patient is a heterosexual sexually-active male, patient must confirm, in writing, that he and/or his female partner will use an effective method of contraception according to local requirements for the length of the trial and for 30 days following completion of the study or early termination
Exclusion Criteria

1. Evidence of iron deficiency defined by Fe:TIBC ratio <15%, or serum ferritin <12 ng/mL
2. Treatment with deferiprone in the past 12 months
3. Previous failure of treatment with deferiprone, or previous discontinuation of treatment with deferiprone due to adverse events
4. Conditions known to contraindicate the use of deferiprone (history of agranulocytosis or recurrent episodes of neutropenia)
5. A serious, unstable illness during the past 3 months before screening visit including but not limited to: hepatic, renal, gastro-enterologic, respiratory, cardiovascular, endocrinologic, neurologic or immunologic disease
6. Evidence of abnormal liver or renal function (serum liver enzyme level(s) > 3 times upper limit of normal at screening) or abnormal creatinine levels at screening visit
7. Disorders associated with neutropenia (ANC < 1.5 x 10⁹/L) or thrombocytopenia (platelet count < 50 x 10⁹/L) in the 12 months preceding the initiation of the study medication. Exception: for patients whose neutropenia was attributed by the treating physician to episodes of infection or to drugs associated with a decline in the neutrophil count and in whom the ANC has fully recovered at the screening visit
8. History of malignancy
9. QTcF interval > 450 msec
10. HIV positive
11. Myocardial infarction, cardiac arrest or cardiac failure within 1 year before screening visit
12. Bowel disease causing malabsorption
13. History of alcohol or drug abuse
14. Treatment with an investigational drug within 30 days or 5 half-lives (whichever is longer) preceding the baseline visit
15. Currently taking iron chelators
16. Pregnant, nursing females and females of childbearing potential who are heterosexually active and unwilling, or unable, to use an acceptable method of contraception according to local requirements
17. Males who are sexually active and unwilling, or unable, to use an acceptable method of contraception according to local requirements
18. History or presence of hypersensitivity or idiosyncratic reaction to deferiprone
19. Patients (or when applicable parent or patients’ legal representatives) with a mental incapacity, unwillingness or language barriers precluding adequate understanding or cooperation
20. Any condition that, in investigator’s opinion, would adversely affect the patient’s ability to complete the study or its assessments
21. Baclofen pump placement less than two months prior to the screening visit
22. Current and ongoing participation in other clinical studies
Procedures

In both trials, dosage was based on milligrams of DFP per kilogram of body weight, starting at 5 mg/kg b.i.d. and titrated up to 15 mg/kg b.i.d. by Week 12. In TIRCON2012V1, patients in the control group received a matching volume of placebo during the same time periods.

All efficacy measures were administered at baseline (except for the PGI-I, which is a measure of change from baseline), months 6, 12, and 18 or early termination. Iron levels in the globus pallidus were measured by MRI-R2* in a subset of patients (those without a DBS device and able to undergo an MRI scan) at baseline and Month 18. MRI scans were conducted according to a standardized imaging protocol, and the images were sent to central reading by radiologists who were blinded to treatment. None of the MRI-R2* results were disclosed by the radiologist until the last patient completed the trial.

Information was also collected on the use of concomitant medications, with particular attention on any changes in drugs or devices used to relieve symptoms of dystonia. Patients had weekly hematology tests to monitor their absolute neutrophil count (ANC). Patients with two consecutive samples with ANC < 1.5×10⁹/L were withdrawn from the study.

To reduce the confounding effects of concomitant therapies on the assessment of treatment, patients with recent or expected changes in therapies that have the potential to affect dystonia symptoms were excluded from enrolment.
Results

There were proportionally more patients with baseline BAD score close to the maximum score of 32 being randomized to the deferiprone treatment group. To investigate whether a “ceiling effect” might account for the differences observed in BAD in response to treatment with deferiprone, the miITT data were re-analyzed after excluding all patients that would have had the potential to experience a ceiling effect. Using the cut-off of 27 for the baseline BAD score, it is evident that the difference in response to treatment is not lessened by the dropping of patients with a cut-off of 27, even though, as would be expected, fewer subjects lessens the level of statistical significance, as shown in Suppl. Table 1a.

Suppl. Table 1a: Main MMRM analysis excluding baseline BAD > 27 in the TIRCON study

<table>
<thead>
<tr>
<th>Subpopulation</th>
<th>Placebo</th>
<th>DFP</th>
<th>DFP-Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Marginal Mean Change (SE)</td>
<td>N</td>
<td>Marginal Mean Change (SE)</td>
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<tr>
<td>All patients</td>
<td>28</td>
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<td>2.48 (0.63)</td>
</tr>
<tr>
<td>Baseline BAD &lt;=27</td>
<td>26</td>
<td>4.62 (0.96)</td>
<td>42</td>
<td>3.07 (0.81)</td>
</tr>
</tbody>
</table>

To further investigate the impact of ceiling effect, a reanalysis of the data was conducted using 3 different strata of baseline values. To avoid the risk of bias in selection of what might constitute suitable cut-off points, we let the data select the points by choosing tertiles of baseline BAD. The MMRM modelling performed for the primary analysis was repeated for each subgroup defined by the tertiles of the baseline BAD score: ≤13, 13-24, >24. The results are summarized in Suppl. Table 1b below. The analysis reveals that the treatment effect as measured by the marginal mean difference between DFP and placebo was observed for each subgroup, indicating benefit of deferiprone over placebo regardless of the baseline BAD level, and, numerically, the largest observed difference is in those with no potential for a ceiling effect. Weaker levels of significance are attributed to smaller numbers of subjects in each group, compared to the full cohort.
**Suppl. Table 1b:** Main MMRM analysis by subgroups based on the tertiles of baseline BAD

<table>
<thead>
<tr>
<th>Subpopulation</th>
<th>Placebo</th>
<th>DFP</th>
<th>DFP-Placebo Marginal Mean Difference (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n</td>
<td>Marginal Mean Change (SE)</td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>28</td>
<td>58</td>
<td>3.99 (0.82)</td>
<td>-1.51 (-3.19, 0.16)</td>
</tr>
<tr>
<td>Baseline BAD: ≤ 13</td>
<td>12</td>
<td>17</td>
<td>7.65 (1.57)</td>
<td>-1.59 (-5.46, 2.27)</td>
</tr>
<tr>
<td>Baseline BAD: 13-24</td>
<td>10</td>
<td>21</td>
<td>3.60 (1.29)</td>
<td>-1.27 (-3.65, 1.10)</td>
</tr>
<tr>
<td>Baseline BAD: &gt; 24</td>
<td>6</td>
<td>20</td>
<td>1.55 (0.76)</td>
<td>-0.78 (-2.42, 0.87)</td>
</tr>
</tbody>
</table>
Over the 18 months of the extension study, there was no significant difference in the change in BAD score for patients who had been on DFP from the start (1.9±0.5 points in the first 18 months vs 1.4±0.4 points in the second 18 months, p=0.2684) while there was significantly less worsening in the placebo-DFP group (4.4±1.1 points when they were receiving placebo vs 1.4±0.9 points when they were receiving DFP, p=0.0206) (Suppl. Table 2). Placebo-DFP group represents the patients who received placebo during the first 18 months and deferiprone during the subsequent 18 months. DFP-DFP group represent the patients who received deferiprone during the 36 months of both trials. Classical PKAN are patients with age at onset of disease < 6 years. Atypical PKAN are patients with age at onset of disease ≥ 6 years.

Suppl. Table 2. Changes in BAD score in the TIRCON and TIRCON-Extension studies

<table>
<thead>
<tr>
<th>Placebo-DFP Group</th>
<th>TIRCON study</th>
<th>T-EXT study</th>
<th>TIRCON vs. T-EXT p-value(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset of symptoms</td>
<td>N</td>
<td>Baseline Score Mean (SD)</td>
<td>Change from Baseline</td>
</tr>
<tr>
<td>Overall</td>
<td>19</td>
<td>15.9 (8.0)</td>
<td>4.4 (4.8)</td>
</tr>
<tr>
<td>&lt; 6 years (classic PKAN)</td>
<td>8</td>
<td>18.0 (9.3)</td>
<td>5.3 (6.1)</td>
</tr>
<tr>
<td>≥6 years (atypical PKAN)</td>
<td>11</td>
<td>14.5 (6.9)</td>
<td>3.8 (3.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DFP-DFP Group</th>
<th>TIRCON study</th>
<th>T-EXT study</th>
<th>TIRCON vs. T-EXT p-value(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset of symptoms</td>
<td>N</td>
<td>Baseline Score Mean (SD)</td>
<td>Change from Baseline</td>
</tr>
<tr>
<td>Overall</td>
<td>43</td>
<td>19.3 (8.1)</td>
<td>1.9 (3.2)</td>
</tr>
<tr>
<td>&lt; 6 years (classic PKAN)</td>
<td>20</td>
<td>20.9 (7.9)</td>
<td>2.3 (4.2)</td>
</tr>
<tr>
<td>≥6 years (atypical PKAN)</td>
<td>23</td>
<td>18.0 (8.3)</td>
<td>1.6 (1.9)</td>
</tr>
</tbody>
</table>

\(^a\) P-value from paired t-test
Correlation between the BAD scale and the PGI-I
The change of PGI-I at completion of 18 months of study therapy was included as a co-primary endpoint based on a request by a regulatory agency.
At Month 18, the LSmean scores were 4.66 for placebo and 4.55 for DFP, with no significant group difference (p=0.7279) indicating that, overall, patients did not detect either an improvement or a worsening in their condition from baseline.
To the best of our knowledge, the PGI-I had not been previously used in a prospective study in patients with NBIA and no data are currently available on its value for identifying the clinical significance of other study measures. To that extent, the TIRCON study provides valuable data for the determination, if a correlation existed between a measurement of disease progression such as the BAD score and the PGI-I.

Suppl. Figure 1 shows the correlation between the PGI-I and the change in BAD score at Month-18. The analysis reveals a weak correlation (r = 0.29), in which < 10% of the PGI-I variation can be explained by the change in BAD (r square < 0.1), indicating the PGI-I is not an adequate tool for assessment in PKAN over an 18 month period.

Suppl. Figure 1. Correlation between change from baseline in BAD score and PGI-I score at Month 18.
Wee FIM

The WeeFIM, which rates 18 activities of daily living in terms of how much assistance is needed, scores each item from 1 (total dependence) to 7 (complete independence), and generates a global score that ranges from 18 to 126. Thus, a decrease in score indicates worsening. The global score for the placebo group worsened by 2.40 points while that for the DFP group improved by 4.91 points, although the difference was not significant (p=0.2026). For the subscale scores, a significant difference in favor of DFP (p=0.0324) was seen for cognition. Treatment group differences in the domain of cognition reached significance in favor of DFP for problem solving (p=0.0258) and social interaction (p=0.0414), and approached significance for memory (p=0.0574). Suppl. Figure 2 displays a polar graph for each treatment group of all the elements contributing to the global WeeFIM score. For the placebo group, there was either worsening or lack of improvement in all measures; for the DFP group, improvement was seen for 4 of the 5 cognitive components (comprehension, social interaction, problem solving, and memory) and no change on the fifth (expression) but worsening or lack of improvement for the items in the self-care and mobility domains.
Suppl. Figure 2. Polar graph of WeeFIM scores. The blue lines represent scores at baseline, and the red lines represent scores at Month 18. Values that are closer to the center indicate lower functioning, so a red line that is inside the blue line indicates worsening, a red line that overlaps the blue line indicates no change, and a red line that is outside the blue line indicates improvement.
SAFETY

Regarding safety, DFP was well tolerated and rates of adverse events were similar between the treatment groups except for anemia, which was seen more frequent in DFP-treated patients than in placebo patients. An overview of the different categories of safety findings during the randomized phase of the studies is shown in Suppl. Table 3.

Suppl. Table 3.
Overview of the different categories of safety findings during the randomized phase of the studies

<table>
<thead>
<tr>
<th>Number of patients with at least one:</th>
<th>Placebo (N=30)</th>
<th>DFP (N=58)</th>
<th>P-value (Fisher’s exact test)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (n)</td>
<td>% (n)</td>
<td></td>
</tr>
<tr>
<td>Adverse event</td>
<td>100.0 (30)</td>
<td>98.3 (57)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>33.3 (10)</td>
<td>31.0 (18)</td>
<td>0.8146</td>
</tr>
<tr>
<td>Severe adverse event</td>
<td>26.7 (8)</td>
<td>29.3 (17)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Adverse event related to study treatment</td>
<td>43.3 (13)</td>
<td>79.3 (46)</td>
<td>0.0015</td>
</tr>
<tr>
<td>Death</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
<td>NA</td>
</tr>
<tr>
<td>Adverse event leading to withdrawal</td>
<td>0.0 (0)</td>
<td>6.9 (4)</td>
<td>0.2947</td>
</tr>
<tr>
<td>First, middle names or initials</td>
<td>Surnames</td>
<td>Affiliations</td>
<td></td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-----------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Thomas</td>
<td>Klopstock</td>
<td>Department of Neurology, Friedrich-Baur-Institute, Ludwig-Maximilians-University of Munich, Munich, Germany</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>German Center for Neurodegenerative Diseases (DZNE), Munich, Germany</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Munich Cluster for Systems Neurology (SyNergy), Munich, Germany</td>
<td></td>
</tr>
<tr>
<td>Fernando</td>
<td>Tricta</td>
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<td>Zuhal</td>
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<td>Ian</td>
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<td>Christine</td>
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<td>Michael</td>
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<td>Andrew M</td>
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<td>Elliott</td>
<td>Department of Hematology/Oncology, UCSF Benioff Children’s Hospital and Research Center Oakland, Oakland, California, USA</td>
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</table>
Supplement

Methods

Study design

TIRCON2012V1 was conducted at 4 treatment centers located in Germany, Italy, the United Kingdom and United States, and was approved by the respective Ethics Committees (Ludwig Maximilians University, Munich; Istituto Neurologico Carlo Besta, Milan; Yorkshire & The Humber, Leeds East Research; and Children’s Hospital & Research Center Oakland). The sites and Ethics Committees were the same for the single-arm extension study, TIRCON2012V1-EXT. An independent Data and Safety Monitoring Board regularly reviewed the safety data of both trials, and each study was registered on ClinicalTrials.gov prior to enrollment of the first patient (trial registration numbers NCT01741532 and NCT02174848, respectively).

Patients

Recruitment was via the centers’ own patients, referral from other neurologists and by posting information on the NBIA Disorders Association website.

Full list of inclusion and exclusion criteria:

Inclusion Criteria
1. Males or females 4 years of age and older at screening visit
2. Have PKAN, confirmed by genetic testing
3. BAD total score ≥ 3 at the screening visit
4. Patients who have Deep Brain Stimulation (DBS) systems or baclofen pumps in place will be eligible for the study, but they must have had a stable setting for at least two months prior to the screening visit; Enrollment of non-DBS patients will be given priority in order to ensure the majority can undergo imaging
5. Informed consent/assent obtained before any study-related activities
6. Ability and willingness to adhere to the protocol including appointments and evaluation schedule
7. Sexually active female patients of childbearing potential must have a negative pregnancy test result at Screening Visit. In addition, if applicable, females of childbearing potential must use an effective method of contraception according to local requirements, OR have had a tubal ligation, OR have had a hysterectomy, OR participates in a non-heterosexual lifestyle, OR have a male sexual partner has been sterilized
8. If the patient is a heterosexual sexually-active male, patient must confirm, in writing, that he and/or his female partner will use an effective method of contraception according to local requirements for the length of the trial and for 30 days following completion of the study or early termination
**Exclusion Criteria**

1. Evidence of iron deficiency defined by Fe:TIBC ratio <15%, or serum ferritin <12 ng/mL
2. Treatment with deferiprone in the past 12 months
3. Previous failure of treatment with deferiprone, or previous discontinuation of treatment with deferiprone due to adverse events
4. Conditions known to contraindicate the use of deferiprone (history of agranulocytosis or recurrent episodes of neutropenia)
5. A serious, unstable illness during the past 3 months before screening visit including but not limited to: hepatic, renal, gastro-enterologic, respiratory, cardiovascular, endocrinologic, neurologic or immunologic disease
6. Evidence of abnormal liver or renal function (serum liver enzyme level(s) > 3 times upper limit of normal at screening) or abnormal creatinine levels at screening visit
7. Disorders associated with neutropenia (ANC < 1.5 x 10^9/L) or thrombocytopenia (platelet count < 50 x 10^9/L) in the 12 months preceding the initiation of the study medication. Exception: for patients whose neutropenia was attributed by the treating physician to episodes of infection or to drugs associated with a decline in the neutrophil count and in whom the ANC has fully recovered at the screening visit
8. History of malignancy
9. QTcF interval > 450 msec
10. HIV positive
11. Myocardial infarction, cardiac arrest or cardiac failure within 1 year before screening visit
12. Bowel disease causing malabsorption
13. History of alcohol or drug abuse
14. Treatment with an investigational drug within 30 days or 5 half-lives (whichever is longer) preceding the baseline visit
15. Currently taking iron chelators
16. Pregnant, nursing females and females of childbearing potential who are heterosexually active and unwilling, or unable, to use an acceptable method of contraception according to local requirements
17. Males who are sexually active and unwilling, or unable, to use an acceptable method of contraception according to local requirements
18. History or presence of hypersensitivity or idiosyncratic reaction to deferiprone
19. Patients (or when applicable parent or patients’ legal representatives) with a mental incapacity, unwillingness or language barriers precluding adequate understanding or cooperation
20. Any condition that, in investigator’s opinion, would adversely affect the patient’s ability to complete the study or its assessments
21. Baclofen pump placement less than two months prior to the screening visit
22. Current and ongoing participation in other clinical studies
Procedures

In both trials, dosage was based on milligrams of DFP per kilogram of body weight, starting at 5 mg/kg b.i.d. and titrated up to 15 mg/kg b.i.d. by Week 12. In TIRCON2012V1, patients in the control group received a matching volume of placebo during the same time periods.

All efficacy measures were administered at baseline (except for the PGI-I, which is a measure of change from baseline), months 6, 12, and 18 or early termination. Iron levels in the globus pallidus were measured by MRI-R2* in a subset of patients (those without a DBS device and able to undergo an MRI scan) at baseline and Month 18. MRI scans were conducted according to a standardized imaging protocol, and the images were sent to central reading by radiologists who were blinded to treatment. None of the MRI-R2* results were disclosed by the radiologist until the last patient completed the trial.

Information was also collected on the use of concomitant medications, with particular attention on any changes in drugs or devices used to relieve symptoms of dystonia. Patients had weekly hematology tests to monitor their absolute neutrophil count (ANC). Patients with two consecutive samples with ANC < 1.5×10⁹/L were withdrawn from the study.

To reduce the confounding effects of concomitant therapies on the assessment of treatment, patients with recent or expected changes in therapies that have the potential to affect dystonia symptoms were excluded from enrolment.

Role of the funding source

Funding for the study was provided by the European Commission, the US FDA, and ApoPharma Inc., Canada. The US FDA had input into the design and selection of endpoints. The sponsor, ApoPharma, participated in study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.
Results

There were proportionally more patients with baseline BAD score close to the maximum score of 32 being randomized to the deferiprone treatment group. To investigate whether a "ceiling effect" might account for the differences observed in BAD in response to treatment with deferiprone, the mITT data were re-analyzed after excluding all patients that would have had the potential to experience a ceiling effect. Using the cut-off of 27 for the baseline BAD score, it is evident that the difference in response to treatment is not lessened by the dropping of patients with a cut-off of 27, even though, as would be expected, fewer subjects lessens the level of statistical significance, as shown in Suppl. Table 1a.

Suppl. Table 1a: Main MMRM analysis excluding baseline BAD > 27 in the TIRCON study

<table>
<thead>
<tr>
<th>Subpopulation</th>
<th>Placebo</th>
<th>DFP</th>
<th>DFP-Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Marginal Mean Change (SE)</td>
<td>n</td>
<td>Marginal Mean Change (SE)</td>
</tr>
<tr>
<td>All patients</td>
<td>28</td>
<td>3.99 (0.82)</td>
<td>58</td>
</tr>
<tr>
<td>Baseline BAD &lt;=27</td>
<td>26</td>
<td>4.62 (0.96)</td>
<td>42</td>
</tr>
</tbody>
</table>

To further investigate the impact of ceiling effect, a reanalysis of the data was conducted using 3 different strata of baseline values. To avoid the risk of bias in selection of what might constitute suitable cut-off points, we let the data select the points by choosing tertiles of baseline BAD. The MMRM modelling performed for the primary analysis was repeated for each subgroup defined by the tertiles of the baseline BAD score: ≤13, 13-24, >24. The results are summarized in Suppl. Table 1b below. The analysis reveals that the treatment effect as measured by the marginal mean difference between DFP and placebo was observed for each subgroup, indicating benefit of deferiprone over placebo regardless of the baseline BAD level, and, numerically, the largest observed difference is in those with no potential for a ceiling effect. Weaker levels of significance are attributed to smaller numbers of subjects in each group, compared to the full cohort.
**Suppl. Table 1b: Main MMRM analysis by subgroups based on the tertiles of baseline BAD**

<table>
<thead>
<tr>
<th>Subpopulation</th>
<th>Placebo</th>
<th>DFP</th>
<th>DFP-Placebo Marginal Mean Difference (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n</td>
<td>Marginal Mean Change (SE)</td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>28</td>
<td>58</td>
<td>3.99 (0.82)</td>
<td>-1.51 (-3.19, 0.16)</td>
</tr>
<tr>
<td>Baseline BAD: ≤ 13</td>
<td>12</td>
<td>17</td>
<td>7.65 (1.57)</td>
<td>-1.59 (-5.46, 2.27)</td>
</tr>
<tr>
<td>Baseline BAD: 13-24</td>
<td>10</td>
<td>21</td>
<td>3.60 (1.29)</td>
<td>-1.27 (-3.65, 1.10)</td>
</tr>
<tr>
<td>Baseline BAD: &gt; 24</td>
<td>6</td>
<td>20</td>
<td>1.55 (0.76)</td>
<td>-0.78 (-2.42, 0.87)</td>
</tr>
</tbody>
</table>

To investigate whether the inclusion of patients with a baseline BAD score close to or at the maximum score of 32 (ceiling effects) impacted on the results of the BAD score analysis, we performed an unscheduled sensitivity analysis by removing patients from the analysis who (i) had already achieved the maximum BAD score of 32 at baseline, or (ii) had already achieved a maximum BAD score of ≥30 at baseline.

As shown in **Suppl. Table 1** below, results did not change significantly by removing these patients.

**Suppl. Table 1:**
BAD score analysis based on inclusion or exclusion of patients with high BAD scores at baseline

<table>
<thead>
<tr>
<th>Population</th>
<th>Placebo</th>
<th>DFP</th>
<th>DFP-Placebo Mean Difference (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n</td>
<td>Marginal Mean Change (SE)</td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>28</td>
<td>58</td>
<td>3.99 (0.82)</td>
<td>-1.51 (-3.19, 0.16)</td>
</tr>
<tr>
<td>Removing max BAD=32 at Month 18</td>
<td>28</td>
<td>56</td>
<td>4.04 (0.83)</td>
<td>-1.52 (-3.24, 0.18)</td>
</tr>
<tr>
<td>Removing max BAD ≥30 at baseline</td>
<td>28</td>
<td>50</td>
<td>4.30 (0.91)</td>
<td>-1.53 (-3.11, 0.07)</td>
</tr>
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</table>
Over the 18 months of the extension study, there was no significant difference in the change in BAD score for patients who had been on DFP from the start (1.9±0.5 points in the first 18 months vs 1.4±0.4 points in the second 18 months, p=0.2684) while there was significantly less worsening in the placebo-DFP group (4.4±1.1 points when they were receiving placebo vs 1.4±0.9 points when they were receiving DFP, p=0.0206) (Suppl. Table 2). Placebo-DFP group represents the patients who received placebo during the first 18 months and deferiprone during the subsequent 18 months. DFP-DFP group represent the patients who received deferiprone during the 36 months of both trials. Classical PKAN are patients with age at onset of disease < 6 years. Atypical PKAN are patients with age at onset of disease ≥ 6 years.

**Suppl. Table 2. Changes in BAD score in the TIRCON and TIRCON-Extension studies**

<table>
<thead>
<tr>
<th>Age at onset of symptoms</th>
<th>Placebo-DFP Group</th>
<th>DFP-DFP Group</th>
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<tr>
<td></td>
<td>TIRCON study</td>
<td>T-EXT study</td>
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<tr>
<td></td>
<td>Change from Baseline</td>
<td>Change from Baseline</td>
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<tr>
<td>Overall</td>
<td>19</td>
<td>43</td>
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<tr>
<td>Baseline Score Mean (SD)</td>
<td>15.9 (8.0)</td>
<td>19.3 (8.1)</td>
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<td>4.4 (4.8)</td>
<td>1.9 (3.2)</td>
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<td></td>
<td>20.4 (8.1)</td>
<td>21.3 (7.6)</td>
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<td>1.4 (3.7)</td>
<td>1.4 (2.4)</td>
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<tr>
<td>&lt; 6 years (classic PKAN)</td>
<td>8</td>
<td>20</td>
</tr>
<tr>
<td>Baseline Score Mean (SD)</td>
<td>18.0 (9.3)</td>
<td>20.9 (7.9)</td>
</tr>
<tr>
<td></td>
<td>5.3 (6.1)</td>
<td>2.3 (4.2)</td>
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<td></td>
<td>23.3 (6.8)</td>
<td>23.2 (7.2)</td>
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<tr>
<td></td>
<td>4.3 (3.8)</td>
<td>2.0 (3.0)</td>
</tr>
<tr>
<td>≥6 years (atypical PKAN)</td>
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<td>23</td>
</tr>
<tr>
<td>Baseline Score Mean (SD)</td>
<td>14.5 (6.9)</td>
<td>18.0 (8.3)</td>
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<tr>
<td></td>
<td>3.8 (3.9)</td>
<td>1.6 (1.9)</td>
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<tr>
<td></td>
<td>18.3 (8.7)</td>
<td>19.7 (7.8)</td>
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<tr>
<td></td>
<td>-0.6 (1.9)</td>
<td>0.9 (1.7)</td>
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</table>

$^\dagger$ P-value from paired t-test
Suppl. Table 3 provides the results of the randomized study, not using the marginal means from the MMRM model for the assessment of treatment difference in mean change of BAD score.

**Suppl. Table 3.**  
**Observed change in BAD total score at Month 18 by age at onset of symptoms - mITT population**

<table>
<thead>
<tr>
<th>Subpopulation</th>
<th>Placebo</th>
<th>DFP</th>
<th>P-value (T-test)</th>
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<tr>
<td></td>
<td>n</td>
<td>Mean (SD)</td>
<td>n</td>
</tr>
<tr>
<td>All patients</td>
<td>22</td>
<td>3.9 (4.3)</td>
<td>49</td>
</tr>
<tr>
<td>Age at onset of disease: &lt; 6</td>
<td>12</td>
<td>4.8 (5.0)</td>
<td>23</td>
</tr>
<tr>
<td>Age at onset of disease: ≥ 6</td>
<td>15</td>
<td>3.1 (1.6)</td>
<td>26</td>
</tr>
</tbody>
</table>

Comment [KTPD4]: Suppl. Table 3 and the text referring to it have been deleted as they are not referred to in the main manuscript, as noted by Reviewer #2.
Correlation between the BAD scale and the PGI-I

The change of PGI-I at completion of 18 months of study therapy was included as a co-primary endpoint based on a request by a regulatory agency. At Month 18, the LSmean scores were 4.66 for placebo and 4.55 for DFP, with no significant group difference (p=0.7279) indicating that, overall, patients did not detect either an improvement or a worsening in their condition from baseline. To the best of our knowledge, the PGI-I had not been previously used in a prospective study in patients with NBIA and no data are currently available on its value for identifying the clinical significance of other study measures. To that extent, the TIRCON study provides valuable data for the determination if a correlation existed between a measurement of disease progression such as the BAD score and the PGI-I.

Suppl. Figure 21 shows the correlation between the PGI-I and the change in BAD score at Month-18. The analysis reveals a weak correlation (r = 0.29), in which < 10% of the PGI-I variation can be explained by the change in BAD (r square < 0.1), indicating the PGI-I is not an adequate tool for assessment in PKAN over an 18 month period.

Suppl. Figure 21. Correlation between change from baseline in BAD score and PGI-I score at Month 18.

![Correlation between BAD and PGI-I](image)
**Wee FIM**

The WeeFIM, which rates 18 activities of daily living in terms of how much assistance is needed, scores each item from 1 (total dependence) to 7 (complete independence), and generates a global score that ranges from 18 to 126. Thus, a decrease in score indicates worsening. The global score for the placebo group worsened by 2.40 points while that for the DFP group improved by 4.91 points, although the difference was not significant ($p=0.2026$). For the subscale scores, a significant difference in favor of DFP ($p=0.0324$) was seen for cognition. Treatment group differences in the domain of cognition reached significance in favor of DFP for problem solving ($p=0.0258$) and social interaction ($p=0.0414$), and approached significance for memory ($p=0.0574$). **Suppl. Figure 1,2** displays a polar graph for each treatment group of all the elements contributing to the global WeeFIM score. For the placebo group, there was either worsening or lack of improvement in all measures; for the DFP group, improvement was seen for 4 of the 5 cognitive components (comprehension, social interaction, problem solving, and memory) and no change on the fifth (expression) but worsening or lack of improvement for the items in the self-care and mobility domains.
Suppl. Figure 12. Polar graph of WeeFIM scores. The blue lines represent scores at baseline, and the red lines represent scores at Month 18. Values that are closer to the center indicate lower functioning, so a red line that is inside the blue line indicates worsening, a red line that overlaps the blue line indicates no change, and a red line that is outside the blue line indicates improvement.
Correlation between the BAD scale and the PGI-I

The change of PGI-I at completion of 18 months of study therapy was included as a co-primary endpoint based on a request by a regulatory agency. At Month 18, the LSmean scores were 4.66 for placebo and 4.55 for DFP, with no significant group difference (p=0.7279) indicating that, overall, patients did not detect either an improvement or a worsening in their condition from baseline.

To the best of our knowledge, the PGI-I had not been previously used in a prospective study in patients with NBIA and no data are currently available on its value for identifying the clinical significance of other study measures. To that extent, the TIRCON study provides valuable data for the determination, if a correlation existed between a measurement of disease progression such as the BAD score and the PGI-I.

Suppl. Figure 2 shows the correlation between the PGI-I and the change in BAD score at Month 18. The analysis reveals a weak correlation (r = 0.29), in which < 10% of the PGI-I variation can be explained by the change in BAD (r square < 0.1), indicating the PGI-I is not an adequate tool for assessment in PKAN over an 18 month period.
SAFETY

Regarding safety, DFP was well tolerated and rates of adverse events were similar between the treatment groups except for anemia, which was seen more frequent in DFP-treated patients than in placebo patients. An overview of the different categories of safety findings during the randomized phase of the studies is shown in Suppl. Table 3.4, and a listing of individual AEs seen in >10% of patients in Suppl. Table 5.

Suppl. Table 3.4.
Overview of the different categories of safety findings during the randomized phase of the studies

<table>
<thead>
<tr>
<th>Number of patients with at least one:</th>
<th>Placebo (N=30)</th>
<th>DFP (N=58)</th>
<th>P-value (Fisher's exact test)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (n)</td>
<td>% (n)</td>
<td></td>
</tr>
<tr>
<td>Adverse event</td>
<td>100.0 (30)</td>
<td>98.3 (57)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>33.3 (10)</td>
<td>31.0 (18)</td>
<td>0.8146</td>
</tr>
<tr>
<td>Severe adverse event</td>
<td>26.7 (8)</td>
<td>29.3 (17)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Adverse event related to study treatment</td>
<td>43.3 (13)</td>
<td>79.3 (46)</td>
<td>0.0015</td>
</tr>
<tr>
<td>Death</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
<td>NA</td>
</tr>
<tr>
<td>Adverse event leading to withdrawal</td>
<td>0.0 (0)</td>
<td>6.9 (4)</td>
<td>0.2947</td>
</tr>
</tbody>
</table>

Comment [KTPDS]: Statement re listing of AEs was removed as the listing has been moved to the main manuscript.
## Table 5. Summary of adverse events seen in ≥10% of patients – Safety population

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (N=30)</th>
<th>DFP (N=58)</th>
<th>P-value (Fisher's exact test)</th>
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<td>Dystonia</td>
<td>46.7 (14)</td>
<td>43.1 (25)</td>
<td>0.8225</td>
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<td>Pyrexia</td>
<td>43.3 (13)</td>
<td>27.6 (16)</td>
<td>0.1567</td>
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<td>Serum ferritin decreased</td>
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<td>32.8 (19)</td>
<td>0.1341</td>
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<td>Headache</td>
<td>30.0 (9)</td>
<td>22.4 (13)</td>
<td>0.4478</td>
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<td>Nasopharyngitis</td>
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<td>Anaemia</td>
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<td>Department of Neurology, Friedrich-Baur-Institute, Ludwig-Maximilians-University of Munich, Munich, Germany&lt;br&gt;German Center for Neurodegenerative Diseases (DZNE), Munich, Germany&lt;br&gt;Munich Cluster for Systems Neurology (SyNergy), Munich, Germany</td>
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<td>Bernadette Kálmán</td>
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Research in context

Evidence before this study
While designing this trial and during its conduct and analysis, we undertook several systematic reviews of the literature between January 2010 and February 2019. We searched PubMed using the search term (“Pantothenate Kinase-Associated Neurodegeneration” OR “PKAN” OR “Neurodegeneration with brain iron accumulation” OR “NBIA”) AND (“deferiprone” OR “iron chelation” OR “iron chelator” OR “Iron Chelating Agents”). Of 33 publications, 4 reported original data on the use of deferiprone (DFP) in more than one PKAN patient. An open-label pilot trial in 10 patients showed significant reduction of globus pallidus iron content but no clinical improvement after 6 months of treatment. Another small open-label trial including 4 PKAN patients showed significant reduction of globus pallidus iron in 3 of 3 patients, as well as mild-to-moderate motor improvement in 2 of the 4 patients after 12 months of treatment. A follow-up study of these 4 PKAN patients showed a relatively stable course over a total period of 48 months. In another small open-label trial, DFP treatment for 18 months led to a reduction of iron load in globus pallidus in all, and some clinical improvement in 4 of 5 PKAN patients. Taken together, there has been some low-quality evidence from case reports and small uncontrolled pilot trials that DFP may be beneficial in PKAN.

Added value of this study
This study is the first randomized controlled trial of DFP in PKAN, and actually the first randomized trial of any treatment in any form of NBIA. While all previous reports together (single cases and pilot trials) had involved 23 PKAN patients, this study randomized 88 PKAN patients, showing the feasibility of randomized trials even in ultraorphan diseases like PKAN with an estimated prevalence of 1 in 1 million. Moreover, this study had a duration of 18 months in its randomized part plus an open-label extension of another 18 months, finally providing safety and efficacy data for 36 months of DFP treatment. As a result, the combined analysis of the randomized trial and the extension study shows excellent safety and tolerability of DFP in PKAN over 36 month, and strong evidence that DFP leads to a marked reduction in brain iron. Regarding the primary endpoint on the change in Barry-Albright dystonia scale), there was only weak evidence to show potential slowing of disease progression in DFP-treated as compared to placebo-treated patients. The difference seemed to be greater in a predefined subgroup of patients with atypical PKAN. The rate of progression seemed to slow down in patients who switched from placebo to DFP in the extension trial. There was no evidence of change in the co-primary endpoint, Patient Global Impression of Improvement (PGI-I).

Implications of all the available evidence
This study, together with previous findings, shows that iron chelation with deferiprone achieves target engagement (lowering of iron in the basal ganglia) in PKAN. While the clinical endpoints were not met for the modified Intent-to-Treat population in the randomized trial, subgroup analysis and the results of the extension trial indicate some slowing of disease progression by deferiprone. This study will help shape the design of future trials in this ultraorphan disease.
Research in context

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Implications of all the available evidence
This study, together with previous findings, shows that iron chelation with deferiprone achieves target engagement (lowering of iron in the basal ganglia) in PKAN. While the clinical endpoints were not met for the modified Intent-to-Treat population in the randomized trial, subgroup analysis and the results of the extension trial indicate some slowing of disease progression by deferiprone. This study will help shape the design of future trials in this ultraorphan disease.
# Table 1. Patients' demographics, basal ganglia iron loading as assessed by MRI R2* and Barry-Albright Dystonia (BAD) scale at baseline of the randomized and extension studies.

All patients in the extension study received only deferiprone for up to 18 months and their data are grouped by the therapy they received during the 18 preceding months, i.e., deferiprone or placebo, while in the randomized study.

BAD scores at baseline of the randomized study are based on the modified intent-to-treat population, defined as all randomized patients who 1) received at least one dose of study drug, and 2) provided a baseline and at least one post-baseline efficacy assessment. BAD scores at the baseline of the extension study are based on that study's intent-to-treat population, which has the same definition as the modified intent-to-treat population of the randomized study. BAD data obtained at the end of study (Month 18) visit of the randomized study was used as the baseline value of the extension study.

<table>
<thead>
<tr>
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<th>Randomized Study</th>
<th>Extension Study</th>
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<tr>
<td></td>
<td>Placebo</td>
<td>Deferiprone</td>
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<tr>
<td>Age at enrollment (years)</td>
<td></td>
<td></td>
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<tr>
<td>N</td>
<td>30</td>
<td>59</td>
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<tr>
<td>Mean ± SD</td>
<td>19.2 ± 12.5</td>
<td>20.8 ± 10.7</td>
</tr>
<tr>
<td>Min - Max</td>
<td>5 - 55</td>
<td>4 - 52</td>
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<tr>
<td>Age at onset (years)</td>
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<tr>
<td>Mean ± SD</td>
<td>7.5 ± 6.2</td>
<td>8.4 ± 7.2</td>
</tr>
<tr>
<td>Min - Max</td>
<td>1 - 23</td>
<td>1 - 29</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Female N (%)</td>
<td>17 (56.7)</td>
<td>25 (42.4)</td>
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<tr>
<td>Male N (%)</td>
<td>13 (43.3)</td>
<td>34 (57.6)</td>
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<td>Racial Origin</td>
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<td>Asian N (%)</td>
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<td>Black N (%)</td>
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<td>White N (%)</td>
<td>28 (93.3)</td>
<td>51 (86.4)</td>
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<td>Basal ganglia MRI R2* (Hz)</td>
<td>16</td>
<td>24</td>
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<tr>
<td>N</td>
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<td>24</td>
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<tr>
<td>Mean ± SD</td>
<td>93.5 ± 31.2</td>
<td>96.6 ± 31.6</td>
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<tr>
<td>Min, Max</td>
<td>35.7, 167.8</td>
<td>34.0, 152.5</td>
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<td>BAD total score†</td>
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<tr>
<td>N</td>
<td>28</td>
<td>58</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>16.5 ± 8.1</td>
<td>19.6 ± 8.4</td>
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<tr>
<td>Min - Max</td>
<td>2 - 31</td>
<td>1 - 32</td>
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<td>All Patients</td>
<td>Placebo N=28</td>
<td>Marginal mean change in BAD score (95% CI)</td>
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<td></td>
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<td>3.99 (2.38, 5.60)</td>
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<td>Deferiprone N=58</td>
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<td>2.48 (1.25, 3.71)</td>
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<th>Placebo N=12</th>
<th>Marginal mean change in BAD score (95% CI)</th>
<th>DFP-Placebo mean Difference (95% CI)*</th>
<th>P-value*</th>
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<td></td>
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<td>3.72 (1.19, 6.25)</td>
<td>-0.81 (-3.68, 2.06)</td>
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<tr>
<td>Deferiprone N=29</td>
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<td>2.91 (1.09, 4.73)</td>
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<th>Atypical PKAN</th>
<th>Placebo N=16</th>
<th>Marginal mean change in BAD score (95% CI)</th>
<th>DFP-Placebo mean Difference (95% CI)*</th>
<th>P-value*</th>
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<td>4.52 (2.74, 6.30)</td>
<td>-2.19 (-4.00, -0.38)</td>
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<tr>
<td>Deferiprone N=29</td>
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<td>2.33 (0.90, 3.76)</td>
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Table 2. Marginal mean change* and 95% CI in BAD score from baseline to end of study during deferiprone or placebo use up to 18 months in the randomized trial. Classical PKAN are patients with age at onset of disease < 6 years. Atypical PKAN are patients with age at onset of disease ≥ 6 years.
* Based on least squares estimate from the MMRM model
* P-value from MMRM model
Table 3. Summary of adverse events seen in ≥10% of patients – Safety population

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<tr>
<th>Adverse Event</th>
<th>Placebo (N=30) % (n)</th>
<th>DFP (N=58) % (n)</th>
<th>P-value (Fisher's exact test)</th>
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<tr>
<td>Dystonia</td>
<td>46.7 (14)</td>
<td>43.1 (25)</td>
<td>0.8225</td>
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<td>Pyrexia</td>
<td>43.3 (13)</td>
<td>27.6 (16)</td>
<td>0.1567</td>
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<tr>
<td>Serum ferritin decreased</td>
<td>16.7 (5)</td>
<td>32.8 (19)</td>
<td>0.1341</td>
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<td>Headache</td>
<td>30.0 (9)</td>
<td>22.4 (13)</td>
<td>0.4478</td>
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<tr>
<td>Nasopharyngitis</td>
<td>20.0 (6)</td>
<td>19.0 (11)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Anaemia</td>
<td>0.0 (0)</td>
<td>20.7 (12)</td>
<td>0.0067</td>
</tr>
<tr>
<td>Condition aggravated</td>
<td>30.0 (9)</td>
<td>17.2 (10)</td>
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<td>Neutrophil count decreased</td>
<td>10.0 (3)</td>
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<td>0.5294</td>
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<td>Pain in extremity</td>
<td>13.3 (4)</td>
<td>17.2 (10)</td>
<td>0.7641</td>
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<td>Cough</td>
<td>16.7 (5)</td>
<td>17.2 (10)</td>
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<td>Vomiting</td>
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<td>0.2580</td>
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<td>10.0 (3)</td>
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<td>Abdominal pain upper</td>
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<td>Constipation</td>
<td>13.3 (4)</td>
<td>3.4 (2)</td>
<td>0.1746</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>10.0 (3)</td>
<td>6.9 (4)</td>
<td>0.6860</td>
</tr>
<tr>
<td>Gastrointestinal infection</td>
<td>10.0 (3)</td>
<td>5.2 (3)</td>
<td>0.4058</td>
</tr>
<tr>
<td>Freezing phenomenon</td>
<td>10.0 (3)</td>
<td>0.0 (0)</td>
<td>0.0370</td>
</tr>
</tbody>
</table>

Table 3. Summary of adverse events seen in ≥10% of patients. Rates are based on all randomized patients who received at least one dose of study drug.
Figure 1. Patient flow diagram of the randomized study from time of screening to time of completion after 18 months on study therapy or early withdrawal.
Figure 2a
Click here to download Figure: Fig2a.eps

2.a. All PKAN

BAD Total Score Mean Change from Baseline

Month

Placebo

Deferiprone

p = 0.0941

p = 0.1592

p = 0.0761
2.b. Atypical PKAN

Figure 2b
Click here to download Figure: Fig2b.eps
2.c. Classic PKAN

Figure 2c
Click here to download Figure: Fig2c.eps
2.d. Change in BAD over the two studies

Placebo - Deferiprone
N=19, 19

Deferiprone - Deferiprone
N=43, 43

p = 0.0500

p = 0.0206

p = 0.9781

p = 0.2684
Figures 2.a, 2.b, 2.c and 2.d. Marginal mean change (±SE) in BAD total score over time in patients with different classes of PKAN in the randomized study: 2a. All PKAN, 2b. Atypical PKAN and 2c. Classic PKAN. The p-values for each class of PKAN was obtained from a MMRM model for the comparison of the DFP and placebo groups. 2.d. Observed change from baseline in BAD total score over the two studies. The bars on the left panel show the mean (±95% confidence limits) change for the patients who received placebo over the 18 months of the randomized study (red bar) and deferiprone over the 18 months of the extension study (blue bar). The bars on the right panel show the corresponding changes for the patients who received deferiprone in both studies (both bars blue). The p-value was obtained from a t-test for any comparison between the two groups of patients or from a paired t-test for any comparison within the same group of patients.
Figure 3. Illustrative MRI data and response to DFP treatment. Imaging panels show a slice from the conventional T2 weighted scan through the basal ganglia (left) with the R2* maps at baseline (center) and 18 Months (right). The expanded anatomical region illustrated for R2* is marked by the box on the T2w scan. The quantitative R2* maps are presented with hotter colors having higher iron levels (higher R2* values). The center panel shows the mean globus pallidus R2* across both hemispheres for each group at each time point demonstrating the reduction in R2* in the DFP treated group, indicating a reduction in GP iron levels on treatment.
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Point estimate</th>
<th>Lower limit</th>
<th>Upper limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAD Eyes Score</td>
<td>-1.15</td>
<td>-3.15</td>
<td>0.84</td>
</tr>
<tr>
<td>BAD Mouth Score</td>
<td>0.28</td>
<td>-1.72</td>
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<tr>
<td>BAD Neck Score</td>
<td>-2.03</td>
<td>-4.03</td>
<td>-0.04</td>
</tr>
<tr>
<td>BAD Trunk Score</td>
<td>-0.68</td>
<td>-2.68</td>
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</tr>
<tr>
<td>BAD Left Upper Extremity Score</td>
<td>0.00</td>
<td>-1.99</td>
<td>1.99</td>
</tr>
<tr>
<td>BAD Right Upper Extremity Score</td>
<td>-0.47</td>
<td>-2.47</td>
<td>1.53</td>
</tr>
<tr>
<td>BAD Left Lower Extremity Score</td>
<td>-2.10</td>
<td>-4.09</td>
<td>-0.11</td>
</tr>
<tr>
<td>BAD Right Lower Extremity Score</td>
<td>-2.05</td>
<td>-4.05</td>
<td>-0.06</td>
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<tr>
<td>UPDRS Part I Score</td>
<td>-0.36</td>
<td>-2.36</td>
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</tr>
<tr>
<td>UPDRS Part II Score</td>
<td>-0.91</td>
<td>-2.91</td>
<td>1.09</td>
</tr>
<tr>
<td>UPDRS Part III Score</td>
<td>1.24</td>
<td>-0.75</td>
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<tr>
<td>UPDRS Part VI Score</td>
<td>-1.37</td>
<td>-3.37</td>
<td>0.62</td>
</tr>
<tr>
<td>WeeFIM Self-care Score</td>
<td>-0.05</td>
<td>-2.10</td>
<td>2.00</td>
</tr>
<tr>
<td>WeeFIM Mobility Score</td>
<td>-0.10</td>
<td>-2.16</td>
<td>1.96</td>
</tr>
<tr>
<td>WeeFIM Cognition Score</td>
<td>-2.25</td>
<td>-4.30</td>
<td>-0.20</td>
</tr>
<tr>
<td>FIM Self-care Score</td>
<td>-1.57</td>
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<tr>
<td>FIM Mobility Score</td>
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<tr>
<td>FIM Cognition Score</td>
<td>-1.00</td>
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<tr>
<td>PedsQL Total Score - Child</td>
<td>0.03</td>
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<tr>
<td>PedsQL Total Score - Parent</td>
<td>0.56</td>
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<tr>
<td>PSQI Score</td>
<td>0.48</td>
<td>-1.51</td>
<td>2.47</td>
</tr>
</tbody>
</table>

**Figure 4.** Forest plot of all secondary endpoint outcomes. Each black square represents the estimated marginal mean difference between DFP and placebo for an endpoint, and the line indicates the 95% confidence interval for the difference, both standardized by the standard error of the marginal mean difference. For each endpoint, the location of the black square indicates whether the results are in favor of DFP (black square at the left side of 0.00) or in favor of placebo (black square at the right side of 0.00).
Suppl. Figure 2. Correlation between change from baseline in BAD score and PGI-I score at Month 18

Correlation Coefficients
Corr = 0.29, p = 0.0104
Suppl. Figure 1. Polar graph of WeeFIM scores. The blue lines represent scores at baseline, and the red lines represent scores at Month 18. Values that are closer to the center indicate lower functioning, so a red line that is inside the blue line indicates worsening, a red line that overlaps the blue line indicates no change, and a red line that is outside the blue line indicates improvement.
# CONSORT Checklist

<table>
<thead>
<tr>
<th><strong>Title and Abstract</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1a. Title:</strong> Identification as a randomised trial in the title.</td>
<td>✓</td>
</tr>
<tr>
<td><strong>1b. Abstract:</strong> Structured summary of trial design, methods, results, and conclusions</td>
<td>Abstract headings now appears as Background, Methods, Results, and Conclusions. “Funding”, which is covered elsewhere in the article, is deleted.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Introduction</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2a. Background:</strong> Scientific background and explanation of rationale</td>
<td>✓</td>
</tr>
<tr>
<td><strong>2b. Objectives:</strong> Specific objectives or hypotheses</td>
<td>✓</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Methods</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3a. Trial Design:</strong> Description of trial design (such as parallel, factorial) including allocation ratio</td>
<td>✓</td>
</tr>
<tr>
<td><strong>3b. Changes to trial design:</strong> Important changes to methods after trial commencement (such as eligibility criteria), with reasons</td>
<td>NA</td>
</tr>
<tr>
<td><strong>4a. Participants:</strong> Eligibility criteria for participants</td>
<td>✓</td>
</tr>
<tr>
<td><strong>4b. Study settings:</strong> Settings and locations where the data were collected</td>
<td>✓</td>
</tr>
<tr>
<td><strong>5. Interventions:</strong> The interventions for each group with sufficient details to allow replication, including how and when they were actually administered</td>
<td>✓</td>
</tr>
<tr>
<td><strong>6a. Outcomes:</strong> Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed</td>
<td>✓</td>
</tr>
<tr>
<td><strong>6b. Changes to outcomes:</strong> Any changes to trial outcomes after the trial commenced, with reasons</td>
<td>NA</td>
</tr>
<tr>
<td><strong>7a. Sample size:</strong> How sample size was determined</td>
<td>✓</td>
</tr>
<tr>
<td><strong>7b. Interim analyses and stopping guidelines:</strong> When applicable, explanation of any interim analyses and stopping guidelines</td>
<td>NA</td>
</tr>
<tr>
<td><strong>8a. Randomisation: sequence generation:</strong> Method used to generate the random allocation sequence</td>
<td>✓</td>
</tr>
<tr>
<td><strong>8b. Randomisation: type:</strong> Type of randomisation; details of any restriction (such as blocking and block size)</td>
<td>✓</td>
</tr>
<tr>
<td><strong>9. Randomisation: allocation concealment mechanism:</strong></td>
<td>✓</td>
</tr>
<tr>
<td>Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned</td>
<td></td>
</tr>
<tr>
<td>10. <strong>Randomisation: implementation</strong>: Who generated the allocation sequence, who enrolled participants, and who assigned participants to interventions</td>
<td></td>
</tr>
<tr>
<td>11a. <strong>Blinding</strong>: If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how</td>
<td></td>
</tr>
<tr>
<td>11b. <strong>Similarity of interventions</strong>: If relevant, description of the similarity of interventions</td>
<td></td>
</tr>
<tr>
<td>12a. <strong>Statistical methods</strong>: Statistical methods used to compare groups for primary and secondary outcomes</td>
<td></td>
</tr>
<tr>
<td>12b. <strong>Additional analyses</strong>: Methods for additional analyses, such as subgroup analyses and adjusted analyses</td>
<td></td>
</tr>
<tr>
<td>Results</td>
<td></td>
</tr>
<tr>
<td>13a. <strong>Participant Flow</strong>: For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome</td>
<td></td>
</tr>
<tr>
<td>13b. <strong>Losses and exclusions</strong>: For each group, losses and exclusions after randomisation, together with reasons</td>
<td></td>
</tr>
<tr>
<td>14a. <strong>Recruitment</strong>: Dates defining the periods of recruitment and follow-up</td>
<td></td>
</tr>
<tr>
<td>14b. <strong>Reason for stopped trial</strong>: Why the trial ended or was stopped</td>
<td></td>
</tr>
<tr>
<td>15. <strong>Baseline Data</strong>: A table showing baseline demographic and clinical characteristics for each group</td>
<td></td>
</tr>
<tr>
<td>16. <strong>Numbers analysed</strong>: For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups</td>
<td></td>
</tr>
<tr>
<td>17a. <strong>Outcomes and estimation</strong>: For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)</td>
<td></td>
</tr>
<tr>
<td>17b. <strong>Binary outcomes</strong>: For binary outcomes, presentation of both absolute and relative effect sizes is recommended</td>
<td></td>
</tr>
<tr>
<td>18. <strong>Ancillary analyses</strong>: Results of any other analyses performed, including subgroup analyses and adjusted analyses</td>
<td></td>
</tr>
</tbody>
</table>
analyses, distinguishing pre-specified from exploratory

| 19. Harms: All important harms or unintended effects in each group | ✓ |

**Discussion**

| 20. Limitations: Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses | This is addressed, although not in detail. Note that doing so would increase the word count yet further. |

| 21. Generalisability: Generalisability (external validity, applicability) of the trial findings | As above |

| 22. Interpretation: Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence | ✓ |

**Other information**

| 23. Registration: Registration number and name of trial registry | ✓ |

| 24. Protocol: Where the full trial protocol can be accessed, if available | The protocol can be provided to the Lancet editor upon request if required, but will not be made available to readers |

| 25. Funding: Sources of funding and other support (such as supply of drugs), role of funders | ✓ |
Clinical Study Protocol Amendment
No. 6
TIRCON
TIRCON2012V1

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

Version: Amendment 6 Final
Approved by: ApoPharma Inc.
Date: 31 JUL 2013

This protocol supersedes protocol dated 27 FEB 2013

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PROTOCOL SYNOPSIS

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

Protocol Code: TIRCON2012V1

Development Phase: Phase III

Sponsor: ApoPharma Inc.

Principal Investigators:
- Thomas Klopstock, MD – Europe
- Elliott Vichinsky, MD – USA

Study Centre: Multicentre – 5 centres

Planned Study Period: Duration of treatment for an individual patient will be 18 months.

Study Objectives:

Co-Primary:
- To evaluate the change in severity of dystonia (BAD scale) in patients with PKAN treated with deferiprone for 18 months compared to placebo.
- To evaluate the patient's global impression of condition's improvement in patients treated with deferiprone for 18 months compared to placebo (PGI-I).

Secondary:
- To evaluate the effect of deferiprone compared to placebo on the change in globus pallidus iron levels (MRI) (subset of patients).
- To evaluate the effect of deferiprone compared to placebo on motor symptoms (UPDRS);
- To evaluate the effect of deferiprone compared to placebo on a measure of functional independence (WeeFIM or FIM);
- To evaluate the effect of deferiprone compared to placebo on quality of life (PedsQL);
- To evaluate the effect of deferiprone compared to placebo on the
patient’s quality of sleep (PSQI);
  - To evaluate the pharmacokinetics of deferiprone and its 3-O-glucuronide metabolite (subset of patients);
  - To evaluate the safety and tolerability of deferiprone in patients with PKAN.

**Study Design:**

Multi-center, double-blind, randomized, placebo-controlled study in patients with PKAN. Approximately 90 patients will be enrolled and randomized in a 2:1 (deferiprone:placebo) ratio. Block randomization will be used to ensure the same 2:1 ratio will be reached in patients in whom motor symptom onset was observed at < 6 yrs and in patients in whom motor symptom onset was observed at ≥ 6 yrs.

**Investigational Products:**

Deferiprone oral solution (80 mg/ml).

**Treatment (duration, treatment arms, dose, route):**

Patients are to be administered deferiprone or placebo at rising doses ranging from 5 to 15 mg/kg BID. Patients will be given 5 mg/kg BID for the first 6 weeks. If the dose is tolerated and there are no signs of toxicity, the dose will be increased to 10 mg/kg BID for the following 6 weeks. Again, if tolerated and there are no signs of drug toxicity, the dose will be increased to 15 mg/kg BID for the remainder of the study. Placebo patients will be dosed in the same manner.

**Target Population:**

90 male and female patients with PKAN.

**Efficacy Endpoints:**

**Co-Primary:**

- Change in the Barry-Albright Dystonia Scale (BAD) total score from baseline to Month 18 in patients treated with deferiprone compared to placebo, as assessed by central blinded evaluation of video-tapes;

- Patient’s Global Impression of Improvement (PGI-I) from baseline to Month 18 in patients treated with deferiprone compared to placebo.

Study will be considered positive if both co-primary endpoints reach statistical significance.

**Secondary (deferiprone vs. placebo):**

1. Proportion of patients with improved or unchanged BAD scale total
score between baseline and Month 18 (responder analysis).

2. Change from baseline to Month 18 in BAD scale score per body region (eyes, mouth, neck, trunk, each upper and lower extremity), as assessed by central blinded evaluation of video-tapes

3. Proportion of patients showing an improvement on PGI-I at the Month 18 visit (responder analysis);

4. Change from baseline to Month 18 in globus pallidus iron levels as measured by MRI R2* (subset of patients).

5. Change from baseline to Month 18 in UPDRS Parts I, II, III and VI scores, respectively;

6. Change from baseline to Month 18 in global WeeFIM score (or FIM for patients > 18 years);

7. Change from baseline to Month 18 in WeeFIM (or FIM for patients > 18 years) score per item;

8. Change from baseline to Month 18 in quality of life (PedsQL);

9. Change from baseline to Month 18 in quality of sleep (PSQI).

**Safety Endpoints:**
1. Frequency of Adverse Events (AEs);
2. Frequency of Serious Adverse Events (SAEs);
3. Discontinuation due to AEs;
4. Hematology assessments;
5. Blood clinical biochemistry assessments;
6. ECG.

**Pharmacokinetic Endpoints:**
Steady state pharmacokinetics of deferiprone and its 3-O-glucuronide metabolite will be assessed in a subset of up to 24 patients over 12 hours. The following standard pharmacokinetic parameters will be derived from plasma concentrations of deferiprone:

- $C_{\text{max}}$
- $T_{\text{max}}$
- $C_{\text{min}}$
- $AUC_{\text{SS}}$
- $\text{CL/F}$
Sample Size: Sample size estimation is based on BAD scores from literature, where a mean value of 21.0 BAD score points with a standard deviation of 6.3 points was observed in 21 NBIA patients (Timmermann et al, 2010). Assuming a 2:1 randomization, an expected difference in change of BAD score of ≥5 points after 18 months between control and treatment group, a standard deviation of 6.3 points for the change from baseline, and a dropout rate of 30%, a total of 87 patients would be needed to achieve 80% power in detection of this clinically relevant effect size at a two-sided 0.05 level of significance. The impact of the co-primary endpoint (PGI-I) on the power to demonstrate superiority of the treatment group over control should be small as a greater degree of difference in response for this endpoint is expected between the two groups. The rationale behind is that the BAD score is based on assessment of dystonia in eight body regions. To obtain a much higher score, in relation to the standard deviation, the active treatment would need to provide beneficial effect on multiple regions. A much higher score in PGI-I can be achieved even if the active treatment performs well in one region only.

Main Inclusion Criteria:

- Males and females 4 years of age and older at screening visit;
- Patients must have PKAN, confirmed by genetic testing;
- Patients having a BAD total score ≥ 3 at the screening visit;
- Patients who have Deep Brain Stimulation (DBS) systems or Baclofen pumps in place will be eligible for the study, but they must have had a stable setting for at least two months prior to the screening visit, and every effort should be made to maintain the stable setting for the duration of the study:
  - Enrollment of non-DBS patients will be given priority, to maximize the proportion that can undergo imaging;
  - Sexually active female patients of childbearing potential must have a negative pregnancy test result at Screening Visit (if applicable; In cases where the Investigator determines there is no reasonable risk of pregnancy because of significant incapacity, pregnancy testing will not be performed);
  - Fertile sexually active males must use an effective method of contraception or must confirm partner’s use of effective
contraception;

- Informed consent/assent obtained before any study-related activities are undertaken;

- Ability and willingness to adhere to the protocol including appointments and evaluation schedule.

Main Exclusion Criteria:

- Evidence of iron deficiency defined by Fe:TIBC ratio < 15%, or serum ferritin < 12 ng/mL;

- Treatment with deferiprone in the past 12 months;

- Previous failure of treatment with deferiprone, or previous discontinuation of treatment with deferiprone due to adverse events;

- Evidence of abnormal liver or renal function (serum liver enzyme level(s) > 3 times upper limit of normal at screening) or clinically significant abnormal creatinine levels at screening visit;

- Disorders associated with neutropenia (ANC < 1.5 x 10^9/L) or thrombocytopenia (platelet count < 50 x 10^9/L) in the 12 months preceding the initiation of the study medication. Exception: for patients whose neutropenia was attributed by the treating physician to episodes of infection or to drugs associated with a decline in the neutrophil count and in whom the ANC has fully recovered at the screening visit;

- Pregnant or nursing females, females planning to become pregnant, and females of childbearing potential who are sexually active and are unwilling, or unable, to use an acceptable method of contraception according to local requirements;

- Initiation or discontinuation of treatment with baclofen, trihexyphenidyl, clonazepam, tizanidine within 30 days prior to baseline; treatment with botox within 60 days of baseline; and initiation or discontinuation of treatment with tetrabenazine within 90 days prior to baseline;

- Treatment with an investigational drug within 30 days or 5 half-lives (whichever is longer) preceding the baseline visit;

- Currently taking iron chelators;

- Patients who, in the opinion of the physician, represent a high medical or psychological risk;

- History of or active drug or alcohol use or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements;
• Patients and patient’s legal representative (if applicable) with a mental incapacity, unwillingness or language barriers precluding adequate understanding or co-operation;

• Baclofen pump placement less than two months prior to the beginning of the study.

Schedule of Study Procedures:
Following screening and baseline assessments eligible patients will be randomized to deferiprone or placebo.

Efficacy evaluations:
The BAD score will be centrally measured using video-taping at baseline, Months 6, 12 and 18 (or early termination visit) study visits. Video-tapes will be assessed by blinded neurologists expert in movement disorders;
The PGI-I will be performed at Months 6, 12 and 18 (or early termination visit) study visits;
The MRI scan will be performed at baseline and Month 18 (or early termination visit) study visits in a subset of patients without deep brain stimulators for whom the use of anaesthesia (if required for the MRI scan) is deemed acceptable based on Investigator’s judgement;
The UPDRS Part I, II, III and VI will be performed at baseline, Months 6, 12 and 18 (or early termination visit) study visits;
The WeeFIM or FIM instrument will be performed at baseline, Months 6, 12 and 18 (or early termination visit) study visits;
The PedsQL will be performed at baseline, Months 6, 12 and 18 (or early termination visit) study visits;
The PSQI will be performed at baseline, Months 6, 12 and 18 (or early termination visit) study visits.

A Likert scale to evaluate the patient’s state with regards to its PKAN symptoms will be performed at baseline, Months 6, 12 and 18 (or early termination visit) study visits.

Safety evaluations:
Medical history will be collected at screening and reviewed at Month 18 (or early termination visit) study visits;
Physical examination will be performed at screening, baseline, Months 1.5, 3, 6, 12 and 18 (or early termination visit) study visits;
Serology will be performed at screening visit;
Vital signs, clinical chemistry, urinalysis, and pregnancy test will be performed at screening and Months 1.5, 3, 6, 12 and 18 (or early termination) study visits;
12-lead ECG will be performed at screening and Month 18 (or early termination) study visits;

Hematology assessments will be performed at screening and baseline visits, and weekly during the study;

Adverse events and use of concomitant medications will be followed at each study visit.

A safety follow-up visit will be conducted 4 weeks after completion of the study.

**Pharmacokinetic evaluations:**

Steady state pharmacokinetics of deferiprone and its 3-\(O\)-glucuronide metabolite will be studied over 12 hours in a subset of up to 24 patients. Blood samples will be collected at pre-dose and 1, 1.5, 2, 2.5, 3, 4, 6, 8 and 12 hours post-dose.

### Data Analysis / Statistical Methods:

**Co-Primary Efficacy Endpoints**

A Mixed-Effect Model Repeated Measure (MMRM) model will be used as the primary analysis method to assess the change in BAD total score and PGI-I from baseline to Month 18, with baseline value and age of onset of motor symptoms as covariates and treatment group as the main factor in the model. Age of onset of motor symptoms will be used as a stratification factor at randomization and thus will be included as a binary variable in all the models where it is used as a covariate. DBS settings change or use of medications that have the potential to affect dystonia symptoms during the study or the frequency of PRN drug or rescue medication use may confound the treatment effect assessment. These variables will also be included in the MMRM model. PGI-I is already a measurement of change from baseline and thus will be used directly as the outcome variable and baseline BAD score will be included as the baseline value in the model.

**Secondary Efficacy Endpoints**

The MMRM model used for the co-primary efficacy endpoints will also be used for the analysis of the secondary endpoints except for the proportion of responders, which will be analyzed by a logistic regression model.

**Subgroup Analysis**

In order to explore potential differences in treatment effect on efficacy endpoints across population subgroups, subgroup analyses will be performed on the co-primary efficacy endpoints on the following factors: Age at onset
of motor symptom (Age ≥6 vs. Age <6), DBS (Deep Brain Stimulation Yes vs. No), Baclofen pump (Yes vs. No), and Region (US vs. Europe). Forest plots will be drawn to compare subgroups of each factor.

Notable improvements or worsening in patient’s condition that are not captured by the relevant scales will be documented.

**Safety Analysis**

The safety data for continuous variables will be summarized using descriptive statistics and the safety data for discrete variables will be tabulated with frequency tables.

**Pharmacokinetic Analysis**

The pharmacokinetics parameters will be summarized using descriptive statistics.
CLINICAL STUDY ADMINISTRATIVE STRUCTURE

SPONSOR: ApoPharma Inc.
200 Barmac Drive
Weston (Toronto), Ontario
CANADA M9L 2Z7
Tel: +1-416-749-9300
1-800-268-4623
Fax: +1-416-401-3867

CONTRACT RESEARCH ORGANIZATION:
Algorithme Pharma
575, Armand-Frappier Blvd.
Laval, Quebec
Canada H7V 4B3

(Bioanalytical/Pharmacokinetic Analysis)
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<tr>
<td>AE</td>
<td>adverse event</td>
</tr>
<tr>
<td>ADR</td>
<td>adverse drug reaction</td>
</tr>
<tr>
<td>AF</td>
<td>assent form</td>
</tr>
<tr>
<td>ALT</td>
<td>alanine aminotransferase</td>
</tr>
<tr>
<td>ANC</td>
<td>absolute neutrophil count</td>
</tr>
<tr>
<td>ANOVA</td>
<td>analysis of variance</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>analysis of co-variance</td>
</tr>
<tr>
<td>AST</td>
<td>aspartate aminotransferase</td>
</tr>
<tr>
<td>AUC</td>
<td>area under the curve</td>
</tr>
<tr>
<td>BAD</td>
<td>Barry Albright Dystonia</td>
</tr>
<tr>
<td>BID</td>
<td><em>bis in die</em> (twice daily dosing)</td>
</tr>
<tr>
<td>BUN</td>
<td>blood urea nitrogen</td>
</tr>
<tr>
<td>CFR</td>
<td>code of federal regulations</td>
</tr>
<tr>
<td>CL/F</td>
<td>clearance of drug</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>maximum observed plasma concentration over a dosing interval</td>
</tr>
<tr>
<td>CMV</td>
<td>cytomegalovirus</td>
</tr>
<tr>
<td>CTCAE</td>
<td>common terminology criteria for adverse events</td>
</tr>
<tr>
<td>CRA</td>
<td>clinical research associate</td>
</tr>
<tr>
<td>CRF</td>
<td>case report form</td>
</tr>
<tr>
<td>CRO</td>
<td>contract research organization</td>
</tr>
<tr>
<td>CS</td>
<td>clinically significant</td>
</tr>
<tr>
<td>DBS</td>
<td>deep brain stimulation</td>
</tr>
<tr>
<td>DSMB</td>
<td>data safety monitoring board</td>
</tr>
<tr>
<td>eCRF</td>
<td>electronic case report form</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>EDC</td>
<td>electronic data capture</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>Fe:TIBC</td>
<td>iron:total iron binding capacity ratio</td>
</tr>
<tr>
<td>FIM</td>
<td>functional independence measure</td>
</tr>
<tr>
<td>GCP</td>
<td>good clinical practice</td>
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</tbody>
</table>
GCSF    granulocyte colony stimulating factor
GGT    gamma-glutamyltransferase
HDPE    high-density polyethylene
HIV    human immunodeficiency virus
HR    heart rate
ICARS    international co-operative ataxia rating scale
ICF    informed consent form
ICH    international conference on harmonisation
ID    identification
IND    investigational new drug
IRB/IEC    institutional review board/independent ethics committee
ITT    intent to treat
IUD    intrauterine device
LOCF    last observation carried forward
LDH    lactate dehydrogenase
MedDRA    medical dictionary for regulatory activities
ME    medical event
mITT    modified intent to treat
MMRM    mixed-effects model for repeated measures
MRI    magnetic resonance imaging
NBIA    neurodegeneration with brain iron accumulation
NCS    not clinically significant
OC    observed case
OECD    organization for economic co-operation and development
PANK2    pantothenate kinase 2
PDR    patient data report
PEDS QL    pediatric quality of life scale
PKAN    pantothenate kinase-associated neurodegeneration
PP    per-protocol
PRN    pro re nata (as needed)
PSQI    Pittsburgh sleep quality index
QTc/QTcF    adjusted QT interval
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>RDC</td>
<td>remote data capture</td>
</tr>
<tr>
<td>SAE</td>
<td>serious adverse event</td>
</tr>
<tr>
<td>SAP</td>
<td>statistical analysis plan</td>
</tr>
<tr>
<td>SDP</td>
<td>sponsor delegated person</td>
</tr>
<tr>
<td>SOC</td>
<td>system organ class</td>
</tr>
<tr>
<td>SOP</td>
<td>standard operating procedure</td>
</tr>
<tr>
<td>Tmax</td>
<td>time of occurrence of maximum drug concentration</td>
</tr>
<tr>
<td>T1/2</td>
<td>half-life</td>
</tr>
<tr>
<td>UPDRS</td>
<td>unified parkinson’s disease rating scale</td>
</tr>
<tr>
<td>Vd/F</td>
<td>volume of distribution</td>
</tr>
<tr>
<td>WeeFIM</td>
<td>pediatric functional independence measure</td>
</tr>
<tr>
<td>WHO</td>
<td>world health organization</td>
</tr>
<tr>
<td>WHODD</td>
<td>world health organization drug dictionary</td>
</tr>
<tr>
<td>WMA</td>
<td>world medical association</td>
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</table>
1 BACKGROUND AND RATIONALE

This will be a randomized, double-blind, placebo-controlled trial of deferiprone in patients with pantothenate kinase-associated neurodegeneration (PKAN)

1.1 Pantothenate Kinase-Associated Neurodegeneration

Pantothenate kinase-associated neurodegeneration (PKAN) is a rare disorder with progressive dystonia, parkinsonism, spasticity, and brain iron accumulation (Hayflick SJ et al. 2003; Zorzi G et al. 2011). PKAN is the most prevalent form of a group of progressive extrapyramidal disorders called neurodegeneration with brain iron accumulation (NBIA), characterized by iron accumulation in the brain (Hayflick SJ. 2003). Although PKAN accounts for only approximately 50% of cases of NBIA (Kurian MA et al. 2011) until recently all patients with high brain iron were given a diagnosis of PKAN, despite the obvious clinical heterogeneity of the individual patients. With the advent of molecular genetic testing, it has become apparent that there are several genetically distinct disorders classified as NBIA.

PKAN is an autosomal recessive inherited disorder caused by mutations in the pantothenate kinase 2 (PANK2) gene. PANK2 codes for the PANK2 enzyme, which phosphorylates pantothenate, the initial and rate-limiting step in coenzyme A biosynthesis. Coenzyme A has a vital role in adenosine triphosphate synthesis, and in fatty acid and neurotransmitter metabolism. Mitochondrial dysfunction is proposed to result from PANK2 mutations, leading to neurodegeneration. Abnormal PANK2 function will lead to accumulation of the neurotoxic metabolites cysteine and pantetheine (Kurian MA et al. 2011).

Although PANK2 is not directly involved in iron metabolism, its absence or abnormal function may contribute to iron accumulation in the brain, leading to neuronal death via a free-radical pathway.

Because the basal ganglia are involved in mediating the initiation of movements, an accumulation of excess labile iron within this region would be expected to result in poor motor control, as a result of iron-related ROS-mediated damage, although proof that iron causes the neurodegeneration is lacking (Hayflick SJ & Hogarth. 2011). Common physiological features include abnormal movements and posture (dystonia), muscular rigidity and sudden involuntary muscle spasms (spasticity). These features can result in clumsiness, problems with gait and posture, difficulty controlling movement, and problems with speech. Progressive generalized dystonia is a major clinical feature of PKAN and can result in life-threatening complications (Castelnau P et al. 2005). Cranial and limb dystonia crises are frequent and are part of the natural history of the disease. These crises may lead to recurrent trauma to the tongue/mouth or to bone fractures, the latter being due to a combination of dystonic overstraining and inactivity-related osteopenia (Gregory A et al. 2009). Another common feature is degeneration of the retina resulting in progressive night blindness and loss of peripheral vision. Hence, PKAN may manifest itself not only as movement disorders but as retinopathy, deterioration of cognition or hearing, or peripheral nerve changes.
Historically, PKAN has been described as either classical or atypical. The majority of PKAN cases are classical and therefore relatively homogeneous in their phenotype (Gregory A et al. 2009). Classical PKAN develops usually before 6 years of age (average age at development of symptoms is 3.5 years) (Gregory A et al. 2009; Kurian MA et al. 2011). Most patients lose the ability to walk independently 10-15 years after the beginning of symptoms. Many individuals with the classical form of PKAN require a wheelchair by their mid-teens (in some cases, earlier). Individuals with classical PKAN are also more likely to have specific eye problems. Approximately two-thirds of these patients will have retinal degeneration, resulting in tunnel vision, night blindness, and loss of peripheral vision. Loss of peripheral vision may contribute to the more frequent falls and gait disturbances in the early stages. Optic atrophy, a vision impairment caused by gradual degeneration of the nerves of the eyes, is found in 3% of patients (Kurian MA et al. 2011).

Atypical PKAN usually becomes evident after the age of ten years and progresses more slowly. The average age at which symptoms develop is 13 years. Loss of independent ambulation often occurs 15-40 years after the initial development of symptoms. In general, atypical disease is less severe and more slowly progressive than classical PKAN. It is hypothesized that classical PKAN results from complete absence of the enzyme pantothenate kinase, whereas atypical disease results from a severe deficiency, i.e., individuals retain some level of enzyme activity. Clinically, the disease manifests as rigidity, dystonia and chorea (Gregory A et al. 2009).

In the last decade, progress has been made in stratifying NBIA and PKAN according to gene mutations and phenotype. However, no genetic or other specific therapies are available for this condition (Gregory A & Hayflick. 1993; Hayflick SJ. 2010; Zorzi G et al. 2011).

1.2 Deferiprone

Deferiprone (3-hydroxy-1,2-dimethylpyridin-4-one) is a bidentate iron chelator that preferentially binds trivalent iron cations (Fe$^{3+}$) in a 3:1 (deferiprone:iron) complex. Ferriprox® is the ApoPharma oral formulation of deferiprone and is available as immediate release 500 mg or 1000 mg tablets, and as an oral solution of 100 mg/mL. The effectiveness of deferiprone in reducing body iron in transfusional iron overload has been assessed by urinary iron excretion, sequential measurements of serum ferritin levels, iron concentration in the liver and in the heart, and by clinical outcomes such as its ability in preventing iron-induced cardiac disease and prolonging survival. The results of the ApoPharma-sponsored clinical studies and of independent trials demonstrate that therapy with Ferriprox® is associated with good compliance and stabilization or decline of the body iron load.

In humans, deferiprone is rapidly absorbed from the upper part of the gastrointestinal tract after oral administration and appears in blood within 5 to 10 min. The mean time for deferiprone concentrations to peak in serum is 45 to 60 min in fasting patients and approximately 2.2 h in non-fasting patients. Less than 10% of deferiprone is bound to serum proteins. The majority of the administered dose of deferiprone is metabolized.
Deferiprone mainly undergoes Phase II metabolism through $O$-glucuronidation. *In vitro* studies suggest that UDP glucuronosyltransferase 1A6 is primarily responsible for the glucuronidation of deferiprone. The predominant deferiprone metabolite is a 3-$O$-glucuronide conjugate, which is unable to bind iron because of inactivation of the 3-hydroxy functional group. In most patients, more than 90% of deferiprone is eliminated from serum within 5 to 6 hours. The elimination half-life of deferiprone is 2 to 3 hours, with about 75% to 90% of the total deferiprone excreted in urine in the first 24 hours in the form of free deferiprone, the 3-$O$-glucuronide metabolite and iron-deferiprone complex. The pharmacokinetics of deferiprone is modified by food intake. Food decreased the rate of absorption of the parent drug, and the subsequent rate of formation of deferiprone glucuronide in healthy patients, while the overall bioavailability (AUC) remained unchanged.

The safety profile of deferiprone has been extensively characterized in patients with systemic iron overload. The most serious AE associated with deferiprone use is agranulocytosis, defined as a confirmed absolute neutrophil count less than $0.5 \times 10^9/L$.

In pooled clinical trials, the incidence of agranulocytosis was 1.7% of patients. The mechanism of deferiprone-associated agranulocytosis is unknown. Agranulocytosis usually resolves upon discontinuation of deferiprone, but there have been post-marketing reports of agranulocytosis leading to death.

The most common adverse reactions reported during clinical trials were chromaturia, nausea, vomiting, abdominal pain, alanine aminotransferase increased, arthralgia and neutropenia (ApoPharma Inc. 2009).

Deferiprone (Ferriprox®) was first approved for the treatment of iron overload in patients with thalassemia major in 1999 by the European Medicines Agency (EMA) and it is currently approved in over 60 countries. It was approved by the Food and Drug Administration (FDA) in October 2011 for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate. The recommended initial dose of deferiprone® in these patients is 25 mg/kg, orally, three times per day for a total of 75 mg/kg/day. The maximum dose is 33 mg/kg, three times per day for a total of 99 mg/kg/day.

### 1.3 Study Rationale

Deferiprone is proposed as a therapeutic method for the treatment of patients with PKAN given its unique ability to cross the blood brain barrier (Arthur AS *et al.* 1997; Roy S *et al.* 2010) and its neuroprotective effect as an iron chelator (Arthur AS *et al.* 1997; Dexter DT *et al.* 2011; Roy S *et al.* 2010).

Although iron is essential for normal physiological function, excessive amounts of iron or dysregulation of its metabolism is potentially toxic. Increased ‘free’ iron levels in tissues lead to the formation of highly reactive oxygen species, including the extremely damaging hydroxyl radical, causing localized toxicity (Poulsen HE. 2005; Singh KK. 2006).
Neurodegeneration in patients with PKAN appears to be related to the intracellular mismanagement of iron, resulting in localized brain iron accumulation, iron toxicity and eventually cell death. The regions of the brain with the highest amounts of iron accumulation include those that control motor output. Thus, motor impairment associated with PKAN are thought to be due, at least in part, to the oxidative damage/necrosis that occurs as a result of long-term localized iron-induced damage (Kakhlon O et al. 2010). In patients with Friedreich’s Ataxia, another neurodegenerative condition involving regional iron deposition in the brain, deferiprone was able to reduce localized elevated levels of brain iron, as evidenced by MRI scans (Boddaert N et al. 2007).

We therefore propose that if iron can be sequestered from brain regions with excess amounts of labile iron, prior to cell death, the clinical symptoms of PKAN could be reduced. In conditions of iron overload, the accepted therapeutic strategy for dealing with accumulation of iron is administration of iron chelators, which both increases iron excretion and prevents the toxic effects of iron excess. Although patients with PKAN do not have generalized iron overload, they have a mismanagement of intracellular iron, which results in a misdistribution of iron at the local level. One strategy for treating PKAN might be iron redistribution by “reversed siderophores”. The aim of chelation with reversed siderophores would be to bind excess labile cell iron and transfer it, directly or indirectly, to endogenous acceptors, like transferrin, for transport to other compartments inside or outside the cells (Kakhlon O et al. 2010). The oral chelator deferiprone appears to fulfill at least some of the criteria required for a reversed siderophore:

- Ability to gain access to cells (Shanzer A et al. 1991) and effectively scavenge intracellular label iron pools (Zanninelli G et al. 1997), exiting cells bound to the iron as an iron-chelate;
- Selectively bind iron in the various intracellular labile iron pools (Sohn YS et al. 2008) and thereby reduce iron-dependent free radical formation (Glickstein H et al. 2005; Glickstein H et al. 2006; Molina-Holgado F et al. 2007);
- Spare extracellular transferrin-bound iron and potentially transfer chelated iron to apotransferrin (Boddaert N et al. 2007; Breuer W et al. 2001; Evans RW et al. 1992; Sohn YS et al. 2008);
- Donate iron for metabolic reutilization (Sohn YS et al. 2008).

Deferiprone possesses the ability to readily enter cells and bind iron intracellularly. Because of its low molecular weight and favorable physicochemical properties, the drug readily crosses the blood-brain barrier in animal studies (Waldmeier PC et al. 1993) and there is indirect evidence to suggest that it does so in humans as well (Boddaert N et al. 2007). Pharmacokinetic studies have shown that deferiprone is rapidly absorbed, appearing in plasma within 5 to 10 minutes of ingestion, with a peak plasma level within 45-60 minutes. The 3:1 chelator:iron complex is excreted with the free drug and its glucuronide in urine and faeces. Because of its ability to penetrate the blood brain
barrier, enter and exit cells and allow iron to be passed to transferrin (and be subsequently used in normal endogenous processes), deferiprone could be exploited clinically for treating neurodegenerative diseases involving regional iron accumulation.

The therapeutic approach that deferiprone provides involves targeting the site of iron accumulation within the brain, and removing excess iron, providing the potential to slow or halt the debilitation that accompanies the disease.

2 OBJECTIVES

2.1 Co-Primary Objective

- To evaluate the change in severity of dystonia in patients with PKAN treated with deferiprone compared to placebo (BAD);
- To evaluate the patient’s global impression of condition’s improvement in patients treated with deferiprone for 18 months compared to placebo (PGI-I).

2.2 Secondary Objective

The secondary objective is:

- To evaluate the effect of deferiprone compared to placebo on the change in globus pallidus iron levels (MRI) (subset of patients);
- To evaluate the effect of deferiprone compared to placebo on motor symptoms (UPDRS);
- To evaluate the effect of deferiprone compared to placebo on a measure of functional independence (WeeFIM or FIM);
- To evaluate the effect of deferiprone compared to placebo on quality of life (PedsQL);
- To evaluate the effect of deferiprone compared to placebo on the patient’s quality of sleep (PSQI);
- To evaluate the pharmacokinetics of deferiprone and its 3-\textit{O}-glucuronide metabolite (subset of patients);
- To evaluate the safety and tolerability of deferiprone in patients with PKAN.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design

This is a multi-center, double-blind, randomized, placebo-controlled study in patients with PKAN. Approximately 90 patients will be enrolled and randomized with 2:1
(deferiprone:placebo) ratio. Patients will be stratified into two age groups: <6 yrs and ≥6 yrs at onset of motor symptom.

3.2 Discussion of Study Design

This study has been designed to evaluate the efficacy and safety of deferiprone in patients with PKAN. Patients will participate in a Baseline Phase followed by a Treatment Phase.

Baseline Phase:

During the Baseline Phase, patients, and when applicable their legal representatives, who sign an informed consent/assent will undergo initial screening. On the final day of the Baseline Phase, patients’ eligibility will be determined, based on inclusion/exclusion criteria, and qualified patients will enter the Treatment Phase.

Treatment Phase:

The Treatment Phase will be 18 months in duration. At the beginning of the Treatment Phase, patients will be randomized in a double-blinded fashion to receive treatment with either deferiprone or placebo twice daily (BID). The minimum interval between doses of deferiprone should be eight (8) hours. If a dose is missed the patient should receive it at the earliest opportunity, as long as it is at least eight (8) hours before the next dose. The patient should never receive more than two doses within a 24-hour period. A 24-hour period of deferiprone will be from 00:01 hours until 24:00 hours on the following night. Doses must never be doubled up. Deferiprone may be taken with or without food, but if patients experience nausea or vomiting, it may help to take deferiprone with some food. If necessary, the total daily dose of study medication will be adjusted to maintain the prescribed dose weight ratio during study visits.

Patients will initiate deferiprone at a dose of 5 mg/kg BID for the first 6 weeks. If the dose is tolerated and there are no signs of toxicity, the dose will be increased to 10 mg/kg BID for the following 6 weeks at the Investigator’s discretion. Again, if tolerated and there are no signs of drug toxicity, the dose will be increased to 15 mg/kg BID for the remainder of the study at the Investigator’s discretion. The dose may be adjusted during the study depending on tolerability, assessment of safety markers for adverse reactions that are possibly dose dependent such as gastrointestinal upset, increases in serum liver enzymes levels and arthropathies. For patients in whom a clinically significant decrease in serum ferritin is observed, iron supplements may be administered at the Investigator’s discretion.

Efficacy, safety and tolerability evaluations will occur according to the schedule of events (Appendix 20.1). The use of rescue medication should be limited to circumstances judged as absolutely necessary by the Investigator. Rescue medication is defined as the introduction of a new medication, or a change in dosing of a current medication, that is prescribed because of a worsening of the patient’s condition and that has the potential to have an effect on dystonia symptoms. Such medications may include, but are not limited to, baclofen, trihexyphenidyl, clonazepam, tizanidine, tetrabenazine, and botox. If a patient is administered rescue medications for more than
two events, the Investigator should notify the Sponsor to discuss the patient’s continued participation in the study. A list of rescue medications is provided in Appendix 20.3.

Pharmacokinetics evaluation of deferiprone and its 3-O-glucuronide metabolite will be conducted in a subset of up to 24 patients at the Month 6 visit according to the schedule of events (Appendix 20.1).

If a patient withdraws from the study, he or she will return to the clinic for an Early Termination Visit as soon as possible, but no later than 1 month following treatment discontinuation. All of the efficacy and safety evaluations will be performed at the last study visit or the Early Termination visit, whichever comes first.

3.3 Study Sites and Study Duration

The study will be conducted at five sites: four sites in Europe, and one in the United States of America.

Each patient is expected to participate in the study for approximately 20 months (from the Screening Visit to the Follow-up Visit).

4 STUDY POPULATION

4.1 Number of Patients

Ninety male and female patients with PKAN will be randomized into the study (60 patients randomized to deferiprone and 30 patients to placebo). Of the 90 patients with PKAN randomized into the study, a subset of up to 24 patients will be involved in the pharmacokinetics evaluation of deferiprone and its 3-O-glucuronide metabolite.

Patients who are considered Screen Failures might be rescreened following approbation by Sponsor. Patients who withdraw from the study after starting treatment will not be replaced.

4.2 Inclusion Criteria

Patients will be eligible for the study only if they meet all of the following criteria:

1. Males or females 4 years of age and older at screening visit;
2. Have PKAN, confirmed by genetic testing (supporting evidence required);
3. BAD total score ≥ 3 at the screening visit;
4. Patients who have Deep Brain Stimulation (DBS) systems or Baclofen pumps in place will be eligible for the study, but they must have had a stable setting for at least two months prior to the screening visit, and every effort should be made to maintain the stable setting for the duration of the study:
• Enrollment of non-DBS patients will be given priority, to maximize the proportion that can undergo imaging;

5. Informed consent/assent obtained before any study-related activities;

6. Ability and willingness to adhere to the protocol including appointments and evaluation schedule;

7. Sexually active female patients of childbearing potential must have a negative pregnancy test result at Screening Visit (if applicable; In cases where the Investigator determines there is no reasonable risk of pregnancy because of significant incapacity, pregnancy testing will not be performed). In addition, if applicable, females of childbearing potential must:
   • Use an effective method of contraception according to local requirements, OR
   • Have had a tubal ligation (supporting evidence required), OR
   • Have had a hysterectomy (supporting evidence required), OR
   • Participates in a non-heterosexual lifestyle, OR
   • Have a male sexual partner has been sterilized (supporting evidence required).

   Effective methods of contraception according to local requirements may include abstinence from sexual intercourse, or hormonal contraceptives, providing they are used with condom or diaphragm or spermicide. Diaphragm and condom may also be used, providing they are used with spermicide. The primary contraception with hormones should be highly effective with a Pearl index < 1%. Supporting evidence for sterilization consists of a surgical report or letter from the family physician;

8. If the patient is a sexually-active male, patient must confirm that he and/or his female partner will use an effective method of contraception according to local requirements for the length of the trial and for 30 days following completion of the study or early termination. Effective methods of contraception for males include condoms or sterilization or abstinence from sexual intercourse.

4.3 Exclusion Criteria

Patients will not be eligible for the study for any of the following reasons:

1. Evidence of iron deficiency defined by Fe:TIBC ratio <15%, or serum ferritin <12 ng/mL;

2. Treatment with deferiprone in the past 12 months;

3. Previous failure of treatment with deferiprone, or previous discontinuation of treatment with deferiprone due to adverse events;
4. Conditions known to contraindicate the use of deferiprone (history of agranulocytosis or recurrent episodes of neutropenia);

5. A serious, unstable chronic illness not related to PKAN during the past 3 months before screening visit including but not limited to: hepatic, renal, gastro-enterologic, respiratory, cardiovascular, endocrinologic, neurologic or immunologic disease;

6. A serious, unresolved acute illness at the screening visit including but not limited to: hepatic, renal, gastro-enterologic, respiratory, cardiovascular, endocrinologic, neurologic or immunologic disease;

7. Initiation or discontinuation of treatment with baclofen, trihexyphenidyl, clonazepam, tizanidine within 30 days prior to baseline; treatment with botox within 60 days of baseline; and initiation or discontinuation of treatment with tetrabenazine within 90 days prior to baseline;

8. Evidence of abnormal liver or renal function (serum liver enzyme level(s) > 3 times upper limit of normal at screening) or clinically significant abnormal creatinine levels at screening visit;

9. Disorders associated with neutropenia (ANC < 1.5 x 10⁹/L) or thrombocytopenia (platelet count < 50 x 10⁹/L) in the 12 months preceding the initiation of the study medication. Exception: for patients whose neutropenia was attributed by the treating physician to episodes of infection or to drugs associated with a decline in the neutrophil count and in whom the ANC has fully recovered at the screening visit;

10. History of malignancy;

11. QTcF interval > 450 msec at screening;

12. HIV positive;

13. Myocardial infarction, cardiac arrest or cardiac failure within 1 year before screening visit;

14. Bowel disease causing malabsorption;

15. History of or active drug or alcohol use or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements;

16. Treatment with an investigational drug within 30 days or 5 half-lives (whichever is longer) preceding the baseline visit;

17. Currently taking iron chelators;

18. Pregnant or nursing females, females planning to become pregnant, and females of childbearing potential who are sexually active and are unwilling, or unable, to use an acceptable method of contraception according to local requirements;
19. Males who are sexually active and are unwilling, or unable, to use an acceptable method of contraception according to local requirements;

20. History or presence of hypersensitivity or idiosyncratic reaction to deferiprone;

21. Patients and patient’s legal representative (if applicable) with a mental incapacity, unwillingness or language barriers precluding adequate understanding or cooperation;

22. Any condition that, in investigator’s opinion, would adversely affect the patient’s ability to complete the study or its assessments.

23. Baclofen pump placement less than two months prior to the screening visit;

24. Current and ongoing participation in other clinical studies.

4.4 Enrolment Violations

The criteria for enrolment must be followed explicitly. If there is inadvertent enrolment of patients who do not meet enrolment criteria, these patients should be withdrawn from the study.

4.5 Treatment Discontinuations

Patients are free to discontinue treatment at any time without discrimination from the Investigator. A patient may be withdrawn from the study at any time, at the discretion of either the Investigator or the Sponsor (or its delegate), for any of the following reasons:

- Patient request;
- Medical or safety reasons considered significant by the patient, Investigator, and/or Sponsor (or its delegate);
- Requirement for concomitant medication/therapy that is contraindicated;
- Occurrence of other illnesses that affect the patient’s further participation in the study or evaluation of study treatment;
- A protocol deviation that may interfere with study assessments as judged by the Sponsor (or its delegate);
- The patient is repetitively non-compliant with the protocol or instruction of the Investigator;
- Significant changes in QTc interval (defined as QTcF change of greater than 60 ms) are noted;
- Patient participation in other clinical studies throughout this study;
Any other situation where, in the opinion of the Investigator, continuation of the study would not be in the best interest of the patient.

A patient must be withdrawn from the study if any of the following conditions apply:

- Pregnant or planning to become pregnant (see Section 10.2 Procedures in case of Pregnancy);
- Occurrence of any adverse event characterized as life-threatening or disabling not associated with the patient’s condition;
- Non-compliance with weekly blood counts (three or more consecutively missed visits will result in automatic withdrawal);
- Termination of the study by the Sponsor;
- Patient experiences moderate neutropenia or severe neutropenia/agranulocytosis (Refer to Section 9.2.4.9 for follow-up procedures).

A patient has the right to withdraw from the study at any time and for any reason without consequence to future care by the Investigator or study center. Whenever possible, a reason for withdrawal will be obtained.

When a patient decides to withdraw participation in the study, he/she should always be contacted to determine, if possible, the reason for withdrawing from the study, any adverse events (AEs) and used any concomitant medications. All investigational product and materials should be returned. If any AEs occurred, the Investigator must attempt to follow up the outcome for 30 days post-termination.

Data collected for patients who withdraw from the study after receiving the study drug will be evaluated for efficacy and safety (if possible).

If, for any reason, the Sponsor (or its delegate) and/or Investigator decide to withdraw a patient before completing the study, the reason for withdrawal must be entered on the source document and on the Disposition page of the electronic Case Report Form (eCRF), and all other appropriate eCRF pages must be completed. A withdrawn patient should return for the Early Termination Visit and a Follow-up Visit.

After a patient is randomized, it is the Investigator’s responsibility to make a reasonable effort to correct any deviation from the protocol and to maintain the patient in the study, if no safety issues are involved.

### 4.6 Treatment Interruptions

Treatment will be interrupted for ANY of the following reasons:

- If the patient develops an infection while on study medication, therapy must be interrupted based on Investigator’s judgement and neutrophil count should be obtained and monitored more frequently if ANC <1.5 x 10^9/L.
If a patient develops a fever (defined as 38.5 ºC or greater), therapy must be interrupted immediately and a CBC and differential should be obtained. Patients should be advised to report promptly to their physician any symptoms indicative of infection such as fever, or flu-like symptoms. Patients will be provided with an emergency services card with contact information and patients will be advised to carry this card at all times. Therapy with study medication can be re-initiated once all symptoms have been resolved and it is deemed safe by the Investigator.

4.7 Pregnancy

All sexually active female participants of childbearing potential will be administered a pregnancy test prior to drug treatment (if applicable; in cases where the Investigator determines there is no reasonable risk of pregnancy because of significant incapacity, pregnancy testing will not be performed). A negative test will be required prior study entry. Patients of childbearing potential should not become pregnant during the study and therefore must agree to use an approved method of contraception (as defined in Appendix 20.2) for 30 days prior to Day 1 (at least 3 months for hormonal contraceptives), throughout the course of the trial and for 30 days following.

In the situation where a female patient is withdrawn from the study because of a pregnancy, the medication must be stopped immediately, the sponsor must be informed immediately via the pregnancy report form and the patient must be closely followed-up during her pregnancy. Update reports should be provided to the Sponsor’s Pharmacovigilance group at mid-pregnancy and at delivery or at termination of the pregnancy.

Male patients must inform investigator if their female partner becomes pregnant during the trial or within one month after trial completion.

5 TREATMENT ALLOCATION

5.1 Randomization

Study medication will be allocated to patients according to a randomization list issued by the Sponsor’s biostatisticians, using a computer random number generator. Approximately 90 patients from 5 study sites will be randomized into this study. A centralized randomization will be used for all study sites. Patients will be randomly assigned at a 2:1 ratio to take either deferiprone or placebo. A stratified randomization will be performed based on patient’s age at disease diagnostic, hereby two separate sets of randomization lists will be generated for the age group of < 6 years at motor symptom onset and the age group of ≥ 6 years at motor symptom onset. A block randomization of the multiple of size 3 will be employed so that approximately the 2:1 ratio between deferiprone and placebo can be maintained during the study.

The randomization lists will consist of randomization code and treatment code. A randomization code will consist of nine alphanumeric characters. The first six
characters will represent age group (AGE<6 or AGE≥6) and will be followed by a hyphen. The next three numeric characters will be a three-digit number that will start at 001 and increase sequentially. For example, the randomization codes “AGE<6-001” and “AGE≥6-001” will represent the first patient to be randomized from the age group of < 6 years at motor symptom onset and the age group of ≥ 6 years at motor symptom onset, respectively. Each randomization code will have a treatment code of either “DEFERIPRONE’ or “PLACEBO”.

Once the patient has met all Inclusion Criteria and no Exclusion Criteria, the site will submit a completed Patient Eligibility/Randomization Form signed by the Investigator to the Sponsor. Once the completed form is reviewed by the Sponsor, the confirmation indicating the randomization code and study medication bottle number for the patient will be sent to the site. The randomization code and the study medication bottle number will be documented in the CRF and accountability log.

5.2 Allocation of Patient Numbers

After signing of the Informed Consent/Assent Form (ICF/AF) by patients and/or patients’ legal representatives, if applicable, patients will be assigned a unique patient ID number.

A patient ID number will contain a six-digit number. The first three numbers represent the site code (00X for the X site). This number is to be used in combination with a three-digit rolling number that will be sequentially assigned by the site to patients who sign the ICF/AF. This number would start at 001 for each site. For example, if site 00X has eight patients, the patient ID number would be 00X001 to 00X008. The patient ID number would start again for site 002 at 002001. If a patient is withdrawn after receiving his or her patient ID number, the number will not be reused. For the purpose of the trial, patients will be referred to by their patient ID number.

6 STUDY PROCEDURES

6.1 Entry Procedures

An Informed Consent/Assent Form (ICF/AF) approved by a recognized IRB/IEC, and local regulatory bodies, if applicable, will be signed and dated by the patient and when applicable, the patient’s authorized legal representative prior to the patient’s participation in this study. The patient and/or legal representative, if applicable, will then be provided with a copy of the signed ICF/AF. The original ICF/AF will be kept by the Investigator. Patients and/or parent and/or legal representative who sign an ICF/AF will undergo screening procedures.

6.2 Screening Visit (Day -30 to DAY -1)

Assessment of eligibility:

The following procedures will take place at the Screening visit:
- Explain the study to the patients and/or parent/legal representative and obtain written informed consent/assent and provide a copy to the patient and/or parent/legal representative;

- Assign the patient ID number (see Section 5.2);

- Confirm genetic PKAN diagnosis (supporting evidence required) or collect blood sample for genetic confirmation of PKAN diagnosis;

- Record demographic information;

- Obtain medical history;

- Record prior and current medications for at least three months prior to screening;

- Collect blood sample for hematology, biochemistry and serology (to be conducted within 14 days prior to starting study treatment). An ANC value of > 1.5 x 10⁹/L and platelet count of > 50 x 10⁹/L will be required for start of dosing;

- Collect blood sample for pregnancy testing for all sexually active females of childbearing potential. A negative result will be required for start of dosing (if applicable; in cases where the Investigator determines there is no reasonable risk of pregnancy because of significant incapacity, pregnancy testing will not be performed);

- Collect urine for urinalysis (to be conducted within 14 days prior to starting study treatment);

- Take vital signs (including weight and height);

- Perform 12-lead ECG (to be conducted within 14 days prior to starting study treatment);

- Complete the BAD scale (to be completed by a Qualified Investigator or a qualified delegate);

- Conduct contraceptive counselling for all sexually active patients;

- Perform physical examination (to be completed by a Qualified Investigator, or qualified delegate);

- Review inclusion/exclusion criteria;

- Determine if patient has had any medical events. If so document them as specified in Section 9.2.4.3;

- Instruct the patient and/or parent/legal representative of the following:
  
  - For patients treated on a regular dosing regimen with a medication that has the potential to have an effect on dystonia prior to start of this study:
    - Medication(s) must have been initiated at least 30 days prior to baseline for baclofen, trihexyphenidyl, clonazepam, tizanidine; 60 days prior to baseline for botox; and 90 days prior to baseline for tetrabenazine. The
patient must stay on the same dose and dosing regimen up to the baseline visit.

- Remind the patient to stay on the same dose and dosing regimen for the duration of the study. Any changes should be limited to circumstances judged as absolutely necessary by the Investigator.

  o For patients treated with baclofen, trihexyphenidyl, clonazepam, tizanidine, botox, or tetrabenazine on a PRN (as needed) dosing regimen prior to the start of this study:

    - Instruct the patient to interrupt treatment as per the table below:

<table>
<thead>
<tr>
<th>Medication</th>
<th>Treatment interruption period prior to baseline visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baclofen</td>
<td>30 days</td>
</tr>
<tr>
<td>Trihexyphenidyl</td>
<td>30 days</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>30 days</td>
</tr>
<tr>
<td>Tizanidine</td>
<td>30 days</td>
</tr>
<tr>
<td>Botox</td>
<td>60 days</td>
</tr>
<tr>
<td>Tetrabenazine</td>
<td>90 days</td>
</tr>
</tbody>
</table>

  o Remind the patient that the DBS stimulation parameters or Baclofen pump settings must remain stable up to the baseline visit.

  - Schedule next study visit.

### Eligibility/Randomization:

Once the above data have been collected, it should be reviewed against the Inclusion/Exclusion Criteria to confirm the patient’s eligibility to enter the trial. If the patient is determined to be eligible, complete the Patient Eligibility/Randomization Form and submit the completed form signed by the Investigator to ApoPharma Inc.

### 6.3 Baseline Visit (Day 0)

- Verify that the dose and dosing regimen of patients treated on a regular dosing regimen with a medication that has the potential to have an effect on dystonia symptoms prior to start of this study remained stable since the screening visit (refer to Appendix 20.3 for a list of medications);
- Verify that patients treated with baclofen, trihexyphenidyl, clonazepam, tizanidine, botox, or tetrabenazine on a PRN (as needed) dosing regimen prior to the start of this study interrupted treatment according to the following table.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Treatment interruption period prior to baseline visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baclofen</td>
<td>30 days</td>
</tr>
<tr>
<td>Trihexyphenidyl</td>
<td>30 days</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>30 days</td>
</tr>
<tr>
<td>Tizanidine</td>
<td>30 days</td>
</tr>
<tr>
<td>Botox</td>
<td>60 days</td>
</tr>
<tr>
<td>Tetrabenazine</td>
<td>90 days</td>
</tr>
</tbody>
</table>

- Verify that the DBS stimulation parameters or Baclofen pump settings remained stable since the screening visit
- Take vital signs (including weight). Patient must be afebrile prior to therapy start;
- Collect urine sample for pregnancy testing for all sexually active females of childbearing potential. A negative result will be required for start of dosing (if applicable; In cases where the Investigator determines there is no reasonable risk of pregnancy because of significant incapacity, pregnancy testing will not be performed);
- Conduct contraceptive counselling for all sexually active patients;
- Determine if patient has had any medical events or used any new medications/changed medications since the screening visit. If so document them as specified in Sections 9.2.1 and 9.2.4.3;
- Complete the Likert scale;
- A Qualified Investigator or a qualified delegate must complete the following:
  - Record administration of BAD in a standardized manner on videotape and transmit tape to the evaluation center;
  - Complete UPDRS Parts I, II, III and VI;
  - Complete WeeFIM or FIM scales;
  - Complete PedsQL;
  - Complete PSQI scale;
Perform brain MRI of globus pallidus (subset of patients) and transmit to a central laboratory for interpretation (to be conducted within one month of starting study treatment; will be considered as the baseline procedure);

Perform dose calculation;

Dispense study medication as per Section 8.4;

Instruct the patient on how to take the medication;

Remind the patient that all used (empty bottles) and unused medication must be returned at Month 1.5 study visit;

Remind the patient to carefully keep track of adverse events and medication used;

Remind the patient that if treatment is stopped early, patient must return to the clinic for an Early Termination Visit as soon as possible, but no later than 1 month following treatment discontinuation;

Remind patients to interrupt therapy immediately if they develop a fever (defined as 38.5°C or greater). Patients must be advised to report promptly to the Investigator any symptoms indicative of infection such as fever, and flu-like symptoms.

Provide patient with an emergency card and advise them to carry this card at all times

For patients treated prior to start of this study on either a regular or a PRN (as needed) dosing regimen with a medication that has the potential to have an effect on dystonia symptoms (refer to Appendix 20.3 for a list of medications):

- Remind the patient to stay on the same dose and dosing regimen for the duration of the study. Any change in dose and dosing regimen should be limited to circumstances judged as absolutely necessary by the Investigator.

Remind the patient that every effort should be made to maintain the same DBS stimulation parameters or Baclofen pump settings for the duration of the study. Any changes in settings should be limited to circumstances judged as absolutely necessary by the Investigator.

Schedule next study visit.

6.4 Week 1, 2, 3, 4 and 5 Telephone Contacts

The patient and/or legal representative must be contacted by telephone weekly (every 7 ± 3 days) on Weeks 1, 2, 3, 4 and 5 to ensure the treatment is proceeding satisfactorily.

If the patient appears to be having difficulty with the treatment, patient and/or legal representative should be contacted again, as frequently as necessary.
Remind the patient/legal representative that if treatment is stopped early, patient must return to the clinic for an Early Termination Visit as soon as possible, but no later than 1 month following treatment discontinuation.

Remind patients to interrupt therapy immediately if they develop a fever (defined as 38.5 ºC or greater). Patients must be advised to report promptly to the Investigator any symptoms indicative of infection such as fever and flu-like symptoms.

All telephone contacts must be fully documented as followed:

- Date and time of contact;
- Person contacted (patients, parent, legal representative);
- Remind the patient and/or legal representative of the study medication dose and instructions on how to take medication;
- Any adverse events, serious adverse events or used any concomitant medications/therapies. If so, document them as specified in Sections 9.2.4.3, 9.2.4.8 and 9.2.1;
- Reconfirm the next study visit;
- Name and signature of the person contacting the patient.

### 6.5 Weekly Assessment

Weekly assessment can be conducted at local laboratories and/or local doctor offices.

Weekly (every 7 ± 3 days) assessment will consist of the following procedure:

- Collect blood sample for hematology.

### 6.6 Month 1.5 Visit (Week 6)

For patients living far away from study site and with conditions not allowing frequent travel, Month 1.5 visit may be conducted at patient’s local doctor office. In that case, specific information regarding this study and the procedures for that visit will be given to the patient and/or legal representative and local doctor.

Month 1.5 visit assessments will consist of the following procedures. The visit could occur between -7 to +7 days from the indicated visit day.

- Perform physical examination (to be completed by a Qualified Investigator, or qualified delegate);
- Take vital signs (including weight);
- Collect blood sample for hematology and biochemistry;
- Collect blood sample for pregnancy testing for all sexually active females of childbearing potential. A negative result will be required for study continuation (if applicable; In cases where the Investigator determines there is no reasonable
risk of pregnancy because of significant incapacity, pregnancy testing will not be performed);

- Collect urine for urinalysis;
- Determine if patient has had any adverse events, serious adverse events or used any concomitant medications/therapies. If so, document them as specified in Sections 9.2.4.3, 9.2.4.8 and 9.2.1;
- Receive and account for the medication dispensed at the previous applicable visit;
- Determine, based on the investigator’s evaluation of the patient’s tolerance to treatment, if her/his dose can be increased to 10 mg/kg BID;
- Conduct contraceptive counselling for all sexually active patients;
- Perform dose calculation;
- Dispense study medication as per Section 8.4;
- Instruct the patient on how to take the medication;
- Remind the patient that all used (empty bottles) and unused medication must be returned at Month 3 study visit;
- Remind the patient to carefully keep track of adverse events and medication used;
- Remind the patient that if treatment is stopped early, patient must return to the clinic for an Early Termination Visit as soon as possible, but no later than 1 month following treatment discontinuation;
- Remind patients to interrupt therapy immediately if they develop a fever (defined as 38.5 °C or greater). Patients must be advised to report promptly to the Investigator any symptoms indicative of infection such as fever and flu-like symptoms.
- For patients treated on either a regular or a PRN (as needed) dosing regimen with a medication that has the potential to have an effect on dystonia symptoms (refer to Appendix 20.3 for a list of medications):
  - Remind the patient to stay on the same dose and dosing regimen for the duration of the study. Any change in dose and dosing regimen should be limited to circumstances judged as absolutely necessary by the Investigator.
- Remind the patient that every effort should be made to maintain the same DBS stimulation parameters or Baclofen pump settings for the duration of the study. Any changes in settings should be limited to circumstances judged as absolutely necessary by the Investigator.
- Schedule next study visit.
6.7 Month 2 Telephone Contact (Week 8)

The patient and/or legal representative must be contacted by telephone on Week 8 to ensure the treatment is proceeding satisfactorily. This telephone contact should occur between -3 to +3 days from the indicated day.

If the patient appears to be having difficulty with the treatment, patient and/or legal representative should be contacted again, as frequently as necessary.

Remind the patient/legal representative that if treatment is stopped early, patient must return to the clinic for an Early Termination Visit as soon as possible, but no later than 1 month following treatment discontinuation.

Remind patients to interrupt therapy immediately if they develop a fever (defined as 38.5 °C or greater). Patients must be advised to report promptly to the Investigator any symptoms indicative of infection such as fever and flu-like symptoms.

All telephone contacts must be fully documented as followed:

- Date and time of contact;
- Person contacted (patients, parent, legal representative);
- Remind the patient and/or legal representative of the study medication dose and instructions on how to take medication;
- Any adverse events, serious adverse events or used any concomitant medications/therapies. If so, document them as specified in Sections 9.2.4.3, 9.2.4.8 and 9.2.1;
- Reconfirm the next study visit;
- Name and signature of the person contacting the patient.

6.8 Month 3 Visit (week 12)

For patients living far away from study site and with conditions not allowing frequent travel, Month 3 visit may be conducted at patient’s local doctor office. In that case, specific information regarding this study and the procedures for that visit will be given to the patient and/or legal representative and local doctor.

Month 3 visit assessments will consist of the following procedures. The visit could occur between -7 to +7 days from the indicated visit day.

- Perform physical examination (to be completed by a Qualified Investigator, or qualified delegate);
- Take vital signs (including weight);
- Collect blood sample for hematology and biochemistry;
- Collect blood sample for pregnancy testing for all sexually active females of childbearing potential. A negative result will be required for study continuation (if applicable; In cases where the Investigator determines there is no reasonable
risk of pregnancy because of significant incapacity, pregnancy testing will not be performed);

- Collect urine for urinalysis;

- Determine if patient has had any adverse events, serious adverse events or used any concomitant medications/therapies. If so document them as specified in Sections 9.2.4.3, 9.2.4.8 and 9.2.1;

- Receive and account for the medication dispensed at the previous applicable visit;

- Conduct contraceptive counselling for all sexually active patients;

- Determine, based on the investigator’s evaluation of the patient’s tolerance to treatment, if her/his dose can be increased to 15 mg/kg BID;

- Perform dose calculation;

- Dispense study medication as per Section 8.4;

- Instruct the patient on how to take the medication;

- Remind the patient that all used (empty bottles) and unused medication must be returned at Month 6 study visit;

- Remind the patient to carefully keep track of adverse events and medication used;

- Remind the patient that if treatment is stopped early, patient must return to the clinic for an Early Termination Visit as soon as possible, but no later than 1 month following treatment discontinuation;

- Remind patients to interrupt therapy immediately if they develop a fever (defined as 38.5 °C or greater). Patients must be advised to report promptly to the Investigator any symptoms indicative of infection such as fever and flu-like symptoms.

- Schedule next study visit;

- Remind patient participating in the pharmacokinetics evaluation that she/he must report to the site prior to dosing on Month 6 visit.

- Instruct the patient and/or parent/legal representative of the following:

  - For patients treated on a regular dosing regimen with a medication that has the potential to have an effect on dystonia symptoms (such medication may include, but is not limited to, baclofen, trihexyphenidyl, clonazepam, tizanidine, botox, and tetrabenazine):

    - Remind the patient to stay on the same dose and dosing regimen for the duration of the study. Any change in dose and dosing regimen should be limited to circumstances judged as absolutely necessary by the Investigator.
o For patients treated with baclofen, trihexyphenidyl, clonazepam, tizanidine, botox, or tetrabenazine on a PRN (as needed) dosing regimen:

- Remind the patient to make an effort to interrupt treatment as per the table below. Administration of these medications during this period should be limited to circumstances judged as absolutely necessary by the Investigator.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Treatment interruption period prior to Month 6 visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baclofen</td>
<td>30 days</td>
</tr>
<tr>
<td>Trihexyphenidyl</td>
<td>30 days</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>30 days</td>
</tr>
<tr>
<td>Tizanidine</td>
<td>30 days</td>
</tr>
<tr>
<td>Botox</td>
<td>60 days</td>
</tr>
<tr>
<td>Tetrabenazine</td>
<td>90 days</td>
</tr>
</tbody>
</table>

o Remind the patient that every effort should be made to maintain the same DBS stimulation parameters or Baclofen pump settings for the duration of the study. Any changes in settings should be limited to circumstances judged as absolutely necessary by the Investigator.

### 6.9 Month 6 and Pharmacokinetics Visit (Week 26)

**Patients participating in the pharmacokinetics evaluation must report to the site prior to dosing.** Month 6 (Week 26) visit assessments will consist of the following procedures. The visit could occur between -14 to +14 days from the indicated visit day.

For the subset of patients participating in the pharmacokinetic evaluation, please proceed with the pharmacokinetic assessments as per Section 6.9.1 below.

- Verify if any changes were made to the dose and dosing regimen of patients treated on a regular dosing regimen with a medication that has the potential to have an effect on dystonia symptoms (refer to Appendix 20.3 for a list of medications);

- Verify if patients treated with baclofen, trihexyphenidyl, clonazepam, tizanidine, botox, or tetrabenazine on a PRN (as needed) dosing regimen interrupted treatment according to the following table:

<table>
<thead>
<tr>
<th>Medication</th>
<th>Treatment interruption period prior to Month 6 visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication</td>
<td>Duration</td>
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<tr>
<td>------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Baclofen</td>
<td>30 days</td>
</tr>
<tr>
<td>Trihexyphenidyl</td>
<td>30 days</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>30 days</td>
</tr>
<tr>
<td>Tizanidine</td>
<td>30 days</td>
</tr>
<tr>
<td>Botox</td>
<td>60 days</td>
</tr>
<tr>
<td>Tetrabenazine</td>
<td>90 days</td>
</tr>
</tbody>
</table>

- Verify if any changes were made to DBS stimulation parameters or Baclofen pump settings;
- Complete the Likert scale;
- A Qualified Investigator or a qualified delegate must complete the following:
  - Perform physical examination;
  - Record administration of BAD in a standardized manner on videotape and transmit tape to the evaluation center;
  - Complete UPDRS Parts I, II, III and VI;
  - Complete WeeFIM or FIM scales;
  - Complete PedsQL;
  - Complete PSQI scale;
  - Administer PGI-I scale;
- Take vital signs (including weight);
- Collect blood sample for hematology and biochemistry;
- Collect blood sample for pregnancy testing for all sexually active females of childbearing potential. A negative result will be required for study continuation (if applicable; In cases where the Investigator determines there is no reasonable risk of pregnancy because of significant incapacity, pregnancy testing will not be performed);
- Collect urine for urinalysis;
- Determine if patient has had any adverse events, serious adverse events or used any concomitant medications/therapies. If so document them as specified in Sections 9.2.4.3, 9.2.4.8 and 9.2.1;
- Receive and account for the medication dispensed at the previous applicable visit;
- Conduct contraceptive counselling for all sexually active patients;
- Verify/adjust dose level as applicable;
• Dispense study medication as per Section 8.4;
• Instruct the patient on how to take the medication;
• Remind the patient that all used (empty bottles) and unused medication must be returned at Month 12 study visit;
• Remind the patient to carefully keep track of adverse events and medication used;
• Remind the patient that if treatment is stopped early, patient must return to the clinic for an Early Termination Visit as soon as possible, but no later than 1 month following treatment discontinuation;
• Remind patients to interrupt therapy immediately if they develop a fever (defined as 38.5 °C or greater). Patients must be advised to report promptly to the Investigator any symptoms indicative of infection such as fever and flu-like symptoms.
• Instruct the patient and/or parent/ legal representative of the following:
  o For patients treated on a regular dosing regimen with a medication that has the potential to have an effect on dystonia symptoms (such medication may include, but is not limited to baclofen, trihexyphenidyl, clonazepam, tizanidine, tetrabenazine and botox):
    - Remind the patient to make an effort to stay on the same dose and dosing regimen for the duration of the study. Any change in dose and dosing regimen should be limited to circumstances judged as absolutely necessary by the Investigator
  o For patients treated with baclofen, trihexyphenidyl, clonazepam, tizanidine, botox, or tetrabenazine on a PRN (as needed) dosing regimen:
    - Remind the patient to interrupt treatment as per the table below. Administration of these medications during this period should be limited to circumstances judged as absolutely necessary by the Investigator:

<table>
<thead>
<tr>
<th>Medication</th>
<th>Treatment interruption period prior to Month 12 visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baclofen</td>
<td>30 days</td>
</tr>
<tr>
<td>Trihexyphenidyl</td>
<td>30 days</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>30 days</td>
</tr>
<tr>
<td>Tizanidine</td>
<td>30 days</td>
</tr>
<tr>
<td>Botox</td>
<td>60 days</td>
</tr>
<tr>
<td>Tetrabenazine</td>
<td>90 days</td>
</tr>
</tbody>
</table>
Remind the patient that every effort should be made to maintain the same DBS stimulation parameters or Baclofen pump settings for the duration of the study. Any changes in settings should be limited to circumstances judged as absolutely necessary by the Investigator.

- Schedule next study visit.

### 6.9.1 Pharmacokinetics Assessment (Subset of patients)

Steady state pharmacokinetics of deferiprone and its 3-\textit{O}-glucuronide metabolite will be assessed in a subset of up to 24 patients over 12 hours. In this subset of patients please perform the following assessments:

- Collect pharmacokinetic pre-dose blood sample;
- Administer dose of study medication;
- Collect pharmacokinetic blood sample at the following time points post-dose: 1, 1.5, 2, 2.5, 3, 4, 6, 8 and 12 hours;

### 6.10 Month 9 Telephone Contact (Week 40)

The patient and/or legal representative must be contacted by telephone on Month 9 to ensure the treatment is proceeding satisfactorily. This telephone contact should occur between -7 to +7 days from the indicated day.

If the patient appears to be having difficulty with the treatment, patient and/or legal representative should be contacted again, as frequently as necessary.

Remind the patient/legal representative that if treatment is stopped early, patient must return to the clinic for an Early Termination Visit as soon as possible, but no later than 1 month following treatment discontinuation.

Remind patients to interrupt therapy immediately if they develop a fever (defined as 38.5 °C or greater). Patients must be advised to report promptly to the Investigator any symptoms indicative of infection such as fever and flu-like symptoms.

All telephone contacts must be fully documented as followed:

- Date and time of contact;
- Person contacted (patients, parent, legal representative);
- Remind the patient and/or legal representative of the study medication dose and instructions on how to take medication;
- Any adverse events, serious adverse events or used any concomitant medications/therapies. If so, document them as specified in Sections 9.2.4.3, 9.2.4.8 and 9.2.1;
- Reconfirm the next study visit;
- Name and signature of the person contacting the patient.

### 6.11 Month 12 Visit (Week 52)

Month 12 (Week 52) visit assessments will consist of the following procedures. This visit could occur between -14 to +14 days from the indicated visit day.

- Verify if any changes were made to the dose and dosing regimen of patients treated on a regular dosing regimen with a medication that has the potential to have an effect on dystonia symptoms (refer to Appendix 20.3 for a list of medications);

- Verify if patients treated with baclofen, trihexyphenidyl, clonazepam, tizanidine, botox, or tetrabenazine on a PRN (as needed) dosing regimen interrupted treatment according to the following table:

<table>
<thead>
<tr>
<th>Medication</th>
<th>Treatment interruption period prior to Month 12 visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baclofen</td>
<td>30 days</td>
</tr>
<tr>
<td>Trihexyphenidyl</td>
<td>30 days</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>30 days</td>
</tr>
<tr>
<td>Tizanidine</td>
<td>30 days</td>
</tr>
<tr>
<td>Botox</td>
<td>60 days</td>
</tr>
<tr>
<td>Tetrabenazine</td>
<td>90 days</td>
</tr>
</tbody>
</table>

- Verify if any changes were made to DBS stimulation parameters or Baclofen pump settings;

- Complete the Likert scale;

- A Qualified Investigator or a qualified delegate must complete the following:
  - Perform physical examination;
  - Record administration of BAD in a standardized manner on videotape and transmit tape to the evaluation center;
  - Complete UPDRS Parts I, II, III and VI;
  - Complete WeeFIM or FIM scales;
  - Complete PedsQL;
  - Complete PSQI scale;
  - Administer PGI-I scale;
- Take vital signs (including weight and height);
- Collect blood sample for hematology and biochemistry;
- Collect blood sample for pregnancy testing for all sexually active females of childbearing potential. A negative result will be required for study continuation (if applicable; In cases where the Investigator determines there is no reasonable risk of pregnancy because of significant incapacity, pregnancy testing will not be performed);
- Collect urine for urinalysis;
- Determine if patient has had any adverse events, serious adverse events or used any concomitant medications/therapies. If so document them as specified in Sections 9.2.4.3, 9.2.4.8 and 9.2.1;
- Receive and account for the medication dispensed at the previous applicable visit;
- Conduct contraceptive counselling for all sexually active patients;
- Verify/adjust dose level as applicable;
- Dispense study medication as per Section 8.4;
- Instruct the patient on how to take the medication;
- Remind the patient that all used (empty bottles) and unused medication must be returned at Month 18 study visit;
- Remind the patient to carefully keep track of adverse events and medication used;
- Remind the patient that if treatment is stopped early, patient must return to the clinic for an Early Termination Visit as soon as possible, but no later than 1 month following treatment discontinuation;
- Remind patients to interrupt therapy immediately if they develop a fever (defined as 38.5 °C or greater). Patients must be advised to report promptly to the Investigator any symptoms indicative of infection such as fever and flu-like symptoms.
- Instruct the patient and/or parent/ legal representative of the following:
  - For patients on a regular dosing regimen with a medication that has the potential to affect dystonia symptoms (such medication may include, but is not limited to baclofen, trihexyphenidyl, clonazepam, tizanidine, tetrabenazine and botox):
    - Remind the patient to stay on the same dose and dosing regimen for the duration of the study. Any change in dose and dosing regimen should be limited to circumstances judged as absolutely necessary by the Investigator.
  - For patients treated with baclofen, trihexyphenidyl, clonazepam, tizanidine, botox, or tetrabenazine on a PRN (as needed) dosing regimen:
- Remind the patient to make an effort to interrupt treatment as per the table below. Administration of these medications during this period should be limited to circumstances judged as absolutely necessary by the Investigator:

<table>
<thead>
<tr>
<th>Medication</th>
<th>Treatment interruption period prior to Month 18 visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baclofen</td>
<td>30 days</td>
</tr>
<tr>
<td>Trihexyphenidyl</td>
<td>30 days</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>30 days</td>
</tr>
<tr>
<td>Tizanidine</td>
<td>30 days</td>
</tr>
<tr>
<td>Botox</td>
<td>60 days</td>
</tr>
<tr>
<td>Tetrabenazine</td>
<td>90 days</td>
</tr>
</tbody>
</table>

- Remind the patient that every effort should be made to maintain the same DBS stimulation parameters or Baclofen pump settings for the duration of the study. Any changes in settings should be limited to circumstances judged as absolutely necessary by the Investigator.

- Schedule next study visit.

### 6.12 Month 15 Telephone Contact (Week 64)

The patient and/or legal representative must be contacted by telephone on Month 15 (week 64) to ensure the treatment is proceeding satisfactorily. This telephone contact should occur between -7 to +7 days from the indicated day.

If the patient appears to be having difficulty with the treatment, patient and/or legal representative should be contacted again, as frequently as necessary.

Remind the patient/legal representative that if treatment is stopped early, patient must return to the clinic for an Early Termination Visit as soon as possible, but no later than 1 month following treatment discontinuation.

Remind patients to interrupt therapy immediately if they develop a fever (defined as 38.5 °C or greater). Patients must be advised to report promptly to the Investigator any symptoms indicative of infection such as fever and flu-like symptoms.

All telephone contacts must be fully documented as followed:

- Date and time of contact;
- Person contacted (patients, parent, legal representative);
Remind the patient and/or legal representative of the study medication dose and instructions on how to take medication;

Any adverse events, serious adverse events or used any concomitant medications/therapies. If so, document them as specified in Sections 9.2.4.3, 9.2.4.8 and 9.2.1;

Reconfirm the next study visit;

Name and signature of the person contacting the patient.

6.13 Month 18 (Week 78) or Early Termination Visit (End of Study Assessment)

The End of Study assessment (at Week 78 ± 14 days from the start of treatment) or Early Termination will consist of the following procedures:

- Verify if any changes were made to the dose or dosing regimen of patients treated on a regular dosing regimen with a medication that has the potential to have an effect on dystonia symptoms (refer to Appendix 20.3 for a list of medications);

- Verify if patients treated with baclofen, trihexyphenidyl, clonazepam, tizanidine, botox, or tetrabenazine on a PRN (as needed) dosing regimen interrupted treatment according to the following table:

<table>
<thead>
<tr>
<th>Medication</th>
<th>Treatment interruption period prior to Month 18 visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baclofen</td>
<td>30 days</td>
</tr>
<tr>
<td>Trihexyphenidyl</td>
<td>30 days</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>30 days</td>
</tr>
<tr>
<td>Tizanidine</td>
<td>30 days</td>
</tr>
<tr>
<td>Botox</td>
<td>60 days</td>
</tr>
<tr>
<td>Tetrabenazine</td>
<td>90 days</td>
</tr>
</tbody>
</table>

- Verify if any changes were made to DBS stimulation parameters or Baclofen pump settings;

- Complete the Likert scale;

- A Qualified Investigator or a qualified delegate must complete the following:
  - Perform physical examination;
  - Record administration of BAD in a standardized manner on videotape and transmit tape to the evaluation center;
o Complete UPDRS Parts I, II, III and VI;
o Complete WeeFIM or FIM scales;
o Complete PedsQL;
o Complete PSQI scale;
o Administer PGI-I scale;

• Take vital signs (including weight and height);
• Perform 12-lead ECG;
• Review medical history and concurrent medications;
• Collect blood sample for hematology and biochemistry;
• Collect blood sample for pregnancy testing for all sexually active females of childbearing potential (if applicable; In cases where the Investigator determines there is no reasonable risk of pregnancy because of significant incapacity, pregnancy testing will not be performed);
• Collect urine for urinalysis;
• Conduct contraceptive counselling for all sexually active patients;
• Determine if patient has had any adverse events, serious adverse events or used any concomitant medications/therapies. If so document them as specified in Sections 9.2.4.3, 9.2.4.8 and 9.2.1;
• Perform brain MRI of globus pallidus (subset of patients) and transmit to a central laboratory for interpretation;
• Receive and account for the medication dispensed at the previous applicable visit;
• Explain to the patient that she or he should inform the site if the she/he experience any serious medical problems (SAEs) in the 30 days following the last dose;
• Schedule follow-up study visit, as applicable.

Any ongoing AEs and/or SAEs should be followed until one of the following:
o Resolution OR
o Condition stabilizes OR
o Event is otherwise explained OR
o Lost to Follow-up.
6.14 Premature Discontinuation (Early Termination)

Patients can be withdrawn from the study at any time. Reasons for withdrawal will be documented in the eCRF and early termination visit procedures should be performed within 1 month of treatment discontinuation.

These data should be recorded and entered in the study database, as they comprise essential evaluations that should be done prior to discharging any patient from the study.

6.15 Follow-Up Visit

A follow-up visit will occur 4 weeks following Month 18 or Early Termination Visit. This visit will be conducted only in patients not enrolled in maintenance protocol or compassionate use program (if applicable). The following assessments will be performed:

- Review prior and current concomitant medications/therapies;
- Perform physical examination;
- Collect blood sample for hematology;
- Take vital signs, including weight;
- Collect AEs that have occurred within 14 days after treatment discontinuation;
- Determine if patient has had any serious adverse events in the 30 days following the last dose. If so document them as specified in Section 9.2.4.8.

7 TREATMENT

7.1 Study Medication

The treatment phase of the study will last for 18 months, beginning on the day of the first dose of the study medication. Dispense the study medication as per Section 8.4.

Eligible patients will receive deferiprone oral solution 80 mg/ml (ApoPharma Toronto, Ontario, Canada) or the matching placebo oral solution.

Patients are to be administered deferiprone or placebo in a double-blinded fashion twice daily (BID). The minimum interval between doses of deferiprone should be eight (8) hours. If a dose is missed the patient should receive it at the earliest opportunity, as long as it is at least eight (8) hours before the next dose. The patient should never receive more than two doses within a 24-hour period. A 24-hour period of deferiprone will be from 00:01 hours until 24:00 hours on the following night. Doses must never be doubled up. Deferiprone may be taken with or without food, but if patients experience nausea or vomiting, it may help to take Deferiprone with some food. If necessary, the total daily dose of study medication will be adjusted to maintain the prescribed dose weight ratio during study visits.
Patients will initiate deferiprone at a dose of 5 mg/kg BID for the first 6 weeks. If the dose is tolerated and there are no signs of toxicity, the dose will be increased to 10 mg/kg BID for the following 6 weeks. Again, if tolerated and there are no signs of drug toxicity, the dose will be increased to 15 mg/kg BID for the remainder of the study. The dose may be adjusted during the study depending on tolerability, assessment of safety markers for adverse reactions that are possibly dose dependent such as gastrointestinal upset, increases in serum liver enzymes levels and arthropathies. For patients in whom a clinically significant decrease in serum ferritin is observed, iron supplements may be administered at the Investigator’s discretion.

As per Section 4.6.5 and 4.6.6 of the ICH Consolidated Guideline on GCP, the investigator is responsible to ensure that the investigational products are used only in accordance with the approved protocol; that the correct use of the medication has been clearly explained by the investigator or delegate to each patient and that the patient continues to take the medication according to those instructions throughout the trial.

If the preliminary evidence indicates deferiprone is safe and effective in patients with PKAN, a compassionate use of deferiprone may be offered to patients (irrespective of whether they were in the deferiprone or in the placebo arm) until approval of deferiprone for use in patients with PKAN, or until termination of development of deferiprone for PKAN.

### 7.2 Rationale for Selection of Doses

Two published studies, evaluating the safety and efficacy of the use of deferiprone in PKAN patients, were used to establish the selection of doses used in this study.

The first study was a 12-month, multi-center, unblinded, single-arm pilot study that was conducted to evaluate the safety and efficacy of deferiprone for reducing cerebral iron accumulation in patients with a clinical diagnosis of NBIA (Abbruzzese G et al. 2011). Four patients with genetically-confirmed PKAN, and two with parkinsonism and focal dystonia (specific condition unidentified due to inconclusive genetic tests) received 15 mg/kg deferiprone twice a day. Magnetic resonance imaging and neurological examinations were conducted at baseline, 6 and 12 months.

Chelation treatment caused no apparent hematologic or neurologic side effects. Magnetic resonance imaging quantitative iron assessment on three patients (due to the presence of signal interferences from metallic oral devices in other patients) revealed decreased iron accumulation in the globus pallidus of the three patients. Clinical rating scales (UPDRS/III, UDRS and ICARS) and blinded video rating evaluations documented mild-to-moderate motor improvement in three patients.

These results suggest that chelating treatment might be effective in improving neurologic manifestations associated with iron accumulation.

The second study was a 6-month pilot study conducted to evaluate the safety and efficacy of deferiprone in 10 patients affected by PKAN (Zorzi G et al. 2011).
Patients received deferiprone 25 mg/kg/day orally in two divided doses (12.5 mg/kg twice a day) for 6 months.

Deferiprone was well tolerated overall, and associated with a significant median reduction in globus pallidus iron content, as assessed by magnetic resonance imaging. There was no change in the scores, using the Burke-Fahn and Marsden Dystonia Rating scales. However, the authors concluded that future trials with a longer treatment period are warranted.

In addition to the published literature cases and studies on patients with PKAN, two case reports demonstrating the effect of deferiprone in patients with PKAN were made available through the Company’s compassionate use program. Both PKAN cases were patients of Dr. Elliott Vichinsky from the Children’s Hospital and Research Center in Oakland, United States.

The first case was a young, third-grade (8-year-old) patient diagnosed with PKAN. In March 2006, he underwent placement of bilateral DBS in hopes of reducing symptoms of dystonia. He continued to deteriorate.

Deferiprone was obtained in November 2007 under a treatment Investigational New Drug (IND). Deferiprone therapy was initiated at 20 mg/kg/day and gradually increased to 30 mg/kg/day. At that time, he was wheelchair-dependent with major dystonic movements and had difficulty speaking.

During the 15 months of treatment with weekly laboratory testing, he demonstrated no significant laboratory abnormalities. Significant clinical improvement was noted.

The second case was a 12-year-old patient with PKAN who began deferiprone treatment for severe progressive dystonia and spastic cerebral palsy with opisthotonic posturing. He was unable to sit in a wheelchair and could only be accommodated in a wagon. He was also legally blind secondary to retinitis pigmentosa and unable to speak. Prior to age 10, the child had no physical limitations. At age 10 he had a rapid clinical deterioration, despite interventions including DBS and intrathecal baclofen.

Since September 2009 the patient has been maintained on deferiprone at dose of 28 mg/kg/day (14 mg/kg BID). There has been a dramatic progressive improvement in the patient’s condition that has resulted in national attention by the media and the NBIA Disorders Association. In January 2010, he was able to sit in a wheelchair with improved head control and muscle strength. He was able to purposefully move his arms above his head and relax his hands. Fine motor skills improved; with his index finger he could activate his wheelchair. His range of motion and activities of daily life improved. For the first time, he sustained oral rather than nasogastric feeding. His pain scale ratings using a Face, Legs, Arm, Cry, Consolability Scale (FLACC) were significantly lower. In April 2010, he was talking in phrases of 2 to 5 words long. His neck spasms significantly decreased. In the last year, the patient has continued to make progress and is undergoing surgical correction of his contracture with the goal of ambulation outside of a wheelchair. He continues to show no toxicity from deferiprone therapy.
An additional PKAN case treated with deferiprone was reported in Italy (Zuccarelli A et al. 2008). The patient was diagnosed with PKAN in June 2005, when she was 8 years old. Clinical situation did not improve but got progressively worse after the patient started taking pantothenic acid, idebenone and baclofen. The patient started therapy with deferiprone in December 2007, at 25 mg/kg in a single morning dose. The patient tolerated the therapy well and clinical conditions improved. There was improvement in the muscle tone of her limbs, a reduction in the excursion of the tibiotarsal joints and the patient has also started to eat autonomously, say a few words and take a few steps without support.

The proposed starting dose for this study is 5 mg/kg BID; lower than the doses described in literature that have been well tolerated by PKAN patients. Patients’ dose will be increased (to a maximum of 15 mg/kg BID) only after safety and tolerability have been demonstrated at this low dose.

### 7.3 Concomitant Therapy

Medications considered necessary for the patient’s welfare may be given at the discretion of the Investigator. The administration of all medication (including study product) must be recorded in the source document and the appropriate sections of the eCRF. During treatment with deferiprone oral solution, patients must not receive any other investigational product or any drugs that are known to cause neutropenia or agranulocytosis. See Appendix 20.4 for list of prohibited drugs.

### 7.4 Rescue Medication

The use of rescue medication should be limited to circumstances judged as absolutely necessary by the Investigator. Rescue medication is defined as the introduction of a new medication, or a change in dosing of a current medication, that is prescribed because of a worsening of the patient’s condition and that has the potential to have an effect on dystonia symptoms. Such medication may include, but are not limited to, baclofen, trihexyphenidyl, clonazepam, tizanidine, tetrabenazine and botox. If a patient is administered rescue medications for more than two events, the Investigator should notify the Sponsor to discuss the patient’s continued participation in the study. A list of rescue medications is provided in Appendix 20.3.

### 7.5 Treatment Compliance

Patients will be instructed on how to take the study medication. Compliance will be evaluated by calculating the volume of medication dispensed and the volume of unused drug supply remaining in the bottle. The investigator should discuss compliance with the patient and, if applicable, his/her parent or legal representative at each visit.
8 MATERIALS AND SUPPLIES

8.1 Study Medication

Deferiprone oral solution, 80 mg/mL and the matching placebo oral solution will be manufactured and distributed by Apotex Inc., Richmond Hill, Ontario, Canada and will have been tested and released according to relevant standards and regulations.

All study medication will be supplied to study sites by the Sponsor.

8.2 Packaging and Labelling

All study medication will be supplied in 500 mL round amber PET bottles with white polypropylene child-resistant pictorial caps and with syringes for dosing.

The contents of the label will be in accordance with all applicable regulatory requirements. The label will include protocol number, expiry date, lot/batch number, investigational statement, storage temperature, study medication bottle number, dosage and name and address of the Sponsor.

8.3 Storage and Disposition of Study Medications

A “Product Receipt Form and Temperature Verification log”, will be provided by the Sponsor with each shipment of investigational product to each study site. The Investigator or designate will sign and date this receipt to acknowledge receiving the product and add the time the “TempTale 4” (Sensitech Inc.) monitoring device was removed and stopped. The Investigator will fax a copy of this receipt form to the Sponsor and retain the original in their Master File.

After receipt of a supply of the study medication(s) by the Investigator or designate, the study medication will be stored in a locked room/cabinet at each site. The supply of study medication will be kept at room temperature (15-30ºC) in a secure location under the control of the Investigator. The clinical centres will use a digital temperature monitoring device and a temperature log to facilitate daily recording of the temperature of the study medication storage facility.

8.4 Drug Dispensing Procedures

Patients will be dispensed study medication at baseline, and Months 1.5, 3, 6 and 12 visits. Dispensing of study medication should be done by appropriately qualified staff (i.e. Physician, Pharmacist, Nurse).

Patients reporting that their medication has been lost or misplaced will be asked to attend the study site to receive replacement medication. This visit will be an Unscheduled Visit and details of this visit will be recorded in the eCRF. Requests for replacement must be made in writing to the Clinical Research Associate (CRA), who will review and forward the request for replacement drug to the Sponsor, who will ensure that the site is supplied with appropriate treatment. All information related to
lost/misplaced medication and the replacement medication will be recorded in the drug accountability forms.

8.5 Study Medications Accountability and Inventory Control

A “Site Investigational Drug Inventory Record” and “Patient Investigational Drug Dispensing Record” form will be provided by the Sponsor to the Investigator.

Investigational product accountability lies with the Investigator at all times. The Investigator must maintain an updated Site Investigational Drug Inventory Record at the study site. This log will include:

- Name of Sponsor
- Name of Investigator
- Study identifier
- Date and quantity of investigational product received from the Sponsor
- Lot/Batch number
- Study medication bottle number

For each patient, the Investigator must maintain an updated Patient Investigational Drug Dispensing Record. This log will include:

- Patient identification number
- Date of dispensing and return
- Dispenser’s initials
- Quantity dispensed and returned
- Study medication bottle number

Patients will be instructed on the administration of the investigational product.

At the conclusion of the study, a final inventory must be performed by the investigator (or delegate). If any bottles or quantity of medication in a bottle are missing, this must be indicated on the study drug accountability form, together with an explanation of the discrepancy. These forms must be available for clinical monitoring as well as for audit and regulatory authority inspection purposes at any time.

All investigational products that have been returned by the patient or that are unused for any other reasons will be returned to the Sponsor or discarded at the pharmacy according to their internal procedures which must include the issuance of appropriate signed destruction certificates including mode of destruction and complete drug accountability of destroyed materials.
9 MEASUREMENTS AND EVALUATIONS

The following efficacy and safety measurements/evaluations will be performed at visits outlined in Appendix 20.1 – Schedule of Events.

9.1 Efficacy

9.1.1 Barry-Albright Dystonia Scale

Dystonia is defined as sustained muscle contractions causing twisting and repetitive movements or abnormal postures. The Barry-Albright Dystonia (BAD) scale is a reliable and responsive rating scale for dystonia that interferes with function. It consists of a five-point ordinal scale for secondary dystonia, which rates severity of dystonia in eight body regions; eyes, mouth, neck, trunk, each upper and each lower extremity (Barry MJ et al. 1999). The individual scores will be summed to provide a total score. The BAD total score ranges from 0 to 32 and the larger the score is, the more severe the patient’s dystonia is (Appendix 20.5.1).

The BAD scale will be administered at screening, baseline, Months 6, 12 and 18 (or early termination visit) study visits.

An Operations Manual will be prepared by a selected group of experts to define a standardized way to administer and read the BAD test. The standardized administration will include a provocation test to better capture episodic or non-continuous symptoms. The BAD scale will be completed at screening by a qualified Investigator or a qualified delegate. At the baseline, Months 6, 12 and 18 (or early termination visit) study visits, a qualified Investigator will administer and video-record the administration of the BAD test and transmit the videotape to a designated center of experts for objective evaluation. Results will be entered by the study site staff in the eCRF.

9.1.2 Patient’s Global Impression of Improvement

The Patient Global Impression of Improvement (PGI-I) is a global index used to rate the response of a condition to a therapy. Patient will be asked at Month 6, 12 and 18 (or early termination visit) study visits to rate their total improvement since the beginning of the study. A 7 point rating scale will be used as: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; or 7, very much worse (Appendix 20.5.2). In cases where the patient cannot complete the scale by him/herself, the parent or legal representative will complete the scale.

Results will be entered by the study site staff in the eCRF.

9.1.3 Globus Pallidus MRI

Neurodegeneration in patients with PKAN appears to be related to the intracellular mismanagement of iron, resulting in localized brain iron accumulation, iron toxicity and
eventually cell death. The regions of the brain with the highest amounts of iron accumulation include those that control motor output; specifically, the globus pallidus.

An MRI scan will be performed at baseline and Month 18 (or early termination visit) study visits in a subset of patients without deep brain stimulators for whom the use of anesthesia (if required for the MRI scan) is deemed acceptable based on Investigator’s judgement. MRI of the globus pallidus will be transferred to the Newcastle Magnetic Resonance Centre at the University of Newcastle and assessed by staff blinded to study treatment. R2* will be measured directly from the R2* map which will be calculated from the multiGE sequence. Results will be entered by the study site staff in the eCRF.

### 9.1.4 UPDRS

The Unified Parkinson’s Disease Rating Scale (UPDRS) has long been the major rating scale that is used to assess severity of symptoms of Parkinson’s disease. The original version of the scale assessed daily activities, motor skills and mental capacity (including behavior and mood). An updated version of the scale was recently developed. The updated version adds new assessments of non-motor symptoms. The UPDRS scale is made up of the following sections: Part I: Mentation, Behaviour and Mood; Part II: Activities of Daily Living; Part III: Motor Examination; Part IV: Complications of Therapy; Part V: Modified Hoehn and Yahr staging; and Part VI: Schwab and England Activities of Daily Living Scale (Appendix 20.5.3).

The Investigator or qualified delegate will complete Parts I, II, III and VI at baseline, Months 6, 12 and 18 (or early termination visit) study visits. Results will be entered by the study site staff in the eCRF.

### 9.1.5 WeeFIM scale (or FIM score for patients > 18 years)

The Functional Independence Measure (FIM) (Appendix 20.5.4) or pediatric version (WeeFIM) (Appendix 20.5.5) scale assesses physical and cognitive disability in four areas (self care, mobility, communication and social cognition). Items are scored on the level of assistance required for an individual to perform activities of daily living; a score of 1-2 indicates that the patient is completely dependent on a helper to perform the tasks, a score of 3-5 indicates that the patient is moderately dependent on a helper to perform the tasks and a score of 6-7 indicates that no help is required to perform the tasks. Scores from each of the four areas are added to obtain the global FIM score.

The Investigator or qualified delegate will complete the WeeFIM or FIM scales at baseline, Months 6, 12 and 18 (or early termination visit) study visits. Results will be entered by the study site staff in the eCRF.

### 9.1.6 Peds QL
The Pediatric Quality of Life (Peds QL) is a questionnaire used to measure functional health and well-being from the patient's point of view. Versions of the Peds QL questionnaire exist for children, young adults (18-25 yrs) and for adults (>25 yrs). Patients are asked to complete the survey based on how they have felt over the past 4 weeks (1 month). Twenty-three questions are used to generate an overall score (Appendix 20.5.6).

The Peds QL will be completed by the patient or legal representative at baseline, Months 6, 12 and 18 (or early termination visit) study visits. Results will be entered by the study site staff in the eCRF.

**9.1.7 Pittsburgh Sleep Quality Index PSQI**

The Pittsburgh Sleep Quality Index (PSQI) is a self-rated questionnaire which assesses sleep quality and disturbances over a 1-month time interval. Nineteen individual items generate seven “component” scores: Subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction (Appendix 20.5.7).

The PSQI will be completed by the patient or legal representative at baseline, Months 6, 12 and 18 (or early termination visit) study visits. Results will be entered by the study site staff in the eCRF.

**9.1.8 Likert Scale**

The Likert scale is a psychometric scale used in this study to rate the patient’s state with regards to its PKAN symptoms on a specific day. Patients will be asked at Baseline, Month 6, 12 and 18 (or early termination visit) study visits how they would rate their day with regards to their PKAN symptoms on that day. A 5 point rating scale will be used as: 1, very good; 2, good; 3, neutral; 4, bad; 5, very bad (Appendix 20.5.8). In cases where the patient cannot complete the scale by him/herself, the parent or legal representative will complete the scale.

Results will be entered by the study site staff in the eCRF.

Notable improvements or worsening in patient’s condition, which are not captured by the relevant scales will be documented.

**9.2 Safety**

The Investigator is responsible for monitoring the safety of patients who have entered the study. Safety and tolerability of deferiprone oral solution will be assessed during
the study by physical examinations, clinical laboratory tests and spontaneous reporting of symptoms by patients, nursing and physicians’ observations.

9.2.1 Medical History, Physical Examination, Vital Signs and Prior and Concomitant Medication/Therapy Use

- Medical history will be performed at screening and reviewed at Month18 (or early termination visit) study visits. History of PKAN symptoms, including dystonia, will be collected for the two years prior to the screening visit. Only improvements of certain conditions will be captured at Month 18, as any worsening/new occurrences will be captured as AEs.

- Physical examination will consist of an exam of the head, ears, eyes, nose, throat and neck, the respiratory system, cardiovascular system, gastrointestinal system, musculoskeletal system, central and peripheral system, skin, thyroid and general constitution. Physical examination will be performed at screening, baseline, Month 1.5, 3, 6, 12 and 18 (or early termination visit) study visits. Any abnormalities noted at the screening and baseline visits will be recorded as medical history while any abnormalities noted during treatment will be recorded as adverse events.

- Vital signs (temperature, and resting heart rate, respiration rate and blood pressure) and weight will be taken at screening and each study visit. Height will be measured only at screening, Month 12 and 18 (or early termination) study visits.

- Information about prior or concomitant medications/therapies will be collected at each study visit following start of dosing with deferiprone. The following must be recorded in the Source Documents and eCRFs:
  - All medications used within 3 months prior to the screening visit;
  - All medications and therapies taken for dystonia symptoms, including DBS, within two years prior to the screening visit and during the study
    - Frequency of change and reason for change in dosage and settings must also be documented
  - Any medications that the patient continues to take during the trial;
  - Any medications which the patient starts to take during the trial.
  - The name, dose, route, frequency, indication, and start and stop dates of all medications used during the trial must be noted in the Source Documents and eCRFs as well as whether or not the medication was used to treat a medical event/adverse event.
9.2.2 Clinical Laboratory Tests

Lab reports must be reviewed and interpreted by the investigator. Any clinically relevant changes which are not part of a larger medical condition which is already recorded as an adverse event, and which occur during the trial must be recorded on the source documents and the Adverse Events section of the eCRF.

The following clinical laboratory tests will be performed:

Hematology:
Hematology assessments (full blood test including total WBC, ANC, platelet count and haemoglobin) will be performed at screening, baseline and weekly after the start of dosing.

Biochemistry:
Biochemistry assessments will be performed at the screening and Month 1.5, 3, 6, 12 and 18 (or early termination) study visits. Biochemistry evaluation will consist of serum ferritin; total protein; GGT; LDH; sodium, potassium, chloride, glucose; total, direct and indirect bilirubin; AST; ALT; albumin; blood urea nitrogen; calcium; creatinine; uric acid; alkaline phosphatase; and amylase.

Serology:
Serology assessments will be performed at screening visit. Serology evaluation will consist of HIV testing.

Urinalysis:
Urinalysis assessments will be performed at screening and Month 1.5, 3, 6, 12 and 18 (or early termination) study visits. Urinalysis evaluation will consist of pH, specific gravity, glucose, protein, ketones, blood by urine dipstick. If indicated by the dipstick, sediment microscopy will be performed.

Pregnancy Test:
Serum pregnancy tests will be performed at screening and Month 1.5, 3, 6, 12 and 18 (or early termination) study visits for all sexually active females of childbearing potential (if applicable)*. Urine pregnancy test will be performed at the baseline visit for all sexually active females of childbearing potential (if applicable)*.

* In cases where the Investigator determines there is no reasonable risk of pregnancy because of significant incapacity, pregnancy testing will not be performed

9.2.3 ECG

A standard 12-lead ECG shall be performed at screening and Month 18 (or early termination) study visits. At a minimum, the following parameters will be assessed: HR, PR, QRS, QT, QTcF, QTcB. 12-Lead ECG will be interpreted by local cardiologists. The overall interpretation will also be documented.
9.2.4 Adverse/Medical Events and Serious Adverse Events

All adverse/medical events encountered during the study will be reported on the source documents and the eCRF and carefully monitored and assessed in terms of their seriousness, severity, and relationship to the study or study drug. Adverse/medical events will be followed until the event is resolved or explained or the patient is lost to follow up. It is the responsibility of the Investigator to ensure that adequate medical care is provided to patients during the study. All SAEs occurring within 30 days following the completion/discontinuation of the study must be reported to the Sponsor regardless of the suspected drug/event causal relationship. SAEs for which the Investigator suspects causal relationship to the study drug must be reported to the Sponsor irrespective of the time elapsed since the last dose of the study drug.

9.2.4.1 Definition of Medical/Adverse Events

Medical Event: Any new untoward medical occurrence or worsening of a pre-existing condition in a patient that occurs after signing the ICF, but before receiving an investigational product.

Adverse Event: An AE is any untoward medical occurrence in a clinical investigation in a patient administered a pharmaceutical or other therapeutic product, not necessarily having a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign, symptom or disease temporally associated with the use of a product, whether or not considered related to that product.

An AE does include:
- exacerbation of a pre-existing illness
- an increase in frequency or intensity of a pre-existing episodic event or condition
- a condition detected or diagnosed after study treatment administration, even though it may have been present prior to the start of the study
- a continuous persistent disease or symptom present at baseline that worsens following the start of the study

An AE does not include:
- a pre-existing disease or condition present or detected at the start of the study that does not worsen
- the disease or disorder being studied, or a sign or symptom associated with the disease or disorder, unless it has worsened
- an overdose of either the study treatment or concurrent medication without any signs of symptoms

9.2.4.2 Adverse/Medical Event Considerations

Note that the definition of AEs/MEs could include accidents (e.g., motor vehicle accidents) and the reasons for changes in concomitant medication (drug and/or dose),
medical, nursing and/or pharmacy consultation, admission to hospital and surgical operations, and the worsening of a pre-existing medical condition.

Planned hospital admissions and/or surgical operations/procedures for an illness or disease that existed before the investigational product was given or the patient was enrolled in a clinical trial are not to be considered AEs/MEs, unless a worsening of the illness or disease lead to an earlier hospitalization.

If a patient’s dosage is reduced or treatment is discontinued as a result of an AE, study site personnel must clearly document the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

Prior to enrolment, study site personnel will note the occurrence and nature of each patient’s medical condition(s) in the source documents and the appropriate section of the eCRF. During the study, site personnel will again note any change in the condition(s) and the occurrence and nature of any AEs/MEs.

Laboratory results will be recorded in a central database. Nonetheless abnormal laboratory findings (e.g., clinical chemistry, hematology, urinalysis), ECG abnormalities or other abnormal assessments (e.g. vital signs) which are not part of a larger medical condition which is already recorded as an adverse event and which are judged by the investigator to be clinically significant must be recorded as AEs or SAEs if they meet the definition of an AE as defined in Section 9.2.4.1 or SAE as defined in Section 9.2.4.6. The investigator should exercise his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

9.2.4.3 Procedures for Adverse/Medical Event Monitoring and Recording

MEs will be collected from the time the ICF is signed and AEs will be collected from the time the treatment starts.

Patients will be instructed to report AEs/MEs to the Investigator. Reports of adverse events will be elicited using a verbal probe and recorded in the source documentation and on the Adverse Event page of the Case Report Form. The investigator or delegate should always ask the same open-ended and non-leading verbal questioning of the patient should be used to inquire about AE/ME occurrence. Appropriate questions include:

“How are you feeling?” or “How do you feel?” or for pediatric studies, “How does your child seem to feel?”

“Have you had any (other) medical problems since your last visit/assessment?” or “Have you felt any different in any way since starting the new medication/treatment or since your last visit/assessment?” or for pediatric studies, “Has your child had any (other) medical problem or seemed to act differently in any way since his/her last visit/assessment?”

“Have you taken any new medicines, other than those provided in this study, since your last visit/assessment?” or for pediatric studies, “Has your child needed to take any medicines, other than those provided in this study, since his/her last visit/assessment?”
Based on the patient’s response to this question, the investigator should ask additional questions relevant to the specific complaint, such as:

- How severe is/was the symptom?
- How often did the symptom occur?
- How long did the symptom last?

All AEs/MEs will be recorded and evaluated for their seriousness, severity, and relationship to the investigational product or study by the Investigator.

The investigator should attempt to establish a diagnosis of the Adverse Event based on signs, symptoms, and/or other clinical information. Wherever possible, a diagnosis should be documented rather than the individual signs/symptoms.

The investigator must also question the patient about any previously reported adverse events that have not resolved.

The investigator will then rate the intensity, seriousness, and causality of the AEs and will also document any measures taken to address the AE. Causality should be rated in terms of relationship to the study medication as follows: not related, possibly related, probably related, definitely related. See Section 9.2.4.4 for further definitions of relationship to study medication. All of this information should be clearly recorded in the Source Documents.

The investigator should employ this probe at each assessment. AEs will be collected throughout the study.

All AEs must be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the patient is lost to follow-up. The investigator is responsible to ensure that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the AE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

### 9.2.4.4 Causality

The relationship of an adverse event to study drug should be determined by the Investigator or study physician after thorough consideration of all facts that are available. Assessment of causality is based on considering associative connections (time or place), pharmacological explanations, previous knowledge of the drug, presence of characteristic clinical or pathological phenomena, exclusion of other causes, and/or absence of alternative explanations. The causal relationship of an adverse event to study drug will be assessed according to the following criteria (based on World Health Organization definitions):
9.2.4.5 **Severity**

Severity refers to the accumulated intensity of discomfort/impairment of health since the last recording of AEs. The investigator will rate the intensity, seriousness, and causality of the AEs. To achieve maximum consistency in the assessment of severity of adverse/medical events, it is recommended that National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) scale be used whenever possible, to assist the investigator in determining the severity of adverse/medical event. Severity of adverse/medical events will be reported on the CRF as mild, moderate, or severe according to the definitions provided below. Grading based on CTCAE scale will not be entered into the CRFs.

<table>
<thead>
<tr>
<th>Severity</th>
<th>Corresponding NCI CTCAE Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild:</strong> awareness of a sign or symptom but easily tolerated</td>
<td>1</td>
</tr>
<tr>
<td><strong>Moderate:</strong> discomfort sufficient to cause interference with normal daily activities</td>
<td>2</td>
</tr>
<tr>
<td><strong>Severe:</strong> resulting in inability to do work or perform normal daily activities</td>
<td>3-5</td>
</tr>
</tbody>
</table>

9.2.4.6 **Serious Adverse Event**
An SAE is any adverse event occurring at any dose that results in any of the following outcomes:

1) Death
2) A life-threatening adverse event
3) Inpatient hospitalization or prolongation of existing hospitalization
4) A persistent or significant disability or incapacity
5) A congenital anomaly in the offspring of a patient who received the study treatment
6) Important medical events that may not result in death, be life threatening, or require hospitalization but which in the investigator’s judgement may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or treatment-related substance abuse.

Clarifications:

- Life threatening means that the patient was, in the view of the investigator, at immediate risk of death from the event as it occurred. This definition does not include an event that, had it occurred in a more severe form, might have caused death.
- Hospitalisation for elective treatment of a pre-existing condition that did not worsen during the study is not considered an AE.
- Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation, the event is an SAE.
- “Inpatient” hospitalisation means the patient has been formally admitted to a hospital for medical reasons. This may or may not be overnight. It does not include presentation at a casualty or emergency room unless the event meets one of the other criteria for being a Serious Adverse Event.
- With regard to the criteria in (6) above, medical and scientific judgement should be used in deciding whether prompt reporting is appropriate in this situation.

9.2.4.7 Procedures for Serious Adverse Event Reporting

Patients will be instructed to report SAEs to the Investigator immediately (within 24 hours) by telephone. The Investigator must report all SAEs to the Sponsor within 24 hours of occurrence or notification by the patient. These events must be faxed to the
Sponsor using ApoPharma’s standard SAE form. The Sponsor (or its delegate) will provide a list of project contacts for SAE receipt, fax numbers and telephone numbers. The Investigator will always provide an assessment of causality at the time of the initial report.

A follow-up SAE form must be completed by the responsible Investigator/delegate and faxed to the Sponsor within 5 calendar days. Furthermore, as additional relevant follow-up information becomes available, the Investigator must complete a follow-up SAE form and fax it to the Sponsor. The Sponsor (or its delegate) will submit serious adverse drug reactions (SADRs) to the appropriate Regulatory Agencies, in line with local regulatory requirements and timelines.

Investigators must also report all SAEs to their respective IRB/IEC responsible for the study. The Sponsor (or its delegate) will promptly inform all other sites of SAEs occurring at a single site, at least possibly related to the study medication and unexpected. All site Investigators will report these events to their IRB/IEC following the same timelines as above or following local IRB/IEC policy, whichever takes precedence. SAEs will be monitored until they are resolved or condition has stabilized or patient is lost to follow-up. The Sponsor will be informed of the resolutions.

9.2.4.8 Follow-up and Documenting of SAEs

SAEs that occur during the study and for 30 days after the patient takes his/her last dose of Study Medication must be documented in the patient’s medical record and on the SAE Report. A separate SAE Report form should be used for each SAE. The investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the SAE and not the individual signs/symptoms.

All SAEs must be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the patient is lost to follow-up. The investigator is responsible to ensure that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

The sponsor may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations. If a patient dies during participation in the study or during a recognized follow-up period, the sponsor should be provided with a copy of any post-mortem findings, including histopathology. New or updated information should be recorded on the originally completed SAE page, with all changes signed and dated by the investigator.

The CRA will verify the Original SAE Report form against the Source Documents at the next monitoring visit.
9.2.4.9 Adverse Event of Special Interest – Neutropenia (Definitions and Management)

Definitions

**Mild Neutropenia**: A confirmed ANC $\geq 1.0 \times 10^9$/L and $< 1.5 \times 10^9$/L.

**Moderate Neutropenia**: A confirmed ANC $\geq 0.5 \times 10^9$/L and $< 1.0 \times 10^9$/L.

**Severe Neutropenia/Agranulocytosis**: A confirmed ANC $< 0.5 \times 10^9$/L.

An Absolute Neutrophil Count (ANC) is confirmed as being less than a specified value if counts on two consecutive counts are both less than the specified value. If both consecutive counts are below $1.5 \times 10^9$/L but not in the same severity category of neutropenia, a third count will be required to determine the severity.

Management

All patients and their primary physicians will be promptly notified when neutropenia occurs. All patients would have been given thermometers at the onset of the study and trained in their use. Any patient with a fever defined as 38.5°C or greater will be instructed to immediately discontinue treatment, obtain a CBC and differential and notify their primary physician in order to detect sudden neutropenia in addition to routine weekly laboratory counts. If the site principle investigator is not the responsible clinical physician, daily contact must be maintained with the primary care physician.

**Mild Neutropenia** (Two consecutive Absolute Neutrophil Counts $\geq 1.0 \times 10^9$/L and $< 1.5 \times 10^9$/L):

Patients who experience mild neutropenia (ANC $\geq 1.0 \times 10^9$/L and $< 1.5 \times 10^9$/L) will be followed daily until two consecutive ANCs are $\geq 1.5 \times 10^9$/L. The following procedure must be followed:
- Discontinue treatment immediately

- Provide protective isolation (if possible).

- Call the 24-hour number to contact an investigator that will be responsible to answer toxicity questions.

- Notify the Sponsor by fax.

- Examine patient the same day to physical examination and review drug history (if possible). If the patient cannot be examined the same day, contact the patient by phone to obtain AEs and concomitant medications/therapies.

- Therapy re-initiation:
  - If the patient is not febrile or does not have an infection, therapy with study medication can be re-initiated once two successive ANCs are >1.5 x 10^9/L and it is deemed safe by the Investigator.
  - If the patient is febrile or have an infection, therapy with study medication can be re-initiated once all symptoms have been resolved and it is deemed safe by the Investigator.

**Moderate Neutropenia** (Two consecutive Absolute Neutrophil Counts ≥ 0.5 x 10^9/L and < 1.0 x 10^9/L):

Patients who experience moderate neutropenia (ANC ≥ 0.5 x 10^9/L and < 1.0 x 10^9/L) will be followed daily until two successive ANCs are ≥1.5 x 10^9/L. The following procedure must be followed:

- Discontinue treatment immediately

- The patient will be withdrawn from the study and monitored until resolution of the event.

- Provide protective isolation; if clinically indicated, admit patient to hospital and obtain q4h vital signs.
All patients with fever 38.5°C or greater and moderate neutropenia will be seen by their physician within 4 hours and undergo an infectious evaluation, including at least a blood culture. Antibiotics will be initiated prior to results of cultures and will be maintained until patient becomes afebrile, resolution of moderate-severe neutropenia, and negative blood cultures for a minimum of 72 or more hours. Antibiotics chosen should be based on local microbial prevalence and antibiotic sensitivity patterns. Broad spectrum antibiotics should be used in order to cover the risk of gram negative and gram positive organisms.

- Call the 24-hour number to contact an investigator that will be responsible to answer toxicity questions.
- Notify the Sponsor by fax.
- Review patient the same day including drug history and physical examination.
- If possible obtain viral studies (CMV, parvovirus, hepatitis A/B/C), serum ALT, BUN, creatinine, and 10 mL serum split into two 5-mL aliquots for frozen storage.

### Severe Neutropenia/Agranulocytosis (Two consecutive Absolute Neutrophil Counts < 0.5 x 10⁹/L):

Patients who experience severe neutropenia/agranulocytosis (ANC < 0.5 x 10⁹/L) will be followed daily until two successive ANCs are ≥1.5 x 10⁹/L. The following procedure must be followed:

- Discontinue treatment immediately.
- The patient will be withdrawn from the study and monitored until resolution of the event.
- Provide protective isolation; if clinically indicated, admit patient to hospital and obtain q4h vital signs. (It is recommended to hospitalize patients with severe neutropenia (ANC < 0.5 x 10⁹/L)).
- Obtain q4h temperatures from patient (monitored by family at home if patient is not in the hospital).
- All patients with fever 38.5°C or greater and moderate neutropenia will be seen by their physician within 4 hours and undergo an infectious evaluation, including at least a blood culture. Antibiotics will be initiated prior to results of cultures and will be maintained until patient becomes afebrile, resolution of moderate-severe neutropenia, and negative blood cultures for a minimum of 72 or more hours. Antibiotics chosen should be based on local microbial prevalence and antibiotic sensitivity patterns. Broad spectrum antibiotics should be used in order to cover the risk of gram negative and gram positive organisms.
prevalence and antibiotic sensitivity patterns. Broad spectrum antibiotics should be used in order to cover the risk of gram negative and gram positive organisms.

- Call the 24-hour number to contact an investigator that will be responsible to answer toxicity questions.
- Notify the Sponsor by fax.
- Review patient the same day including drug history and physical examination.
- If possible obtain viral studies (CMV, parvovirus, hepatitis A/B/C), serum ALT, BUN, creatinine, and 10 mL serum split into two 5-mL aliquots for frozen storage.
- Collect a blood sample to attempt to identify genetic or other biomarkers related to agranulocytosis (patient’s consent needs to be obtained).
- If possible obtain bone marrow aspirate for:
  - Histology
  - Progenitor culture
  - Frozen storage (1 mL sample)
- If possible obtain bone marrow biopsy (minimum length 3 mm).
- Perform septic work-up including chest X-ray, blood, urine and throat, cultures.
- If warranted, administer granulocyte stimulating factors, such as G-CSF 10 μg/kg, as an inpatient if possible, beginning the same day that the ANC is confirmed as < 0.5 x 10^9/L; administer daily until ANC is > 1.5 x 10^9/L on two consecutive days.
- If ANC < 0.5 x 10^9/L for 7 days, repeat bone marrow biopsy and aspirate weekly during the period of agranulocytosis, if warranted.

### 9.3 Pharmacokinetics

Blood samples for the pharmacokinetic analyses of deferiprone and its 3-\textit{O}-glucuronide metabolite will be collected at specific timepoints/schedule during the Month 6 visit. Blood samples will be collected at pre-dose and 1, 1.5, 2, 2.5, 3, 4, 6, 8 and 12 hours post-dose. Pharmacokinetic parameters will be derived by non-compartmental analysis. The following parameters will be derived from individual plasma deferiprone and its 3-\textit{O}-glucuronide metabolite concentration-time profiles:

- $C_{\text{max}}$  Maximum observed plasma concentration over a dosing interval
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{\text{max}}$</td>
<td>Time of occurrence of $C_{\text{max}}$</td>
</tr>
<tr>
<td>$C_{\text{min}}$</td>
<td>Minimum observed plasma concentration over a dosing interval</td>
</tr>
<tr>
<td>$\text{AUC}_{\text{SS}}$</td>
<td>Area under the plasma concentration versus time curve within a complete dosing interval at steady state</td>
</tr>
<tr>
<td>CL/F</td>
<td>Apparent clearance</td>
</tr>
<tr>
<td>$T_{1/2}$</td>
<td>Elimination half-life at steady state</td>
</tr>
<tr>
<td>Vd/F</td>
<td>Apparent volume of distribution</td>
</tr>
</tbody>
</table>

### 10 PROCEDURES IN CASE OF MEDICAL EMERGENCY

The Investigator is responsible for ensuring that procedures and expertise are available to cope with medical emergencies during the study period. An emergency may constitute a SAE.

Each site will be provided with code break instructions. In the event of an emergency, the randomisation code may only be broken if knowledge of the respective treatment is necessary for adequate treatment of the emergency. Further information regarding contacts will be provided in the SAE Report Form Completion Guidelines.

#### 10.1 Precautions/Overdosage

Deferiprone use can be associated with neutropenia, including agranulocytosis. All patients must have their neutrophil count monitored weekly and have therapy interrupted at the first sign of neutropenia. Recommended management of neutropenia is outlined in Section 9.2.4.9. Treatment with deferiprone should not be initiated in patients with a history of recurrent neutropenia or a single episode of agranulocytosis.

Overdose per se will not be reported as an AE, unless associated with one. The signs and symptoms or clinical sequelae resulting from overdose will be reported if they fulfill the AE or SAE definition.

Neurological disorders such as cerebellar symptoms, diplopia, lateral nystagmus, psychomotor slowdown, hand movements and axial hypotonia, have been observed in 2 children with thalassemia who were treated with deferiprone for more than 1 year with more than twice the maximum recommended dose of 99 mg/kg/day for transfusion-related iron overload. The neurological disorders progressively regressed after deferiprone discontinuation.

#### 10.2 Procedures in Case of Pregnancy

If a female study patient or a female partner of a male study patient becomes pregnant, or plans to become pregnant, during the course of the study, the patient must inform the investigator and the patient will be immediately withdrawn from the Clinical trial. The
investigator must report all pregnancies that occur during the study and within 30 days after the last dose of study medication using the Pregnancy Reporting Form and AE page of the CRF within 24 hours. The patient will be followed up and the pregnancy outcome will be reported. Pregnancy outcomes include live birth, spontaneous abortions (loss of pregnancy before 20 weeks of gestation), elective termination, fetal death/still births (loss of pregnancy after 20 weeks of gestation). Within any of these categories the fetus or infant must be evaluated for the presence of any congenital anomalies. Any maternal/fetal complications should be also reported. If possible, the health of the child will be followed for 1 year.

The same pregnancy and post-gestation monitoring procedures will also apply in the case that a male patient reports that his female partner has become pregnant. In this case, however, there will be no requirement for the patient to withdraw from the trial.

11 LABORATORY PROCEDURES

Specimens will be collected by venipuncture. Each serum separator tube will be labelled with the sample code, patient ID number, date the sample was drawn (dd/mmm/yyyy), participant's date of birth (dd/mmm/yyyy). All samples will be sent to the local lab.

Investigators must document their review of each laboratory report by signing or initialling, and dating each report.

Laboratory values that fall outside a clinically accepted range or values that differ significantly from previous values must be evaluated and commented on by the Investigator by marking each value CS (clinically significant) or NCS (not clinically significant). Any laboratory value that is clinically significant or that differs importantly from a previous value should be further explained on the laboratory report and should be reported as an AE. The Investigator may use the CTCAE scale as a guide to determine the severity of the laboratory finding.

Images of patients undergoing MRI imaging will be identified with the patient ID number and will locally receive image identifier codes (one for each local imaging procedure). Images will be electronically transferred to a designated image analysis center at the University of Newcastle.

12 STUDY COMMITTEES

12.1 Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will be established to monitor the safety of patients during the course of the study. The DSMB will be responsible for overseeing the conduct of the trial and will be empowered to recommend stopping the trial if in their judgement continuation is not ethically acceptable on the grounds of safety.
The following will trigger an evaluation by the data safety monitoring board (DSMB) for recommending stopping the study at any time point following initiation of study medication:

1. Death or life-threatening event that is deemed to be at least possibly related to the study medication by either the Investigator, or the Sponsor in any of the patients randomized in the study.

2. Occurrence of Serious Adverse Events that:
   a. are not associated with exacerbation of a pre-existing condition and;
   b. are deemed to be at least possibly related to the study medication by either the Investigator, or the Sponsor and;
   c. affect at least 2 subjects randomized and exposed to active medication in the study.

No study stopping decision will be made without prior consultation with the Sponsor, FDA and EMA.

The operating model and the frequency of the interim safety review meetings will be laid out in the DSMB charter. The DSMB will be constituted prior to the enrolment of any patients into the study. The DSMB will be notified of any changes to the protocol or the study conduct. The DSMB will be included in the review of any substantive changes to the protocol that could affect patient safety prior to their submission to IRB/IEC for implementation approval. All DSMB meeting minutes and board composition will be submitted to the regulatory authorities with the Final Clinical Report.

13 DATA HANDLING and STATISTICAL ANALYSIS

13.1 Data-collection and Handling Procedures

13.1.1 Documentation of Data

All subject data obtained during the study will be entered by the Investigator or designee using the electronic Case Report Forms (eCRFs) provided the Sponsor. Clinical data will be entered and stored into a validated database. The data will be coded using the MedDRA (Medical Dictionary for Regulatory Activities) and WHODDD (World Health Organization Drug Dictionary) dictionaries. The electronic CRFs will be provided in the Remote Data Capture (RDC) system hosted by the Sponsor. Trained users will access the system via a secured gateway. Users will be authorized to access data only for their own study site. Data will be entered directly into the system from the source documents in lieu of the paper CRFs. On line and off line edit checks will be used to prompt the user to provide clean and accurate data. Clinical Data Management will code and monitor the data for accuracy. An electronic signature will be required by the Investigator on the eCRFs and the monitor will verify the eCRFs on line.
13.1.2 Corrections to Study Documentation

Any errors in the study documentation must be crossed out with a single line, leaving the original entry legible. The correction must then be dated and initialed. Incorrect entries must not be covered with correcting fluid, obliterated, or made illegible in any way.

13.1.3 Data Processing

Data will be entered by clinical study site personnel from the source data directly into the eCRF. Support is provided to data entry users at the site via a Help Desk.

During the study, the statistician will have read-only access to the data for program development. Integrity of the database will be assured by limiting access through passwords and account control and through regular, secure backups of both the clinical data management files and SAS-related files.

13.1.4 Coding

The following coding dictionaries will be used:

Medical History: MedDRA
Adverse events: MedDRA
Drugs: WHO Drug Dictionary

13.1.5 Data-Handling

Discrepancies are reviewed and resolved on-line by the clinical study site users or reviewed off line by Clinical Data Management, CRO and/or Sponsor and sent to the study site. A Patient Data Report (PDR) is a generated compilation of data from the database that is presented in a pdf document. The PDR originates from the same HTML files as the electronic case report forms (eCRFs) and can either be generated with no data, with patient and eCRF information (such as patient ID number #, site name, etc.), and/or with all collected response data. This report can be used for electronic submissions and as a print out for review. A copy of the final PDRs is sent to the clinical study site after database freeze.

13.1.6 Missing, Unused and Spurious Data

All missing data will be subject to data queries as specified above. All eCRF data will be included into the electronic database and will be considered for analysis as specified in the statistical analysis plan.
13.2 Statistical Analysis

13.2.1 Co-Primary Efficacy Endpoint

- Change in the BAD total score from baseline to Month 18 in patients treated with deferiprone compared to placebo, as assessed by central blinded evaluation of video-tapes;

- Patient’s global impression of improvement from baseline to Month 18 in patients treated with deferiprone compared to placebo.

Study will be considered positive if both co-primary endpoints reach statistical significance.

13.2.2 Secondary Efficacy Endpoints

- Proportion of patients with improved or unchanged BAD scale total score between baseline and Month 18 (defined as responders, with change in total score from baseline to Month 18 to be ≤0).

- Change in BAD scale per body region (eyes, mouth, neck, trunk, each upper/lower extremity) from baseline to Month 18;

- Proportion of patients showing an improvement on PGI-I at the Month 18 visit (responders are defined as patients whose conditions have not deteriorated; patients who have “not change”, or are “minimally improved”, “much improved” or “very much improved” in the PGI-I questionnaire at the last study visit);

- Change in globus pallidus iron levels as measured by MRI R2* from baseline to Month 18;

- Change from baseline to Month 18 in UPDRS Parts I, II, III and VI scores;

- Change in global WeeFIM score (or FIM for patients > 18 years) from baseline to Month 18;

- Change in WeeFIM (or FIM for patients > 18 years) score per item from baseline to Month 18;

- Change in quality of life (PedsQL) from baseline to Month 18;

- Change in quality of sleep (PSQI) from baseline to Month 18.

13.2.3 Safety Endpoints

- Frequency of Adverse Events (AEs);

- Frequency of Serious Adverse Events (SAEs);

- Discontinuation due to AEs;

- Hematology assessments;

- Blood clinical biochemistry assessments;
13.2.4 Pharmacokinetics Endpoints

To examine the steady state pharmacokinetic profile of deferiprone and deferiprone 3-\textit{O}-glucuronide following the administration of twice daily deferiprone oral dose, the following analyses will be performed:

PK parameters for serum deferiprone and deferiprone 3-\textit{O}-glucuronide will be calculated as follows:

\begin{itemize}
  \item $C_{\text{max}}$: Maximum observed plasma concentration over a dosing interval
  \item $T_{\text{max}}$: Time or occurrence of $C_{\text{max}}$
  \item $C_{\text{min}}$: Minimum observed plasma concentration over a dosing interval
  \item $AUC_{\text{SS}}$: Area under the plasma concentration versus time curve within a complete dosing interval at steady state
  \item $\text{CL/F}$: Clearance
  \item $T_{\frac{1}{2}}$: Half-life
  \item $V_{\text{d/F}}$: Volume of distribution
\end{itemize}

Parameters will not be calculated for subjects with only 2 or fewer time points with detectable concentrations.

13.2.5 Determination of Sample Size

Sample size estimation is based on BAD scores from literature, where a mean value of 21.0 BAD score points with a standard deviation of 6.3 points was observed in 21 NBIA patients (Timmermann et al, 2010). Assuming a 2:1 randomization, an expected difference in change of BAD score of $\geq 5$ points after 18 months between control and treatment group, a standard deviation of 6.3 points for the change from baseline, and a drop-out rate of 30%, a total of 90 patients would be needed to achieve 80% power in detection of this clinically relevant effect size at a two-sided 0.05 level of significance.

The impact of the co-primary endpoint (PGI-I) on the power to demonstrate superiority of the treatment group over control should be small as a greater degree of difference in response for this endpoint is expected between the two groups. The rationale behind is that the BAD score is based on assessment of dystonia in eight body regions. To obtain a much higher score, in relation to the standard deviation, the active treatment would need to provide beneficial effect on multiple regions. A much higher score in PGI-I can be achieved even if the active treatment performs well in one region only.
13.2.6 Study Population

Study populations intended for analysis will be defined as follows: Intent-to-treat (ITT), Modified Intent-to-treat (mITT), Per-Protocol (PP), Safety and Pharmacokinetics. The mITT population will represent the primary analysis population to evaluate the treatment groups on all efficacy endpoints. The co-primary efficacy endpoints will also be analyzed for the PP population, which is the secondary analysis population.

13.2.6.1 Intent-to-treat Population

The ITT population is defined as all randomized patients.

13.2.6.2 Modified Intent-to-treat Population

The mITT population is defined as all randomized patients who received at least one dose of study drug and have a baseline and at least one post-baseline efficacy assessment. All efficacy analyses will be based on the mITT population.

13.2.6.3 Per-Protocol Population

The PP population will include all randomized patients who complete the study, have no major protocol violations, and have an efficacy assessment at the end of the study. Prior to database lock, protocol violations will be reviewed for their seriousness and patients with major violations will be excluded from the PP population. Only the co-primary efficacy endpoints will be analyzed for the PP population.

13.2.6.4 Safety Population

The Safety population will include all randomized patients who took at least one dose of study drug.

13.2.6.5 Pharmacokinetics Population

The Pharmacokinetics population will include all patients participating in the pharmacokinetic evaluation who have sufficient PK data to derive at least one PK parameter.
13.3 Statistical Analysis Plan

A separate statistical analysis plan (SAP) detailing the specifications given below will be prepared and approved prior database lock. Any changes in the planned statistical methods will be documented in the final study report.

13.4 Definition of Analysis

For safety data analysis, no imputation will be performed on the missing data and analysis will be based on observed cases (OC).

For continuous efficacy data, a Mixed-Effect Model Repeated Measure (MMRM) model will be used as the primary analysis method and the analysis will be based on observed cases data set. As a sensitivity analysis, an analysis of covariance (ANCOVA) model will be used as the secondary analysis method with missing data being imputed using the imputation rule as described below.

For patients who were terminated from the study prior to Month 18, if their last efficacy measures were obtained within 90 days of Month 18, the data obtained will be treated as the Month 18 data. For early termination that occurred outside this window, the last observation carried forward (LOCF) method will be used to fill the missing data when the early termination was not caused by worsening of disease conditions or inadequate efficacy of the drug. For early termination due to worsening of disease conditions or inadequate efficacy of the drug, as indicated in the CRF, the “worst score” method will be used. That is, for continuous variables such as BAD total score at a particular time point, the average score of the placebo arm at that time point will be used to impute the missing data of the placebo group while the worst score of all patients for the active group will be used to impute the missing data at that time point. Similarly, for categorical variable such as responder, the worst category (treatment failure) will be assigned for the missing data. For missing data due to missed visit, the LOCF method will be used to fill the void.

13.4.1 Planned Analysis

13.4.1.1 Patient Disposition and Drug Exposure

Patient disposition, based on the ITT population, will be summarized and presented, including the number and percentages of patients who were screened, were enrolled, completed the study, and withdrawn (including reasons for withdrawals).

For each patient, the number of doses taken will be computed from the study drug dispensing and accountability CRFs obtained at each visit. The extent of exposure to the study medication as well as the number of doses taken during study will be summarized with descriptive statistics.
13.4.1.2 Patient Characteristics

Baseline characteristics will be summarized by: mean, standard deviation, minimum, median and maximum values (by mITT and PP populations). Medical history and prior medications will be summarized descriptively (number of patients and percentage).

13.4.1.3 Efficacy Analyses

Co-Primary Efficacy Endpoints

A Mixed-Effect Model Repeated Measure (MMRM) model will be used as the primary analysis method to assess the change in BAD total score and PGI-I from baseline to Month 18, with baseline value and age of onset of motor symptoms as covariates and treatment group as the main factor in the model. Age of onset of motor symptoms will be used as a stratification factor at randomization and thus will be included as a binary variable in all the models where it is used as a covariate. DBS settings change or use of medications that has the potential to affect dystonia symptoms during the study or the frequency of PRN drug or rescue medication use may confound the treatment effect assessment. These variables will also be included in the MMRM model appropriately. PGI-I is already a measurement of change from baseline and thus will be used directly as the outcome variable, and baseline BAD score will be included as the baseline value in the model.

The MIXED procedure in SAS will be used for the MMRM model analysis using the observed data. Data within each patient at different visits will be considered repeated measures. UN (Unstructured) covariance structure will be used to model the correlation between repeated measures within the same patient and Kenward and Roger’s method will be used to estimate the denominator degrees of freedom. The 95% confidence interval (CI) for the difference between the two treatments will be calculated by the LSMEANS statement.

As a sensitivity analysis, an analysis of covariance (ANCOVA) model will be used as the secondary analysis method to assess the change in value from baseline to Month 18 for co-primary efficacy endpoints only. The model will be similar to the MMRM model. The LOCF imputation method described in Section 13.4 will be employed for imputing missing data.

If the blinded review of the efficacy data performed before the breaking of the treatment codes indicates a severe non-normality of the data, an appropriate transformation (for example, log transformation) will be applied to the data, or nonparametric statistical methods based on ranks will be employed, if warranted. This analysis will be treated as a secondary analysis and will be analyzed with the ANCOVA model only.
Secondary Efficacy Endpoints

The MMRM model will also be used for the analysis of the secondary endpoints except for the proportion of responders, which will be analyzed by a logistic regression model with age of onset of motor symptoms and baseline BAD score as covariates and treatment group as the main factor. The GENMOD procedure in SAS will be used to perform the logistic regression.

With regard to the secondary efficacy endpoints, DBS settings change or use of medications that has the potential to affect dystonia symptoms during the study or the frequency of PRN drug or rescue medication use may also confound the treatment effect assessment. These variables will also be included in the MMRM model and the logistic regression model appropriately.

Subgroup Analysis

In order to explore potential differences in treatment effect on efficacy endpoints across population subgroups, subgroup analyses will be performed on the co-primary efficacy endpoints for the mITT population on the following factors: Age at onset of motor symptom (Age ≥6 vs. Age <6), DBS (Deep Brain Stimulation Yes vs. No), Baclofen pump (Yes vs. No), and Region (US vs. Europe). Forest plots will be drawn to compare subgroups of each factor.

13.4.1.4 Safety Analyses

All safety data collected will be presented in listings and summary tables to give an overview of the safety findings.

Adverse Events

A summary table of adverse events will include the following information:

- number of patients exposed to study treatment,
- number of patients experiencing at least one AE,
- number of patients experiencing at least one severe AE,
- number of patients experiencing at least one serious AE,
- number of patients experiencing at least one drug-related AE,
- number of deaths,
- total number of patients withdrawn,
- number of withdrawals due to AEs.
All adverse experiences will be coded using the MedDRA (Medical Dictionary for Regulatory Activities). Adverse events will be defined as: 1) AEs that occurred or worsened (increased in severity and/or frequency) on or after the first dose of study medication. 2) AEs with a missing start date and a stop date on or after the first dose of study medication. 3) AEs with both a missing start and stop date. AEs will be summarized by treatment and by MedDRA SOC and Preferred Term. AEs that occurred within 14 days after treatment discontinuation will be considered AEs. Serious adverse events occurred within 30 days after treatment discontinuation will be included in the database.

Adverse events (AEs) will be summarized using the total number of AEs, the total number and percent of patients who experience an AE, and the number and percent of patients who experienced an AE within each system organ class (and preferred term within a system organ class). AEs will also be presented by severity (mild, moderate, severe), by seriousness (serious, non-serious) and by relationship to study medication (at least possibly related, not-related). The number of patients withdrawn will also be presented.

To count the number of patients who experienced each AE, patients having experienced the same AE multiple times will only be counted once for the corresponding preferred term. Similarly, if a patient experiences multiple AEs within the same system organ class, that patient will be counted only once for that system organ class. AEs will be tabulated presenting the system organ class alphabetically and within each of them, the preferred term will be presented in decreasing order of the total number of patients who experienced each AE. In summaries presenting the incidence of AEs by severity, seriousness and relation to study medication, a patient with multiple events coded to a given preferred term or system organ class will be counted once for that preferred term or system organ class according to the most severe event, the most serious event or the event with the closest relationship to study medication.

Listing of serious adverse events and listing of withdrawals due to AEs will be presented. Patient deaths will be listed separately and discussed with patient narratives.

Vital Signs

Descriptive statistics (mean, median, standard deviation, minimum and maximum) will be presented for temperature, heart rate, respiratory rate, systolic blood pressure, diastolic blood pressure, weight, height, at screening or baseline and each relevant visit. Changes from baseline to each post-baseline time-point will also be presented. Data will also be presented graphically for examination of possible trend.

ECGs

Clinically significant ECG abnormalities will be reported. The number and percentage of patients with normal and abnormal ECG results will be provided.

Biochemistry, Hematology and Urinalysis

Descriptive statistics for each clinical laboratory test will be presented for each scheduled visit. Change from baseline to each visit will also be presented. According to the laboratory normal ranges, laboratory test results will be categorized as low (< lower
normal limit), normal (within normal range), and high (> upper normal limit). Shift tables comparing the distributions of these three categories at baseline versus end of treatment will be presented. Continuous data will also be presented graphically for examination of possible trend. Clinically significant laboratory values will be reported in the adverse event analysis.  

**Concomitant Medications**

Medications will be coded using the WHO Drug dictionary. Medications taken during the course of the trial (on or after the first study drug dose and before or on the study termination date) will be considered as concomitant medications. Medications started after the study termination date will not be reported in tables, but will be presented in patient data listings. Concomitant medications used to treat adverse events will be differentiated from others.

Concomitant medications will be summarized according to the preferred terms only. To count the number of patients who took a medication, a patient taking the same medication multiple times will only be counted once for that medication. Medications will be tabulated in decreasing order of the total number of patients who took each medication. In addition, the total number of patients to ever take any concomitant medications will be presented.

Concomitant medications will be presented based on the Safety population.

13.4.1.5 **Pharmacokinetics Analyses**

Pharmacokinetic parameters will be derived by non-compartmental analysis. Actual sampling times will be used for pharmacokinetic evaluations. Descriptive statistics (Arithmetic means, SD, CV, median, minimum and maximum values) will be presented for the concentrations and the pharmacokinetics parameters. Additional pharmacokinetics analyses may be performed if deemed appropriate.

14 **DATA MANAGEMENT CONSIDERATIONS**

14.1 **Data Management**

The Sponsor’s Clinical Data Management group will be responsible for the processing, coding and validating/cleaning of clinical study data. Patient data will be entered by the Investigator or designee using the electronic Case Report Forms (eCRFs) provided by the Sponsor. Clinical data will be entered and stored into a validated database. The data will be coded using the MedDRA (Medical Dictionary for Regulatory Activities) and WHO Drug dictionary (World Health Organization Drug Dictionary). The eCRFs will be provided in the Remote Data Capture (RDC) system hosted by the Sponsor. Trained users will access the system via a secured gateway. Users will be only authorized to access data for their study site. Data will be entered directly into the system from the source documents in lieu of the paper CRFs. On line and off line edit
checks will be used to prompt the user to provide clean and accurate data. Clinical Data Management will code and monitor the data for accuracy. An electronic signature will be required by the Investigator on the electronic CRFs and the monitor will verify the eCRFs on line.

Clinical data management activities will be performed by the Sponsor in accordance with applicable standards and data cleaning procedures of the Sponsor. An audit trail of all data processing will be stored in the database. The study biostatistician will be notified when all patient data are ready for analysis.

Integrity of the database will be assured by limiting access through username/password combination and account control. Authorized access to the database will be provided to those individuals with an inspection/auditing function (Regulatory Authorities/Quality Assurance); "read only" access will be provided to avoid unintentional corruption of the database.

The database will be backed up daily.

14.2 Source Documents

The Investigator will maintain adequately detailed source documents supporting significant source data for each patient. Source data are defined as all information in original records and/or certified copies of original records of Clinical findings, observations, or other activities in a Clinical trial necessary for the reconstruction and evaluation of the trial. Examples include medical history; physical examination; laboratory results; X-ray/ultrasound findings; and ECG results.

The Investigator will also retain all patients’ specific printouts, reports of tests and procedures performed as requirements of the study. The source documents must be available at the time of any site visit from the Sponsor/CRO and/or regulatory authorities.

During monitoring visits the monitor will need to validate data in the eCRFs against these sources of data.

For every patient, the hospital/patient records should clearly indicate at least and not limited to:

- That he/she participated in the study, e.g. by including patient identification (patient ID number) and study identification (study code or other).
- Medical History.
- A list of prior and concomitant medications/therapies prior to participation in the study.
- A list of treatments, including investigational product(s), received or changed during the study.
- A record of all visits to the study site during the study period, including those for study purposes only.
• A list of all AEs, including SAEs, ADRs, and SADRs

14.3 Electronic Data Capture (EDC)
The Sponsor will provide the Investigators and site staff with training on the system. Data is entered by clinical study site personnel from the source data directly into the eCRF. Support is provided to data entry users at the site via a Help Desk.

Discrepancies are reviewed and resolved on line by the clinical study site users or reviewed off line by Clinical Data Management, CRO and/or Sponsor and sent to the study site. A Patient Data Report (PDR) is a generated compilation of data from the database that is presented in a pdf document. The PDR originates from the same HTML files as the electronic case report forms (eCRFs) and can either be generated with no data, with patient and eCRF information (such as patient ID number #, site name, etc.), and/or with all collected response data. This report can be used for electronic submissions and as a print out for review. A copy of the final PDRs is sent to the clinical study site after database freeze.

15 MONITORING, AUDITS AND INSPECTIONS

15.1 Monitoring
The Sponsor has the obligation to follow this study closely throughout its course. Monitoring of the investigational sites will be conducted by the Sponsor or contracted to a qualified (through audit) CRO who will provide an appropriately trained CRA. The CRA will have regular contacts with the investigational site. These contacts will include visits to confirm that facilities remain acceptable, that the investigational site is adhering to the protocol and that data are being accurately recorded in the CRFs, and to provide information and support the Investigator. The CRA will ensure that the investigational product is accounted for and that written informed consent/assent form (where applicable) was obtained for each patient. Source data will be verified, and the data in the CRF compared with the source data. The source documents must be available at the time of the site visit.

15.2 Audits and Inspections
In accordance with the principles of ICH E6 Guideline for Good Clinical Practice, the study may be inspected by regulatory authorities and audited by the Sponsor or their designees. The Investigator and relevant Clinical support staff will be required to attend audits and inspections and make all necessary documentation and data available upon request.

During the course of the study or after study completion, one or more investigator site audits may be undertaken by auditors from the Sponsor or their delegates. The purpose of these audits is to determine whether or not the study is being/has been conducted and monitored in compliance with the ICH E6 Guideline for Good Clinical Practice,
approved protocol and amendment requirements, applicable local Standard Operating Procedures (SOPs) and local laws and regulations. It is the investigator’s and his/her staff’s responsibility to promptly address deficiencies stemming out of regulatory inspections and the Sponsor’s or delegated audits, as well as to ensure that agreed-upon corrective and preventative actions are implemented promptly.

An inspection by any regulatory authority or a sponsor’s audit may occur at any time during or after completion of the study. If an Investigator is contacted by a regulatory authority for the purpose of conducting an inspection or to discuss any compliance issues, he/she is required to contact the Sponsor immediately who will assist the site in preparation for the audit/inspection.

16 REGULATORY REQUIREMENTS AND OBLIGATIONS

16.1 Informed Consent/Assent

The Investigator or his/her designee will ensure that the patient and/or his/her legal representative is given full and adequate oral and written information about the nature, purpose, possible risks and possible benefits of the study.

The Investigator or his/her designee must make a conscientious effort to be fully satisfied that the patient and/or his/her legal representative has truly understood that for which the consent has been given. The patient and/or his/her legal representative must also be notified that he/she is free to withdraw his/her participation in the study at any time, and that such withdrawal will not affect his/her present or future care.

The patient and/or his/her legal representative should be given ample opportunity to ask questions and discuss the study with the family. The consent document signed by the patient must not be phrased in a manner that might be understood to abrogate the rights of the patient and/or his/her legal representative or the responsibility of the Investigator or Sponsor. The consent/assent form used to obtain the patient’s consent must be the most up-to-date consent/assent form approved by the IRB/IEC.

Written informed consent/assent will be obtained from the study patient and/or legal representative as described in the Declaration of Helsinki, June 1964, as clarified by the World Medical Association (WMA) General Assembly, Washington 2002, CFR Part 50 prior to entering the patient into the study. The consent/assent form will be signed and dated by the patient or legal representative prior to the first study intervention. A completed copy of each patient’s signed and dated consent/assent form will be retained in the patient’s chart.

The patient will be provided with a copy of the signed and dated ICF/assent form. Site variations may occur owing to the individual preferences of each ethics committee. Copies of the consent/assent form intended for use at each Clinic will be forwarded to the Sponsor.

Should a protocol amendment be made, the ICF/assent may need to be revised to reflect the changes to the protocol. The revised consent/assent form will be forwarded to the Sponsor. The Investigator must then ensure firstly that the revised consent/assent form
is reviewed and receives favourable written approval from the IRB or IEC, and secondly that it is signed by all patients subsequently entered in the trial and those currently in the trial. The Investigator must provide written approval from the IRB/IEC to the Sponsor.

16.2 Institutional Review Board/Independent Ethics Committee

The Investigators agree to provide the IRB/IEC with all appropriate documents, including a copy of the protocol/amendments, ICFs, advertising text (if any), Investigator’s brochure (if any) and any written information to be given to the patient. The Investigators must obtain IRB/IEC favourable written approvals for the protocol/amendments, the ICFs and any applicable translations, and any written information to be given to the patient prior to their enrolment, and any advertising to be used for patient recruitment. The Investigator must provide a copy of the written approval of the IRB/IEC to the Sponsor before commencement of the study. The names of the members of IRB/IEC and their title/institutional affiliation will be provided to the Sponsor and the Investigators prior to the start of the study. The Sponsor further requires copies of all correspondence with the IRB/IEC.

In the event that the protocol is amended, the protocol amendment must be approved by the IRB/IEC prior to its implementation, unless the changes are administrative in nature. If an ICF needs to be revised to reflect the changes to the protocol, the revised consent form will be forwarded to the Sponsor for approval prior to the submission to the IRB/IEC. The Investigator must then ensure firstly that the revised consent form is reviewed and receives favourable written approval from the IRB/IEC, and secondly that it is signed by all patients subsequently entered in the trial and those currently in the trial. The Investigator must provide the written approval to the Sponsor.

The Investigator is also obliged to report all SAEs to the IRB/IEC as per local requirements. The Investigator must submit reports of the study at least annually to the IRB/IEC for review.

The Investigator must notify the IRB/IEC that the study has been completed within 3 months of its completion. A final Clinical report will be made available to the IRB/IEC. The Investigator must maintain an accurate and complete record of all submissions made to the IRB/IEC, including a list of reports and documents.

16.3 Patient Data Protection

To ensure the patient’s identity remains unknown to the Sponsor (or its delegate), the Sponsor (or its delegate) will identify all data by patient ID number.

The Investigator must inform patients of the possibility that representatives from regulatory authorities and/or the Sponsor (or its delegate) may require access to hospital or study site records for verification of data pertinent to the study, including medical history.
The Investigator is responsible for keeping a patient identification list or form of all patients entered, including enrolment code, patient ID number, full name, and last known address.

### 16.4 Assumption of Liability and Indemnification

The Sponsor shall indemnify, defend, and hold harmless the Investigator(s) (which term includes the Investigator(s)’s Institutions, employees, agents, representatives and associates) from and against any demands, claims, costs, judgments, liabilities, damages, losses and expenses, including reasonable legal fees (collectively, a “Loss”), that may be suffered or incurred by the Investigator(s) as a result of personal injuries or damage to property due to or arising out of the conduct of this Clinical trial.

Notwithstanding the foregoing, the Sponsor shall have no obligation or liability pursuant to the foregoing indemnity should the Loss result directly or indirectly from the Investigator(s)’s:

a. negligence or wilful misconduct;

b. failure to comply with the terms of the protocol or written instructions regarding the use of any product(s) used in this Clinical trial;

c. failure to adhere to any government regulations or requirements; or

d. failure to conduct the study in accordance with standard medical practice.

The Investigators shall promptly notify the Sponsor in writing of any demand, claim, proceeding or other matter (a “Claim”) for which indemnity may be claimed. The notification shall specify the all known particulars of the Claim, including, if available, the amount of the Claim. If the Investigator(s) fails to give timely notice of any Claim and as a result the Sponsor is prevented from effectively contesting liability for the Claim, the Sponsor shall be relieved of its obligations hereunder. The Investigator(s) shall take all commercially reasonable action to preserve the right to object to and defend against any Claim.

The Investigator(s) shall fully co-operate with the Sponsor with respect to all Claims and shall keep the Sponsor fully advised with respect thereto, including promptly supplying copies of all relevant documentation as it becomes available.

The Sponsor shall have the right but not the obligation, at its expense, and at any and all times participate in or assume control of the negotiation, settlement or defence of any Claim. Should the Sponsor elect not to assume control of the negotiation, settlement or defence of a Claim, the Investigator shall not settle the Claim without the written consent of the Sponsor, which consent shall not be unreasonably withheld.

If the Sponsor assumes control of the defence of a Claim, which it thereafter fails to defend, the Investigator shall be entitled to assume control thereof and the Sponsor shall be bound by the results obtained by the Investigator with respect to the Claim.
16.5 Compliance

This study will be conducted in compliance with the study protocol, ICH GCP E6, the Organization for Economic Co-operation and Development (OECD) Good Laboratory Practices and all applicable regulations, including the Federal Food, Drug and Cosmetic Act, U.S. applicable Code of Federal Regulations Title 21, Parts 50, 54 (financial disclosure), 56, 312 and 314, Directive 2001/20/EC of the European Parliament and of the Council of 04 April 2001, on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good Clinical practices in the conduct of Clinical trials on medicinal products for human use; any IRB requirements relative to Clinical studies and the Declaration of Helsinki (Appendix 20.6), June 1964, as clarified by the WMA General Assembly, Washington 2002 and Directive 2005/28/EC of the European Parliament and of the Council of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products.

16.6 Amendments to the Protocol

No amendments may be made to this protocol without the agreement of both the Sponsor, and the Investigators. All changes to this protocol must be documented by signed protocol amendment.

The amendment will be implemented by the study site from the day the document is signed by the Investigator and the Sponsor, whichever comes later, and once all applicable regulatory and IRB/IEC approvals have been obtained. If the change affects the safety of patients or involves intervening in the patient’s treatment of care, the scope of the investigation or the scientific quality of the study, the amendment must also have IRB/IEC approval, and it also has to be notified to or approved by regulatory authorities before it is implemented. Examples of these types of changes include:

- Any change in drug dosage or duration of exposure of individual patients to the study agent beyond that in the current protocol, or any significant change in the number of patients under study.
- Any significant change in the design of a protocol (such as the addition or dropping of a control group).
- The addition or dropping of a test or procedure.

A change intended to eliminate an apparent immediate hazard to patients may be implemented immediately and without written amendment to this protocol, provided that the regulatory authorities and the IRB/IEC are notified as soon as possible afterwards.

When a proposed change to the protocol meets the statutory criteria for amendment as defined by FDA and EMA substantially alters the study design or potential risk to the patient, the patient’s re-consent to continue participation will be obtained. This action
will require a revised ICF. The revised ICF will require approval from the Sponsor and the IRB/IEC.

16.7 Sponsor’s Obligations

The obligations described below contain excerpts from the ICH guidelines (Good Clinical Practice: Consolidated Guidance: E6, 1996) and the Sponsor’s policy governing Sponsor and Investigator obligations.

The Sponsor (or its delegate) is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded) and reported in compliance with the protocol, GCP guidelines and the appropriate regulatory requirements.

The Sponsor will have the ultimate and final authority in the trial on matters of policy and finance. At the time the study is initiated, the protocol and CRFs will be reviewed thoroughly with the Clinical Investigators and their staff. During the course of the study, the CRA and a Sponsor representative will be available to discuss by telephone, questions regarding AEs, removal of patients from the trial, conduct of the study and other Clinical study matters.

The Sponsor or its delegate will be responsible for:

1. Reporting the occurrence of SAEs to the Investigators and to regulatory agencies of findings that could affect adversely the safety of patients, impact the conduct of the trial, or alter the IRB/IEC approval/favourable opinion to continue the trial.

2. Providing adequate support to the Investigators so that the trial is conducted safely and effectively according to the standards of GCP.

3. Reporting the findings of this study annually, or as required, to regulatory agencies and providing a written report of the study upon its completion.

4. Retaining all documentation and records as required by the relevant regulatory agencies.

5. Monitoring and auditing of data at the Clinical sites for the duration of the trial to ensure the study is being conducted according to ICH GCP E6 as well as any applicable local regulations and laws (e.g. adherence to the protocol, patient enrolment, investigational product accountability, and accuracy of data forms).

16.8 Investigators’ Obligations

1. Investigators must be registered Clinical practitioners, qualified to carry out the study, taking into account the nature of the study and the particular phase and nature of the investigation undertaken.

2. Investigators must provide the Sponsor (or its delegate) with appropriate regulatory documentation and up-to-date curricula vitae for themselves and co-Investigators participating in the Clinical trial. They must also furnish the Sponsor (or its
delegate) with the names of all ancillary staff (pharmacists, nurses, etc.) who are directly involved in the study.

3. Investigators are responsible for providing suitable facilities to allow the study to be conducted efficiently and effectively.

4. Investigators are responsible for obtaining written IRB/IEC approval before initiation of the study from their respective institutions. This also includes an IRB/IEC approval of the ICF and any applicable amendments.

5. Investigators are responsible for obtaining written informed consent/assent from the patients and/or legal representatives, prior to the initiation of any study procedures. The patient should receive a copy of the written ICF.

6. Investigators are responsible for conducting the study according to the protocol for the accurate and complete reporting of results in accordance with GCP, and for maintaining accurate investigational product accountability records.

7. Investigators must record in detail all AEs occurring during the course of the study. They must report all SAEs immediately to the Sponsor (or its delegate) and the IRB/IEC, and notify the Sponsor (or its delegate) immediately when a patient has been removed from the study because of a SAE. The responsible Investigators should institute appropriate diagnostic and therapeutic measures and should keep the patient under observation for as long as it is medically indicated.

8. Investigators must provide completed eCRFs and resolve discrepancies in a timely manner.

9. Investigators must ensure that the study documents are retained in a safe and secure location for 15 years following the completion of the study. No documents may be destroyed without written permission of the Sponsor.

### 16.9 Data Quality Compliance

To ensure accurate, complete, and reliable data, the Sponsor will do the following:

The Clinical Research Division will:

- Provide instructional material to the study sites.
- Sponsor a Start-up Training Session to instruct the Investigators and study coordinators. This session will give instruction on the protocol, the completion of the CRFs, study procedures, GCP and ICH guidelines and the Operations Manual.
- Make periodic visits to the study sites.
- Be available for consultation with the study site personnel by mail, telephone and fax.

The Clinical Data Management Division will:

- Review and evaluate CRF data and use standard computer edits to detect errors in data collection.
• Conduct a quality review of the database.

The Quality Assurance Division will:

• Audit all or parts of the study and all or parts of its documentation including those generated at investigators’ sites, local and central laboratories and support sites.

• Audit the final report to ensure that, as far as can be reasonably established, the methods described and the results reported accurately reflect the raw data generated during the study.

• Conduct, if necessary, process Audits including samples of data and documentation to assure compliance with ICH GCP E6, applicable local regulations, guidelines and laws as well as the study protocol and relevant Sponsor Standard Operating Procedures and Work Instructions.

16.10 Study Reports

One report on safety and efficacy will be prepared by the Sponsor (or its delegate) at the completion of the study. The lead Investigator and/or members of the Steering Committee may have an opportunity to review the study report. The Chair of the Steering Committee and appropriate Sponsor members will be signing the study report to indicate approval.

The Sponsor will be responsible for all submissions to the regulatory agencies.

16.11 Ownership

The terms of the TIRCON FP7 Grant Agreement No. 277984 and the TIRCON internal Consortium Agreement, as agreed upon and signed by all parties, shall apply.

16.12 Publications/Poster/Presentation

The terms of the TIRCON FP7 Grant Agreement No. 277984 and the TIRCON internal Consortium Agreement, as agreed upon and signed by all parties, shall apply.

16.13 Early Study Termination

The Sponsor or its delegate reserves the right to discontinue this trial at any time. The study may be terminated by the Investigator at his/her respective site following consultation with the Sponsor. The Investigator will immediately, on discontinuance of the Clinical trial, in its entirety or at a Clinical trial site, inform both the Clinical trial patients and the IRB/IEC responsible for the study of the discontinuance, provide them with the reasons for the discontinuance and advise them in writing of any potential risks to the health of Clinical trial patients or other persons. It is the Sponsor’s (or its delegate) responsibility to report discontinuance of the study to regulatory agencies, and
provide them with the reasons for the discontinuance and advise them in writing of any potential risks to the health of Clinical trial patients or other persons. The Sponsor (or its delegate) must then inform the Investigators.

In the event of a discontinuation, the Investigators will ensure return of all investigational products to the Sponsor with all outstanding investigational materials (e.g. CRFs, SAE forms) within 1 month. If possible, Investigators should complete all assessments as per the study termination assessments (see Section 6.13).

If there is any conflict between the terms of section 16.13 and the TIRCON FP7 Grant Agreement No. 277984 and the internal Consortium Agreement, the terms of the TIRCON FP7 Grant Agreement No. 277984 and internal Consortium Agreement shall take precedence.

17 CONFIDENTIALITY

The terms of the TIRCON FP7 Grant Agreement No. 277984 and the TIRCON internal Consortium Agreement, as agreed upon and signed by all parties, shall apply.
18 REFERENCES


26. Waldmeier PC, Buchle AM, Steulet AF. Inhibition of catechol-O-methyltransferase (COMT) as well as tyrosine and tryptophan hydroxylase by the orally active iron chelator, 1,2-dimethyl-3-hydroxypyridin-4-one (L1, CP20), in rat brain in vivo. Biochem Pharmacol. 1993; 45(12):2417-24.


29. Zuccarelli A, Sanna PMG, Bellu L, Solinas, & Mulas G. Therapy with Deferiprone in a case of Pantothenate kinase-associated neurodegeneration
(PKAN) [Terapia con Deferiprone in un caso di Neurodegenerazione associata al difetto di pantetonato chinasi (PKAN)]. 2008; (V CONGRESSO NAZIONALE SOSTE Cagliari 16-18 ottobre 2008)
19 SIGNED AGREEMENT TO THE PROTOCOL

19.1 Principal Investigator Signature Page

I confirm that I have read this protocol and I understand it. I agree to conduct this study in accordance with ICH Good Clinical Practice guidelines, all of the specifications in this study protocol, and local regulatory requirements. I will be responsible for obtaining approval from the IRB/IEC responsible for my institution before the start of the study. I will adhere to the protocol and comply with the guidelines. I agree to fully co-operate with compliance checks by allowing access to all documentation by authorized individuals.

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

Study Code: TIRCON2012V1

Study Site:

________________________________________
Investigator Name

________________________________________
Investigator Signature Date: (DD MMM YYYY)

________________________________________
Name of Facility

________________________________________
Location of Facility
19.2 Protocol Approval Signature Page

The undersigned, hereby declare that this study will be carried out under supervision in accordance with the methods described herein.

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

**Study Code:** TIRCON2012V1

---

(Thomas Klopstock, M.D.)
Friedrich-Baur-Institute, Department of Neurology, University of Munich Ziemssenstr, Germany

Date: (DD MMM YYYY)

---

(Competent Authority)

Date: (DD MMM YYYY)

---

(Elliot Vichinsky, M.D.)
Medical Director, Hematology/Oncology Department
Children's Hospital & Research Center Oakland, USA

Date: (DD MMM YYYY)

---

(Fernando Tricca, M.D.)
Vice President, Medical Affairs
ApoPharma Inc., Canada

Date: (DD MMM YYYY)
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(Thomas Klopstock, M.D.)
Friedrich-Baur-Institute, Department of Neurology, University of Munich Ziemsenstr, Germany

Date: (DD MMM YYYY)

(Elliott Vichinsky, M.D.)
Medical Director, Hematology/Oncology Department
Children’s Hospital & Research Center Oakland, USA

Date: (DD MMM YYYY)

(Fernando Tricta, M.D.)
Vice President, Medical Affairs
ApoPharma Inc., Canada

Date: (DD MMM YYYY)
## 20 APPENDICES

### 20.1 Schedule of Events

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<th>STUDY PROCEDURE</th>
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<td>Physical examination</td>
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<td>Hematology</td>
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<td>Biochemistry</td>
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<td>Serology</td>
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<td>Serum pregnancy testing (females only)</td>
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<tr>
<td>STUDY PROCEDURE</td>
<td>Screening/Baseline Phase</td>
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<td>Screening Baseline</td>
<td>Telephone Contact Month 1.5 (Week 6) Visit</td>
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<td>Urine pregnancy testing (females only)</td>
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<td>12-lead ECG</td>
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<td>Likert Scale</td>
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<tr>
<td>BAD (completed by a qualified Investigator or qualified delegate)</td>
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<td>BAD scale Videotaping</td>
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<td>PedsQL</td>
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<td>PSQI</td>
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<tr>
<td>Pharmacokinetic samples collection</td>
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</table>

Urine pregnancy testing (females only), Urinalysis, Vital signs (including weight), Height, 12-lead ECG, Contraceptive counselling, Brain MRI of globus pallidus (subset of patients), Likert Scale, BAD (completed by a qualified Investigator or qualified delegate), BAD scale Videotaping, PGI-I, UPDRS I, II, III and VI, WeeFIM/FIM, PedsQL, PSQI, Pharmacokinetic samples collection.
X - To do

1. Screening procedures must be performed within 14 days prior to baseline visit (start of dosing). Females of childbearing potential must use an approved birth control method at least 30 days prior to baseline visit.
2. Discontinuation: if subject withdraws from the study prior to Month 18, the subject must be seen for an Early Termination Visit within 30 days after treatment discontinuation.
3. Follow-up visit should be conducted 4 weeks after Month 18/Early Termination visit.
20.2 Acceptable Methods of Contraception and Definitions Related to Childbearing Potential

1. Approved methods of contraception will consist of the following for the purposes of this study or must follow local requirements:
   - Oral contraceptive medications with condom, or diaphragm or spermicide
   - Hormonal implants with condom, or diaphragm or spermicide
   - Injectable contraceptive medications with condom, or diaphragm or spermicide
   - Diaphragm or condom used with spermicide.

   If the hormonal contraception is used, it should have a Pearl index <1%.

2. Women who are not able to bear children and therefore do not need to practice a medically accepted method of contraception will include those who:
   - Have had a tubal ligation
   - Are post-menopausal (i.e. last menstrual period was more than 2 years ago)
   - Have had an hysterectomy or oophrectomy
   - Participates in a non-heterosexual lifestyle,
   - Have a male sexual partner has been sterilized (supporting evidence required).

3. Patients who are peri-menopausal (i.e. less than 2 years since their last menstrual period), must have a pregnancy test and must use one of the medically accepted methods listed above (under point 2) if they wish to participate in the study.
20.3 List of Rescue Medications

Any use of the rescue medications listed below must be documented including the reason. Rescue medication is defined as the introduction of a new medication, or a change in dosing of a current medication, that is prescribed because of a worsening of the patient’s condition and that has the potential to have an effect on dystonia symptoms.

1. Baclofen (including baclofen pump)
2. Trihexyphenidyl
3. Clonazepam
4. Tizanidine
5. Tetrabenazine
6. Botox
20.4 List of Prohibited Drugs

The use of the following medications is precluded by protocol TIRCON2012V1. All exceptions must be approved by the Sponsor

1. Any investigational drug
2. Chloramphenicol (CHLOROMYCETIN)
3. Clozapine (CLOZARIL), Doxepin HCl (SINEQUAN), Amitriptyline HCl/Perphenazine (ETRAFON) and other tricyclic antidepressants
4. Clomipramine hydrochloride (ANAFRANIL)
5. Propranolol hydrochloride (INDERAL)
6. Bepredil (VASCOR)
7. Aminogluthethimide (CYTADREN)
8. Interferon (INTRON A)
9. Para-aminophenol (e.g., paracetamol or acetaminophen) or pyrazolone derivatives
10. Phenytoin (DILANTIN), Carbamazepine
11. Chlordiazepoxide (LIBRIUM) and other benzodiazepines
12. Phenylbutazone
13. Mefenamic Acid (PONSTAN)
14. Metoclopramide HCl (REGLAN)
15. Chlorpromazine, prochlorperazine and other phenothiazines
16. Procainamide
17. Levamisole (ERGAMISOLE)
18. Diclofenac Sodium (VOLTAREN)
19. Hydroxyurea (Hydrea)
20. Trimethoprim/sulfamethoxazole (Bactrim/Septra)
21. Aminopyrine
20.5 Rating Scales

20.5.1 BAD

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Barry-Albright Dystonia Scale

Patient’s Number: ____________________________ Date: _____________

Directions: Assess the patient for dystonia in each of the following regions: eyes, mouth, neck, trunk, each upper and lower extremity (8 body regions). Write the scores on the lines provided (whole numbers only). Rate severity based only on dystonia as evidenced by abnormal movements or postures.

Dystonia: sustained muscle contractions causing twisting and repetitive movements or abnormal postures.

Spasticity: velocity-dependent resistance to passive stretch.

Athetosis: distal writhing or contorting movements.

Chorea: brief, rapid, unsustained, irregular movements.

Ataxia: incoordination of movement characterized by wide-based unsteady gait, falling movements.

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Eyes: Signs of dystonia of the eyes include: Prolonged eyelid spasms and/or forced eye deviations.

0 ____ Absence of eye dystonia.
1 ____ Slight. Dystonia less than 10% of the time.
2 ____ Mild. Frequent blinking without prolonged spasms of eye closure and/or eye movements less than 50% of the time.
3 ____ Moderate. Prolonged spasms of eyelid closure, but eyes open most of the time.
4 ____ Severe. Prolonged spasms of eyelid closure, with eyes closed at least 30% of the time.

* ____ Unable to assess eye movements.

Eyes: ______

Mouth: Signs of dystonia of the mouth include: Grimacing, clenched or deviated jaw, forced open mouth, and/or forceful tongue thrusting.

0 ____ Absence of mouth dystonia.
1 ____ Slight. Dystonia less than 10% of the time and does not interfere with speech or feeding.
2 ____ Mild. Dystonia less than 50% of the time and does not interfere with speech or feeding.
3 ____ Moderate. Dystonia more than 50% of the time, or dystonia that interferes with speech or feeding.
4____ **Severe.** Dystonia more than 50% of the time or dystonia that prevents speech or feeding.

*____ Unable to assess mouth movements.

**Mouth:** ______

**Neck:** Signs of dystonia of the neck include: Pulling of the neck into any plane of motion: Extension, flexion, lateral flexion or rotation.

0____ **Absence** of neck dystonia.

1____ **Slight.** Pulling less than 10% of the time and does not interfere with lying, sitting, standing or walking.

2____ **Mild.** Pulling less than 50% of the time and does not interfere with lying, sitting, standing or walking.

3____ **Moderate.** Pulling more than 50% of the time or dystonia that interferes with lying, sitting, standing or walking.

4____ **Severe.** Pulling more than 50% of the time or dystonia that prevents sitting in standard wheelchair, standing or walking (i.e. requires more than standard head rest for seating).

*____ Unable to assess neck movements.

**Neck:** ______

**Trunk:**

0____ **Absence** of trunk dystonia.

1____ **Slight.** Pulling less than 10% of the time and does not interfere with lying, sitting, standing or walking.

2____ **Mild.** Pulling less than 50% of the time and does not interfere with lying, sitting, standing or walking.

3____ **Moderate.** Pulling more than 50% of the time or dystonia that interferes with lying, sitting, standing or walking.

4____ **Severe.** Pulling more than 50% of the time or dystonia that prevents sitting in standard wheelchair, standing or walking.

*____ Unable to assess trunk movements.

**Trunk:** ______

**Upper Extremities:**

0____ **Absence** of upper extremity dystonia.

1____ **Slight.** Dystonia less than 10% of the time and does not interfere with normal positioning or functional activities.

2____ **Mild.** Dystonia less than 50% of the time and does not interfere with normal positioning or functional activities.
3. **Moderate**. Dystonia more than 50% of the time or dystonia that interferes with normal positioning or upper extremity function.
4. **Severe**. Dystonia more than 50% of the time or dystonia that prevents normal positioning or upper extremity function; i.e., arms restrained in wheelchair to prevent injury.
* Unable to assess upper extremity movements.

**Left Upper Extremity:**
**Right Upper Extremity:**

**Lower Extremities:**
0. **Absence** of lower extremity dystonia.
1. **Slight**. Dystonia less than 10% of the time and does not interfere with normal positioning or functional activities.
2. **Mild**. Dystonia less than 50% of the time and does not interfere with normal positioning or functional activities.
3. **Moderate**. Dystonia more than 50% of the time or dystonia that interferes with normal positioning or lower extremity weight bearing or function.
4. **Severe**. Dystonia more than 50% of the time or dystonia that prevents normal positioning or lower extremity weight bearing or function.
* Unable to assess lower extremity movements.

**Left Lower Extremity:**
**Right Lower Extremity:**

**Total Score:**
**Rater’s Initials:**
The Patient Global Impression of Improvement (PGI-I) is a global index used to rate the response of a condition to a therapy. Patients are asked to rate their total improvement since the beginning of the study. A 7 point rating scale is used as:

1, very much improved;
2, much improved;
3, minimally improved;
4, no change;
5, minimally worse;
6, much worse; or
7, very much worse
20.5.3 UPDRS

UNIFIED PARKINSON'S DISEASE RATING SCALE (UPDRS)


**APPENDIX 1**
Unified Parkinson’s Disease Rating Scale
Version 3.0 – February 1987
Definitions of 0-4 Scale

1. MENTATION, BEHAVIOR AND MOOD

1. **Intellectual Impairment:**
   0 = None.
   1 = Mild. Consistent forgetfulness with partial recollection of events and no other difficulties.
   2 = Moderate memory loss, with disorientation and moderate difficulty handling complex problems.
   Mild but definite impairment of function at home with need of occasional prompting.
   3 = Severe memory loss with disorientation for time and often to place. Severe impairment in handling problems.
   4 = Severe memory loss with orientation preserved to person only. Unable to make judgements or solve problems. Requires much help with personal care. Cannot be left alone at all.

2. **Thought Disorder:** (DUE TO DEMENTIA OR DRUG INTOXICATION)
   0 = None.
   1 = Vivid dreaming.
   2 = "Benign" hallucinations with insight retained.
   3 = Occasional to frequent hallucinations or delusions; without insight; could interfere with daily activities.
   4 = Persistent hallucinations, delusions, or florid psychosis. Not able to care for self.

3. **Depression:**
   0 = None.
   1 = Periods of sadness or guilt greater than normal, never sustained for days or weeks.
   2 = Sustained depression (1 week or more).
   3 = Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest).
4 = Sustained depression with vegetative symptoms and suicidal thoughts or intent.

4. Motivation/Initiative:

0 = Normal.
1 = Less assertive than usual; more passive.
2 = Loss of initiative or disinterest in elective (nonroutine) activities.
3 = Loss of initiative or disinterest in day to day (routine) activities.
4 = Withdrawn, complete loss of motivation.

II. ACTIVITIES OF DAILY LIVING (DETERMINE FOR "ON/OFF")

5. Speech:

0 = Normal.
1 = Mildly affected. No difficulty being understood.
2 = Moderately affected. Sometimes asked to repeat statements.
3 = Severely affected. Frequently asked to repeat statements.
4 = Unintelligible most of the time.

6. Salivation:

0 = Normal.
1 = Slight but definite excess of saliva in mouth; may have nighttime drooling.
2 = Moderately excessive saliva; may have minimal drooling.
3 = Marked excess of saliva with some drooling.
4 = Marked drooling, requires constant tissue or handkerchief.

7. Swallowing:

0 = Normal.
1 = Rare choking.
2 = Occasional choking.
3 = Requires soft food.
4 = Requires NG tube or gastrotomy feeding.

8. Handwriting:

0 = Normal.
1 = Slightly slow or small.
2 = Moderately slow or small; all words are legible.
3 = Severely affected; not all words are legible.
4 = The majority of words are not legible.

9. Cutting food and handling utensils:

0 = Normal.
10. **Dressing:**

0 = Normal.
1 = Somewhat slow, but no help needed.
2 = Occasional assistance with buttoning, getting arms in sleeves.
3 = Considerable help required, but can do some things alone.
4 = Helpless.

11. **Hygiene:**

0 = Normal.
1 = Somewhat slow, but no help needed.
2 = Needs help to shower or bathe; or very slow in hygienic care.
3 = Requires assistance for washing, brushing teeth, combing hair, going to bathroom.
4 = Foley catheter or other mechanical aids.

12. **Turning in bed and adjusting bed clothes:**

0 = Normal.
1 = Somewhat slow and clumsy, but no help needed.
2 = Can turn alone or adjust sheets, but with great difficulty.
3 = Can initiate, but not turn or adjust sheets alone.
4 = Helpless.

13. **Falling- (unrelated to freezing):**

0 = None.
1 = Rare falling.
2 = Occasionally falls, less than once per day.
3 = Falls an average of once daily.
4 = Falls more than once daily.

14. **Freezing when walking:**

0 = None.
1 = Rare freezing when walking; may have start hesitation.
2 = Occasional freezing when walking.
3 = Frequent freezing. Occasionally falls from freezing.
4 = Frequent falls from freezing.

15. **Walking:**

0 = Normal.
1 = Mild difficulty. May not swing arms or may tend to drag leg.
2 = Moderate difficulty, but requires little or no assistance.
3 = Severe disturbance of walking, requiring assistance.
4 = Cannot walk at all, even with assistance.

16. *Tremor:*
0 = Absent.
1 = Slight and infrequently present.
2 = Moderate; bothersome to patient.
3 = Severe; interferes with many activities.
4 = Marked; interferes with most activities.

17. *Sensory complaints related to parkinsonism:*
0 = None.
1 = Occasionally has numbness, tingling, or mild aching.
2 = Frequently has numbness, tingling, or aching; not distressing.
3 = Frequent painful sensations.
4 = Excruciating pain.

---

### III. MOTOR EXAMINATION

18. *Speech:*
0 = Normal.
1 = Slight loss of expression, diction and/or volume.
2 = Monotone, slurred but understandable; moderately impaired.
3 = Marked impairment, difficult to understand.
4 = Unintelligible.

19. *Facial Expression:*
0 = Normal.
1 = Minimal hypomimia, could be normal "Poker Face".
2 = Slight but definitely abnormal diminution of facial expression.
3 = Moderate hypomimia; lips parted some of the time.
4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more.

20. *Tremor at rest:*
0 = Absent.
1 = Slight and infrequently present.
2 = Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.
3 = Moderate in amplitude and present most of the time.
4 = Marked in amplitude and present most of the time.
21. Action or Postural Tremor of hands:

0 = Absent.
1 = Slight; present with action.
2 = Moderate in amplitude, present with action.
3 = Moderate in amplitude with posture holding as well as action.
4 = Marked in amplitude; interferes with feeding.

22. Rigidity: (Judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored.)

0 = Absent.
1 = Slight or detectable only when activated by mirror or other movements.
2 = Mild to moderate.
3 = Marked, but full range of motion easily achieved.
4 = Severe, range of motion achieved with difficulty.

23. Finger Taps: (Patient taps thumb with index finger in rapid succession with widest amplitude possible, each hand separately.)

0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

24. Hand Movements: (Patient opens and closes hands in rapid succession with widest amplitude possible, each hand separately.)

0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

25. Rapid Alternating Movements of Hands: (Pronation-supination movements of hands, vertically and horizontally, with as large an amplitude as possible, both hands simultaneously.)

0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

26. Leg Agility: *(Patient taps heel on the ground in rapid succession picking up entire leg. Amplitude should be at least 3 inches.)*

0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

27. Arising from Chair: *(Patient attempts to arise from a straight-back wood or metal chair with arms folder across chest.)*

(Patient attempts to rise from a straightbacked chair, with arms folded across chest.)
0 = Normal.
1 = Slow; or may need more than one attempt.
2 = Pushes self up from arms of seat.
3 = Tends to fall back and may have to try more than one time, but can get up without help.
4 = Unable to arise without help.

28. Posture:

0 = Normal erect.
1 = Not quite erect, slightly stooped posture; could be normal for older person.
2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.
3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.
4 = Marked flexion with extreme abnormality of posture.

29. Gait:

0 = Normal.
1 = Walks slowly, may shuffle with short steps, but no festination (hastening steps) or propulsion.
2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.
3 = Severe disturbance of gait, requiring assistance.
4 = Cannot walk at all, even with assistance.

30. Postural Stability: *(Response to sudden, strong posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared.)*

0 = Normal.
1 = Retropulsion, but recovers unaided.
2 = Absence of postural response; would fall if not caught by examiner.
3 = Very unstable, tends to lose balance spontaneously.
4 = Unable to stand without assistance.

31. **Body Bradykinesia and Hypokinesia:** (Combining slowness, hesitancy, decreased armswing, small amplitude, and poverty of movement in general.)

0 = None.
1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.
2 = Mild degree of slowness and poverty of movement which is definitely abnormal.
   Alternatively, some reduced amplitude.
3 = Moderate slowness, poverty or small amplitude of movement.
4 = Marked slowness, poverty or small amplitude of movement.

---

**IV. COMPLICATIONS OF THERAPY** (In the past week)

**A. Dyskinesias**

32. **Duration:** What proportion of the waking day are dyskinesias present? (Historical information.)

0 = None
1 = 1-25% of day.
2 = 26-50% of day.
3 = 51-75% of day.
4 = 76-100% of day.

33. **Disability:** How disabling are the dyskinesias? (Historical information; may be modified by office examination.)

0 = Not disabling.
1 = Mildly disabling.
2 = Moderately disabling.
3 = Severely disabling.
4 = Completely disabled.

34. **Painful Dyskinesias:** How painful are the dyskinesias?

0 = No painful dyskinesias.
1 = Slight.
2 = Moderate.
3 = Severe.
4 = Marked.

35. **Presence of Early Morning Dystonia:** (Historical information)

0 = No
1 = Yes
B. Clinical Fluctuations

36. *Are "off" periods predictable as to timing after a dose of medication?*

0 = No  
1 = Yes

37. *Are "off" periods unpredictable as to timing after a dose of medication?*

0 = No  
1 = Yes

38. *Do "off" periods come on suddenly, e.g., over a few seconds?*

0 = No  
1 = Yes

39. *What proportion of the waking day is the patient "off" on average?*

0 = None  
1 = 1-25% of day.  
2 = 26-50% of day.  
3 = 51-75% of day.  
4 = 76-100% of day.

C. Other Complications

40. *Does the patient have anorexia, nausea, or vomiting?*

0 = No  
1 = Yes

41. *Any sleep disturbances, e.g., insomnia or hypersomnolence?*

0 = No  
1 = Yes

42. *Does the patient have symptomatic orthostasis?*

0 = No  
1 = Yes

V. MODIFIED HOEHN AND YAHRT STAGING

STAGE 0 = No signs of disease.  
STAGE 1 = Unilateral disease.  
STAGE 1.5 = Unilateral plus axial involvement.
STAGE 2    = Bilateral disease, without impairment of balance.
STAGE 2.5 = Mild bilateral disease, with recovery on pull test.
STAGE 3    = Mild to moderate bilateral disease; some postural instability; physically independent.
STAGE 4    = Severe disability; still able to walk or stand unassisted.
STAGE 5    = Wheelchair bound or bedridden unless aided.

VI. SCHWAB AND ENGLAND ACTIVITIES OF DAILY LIVING SCALE

100% = Completely independent. Able to do all chores without slowness, difficulty or impairment. Essentially normal. Unaware of any difficulty.
90%  = Completely independent. Able to do all chores with some degree of slowness, difficulty and impairment. Might take twice as long. Beginning to be aware of difficulty.
80%  = Completely independent in most chores. Takes twice as long. Conscious of difficulty and slowness.
70%  = Not completely independent. More difficulty with some chores. Three to four times as long in some. Must spend a large part of the day with chores.
60%  = Some dependency. Can do most chores, but exceedingly slowly and with much effort. Errors; some impossible.
50%  = More dependent. Help with half, slower, etc. Difficulty with everything.
40%  = Very dependent. Can assist with all chores, but few alone.
30%  = With effort, now and then does a few chores alone or begins alone. Much help needed.
20%  = Nothing alone. Can be a slight help with some chores. Severe invalid.
10%  = Totally dependent, helpless. Complete invalid.
0%   = Vegetative functions such as swallowing, bladder and bowel functions are not functioning. Bedridden.
### FIM

#### CASE CODING FORM (Page 1 of 2)

**Patient Information**

1. Facility Code
2. Patient Code
3. Birth Date
4. Social Security Number
5. First Name *
6. MI
7. Last Name *
8. Street *
9. City *
10. State *
11. ZIP Code
12. Country *
13. Telephone *

**Case Information**

21. Admission Date
22. Admission Class
23. Discharge Date
24. Program Interruptions
25. Program Interruption Dates

**Medical Information**

26. Impairment Group
27. ASIA Impairment Scale
28. Date of Onset
29. Etiologic Diagnosis
30. Other Diagnoses: Most Significant
31. Complications/Comorbidities
32. Diagnosis for Transfer or Death

**Payer/Charge Information**

18. Payment Source
A. Primary Source
   - Use codes listed for Secondary Source (except 15-None).
B. Secondary Source
   - 01-Medicare 02-Medicaid HCPCS 03-Non-Medicare 04-Private 05-Commercial 06-Medicaid HCPCS 07-Private 08-Workers Compensation 09-Crippled Children’s Service 10-Veteran Affairs 11-VA Health Care 12-Non-Veteran Affairs 13-Other 14-None (only for secondary sources) 15-No Fault Auto

19. Gross Rehabilitation Charges
A. Total
B. Physician Fee

20. Net Rehabilitation Charges
A. Total
B. Physician Fee

---

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Adult FIM Case Coding Form, USA/Canada 07/11/2011*
# Case Coding Form (Page 2 of 2)

## Patient/Case Identification

1. Facility Code
2. Patient Code
21. Admission Date: MM/DD/YYYY

## Admission Information

33. Admit From:
   - 01 Home
   - 02 Board and Care
   - 03 Transitional Living
   - 04 Intermediate Care
   - 05 Skilled Nursing Facility
   - 06 Acute Unit of own Facility
   - 07 Acute Unit of another facility
   - 08 Chronic Hospital
   - 09 Rehabilitation Facility
   - 10 Other
   - 12 Alternate Level of Care Unit
   - 13 Subacute Setting
   - 14 Assisted Living Residence

34. Prehospital Living Setting:
   - Home Care

35. Prehospital Living With:
   - Alone
   - Family/Relatives
   - Friends
   - Other

36. Prehospital Vocational Category:
   - Full-time Work
   - Part-time Work
   - Retired
   - Military
   - Student
   - Unemployed
   - Disabled

37. Prehospital Vocational Effort:
   - Full-time Work
   - Part-time Work
   - Unemployed
   - Disabled

## Discharge Information

38. Discharge To Living Setting:
   - Home Care
   - Board and Care
   - Transitional Living
   - Intermediate Care
   - Skilled Nursing Facility
   - Acute Unit of own Facility
   - Acute Unit of another facility
   - Chronic Hospital
   - Rehabilitation Facility
   - Other
   - Alternate Level of Care Unit
   - Subacute Setting
   - Assisted Living Residence

39. Discharge To Living With:
   - Alone
   - Family/Relatives
   - Friends
   - Other

## Program Information

40. Therapy Date Range:
   - Start of Therapy: MM/DD/YYYY
   - End of Therapy: MM/DD/YYYY

41. Internal Program Name

## Case Notes

## Functional Independence Measure (FIM)

### Self-Care
- A. Eating
- B. Grooming
- C. Bathing
- D. Dressing - Upper
- E. Dressing - Lower
- F. Toileting
- G. Bladder
- H. Bowel
- I. Bed, Chair, Wheelchair
- J. Toilet
- K. Tub, Shower

### Locomotion
- L. Walk/Wheelchair
- M. Stairs

### Communication
- N. Comprehension
- O. Expression

### Social Cognition
- P. Social Interaction
- Q. Problem Solving
- R. Memory

### Admit Score
- Wheelchair
- Non-Wheelchair

### Discharge Score
- D-BAT
- E-BAT

### Goal
- "(Leave blank. Enter if not testable due to risk.)"

## FIM Levels
- No Help
- Complete Independence (Timely, Safety)
- Modified Independence (Device)
- Helper - Modified Dependence
- Supervision (Subject = 100%)
- Minimal Assistance (Subject = 75% or more)
- Moderate Assistance (Subject = 50% or more)
- Helper - Complete Dependence
- Maximal Assistance (Subject = 25% or more)
- Total Assistance or not testable (Subject less than 25%)

---

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# INTERIM OR FOLLOW-UP ASSESSMENT CODING FORM

## PATIENT/CASE IDENTIFICATION

| 1. Facility Code |  
| 2. Patient Code |  
| 21. Admission Date | MM/DD/YYYY |

## ASSESSMENT INFORMATION

| 60. Assessment Type | 2-Interim OR 4-Follow-up |
| 61. Assessment Date | MM/DD/YYYY |

## FOLLOW-UP INFORMATION ONLY

| 62. Follow-up Information Source |  
| 63. Follow-up Assessment Method | 1. In person | 2. Telephone | 3. Mail questionnaire |
| 64. Follow-up Living Setting |  
| 1. Home | 2. Board and Care | 3. Transitional Living |
| 4. Skilled Nursing Facility | 5. Acute Care Facility | 6. Emergency Room |


## FOLLOW-UP Health Maintenance

| A. Primary |  
| 1. Own care | 2. Unpaid person or family |
| 3. Paid attendant or aide | 4. Paid, skilled professional |

| B. Secondary |  
| Use code below for auxiliary follow-up health maintenance. |

| 69. Follow-up Therapy | 1. Home | 2. Outpatient therapy | 3. Home-based paid professional therapy |
| 4. Outpatient and home-based paid professional therapy | 5. Inpatient | 6. Long-Term Care Facility |
| 7. Other | 8. Day Treatment |

## FOLLOW-UP Diagnoses

| A | B | C |
| D | E | F |
| G |

## 71. FUNCTIONAL INDEPENDENCE MEASURE (FIM)

**SELF-CARE**

- A. Eating
- B. Grooming
- C. Bathing
- D. Dressing - Upper
- E. Dressing - Lower
- F. Toileting

**SPHINCTER CONTROL**

- G. Bladder
- H. Bowel

**TRANSFERS**

- I. Bed, Chair, Wheelchair
- J. Toilet
- K. Tub, Shower

**LOCOMOTION**

- L. Walk/Wheelchair
- M. Stairs

**COMMUNICATION**

- N. Comprehension
- O. Expression

**SOCIAL COGNITION**

- P. Social Interaction
- Q. Problem Solving
- R. Memory

*Leave no blanks. Enter 1 if not testable due to risk.*

**FIM LEVELS**

| No Help | 7. Complete Independence (Timely, Safely) |
| 6. Modified Independence (Device) |
| Helper - Modified Dependence |
| 5. Supervision (Subject < 100%) |
| 4. Minimal Assistance (Subject > 75%) |
| 3. Moderate Assistance (Subject < 50%) |
| Helper - Complete Dependence |
| 2. Maximal Assistance (Subject > 25%) |
| 1. Total Assistance or not testable (Subject less than 25%) |

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**Page 117 of 150**
### 20.5.5 WeeFIM

#### WeeFIM™ Assessment Coding Form

<table>
<thead>
<tr>
<th>Case Identification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Facility Code</td>
</tr>
<tr>
<td>2. Patient Code</td>
</tr>
<tr>
<td>3. Admission Date</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Assessment Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. Assessment Type</td>
</tr>
<tr>
<td>(a) Pre-admission (1) Admission (2) 30 Days Only (3) Discharge (4) Follow-up</td>
</tr>
<tr>
<td>5. Assessment Date</td>
</tr>
<tr>
<td>6. Information Source</td>
</tr>
<tr>
<td>Record one item from the list below for follow-up and outpatient only.</td>
</tr>
<tr>
<td>(1) Staff (2) Patient (3) Caregiver (4) Other</td>
</tr>
<tr>
<td>7. Assessment Method</td>
</tr>
<tr>
<td>Record one item from the list below for follow-up and outpatient only.</td>
</tr>
<tr>
<td>(1) In person (2) Telephone (3) Tablet/phone (4) Unable to reach</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Living Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Home (2) Acute care unit of own facility (3) Acute care unit of another facility (4) Rehabilitation facility (5) Residential facility (6) Transitional living center (7) Skilled nursing facility (8) Shelter (9) Other (10) Died</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Living With</th>
</tr>
</thead>
<tbody>
<tr>
<td>Record one item from the list below only if Living Setting (item 8) was recorded (1) Home (2) Two parents (3) One parent (4) Resides (5) Foster care (6) Other</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Educational Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) N/A (2) Early education program (3) Pre-school (4) Kindergarten-12 (5) Other</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Educational Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Regular class (2) Regular class with accommodation (3) Special classes (4) Home based or home schooling (5) Any other (6) Homeless (7) Community</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Health Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Home (2) Skilled professional (3) One parent (4) Foster care (5) Other</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) N/A (2) Home-based professional therapy (3) Both / &amp; (4) Both / &amp; (5) Inpatient hospital / (6) Day treatment / (7) School based / (8) Other</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Therapy Services</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) N/A (2) Physical therapy (3) Occupational therapy (4) Speech therapy (5) Physical &amp; Occupational therapy (6) Physical occupation (7) Other</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gait Training Equipment</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Communication Devices</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Self-Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Eating</td>
</tr>
<tr>
<td>b. Grooming</td>
</tr>
<tr>
<td>c. Bathing</td>
</tr>
<tr>
<td>d. Dressing—Upper Body</td>
</tr>
<tr>
<td>e. Dressing—Lower Body</td>
</tr>
<tr>
<td>f. Toileting</td>
</tr>
<tr>
<td>g. Bladder Management</td>
</tr>
<tr>
<td>h. Bowel Management</td>
</tr>
<tr>
<td>i. Self-Care Total</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mobility</th>
</tr>
</thead>
<tbody>
<tr>
<td>i. Chair, Wheelchair</td>
</tr>
<tr>
<td>j. Toilet</td>
</tr>
<tr>
<td>k. Tub, Shower</td>
</tr>
<tr>
<td>l. Walk, Wheelchair, Crawl</td>
</tr>
<tr>
<td>m. Stairs</td>
</tr>
<tr>
<td>n. Mobility Total</td>
</tr>
<tr>
<td>o. Motor Total</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cognition</th>
</tr>
</thead>
<tbody>
<tr>
<td>n. Comprehension</td>
</tr>
<tr>
<td>o. Expression</td>
</tr>
<tr>
<td>p. Social Interaction</td>
</tr>
<tr>
<td>q. Problem Solving</td>
</tr>
<tr>
<td>r. Memory</td>
</tr>
<tr>
<td>s. Cognition Total</td>
</tr>
<tr>
<td>t. WeeFIM® Total</td>
</tr>
</tbody>
</table>

* Leave no blanks for this column. If an item is not testable due to risk, enter 1.

#### WeeFIM® Instrument

17. WeeFIM® Instrument

Rate the child for each of the items below.

<table>
<thead>
<tr>
<th>Self-Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Eating</td>
</tr>
<tr>
<td>b. Grooming</td>
</tr>
<tr>
<td>c. Bathing</td>
</tr>
<tr>
<td>d. Dressing—Upper Body</td>
</tr>
<tr>
<td>e. Dressing—Lower Body</td>
</tr>
<tr>
<td>f. Toileting</td>
</tr>
<tr>
<td>g. Bladder Management</td>
</tr>
<tr>
<td>h. Bowel Management</td>
</tr>
<tr>
<td>i. Self-Care Total</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mobility</th>
</tr>
</thead>
<tbody>
<tr>
<td>i. Chair, Wheelchair</td>
</tr>
<tr>
<td>j. Toilet</td>
</tr>
<tr>
<td>k. Tub, Shower</td>
</tr>
<tr>
<td>l. Walk, Wheelchair, Crawl</td>
</tr>
<tr>
<td>m. Stairs</td>
</tr>
<tr>
<td>n. Mobility Total</td>
</tr>
<tr>
<td>o. Motor Total</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cognition</th>
</tr>
</thead>
<tbody>
<tr>
<td>n. Comprehension</td>
</tr>
<tr>
<td>o. Expression</td>
</tr>
<tr>
<td>p. Social Interaction</td>
</tr>
<tr>
<td>q. Problem Solving</td>
</tr>
<tr>
<td>r. Memory</td>
</tr>
<tr>
<td>s. Cognition Total</td>
</tr>
<tr>
<td>t. WeeFIM® Total</td>
</tr>
</tbody>
</table>

#### WeeFIM® Rating Levels

| No Helper: |
| Complete independence (no device, timely, safely) |
| Modified independence (device, not timely, or not safely) |
| 6 | 7 |

| Helper - Modified Dependence |
| Supervision (subject performs 100% of the effort) |
| Minimal assistance (subject performs 75% or more of the effort) |
| Moderate assistance (subject performs 50% to 74% of the effort) |
| 4 | 5 | 6 |

| Total Assistance or Not Testable (subject performs less than 25% of the effort) |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 59 | 60 | 61 | 62 | 63 | 64 | 65 | 66 | 67 | 68 | 69 | 70 | 71 | 72 | 73 | 74 | 75 | 76 | 77 | 78 | 79 | 80 | 81 | 82 | 83 | 84 | 85 | 86 | 87 | 88 | 89 | 90 | 91 | 92 | 93 | 94 | 95 | 96 | 97 | 98 | 99 | 100 | 101 | 102 | 103 | 104 | 105 | 106 | 107 | 108 | 109 | 110 | 111 | 112 | 113 | 114 | 115 | 116 | 117 | 118 | 119 | 120 | 121 | 122 | 123 | 124 | 125 | 126 | 127 | 128 | 129 | 130 | 131 | 132 | 133 | 134 | 135 | 136 | 137 | 138 | 139 | 140 | 141 | 142 | 143 | 144 | 145 | 146 | 147 | 148 | 149 | 150 |

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Last revised: 11/17/03

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20.5.6 PedsQL

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PedsQL-4.0-Core – US/English
PedsQL-4.0-Core-YC_eng-USori.doc

PedsQL™
Pediatric Quality of Life Inventory
Version 4.0

PARENT REPORT for TODDLERS (ages 2-4)

DIRECTIONS

On the following page is a list of things that might be a problem for your child. Please tell us how much of a problem each one has been for your child during the past ONE month by circling:

0 if it is never a problem
1 if it is almost never a problem
2 if it is sometimes a problem
3 if it is often a problem
4 if it is almost always a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.
In the past ONE month, how much of a problem has your child had with ...

**PHYSICAL FUNCTIONING (problems with...)**

<table>
<thead>
<tr>
<th>Activity</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Walking</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Running</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Participating in active play or exercise</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Lifting something heavy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Bathing</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. Helping to pick up his or her toys</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. Having hurts or aches</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8. Low energy level</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

**EMOTIONAL FUNCTIONING (problems with...)**

<table>
<thead>
<tr>
<th>Problem</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Feeling afraid or scared</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Feeling sad or blue</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Feeling angry</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Trouble sleeping</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Worrying</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

**SOCIAL FUNCTIONING (problems with...)**

<table>
<thead>
<tr>
<th>Activity</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Playing with other children</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Other kids not wanting to play with him or her</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Getting teased by other children</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Not able to do things that other children his or her age can do</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Keeping up when playing with other children</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

*Please complete this section if your child attends school or daycare*

**SCHOOL FUNCTIONING (problems with...)**

<table>
<thead>
<tr>
<th>Activity</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Doing the same school activities as peers</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Missing school/daycare because of not feeling well</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Missing school/daycare to go to the doctor or Hospital</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
Instructions for interviewer:

I am going to ask you some questions about things that might be a problem for some children. I want to know how much of a problem any of these things might be for you.

Show the child the template and point to the responses as you read.

If it is not at all a problem for you, point to the smiling face

If it is sometimes a problem for you, point to the middle face

If it is a problem for you a lot, point to the frowning face

I will read each question. Point to the pictures to show me how much of a problem it is for you. Let’s try a practice one first.

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at all</th>
<th>Sometimes</th>
<th>A lot</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Is it hard for you to snap your fingers</td>
<td>☺</td>
<td>☹</td>
<td>☹</td>
</tr>
</tbody>
</table>

Ask the child to demonstrate snapping his or her fingers to determine whether or not the question was answered correctly. Repeat the question if the child demonstrates a response that is different from his or her action.
Think about how you have been doing for the last few weeks. Please listen carefully to each sentence and tell me how much of a problem this is for you.

After reading the item, gesture to the template. If the child hesitates or does not seem to understand how to answer, read the response options while pointing at the faces.

### Physical Functioning (problems with…)

<table>
<thead>
<tr>
<th>Item</th>
<th>Not at all</th>
<th>Sometimes</th>
<th>A lot</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Is it hard for you to walk</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>2. Is it hard for you to run</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>3. Is it hard for you to play sports or exercise</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>4. Is it hard for you to pick up big things</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>5. Is it hard for you to take a bath or shower</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>6. Is it hard for you to do chores (like pick up your toys)</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>7. Do you have hurts or aches (Where?)</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>8. Do you ever feel too tired to play</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

Remember, tell me how much of a problem this has been for you for the last few weeks.

### Emotional Functioning (problems with…)

<table>
<thead>
<tr>
<th>Item</th>
<th>Not at all</th>
<th>Sometimes</th>
<th>A lot</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you feel scared</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>2. Do you feel sad</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>3. Do you feel mad</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>4. Do you have trouble sleeping</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>5. Do you worry about what will happen to you</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

### Social Functioning (problems with…)

<table>
<thead>
<tr>
<th>Item</th>
<th>Not at all</th>
<th>Sometimes</th>
<th>A lot</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Is it hard for you to get along with other kids</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>2. Do other kids say they do not want to play with you</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>3. Do other kids tease you</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>4. Can other kids do things that you cannot do</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>5. Is it hard for you to keep up when you play with other Kids</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

### School Functioning (problems with…)

<table>
<thead>
<tr>
<th>Item</th>
<th>Not at all</th>
<th>Sometimes</th>
<th>A lot</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Is it hard for you to pay attention in school</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>2. Do you forget things</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>3. Is it hard to keep up with schoolwork</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>4. Do you miss school because of not feeling good</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>5. Do you miss school because you have to go to the doctor’s or hospital</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>
How much of a problem is this for you?

Not at all  Sometimes  A lot

😊  🙃  🙁
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Pediatric Quality of Life Inventory
Version 4.0

PARENT REPORT for YOUNG CHILDREN (ages 5-7)

DIRECTIONS

On the following page is a list of things that might be a problem for your child. Please tell us how much of a problem each one has been for your child during the past ONE month by circling:

0 if it is never a problem
1 if it is almost never a problem
2 if it is sometimes a problem
3 if it is often a problem
4 if it is almost always a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.
In the past **ONE month**, how much of a **problem** has your child had with …

### PHYSICAL FUNCTIONING (**problems with…**)  

<table>
<thead>
<tr>
<th>Problem</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Walking more than one block</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Running</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Participating in sports activity or exercise</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Lifting something heavy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Taking a bath or shower by him or herself</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. Doing chores, like picking up his or her toys</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. Having hurts or aches</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8. Low energy level</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### EMOTIONAL FUNCTIONING (**problems with…**)  

<table>
<thead>
<tr>
<th>Problem</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Feeling afraid or scared</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Feeling sad or blue</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Feeling angry</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Trouble sleeping</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Worrying about what will happen to him or her</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### SOCIAL FUNCTIONING (**problems with…**)  

<table>
<thead>
<tr>
<th>Problem</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Getting along with other children</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Other kids not wanting to be his or her friend</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Getting teased by other children</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Not able to do things that other children his or her age can do</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Keeping up when playing with other children</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### SCHOOL FUNCTIONING (**problems with…**)  

<table>
<thead>
<tr>
<th>Problem</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Paying attention in class</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Forgetting things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Keeping up with school activities</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Missing school because of not feeling well</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Missing school to go to the doctor or hospital</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
CHILD REPORT (ages 8-12)

DIRECTIONS

On the following page is a list of things that might be a problem for you. Please tell us how much of a problem each one has been for you during the past ONE month by circling:

0 if it is never a problem
1 if it is almost never a problem
2 if it is sometimes a problem
3 if it is often a problem
4 if it is almost always a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.
In the past ONE month, how much of a problem has this been for you …

**ABOUT MY HEALTH AND ACTIVITIES (problems with…)**

<table>
<thead>
<tr>
<th>Problem</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. It is hard for me to walk more than one block</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. It is hard for me to run</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. It is hard for me to do sports activity or exercise</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. It is hard for me to lift something heavy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. It is hard for me to take a bath or shower by myself</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. It is hard for me to do chores around the house</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. I hurt or ache</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8. I have low energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

**ABOUT MY FEELINGS (problems with…)**

<table>
<thead>
<tr>
<th>Feeling</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I feel afraid or scared</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. I feel sad or blue</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. I feel angry</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. I have trouble sleeping</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. I worry about what will happen to me</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

**HOW I GET ALONG WITH OTHERS (problems with…)**

<table>
<thead>
<tr>
<th>Problem</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I have trouble getting along with other kids</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Other kids do not want to be my friend</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Other kids tease me</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. I cannot do things that other kids my age can do</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. It is hard to keep up when I play with other kids</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

**ABOUT SCHOOL (problems with…)**

<table>
<thead>
<tr>
<th>Problem</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. It is hard to pay attention in class</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. I forget things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. I have trouble keeping up with my schoolwork</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. I miss school because of not feeling well</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. I miss school to go to the doctor or hospital</td>
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<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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</tbody>
</table>
PedsQL™
Pediatric Quality of Life Inventory
Version 4.0

PARENT REPORT for CHILDREN (ages 8-12)

DIRECTIONS

On the following page is a list of things that might be a problem for your child. Please tell us how much of a problem each one has been for your child during the past ONE month by circling:

0 if it is never a problem
1 if it is almost never a problem
2 if it is sometimes a problem
3 if it is often a problem
4 if it is almost always a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.
In the past **ONE month**, how much of a **problem** has your child had with…

<table>
<thead>
<tr>
<th>PHYSICAL FUNCTIONING (problems with…)</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Walking more than one block</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Running</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Participating in sports activity or exercise</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Lifting something heavy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Taking a bath or shower by him or herself</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. Doing chores around the house</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. Having hurts or aches</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8. Low energy level</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EMOTIONAL FUNCTIONING (problems with…)</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Feeling afraid or scared</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Feeling sad or blue</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Feeling angry</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Trouble sleeping</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Worrying about what will happen to him or her</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>SOCIAL FUNCTIONING (problems with…)</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Getting along with other children</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Other kids not wanting to be his or her friend</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Getting teased by other children</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Not able to do things that other children his or her age can do</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Keeping up when playing with other children</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SCHOOL FUNCTIONING (problems with…)</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Paying attention in class</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Forgetting things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Keeping up with schoolwork</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Missing school because of not feeling well</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Missing school to go to the doctor or hospital</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
# PedsQL™

## Pediatric Quality of Life Inventory

Version 4.0

## TEEN REPORT (ages 13-18)

**DIRECTIONS**

On the following page is a list of things that might be a problem for you. Please tell us how much of a problem each one has been for you during the past **ONE month** by circling:

- 0 if it is **never** a problem
- 1 if it is **almost never** a problem
- 2 if it is **sometimes** a problem
- 3 if it is **often** a problem
- 4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.
In the past ONE month, how much of a problem has this been for you …

**ABOUT MY HEALTH AND ACTIVITIES (problems with…)**

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. It is hard for me to walk more than one block</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. It is hard for me to run</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. It is hard for me to do sports activity or exercise</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. It is hard for me to lift something heavy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. It is hard for me to take a bath or shower by myself</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. It is hard for me to do chores around the house</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. I hurt or ache</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8. I have low energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

**ABOUT MY FEELINGS (problems with…)**

<table>
<thead>
<tr>
<th></th>
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<th>Almost Never</th>
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<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I feel afraid or scared</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. I feel sad or blue</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. I feel angry</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. I have trouble sleeping</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. I worry about what will happen to me</td>
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<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
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**HOW I GET ALONG WITH OTHERS (problems with…)**

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<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>1. I have trouble getting along with other teens</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Other teens do not want to be my friend</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
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</tr>
<tr>
<td>3. Other teens tease me</td>
<td>0</td>
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<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. I cannot do things that other teens my age can do</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. It is hard to keep up with my peers</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

**ABOUT SCHOOL (problems with…)**

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>1. It is hard to pay attention in class</td>
<td>0</td>
<td>1</td>
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<td>3</td>
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<tr>
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<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. I miss school because of not feeling well</td>
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PARENT REPORT for TEENS (ages 13-18)

DIRECTIONS
On the following page is a list of things that might be a problem for your teen. Please tell us how much of a problem each one has been for your teen during the past ONE month by circling:

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In the past ONE month, how much of a problem has your teen had with …

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<tbody>
<tr>
<td>1. Walking more than one block</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Running</td>
<td>0</td>
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<td>2</td>
<td>3</td>
<td>4</td>
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<tr>
<td>3. Participating in sports activity or exercise</td>
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<tr>
<td>5. Taking a bath or shower by him or herself</td>
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<tr>
<td>6. Doing chores around the house</td>
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<td>3</td>
<td>4</td>
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<tr>
<td>8. Low energy level</td>
<td>0</td>
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<tr>
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<tr>
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<tr>
<td>2. Feeling sad or blue</td>
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<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Feeling angry</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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<tr>
<td>4. Trouble sleeping</td>
<td>0</td>
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<td>2</td>
<td>3</td>
<td>4</td>
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<tr>
<td>5. Worrying about what will happen to him or her</td>
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<td>3</td>
<td>4</td>
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<table>
<thead>
<tr>
<th>SOCIAL FUNCTIONING (problems with…)</th>
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<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
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</thead>
<tbody>
<tr>
<td>1. Getting along with other teens</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Other teens not wanting to be his or her friend</td>
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<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Getting teased by other teens</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Not able to do things that other teens his or her age can do</td>
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<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Keeping up with other teens</td>
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<thead>
<tr>
<th>SCHOOL FUNCTIONING (problems with…)</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Paying attention in class</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Forgetting things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Keeping up with schoolwork</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Missing school because of not feeling well</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Missing school to go to the doctor or hospital</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
PedsQL™
Young Adult Quality of Life Inventory
Version 4.0

YOUNG ADULT REPORT (ages 18-25)

DIRECTIONS

On the following page is a list of things that might be a problem for you. Please tell us how much of a problem each one has been for you during the past ONE month by circling:

0 if it is never a problem
1 if it is almost never a problem
2 if it is sometimes a problem
3 if it is often a problem
4 if it is almost always a problem

There are no right or wrong answers. If you do not understand a question, please ask for help.
In the past ONE month, how much of a problem has this been for you …

### ABOUT MY HEALTH AND ACTIVITIES (problems with…)

<table>
<thead>
<tr>
<th>Problem</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. It is hard for me to walk more than one block</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. It is hard for me to run</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. It is hard for me to do sports activity or exercise</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. It is hard for me to lift something heavy</td>
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<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. It is hard for me to take a bath or shower by myself</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. It is hard for me to do chores around the house</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. I hurt or feel pain</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8. I have low energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### ABOUT MY FEELINGS (problems with…)

<table>
<thead>
<tr>
<th>Problem</th>
<th>Never</th>
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</tr>
</thead>
<tbody>
<tr>
<td>1. I feel afraid or scared</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. I feel sad or blue</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. I feel angry</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. I have trouble sleeping</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. I worry about what will happen to me</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### HOW I GET ALONG WITH OTHERS (problems with…)

<table>
<thead>
<tr>
<th>Problem</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I have trouble getting along with other young adults</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Other young adults do not want to be my friend</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Other young adults tease me</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. I cannot do things that others my age can do</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. It is hard to keep up with my peers</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### ABOUT MY WORK/STUDIES (problems with…)

<table>
<thead>
<tr>
<th>Problem</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. It is hard to pay attention at work or school</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. I forget things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. I have trouble keeping up with my work or studies</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. I miss work or school because of not feeling well</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. I miss work or school to go to the doctor or hospital</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
PedsQL™
Pediatric Quality of Life Inventory
Version 4.0

PARENT REPORT for YOUNG ADULTS (ages 18-25)

DIRECTIONS

On the following page is a list of things that might be a problem for your child. Please tell us how much of a problem each one has been for your child during the past ONE month by circling:

0 if it is never a problem
1 if it is almost never a problem
2 if it is sometimes a problem
3 if it is often a problem
4 if it is almost always a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.
In the past ONE month, how much of a **problem** has your child had with …

<table>
<thead>
<tr>
<th>PHYSICAL FUNCTIONING (PROBLEMS WITH…)</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Walking more than one block</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Running</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Participating in sports activity or exercise</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Lifting something heavy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Taking a bath or shower by him or herself</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. Doing chores around the house</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. Having hurts or aches</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8. Low energy level</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EMOTIONAL FUNCTIONING (PROBLEMS WITH…)</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Feeling afraid or scared</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Feeling sad or blue</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Feeling angry</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Trouble sleeping</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Worrying about what will happen to him or her</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SOCIAL FUNCTIONING (PROBLEMS WITH…)</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Getting along with other young adults</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Other young adults not wanting to be his or her friend</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Getting teased by other young adults</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Not able to do things that others his or her age can do</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Keeping up with other young adults</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SCHOOL FUNCTIONING (PROBLEMS WITH…)</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Paying attention at work or school</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Forgetting things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Keeping up with work or studies</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Missing work or school because of not feeling well</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Missing work or school to go to the doctor or hospital</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
PedsQL™

Adult Quality of Life Inventory

Version 4.0

ADULT REPORT

DIRECTIONS

On the following page is a list of things that might be a problem for you. Please tell us how much of a problem each one has been for you during the past ONE month by circling:

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1 if it is almost never a problem
2 if it is sometimes a problem
3 if it is often a problem
4 if it is almost always a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.
In the past **ONE month**, how much of a **problem** has this been for you …

### ABOUT MY HEALTH AND ACTIVITIES (*problems with…*)

<table>
<thead>
<tr>
<th>Problem</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. It is hard for me to walk more than one block</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. It is hard for me to run</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. It is hard for me to do sports activity or exercise</td>
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<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. It is hard for me to lift something heavy</td>
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<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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<tr>
<td>5. It is hard for me to take a bath or shower by myself</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. It is hard for me to do chores around the house</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. I hurt or ache</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8. I have low energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### ABOUT MY FEELINGS (*problems with…*)

<table>
<thead>
<tr>
<th>Problem</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
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</thead>
<tbody>
<tr>
<td>1. I feel afraid or scared</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. I feel sad or blue</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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<tr>
<td>3. I feel angry</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. I have trouble sleeping</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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<td>5. I worry about what will happen to me</td>
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<td>3</td>
<td>4</td>
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</table>

### HOW I GET ALONG WITH OTHERS (*problems with…*)

<table>
<thead>
<tr>
<th>Problem</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I have trouble getting along with other adults</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Other adults do not want to be my friend</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Other adults tease me</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. I cannot do things that others my age can do</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. It is hard to keep up with my peers</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### ABOUT MY WORK/STUDIES (*problems with…*)

<table>
<thead>
<tr>
<th>Problem</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. It is hard to pay attention at work or school</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. I forget things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. I have trouble keeping up with my work or studies</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. I miss work or school because of not feeling well</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. I miss work or school to go to the doctor or hospital</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
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</tr>
</tbody>
</table>
20.5.7 PSQI

PITTSBURGH SLEEP QUALITY INDEX

INSTRUCTIONS:

The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month.

Please answer all questions.

1. During the past month, what time have you usually gone to bed at night?
   
   BED TIME ___________

2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?
   
   NUMBER OF MINUTES ___________

3. During the past month, what time have you usually gotten up in the morning?
   
   GETTING UP TIME ___________

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.)
   
   HOURS OF SLEEP PER NIGHT ___________

For each of the remaining questions, check the one best response. Please answer all questions.

5. During the past month, how often have you had trouble sleeping because you . . .

   a) Cannot get to sleep within 30 minutes

      Not during the past month_____  Less than once a week_____  Once or twice a week_____  Three or more times a week_____ 

   b) Wake up in the middle of the night or early morning

      Not during the past month_____  Less than once a week_____  Once or twice a week_____  Three or more times a week_____ 

   c) Have to get up to use the bathroom


d) Cannot breathe comfortably

Not during the past month _____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

e) Cough or snore loudly

Not during the past month _____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

f) Feel too cold

Not during the past month _____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

g) Feel too hot

Not during the past month _____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

h) Had bad dreams

Not during the past month _____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

i) Have pain

Not during the past month _____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

j) Other reason(s), please describe__________________________________________
__________________________________________________________________________

How often during the past month have you had trouble sleeping because of this?

Not during the past month _____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

6. During the past month, how would you rate your sleep quality overall?

    Very good __________
    Fairly good __________
7. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Not during the past month</th>
<th>Less than once a week</th>
<th>Once or twice a week</th>
<th>Three or more times a week</th>
</tr>
</thead>
</table>

8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Not during the past month</th>
<th>Less than once a week</th>
<th>Once or twice a week</th>
<th>Three or more times a week</th>
</tr>
</thead>
</table>

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

<table>
<thead>
<tr>
<th>Problem severity</th>
<th>No problem at all</th>
<th>Only a very slight problem</th>
<th>Somewhat of a problem</th>
<th>A very big problem</th>
</tr>
</thead>
</table>

10. Do you have a bed partner or room mate?

<table>
<thead>
<tr>
<th>Bed or Room Mate Status</th>
<th>No bed partner or room mate</th>
<th>Partner/room mate in other room</th>
<th>Partner in same room, but not same bed</th>
<th>Partner in same bed</th>
</tr>
</thead>
</table>

If you have a room mate or bed partner, ask him/her how often in the past month you have had . . .

a) Loud snoring

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Not during the past month</th>
<th>Less than once a week</th>
<th>Once or twice a week</th>
<th>Three or more times a week</th>
</tr>
</thead>
</table>

b) Long pauses between breaths while asleep

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Not during the past month</th>
<th>Less than once a week</th>
<th>Once or twice a week</th>
<th>Three or more times a week</th>
</tr>
</thead>
</table>

c) Legs twitching or jerking while you sleep

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Not during the past month</th>
<th>Less than once a week</th>
<th>Once or twice a week</th>
<th>Three or more times a week</th>
</tr>
</thead>
</table>
d) Episodes of disorientation or confusion during sleep
Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

e) Other restlessness while you sleep; please describe_____________________________________________________________
___________________________________________________________________________
Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____
20.5.8 Likert Scale

The Likert scale is a psychometric scale used in this study to rate the patient’s state with regards to its PKAN symptoms on a specific day. Patients will be asked at Baseline, Month 6, 12 and 18 (or early termination visit) study visits how they would rate their day with regards to their PKAN symptoms on that day. A 5 point rating scale will be used as:

1, very good;
2, good;
3, neutral;
4, bad;
5, very bad.
20.6 Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects
Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of
Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject’s freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject’s dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE
31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

• The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or

• Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient’s decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.