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

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Summary

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

Methods We did an 18-month, randomised, double-blind, placebo-controlled trial (TIRCON2012V1), followed by a pre-planned 18-month, open-label extension study, in patients with PKAN in four hospitals in Germany, Italy, England, and the USA. Patients aged 4 years or older with a genetically confirmed diagnosis of PKAN, a total score of at least 3 points on the Barry-Albright Dystonia (BAD) scale, and no evidence of iron deficiency, neutropenia, or abnormal hepatic or renal function, were randomly allocated (2:1) to receive an oral solution of either deferiprone (30 mg/kg per day divided into two equal doses) or placebo for 18 months. Randomisation was done with a centralised computer random number generator and with stratification based on age group at onset of symptoms. Patients were allocated to groups by a randomisation team not masked for study intervention that was independent of the study. Patients, caregivers, and investigators were masked to treatment allocation. Co-primary endpoints were the change from baseline to month 18 in the total score on the BAD scale (which measures severity of dystonia in eight body regions) and the score at month 18 on the Patient Global Impression of Improvement (PGI-I) scale, which is a patient-reported interpretation of symptom improvement. Efficacy analyses were done on all patients who received at least one dose of the study drug and who provided a baseline and at least one post-baseline efficacy assessment. Safety analyses were done for all patients who received at least one dose of the study drug. Patients who completed the randomised trial were eligible to enrol in a single-arm, open-label extension study of another 18 months, in which all participants received deferiprone with the same regimen as the main study. The trial was registered on ClinicalTrials.gov, number NCT01741532, and EudraCT, number 2012-000845-11.

Findings Following a screening of 100 prospective patients, 88 were randomly assigned to the deferiprone group (n=58) or placebo group (n=30) between Dec 13, 2012, and April 21, 2015. Of these, 76 patients completed the study (49 in the deferiprone group and 27 in the placebo group). After 18 months, the BAD score worsened by a mean of 2·48 points (SE 0·63) in patients in the deferiprone group versus 3·99 points (0·82) for patients in the control group (difference –1·51 points, 95% CI –3·19 to 0·16, p=0·076). No subjective change was detected as assessed by the PGI-I scale: mean scores at month 18 were 4·6 points (SE 0·3) for patients in the deferiprone group versus 4·7 points (0·4) for those in the placebo group (p=0·728). In the extension study, patients continuing deferiprone retained a similar rate of disease progression as assessed by the BAD scale (1·9 points [0·5] in the first 18 months *vs* 1·4 points [0·4] in the second 18 months, p=0·268), whereas progression in patients switching from placebo to deferiprone seemed to slow (4·4 points [1·1] *vs* 1·4 points [0·9], p=0·021). Patients did not detect a change in their condition after the additional 18 months of treatment as assessed by the PGI-I scale, with mean scores of 4·1 points [0·2] in the deferiprone–deferiprone group and of 4·7 points [0·3] in the placebo–deferiprone group. Deferiprone was well tolerated and adverse events were similar between the treatment groups, except for anaemia, which was seen in 12 (21%) of 58 patients in the deferiprone group, but was not seen in any patients in the placebo group. No patient discontinued therapy because of anaemia, and three discontinued because of moderate neutropenia. There was one death in each group of the extension study and both were secondary to aspiration. Neither of these events was considered related to deferiprone use.

Interpretation Deferiprone was well tolerated, achieved target engagement (lowering of iron in the basal ganglia), and seemed to somewhat slow disease progression at 18 months, although not significantly, as assessed by the BAD scale. These findings were corroborated by the results of an additional 18 months of treatment in the extension study. The

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subjective PGI-I scale was largely unchanged during both study periods, indicating that might not be an adequate tool for assessment of disease progression in patients with PKAN. Our trial provides the first indication of a decrease in disease progression in patients with neurodegeneration with brain iron accumulation. The extensive information collected and long follow-up of patients in the trial will improve the definition of appropriate endpoints, increase the understanding of the natural history, and thus help to shape the design of future trials in this ultra-orphan disease.

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Introduction

Neurodegeneration with brain iron accumulation (NBIA) is a clinically and genetically heterogeneous group of rare hereditary neurodegenerative disorders characterised by high concentrations 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 localises to mitochondria and is essential for the biosynthesis of coenzyme A, which in turn is vital for ATP synthesis and fatty acid and neurotransmitter metabolism. Absence or abnormal function of PANK2 can contribute to iron accumulation in specific brain regions.[3] The time of onset of clinical signs ranges from infancy to adulthood, progression ranges from rapid to slow, and symptoms can vary greatly. Disease characteristics include progressive dystonia, parkinsonism, rigidity, and spasticity. The factors that influence disease severity and progression rate of PKAN are unknown. No disease-modifying therapies are yet available in PKAN or any form of NBIA.[4–6]

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

Research in context

Evidence before this study

When designing this trial and during its conduct and analysis, we undertook several systematic reviews of the literature between 11 Jan, 2010, and 26 Feb, 2019. We searched PubMed using the search terms ("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, four reported original data on the use of deferiprone in more than one patient with pantothenate kinase-associated neurodegeneration (PKAN). An open-label pilot trial in ten patients showed significant reduction of iron load in the globus pallidus but no clinical improvement after 6 months of treatment. Another small, open-label trial including four patients with PKAN showed significant reduction of iron in the globus pallidus in three of three evaluable patients, as well as mild-to-moderate motor improvement in two of the four patients after 12 months of treatment. A follow-up study of these four patients showed a relatively stable course of disease over 48 months. In another small, open-label trial, deferiprone treatment for 18 months reduced iron load in the globus pallidus of all and some clinical improvement in four of five patients with PKAN. These findings provide some low-quality evidence from case reports and small uncontrolled pilot trials that deferiprone might be beneficial in treating patients with PKAN.

Added value of this study

To our knowledge, this study is the first randomised controlled trial of deferiprone in patients with PKAN, and is the first randomised trial of any treatment in any form of neurodegeneration with brain iron accumulation (NBIA). Although all previous reports together (single cases and pilot trials) had involved 23 patients with PKAN, this study randomly assigned 88 PKAN patients, showing the feasibility of randomised trials even in ultra-orphan diseases with an estimated prevalence of one in 1 million. Moreover, this study lasted 18 months in its randomised part and included an open-label extension study of another 18 months, ultimately providing safety and efficacy data for 36 months of deferiprone treatment. As a result, the combined analysis of the randomised trial and the extension study shows excellent safety and tolerability of deferiprone in PKAN over 36 months, and strong evidence that deferiprone 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 patients treated with deferiprone compared with those treated with placebo. The difference seemed to be greater in a predefined subgroup of patients with atypical PKAN. Disease progression seemed to slow down in patients who switched from placebo to deferiprone in the extension trial. There was no evidence of change in the co-primary endpoint, the Patient Global Impression of Improvement scale.

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 patients with PKAN. Although the clinical endpoints were not met for the intention-to-treat population in the randomised trial, subgroup analysis and the results of the extension trial indicate some slowing of disease progression by deferiprone. This study might help to shape the design of future trials in this ultra-orphan disease.

evident after 10 years of age, is less severe, and progresses more slowly than classic PKAN.[3,7] It is hypothesised that classic PKAN results from complete absence of the PANK2 enzyme, whereas atypical disease results from severe deficiency.[3]

Although 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 localised toxicity.[8,9] Although proof that iron causes neurodegeneration in PKAN and most other NBIAs is insufficient, preferential iron accumulation in the basal ganglia probably explains the predominant phenotype of this movement disorder.[10] Accordingly, iron chelation holds the potential to decrease brain iron concentrations in NBIA, which could retard disease progression.

Deferiprone (3-hydroxy-1,2-dimethylpyridin-4-one) is an oral iron chelator approved for the treatment of transfusional iron overload in patients with thalassaemia. Deferiprone crosses the blood–brain barrier, chelates excess iron from intracellular organelles, and can transfer it to biological receptors, such as transferrin.[11] Few safety and efficacy data exist on patients with brain iron accumulation. On the basis of the available data in patients with PKAN or other neurodegenerative disorders who received deferiprone,[6,12–20] it was hypothesised that deferiprone could reduce brain iron, which might lead to clinical benefit. We aimed to assess whether deferiprone could reduce the clinical symptoms of PKAN or slow its progression. This Article describes the results of the TIRCON2012V1 study, which is, to our knowledge, the first randomised clinical trial of a putative therapeutic drug 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 appendix (p 1).

Study design

TIRCON2012V1 was an 18-month, multicentre, randomised, double-blind, placebo-controlled trial that evaluated the safety and efficacy of deferiprone in patients with PKAN in four hospitals in Germany, Italy, England, and the USA. Patients who completed the randomised trial were eligible to enrol in a single-arm open-label extension study of another 18 months, TIRCON2012V1-EXT, in which all participants received deferiprone.

An independent Data and Safety Monitoring Board regularly reviewed the safety data of both trials, and each study was registered on ClinicalTrials.gov before enrolment of the first patient. The trial was approved by the respective Ethics Committees of the study centres (Ludwig Maximilians University, Munich, Germany; Istituto Neurologico Carlo Besta, Milan, Italy; Yorkshire and the Humber—Leeds East health research authority, Leeds, UK; and Children's Hospital and Research Center, Oakland, CA, USA).

Participants

Patients aged at least 4 years were eligible for enrolment in TIRCON2012V1 if: they had a diagnosis of PKAN confirmed by genetic testing; a total score of 3 points or more on the Barry-Albright Dystonia (BAD) scale, which ranges from 0 (best) to 32 (worst); and no evidence of iron deficiency, neutropenia, or abnormal hepatic or renal function. 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 and exclusion criteria is provided in the appendix (p 1). The use of symptomatic treatments for dystonia (eg, baclofen, trihexyphenidyl, clonazepam, tizanidine, or botulinum toxin) was permitted; however, to reduce confounds, individuals were excluded if they had recent (within 2 months) or anticipated changes in any ongoing regimen to treat dystonia (ie, medication or a device for deep brain stimulation). Written informed consent was obtained from each participant or the parent or legal guardian before any procedures were done.

Randomisation and masking

In TIRCON2012V1, patients were assigned (in a 2:1 ratio) to receive either an oral solution of deferiprone up to 30 mg/kg per day divided into two doses (deferiprone group) or matching placebo (identical packaging, appearance, and taste; placebo group), using block randomisation in block sizes of six. Investigators were in charge of confirming eligibility and an independent team was responsible for random group assignment. The randomisation list was generated using a computer random number generator. A centralised randomisation process was used for all study sites, and patients were allocated to groups by an unmasked randomisation team that was independent of the study. Group allocation was concealed through a centralised randomisation process with a computer-generated randomisation list. Randomisation was stratified on the basis of the patient's age at onset of motor symptoms, with one list generated for individuals who had been younger than 6 years at the onset of motor symptoms (classic PKAN) and another list generated for those who had been 6 years or older (atypical PKAN). Patients, caregivers, study staff, and the neurologists who analysed videotapes for determination of BAD scores were unaware of treatment assignment, as were the radiologists who analysed the MRI images to determine iron concentrations in the globus pallidus.

See Online for appendix

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

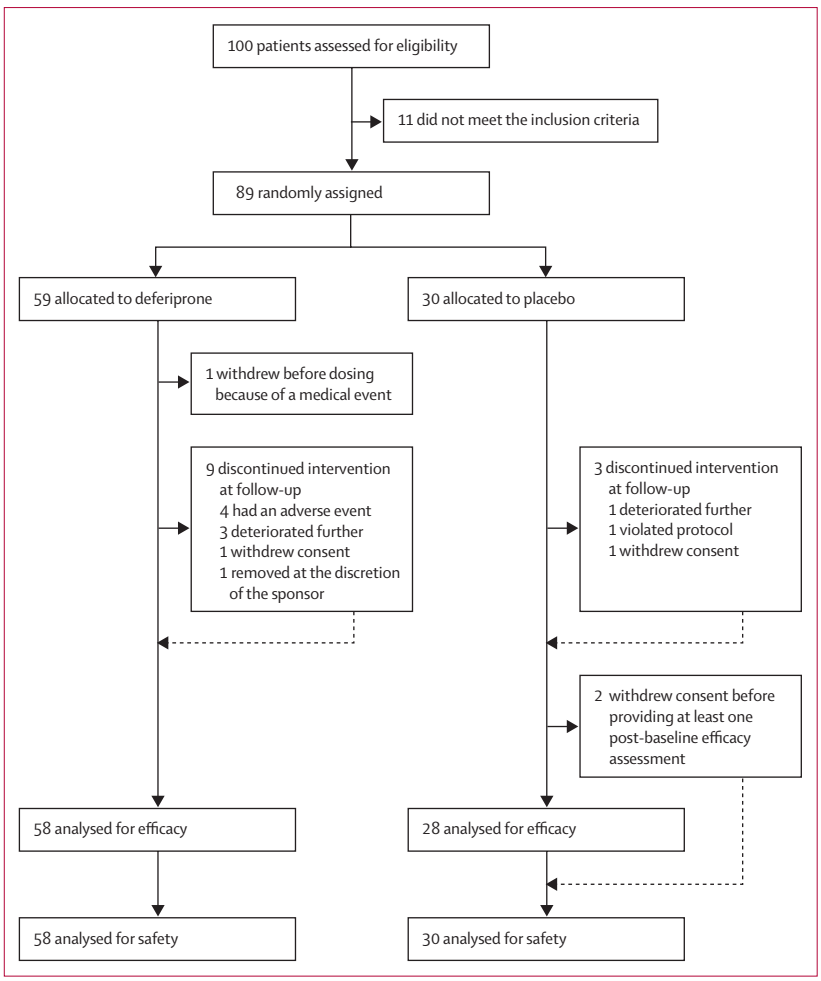

Figure 1: **Profile of the main study from screening until completion at month 18**

Procedures

Participants took the assigned study product twice daily every day for 18 months (appendix p 3). 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. Following the baseline visit of the main study, patients had safety and efficacy assessments at the following intervals: month 1·5 (week 6), 3, 6, 12, and 18. Patients were also contacted by phone weekly for the first 6 weeks and then on month 2, 9, and 15. During the extension study, patients were contacted by phone weekly during the first 2 weeks of the study and then had site visits every 6 months.

Efficacy assessed every 6 months used the following measures: (1) the BAD scale, which measures the severity of dystonia in eight 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) scale, 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) compared with how they had felt at baseline; (3) parts I, II, III, and VI of the Unified Parkinson's Disease Rating Scale (UPDRS) for assessment of motor symptoms that resemble those of patients with Parkinson's disease, as well as some quality of life aspects; (4) the Functional Independence Measure (FIM) or WeeFIM (paediatric 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 done and videotaped at the site, and the videotapes were sent to a central site for masked assessment by experts on movement disorders. We do not report the Likert scale here, which was mentioned as an efficacy evaluation in our protocol paper, because it overlaps with elements from the other scales we used. Iron concentrations in the globus pallidus were measured by MRI-R2* mapping in a subset of patients at baseline and month 18. Safety assessments were done at each visit and involved collecting data on adverse events, clinical laboratory tests, physical examination, vital signs, and electrocardiogram (ECG; at screening and month 18 only).

In the extension study, patients who had been randomly assigned to deferiprone continued to receive it and those who had been assigned to placebo were switched to deferiprone. Again, efficacy assessments were made every 6 months. Safety evaluations were the same as in the main trial but efficacy measures were made only with the BAD scale and PGI-I.

Outcomes

In the randomised trial, the co-primary efficacy endpoints were change from baseline to month 18 in the BAD total score and the PGI-I score of improvement from baseline to month 18. The outcome was to be considered positive if the group differences in both co-primary endpoints reached significance ($p<0·05$).

Secondary efficacy endpoints were iron concentrations in the globus pallidus (as assessed by MRI-R2*), change from baseline to month 18 in the BAD score for each body region (eight regions), the FIM or WeeFIM, UPDRS, PedsQL, and PSQI scales, and the proportions of patients at month 18 with improved or unchanged BAD total scores and PGI-I scores. Blood samples for the pharmacokinetic analyses of deferiprone and its main metabolite, deferiprone 3-O-glucuronide, were collected from a subset of 13 patients during the month-6 visit, before dosing and at 1, 1·5, 2, 2·5, 3, 4, 6, 8, and 12 h after dosing. All samples were analysed but pharmacokinetic parameters were evaluated only for the patients who were receiving deferiprone (n=9), not for those receiving placebo (n=4). The results on pharmacokinetics reported in our study for patients with PKAN receiving deferiprone at a dose of 15 mg/kg were similar to what has been previously observed in studies in healthy volunteers.[21] We

did not report our results because of this consistency and because of space limitations. For the safety endpoints, the intervention groups were compared for their 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 and PGI-I scores.

Statistical analysis

At the time of planning the randomised trial, to our knowledge, there were no published studies with data sufficient to estimate sample size on the basis of either the natural history of the disease or the expected impact from a drug 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 most probably had 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.[22] We 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 deferiprone group of 5 points or more. Assuming a standard deviation of 6·3 points, a randomisation ratio of 2:1, and 30% drop out, 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 enrol.

Safety analyses were based on all randomised patients who received at least one dose of the study drug. Efficacy analyses were based on the intention-to-treat population, defined as all randomised patients who received at least one dose of study drug and 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 timepoints (months 6, 12, and 18), with baseline value and age of onset of motor symptoms (before 6 years *vs* 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 settings for deep brain stimulation 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 scale. 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, subgroup analyses using a similar MMRM model were done on the co-primary efficacy endpoints on the basis of pre-established factors, such as age at onset of motor symptoms (classic or atypical PKAN), use of deep brain stimulation, and use of a baclofen pump. The results are not reported in the Article as they were either uninformative because of the small number of patients using deep brain stimulation or baclofen pumps, or did not differ from the results of the main analysis. The safety data for continuous variables were summarised using descriptive statistics, and the safety data for discrete variables were tabulated with frequency tables. The trial was registered with ClinicalTrials.gov, number NCT01741532, and EudraCT, number 2012-000845-11.

In the extension study, changes in the BAD scale and PGI-I scores were summarised using descriptive statistics. The last observation carried forward (LOCF) method 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

	Randomised study		Extension study	
	Placebo group	Deferiprone group	Placebo-deferiprone group	Deferiprone-deferiprone group
Age at enrolment (years)				
N	30	59	19	43
Mean (SD)	19·2 (12·5)	20·8 (10·7)	18·2 (10·0)	22·7 (9·6)
Range	5–55	4–52	6–40	6–47
Age at onset (years)				
Mean (SD)	7·5 (6·2)	8·4 (7·2)	8·0 (6·4)	8·2 (6·2)
Min–max	1–23	1–29	1–23	1–19
Sex				
Female	17 (57%)	25 (42%)	11 (58%)	16 (37%)
Male	13 (43%)	34 (58%)	8 (42%)	27 (63%)
Racial origin				
Asian	1 (3%)	6 (10%)	0	3 (7%)
Black	0	2 (3%)	0	0
Unknown	1 (3%)	0	1 (5%)	0
White	28 (93%)	51 (86%)	18 (95%)	40 (93%)
Basal ganglia MRI R2* (Hz)				
N	16	24	NA	NA
Mean (SD)	93·5 (31·2)	96·6 (31·6)	NA	NA
Min–max	35·7–167·8	34·0–152·5	NA	NA
BAD total score†				
N	28	58	19	43
Mean (SD)	16·5 (8·1)	19·6 (8·4)	20·4 (8·1)	21·3 (7·6)
Min–max	2–31	1–32	3–30	3–30

Data are number of participants (%), unless otherwise indicated. Percentages might not total 100% because of rounding. 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 (ie, deferiprone or placebo), while in the randomised study. NA=not applicable. BAD=Barry-Albright dystonia. *BAD scores at baseline of the randomised study are based on the intent-to-treat population, defined as all randomised 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 intent-to-treat population of the randomised study. BAD data obtained at the end of study (month 18) visit of the randomised study was used as the baseline value of the extension study.

Table 1: **Patients' demographics, basal ganglia iron loading as assessed by MRI R2*, and BAD scale at baseline of the randomised and extension studies**

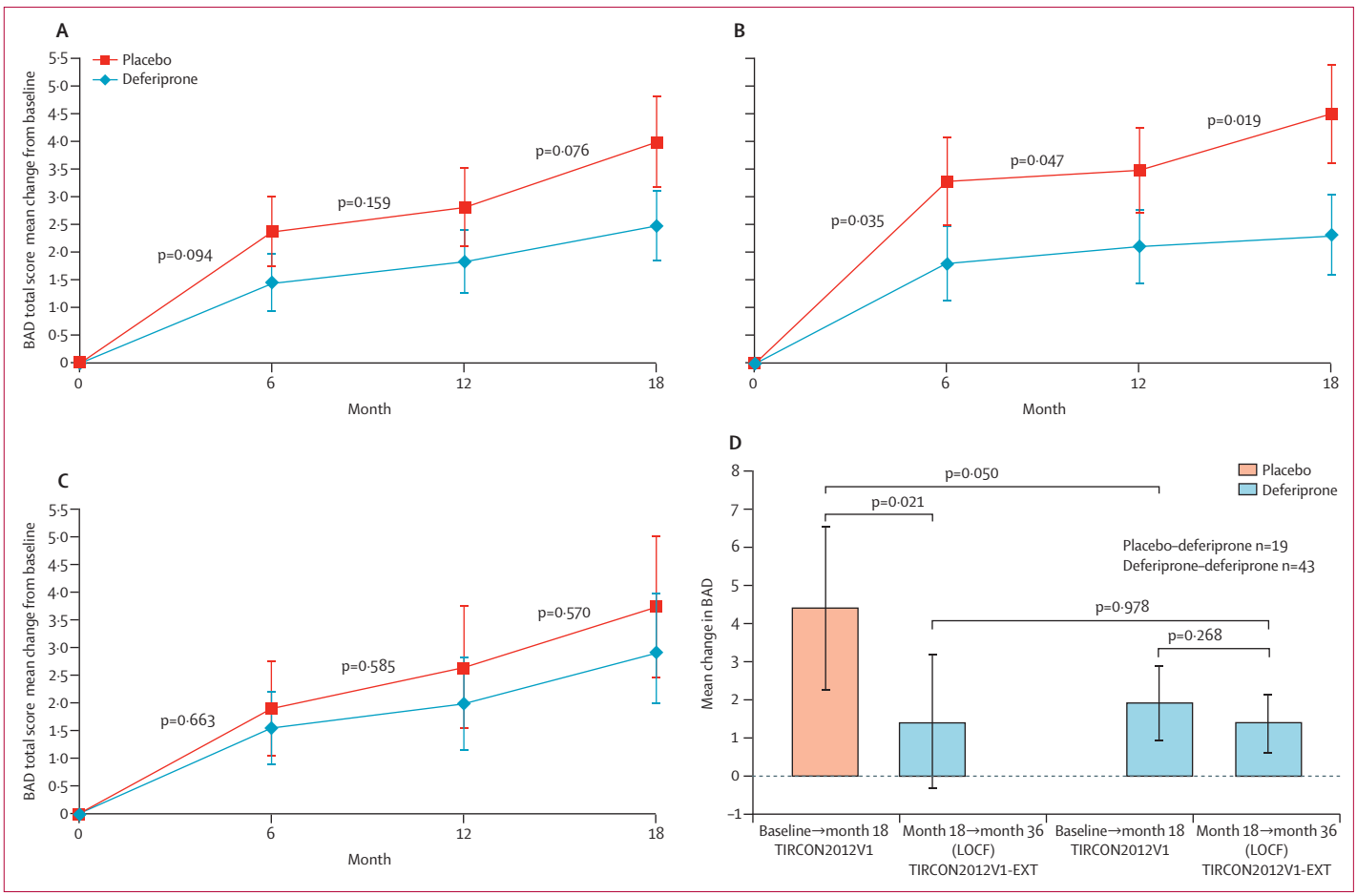

Figure 2: **Marginal mean change in BAD total score over time in patients with different classes of PKAN in the randomised study**
(A) All PKAN patients. (B) Patients with atypical PKAN. (C) Patients with classic PKAN. Error bars represent SE. The p values for each class of PKAN were obtained from a mixed model for repeated measures for the comparison of the deferiprone and placebo groups. (D) Mean change and 95% CI from baseline in BAD total score over the main and extension studies (18 + 18 months) for patients in the placebo–deferiprone (left) and the deferiprone–deferiprone (right) groups. P values were obtained from a Student's *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. BAD=Barry-Albright Dystonia. LOCF=last observation carried forward. PKAN=pantothenate kinase-associated neurodegeneration.

	Patients (n)		Marginal mean change in BAD score (95% CI)		Deferiprone–placebo mean difference (95% CI)*	p value†
	Placebo	Deferiprone	Placebo	Deferiprone		
All patients	28	58	3·99 (2·38–5·60)	2·48 (1·25–3·71)	−1·51 (−3·19 to 0·16)	0·076
Classical PKAN	12	29	3·72 (1·19–6·25)	2·91 (1·09–4·73)	−0·81 (−3·68 to 2·06)	0·570
Atypical PKAN	16	29	4·52 (2·74–6·30)	2·33 (0·90–3·76)	−2·19 (−4·00 to −0·38)	0·019

Patients with classical PKAN are aged less than 6 years at disease onset. Patients with atypical PKAN are aged at least 6 years at disease onset. BAD=Barry-Albright dystonia. MMRM=mixed model for repeated measures. PKAN=pantothenate kinase-associated neurodegeneration. *Based on least squares estimates from the MMRM model. †p value from MMRM model

Table 2: **Marginal mean change in BAD score from baseline to end of study during deferiprone or placebo use up to 18 months in the randomised trial**

randomised and the extension studies, whereas Student's *t* test was used for within-study comparison of treatment groups. All statistical analyses were done with SAS (version 9.3). The extension study was registered with ClinicalTrials.gov, number NCT02174848.

Role of the funding source

Funding for the study was provided by the European Commission, the US Food and Drug Administration, 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

Following a screening of 100 prospective patients, 89 of 90 planned participants were enrolled between Dec 13, 2012, and April 21, 2015. 59 were randomly assigned to receive deferiprone and 30 to receive placebo (figure 1). One patient assigned to the deferiprone group

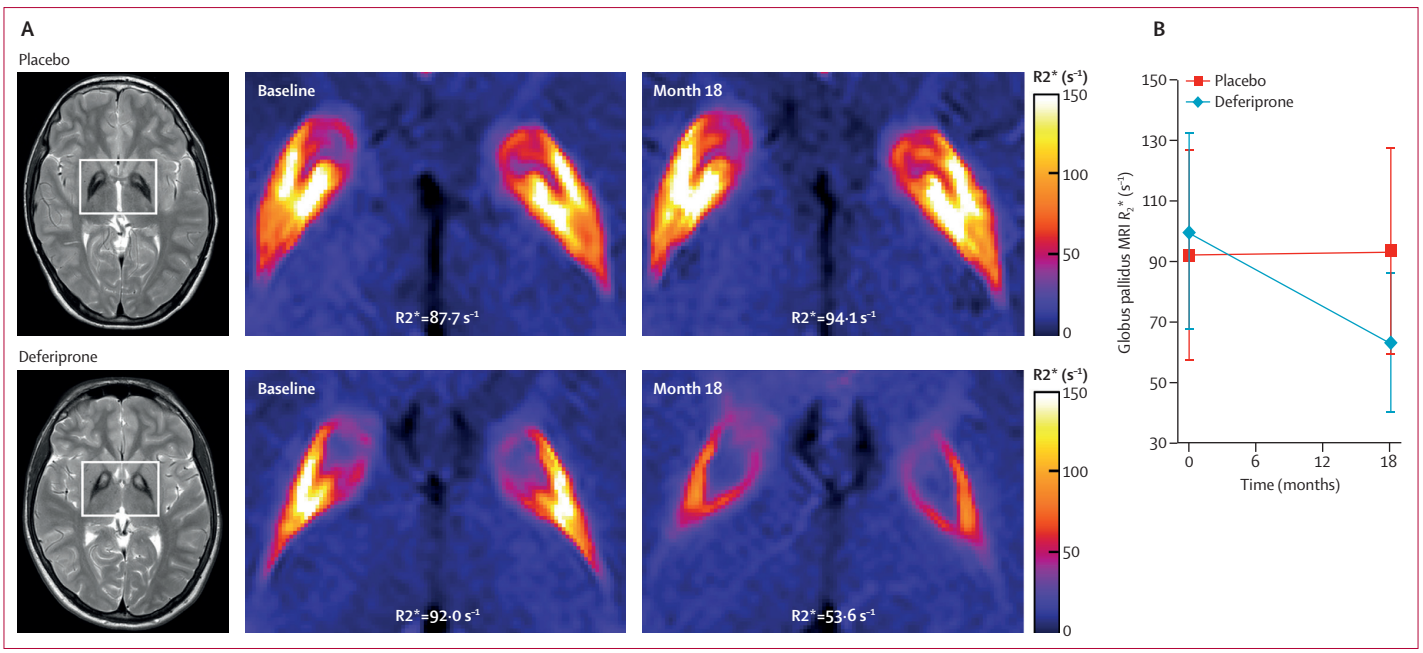

Figure 3: **Illustrative MRI data and response to deferiprone treatment**
(A) Images show slices from the conventional T2-weighted scan through the basal ganglia (left) with the R2* maps at baseline (centre) and at 18 months (right). The expanded anatomical regions illustrated for R2* are marked by the boxes on the T2-weighted scans. The quantitative R2* maps are shown with hotter colours representing increased iron concentrations and corresponding increased R2* values. (B) Mean (SD) R2* of the globus pallidus across both hemispheres for each group at each timepoint, showing the reduction in R2* signal in the deferiprone group that corresponds to a reduction of iron load in this brain region due to treatment.

withdrew before receiving the first dose because of a medical event, and two assigned to placebo withdrew consent after receiving the study drug but before providing any post-baseline efficacy data. Accordingly, there were 58 patients in the deferiprone group evaluable for both safety and efficacy, and 30 in the placebo group evaluable for safety and 28 for efficacy. 76 (85%) of 89 patients completed the trial and 12 (excluding the one patient who was never dosed) withdrew: three (10%) in the placebo group and nine (15%) in the deferiprone group. Four patients (all in the deferiprone group) withdrew because of an adverse event. Of these withdrawals, three were for moderate neutropenia (confirmed absolute neutrophil counts ≥ $0{\cdot}5\times10^9$ – $<1{\cdot}0\times10^9$ cells/L), for which withdrawal was mandated by the study protocol, and one 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, baseline BAD score, or amount of iron in the relevant brain areas (table 1). Stratification was used to ensure that each treatment group had approximately equal proportions of patients with classic or atypical PKAN, as determined by age at onset of motor symptoms. From the 86 patients who were evaluable for efficacy, there were 12 patients with classic and 16 with atypical presentation in the placebo group, and 29 with each type in the deferiprone group. Mean age at randomisation differed considerably between the subgroups (SD 13·7 years for patients with classic and 26·5 years for those with atypical PKAN), but disease duration (approximately 13 years) was similar for both groups. As we expected, the disease had progressed further in patients with classic PKAN, as indicated by baseline BAD scores (20·3 [SD 8·9] *vs* 17·0 [7·6]), but the difference was not significant (p=0·075).

Concomitant treatments for dystonia symptoms were an important consideration because of their possible confounding effect on the BAD score. Most participants (18 [60%] patients receiving placebo and 42 [72%] patients receiving deferiprone) were taking at least one medication for dystonia at baseline; 25 patients (six [20%] and 19 [32%], respectively) had a deep brain stimulation system in place; and three patients (one [3%] and two [3%], respectively) had a baclofen pump in place. Treatment groups were similar regarding the use of any medication or device for the treatment of dystonia at baseline (appendix p 4). 18 (60%) of 30 patients receiving placebo and 42 (72%) of 58 receiving deferiprone reported taking at least one such medication, with the most common being baclofen (14 [47%] of patients in the placebo group and 27 [47%] of patients in the deferiprone group), trihexyphenidyl (nine [30%] and 25 [43%]), clonazepam (seven [23%] and 12 [21%]), and diazepam (four [13%] and five [9%]). No other medication was being taken by more than four patients in a group. During the study, additional dystonia medications administered on an as-needed basis were taken by a higher proportion of patients in the placebo group (six [21%]) than patients in the deferiprone

	Deferiprone		Placebo		Point estimate (95% CI)
	Patients (n)	Marginal mean (SE)	Patients (n)	Marginal mean (SE)	
BAD eyes score	58	0·40 (0·15)	28	0·60 (0·19)	−1·15 (−3·15 to 0·84)
BAD mouth score	58	0·43 (0·14)	28	0·39 (0·18)	0·28 (−1·72 to 2·28)
BAD neck score	58	0·31 (0·17)	28	0·75 (0·22)	−2·03 (−4·03 to −0·04)
BAD trunk score	58	0·32 (0·17)	28	0·46 (0·22)	−0·68 (−2·68 to 1·32)
BAD left upper extremity score	58	0·22 (0·15)	28	0·22 (0·19)	0·00 (−1·99 to 1·99)
BAD right upper extremity score	58	0·34 (0·15)	28	0·43 (0·19)	−0·47 (−2·47 to 1·53)
BAD left lower extremity score	58	0·26 (0·11)	28	0·54 (0·14)	−2·10 (−4·09 to −0·11)
BAD right lower extremity score	58	0·30 (0·10)	28	0·54 (0·12)	−2·05 (−4·05 to −0·06)
UPDRS part I score	58	−0·25 (0·43)	28	−0·07 (0·55)	−0·36 (−2·36 to 1·64)
UPDRS part II score	58	1·09 (1·19)	28	2·36 (1·52)	−0·91 (−2·91 to 1·09)
UPDRS part III score	58	5·38 (2·20)	28	2·06 (2·79)	1·24 (−0·75 to 3·24)
UPDRS part VI score	57	2·17 (2·94)	28	7·66 (3·85)	−1·37 (−3·37 to 0·62)
WeeFIM self-care score	21	2·11 (3·06)	14	2·26 (3·11)	−0·05 (−2·10 to 2·00)
WeeFIM mobility score	21	0·48 (2·03)	14	0·69 (2·02)	−0·10 (−2·16 to 1·96)
WeeFIM cognition score	21	−6·24 (2·56)	14	0·06 (2·63)	−2·25 (−4·30 to −0·20)
FIM self-care score	37	−1·72 (1·14)	14	0·75 (1·63)	−1·57 (−3·60 to 0·46)
FIM mobility score	37	−0·28 (0·97)	14	0·81 (1·38)	−0·83 (−2·85 to 1·19)
FIM cognition score	37	−2·07 (1·02)	14	−1·07 (1·42)	−1·00 (−3·75 to 1·75)
PedsQL total score—child	42	−1·21 (3·68)	25	−1·34 (4·49)	0·03 (−1·98 to 2·04)
PedsQL total score—parent	41	4·90 (3·99)	19	2·37 (4·90)	0·56 (−1·46 to 2·58)
PSQI score	56	0·48 (0·61)	26	0·14 (0·80)	0·48 (−1·51 to 2·47)

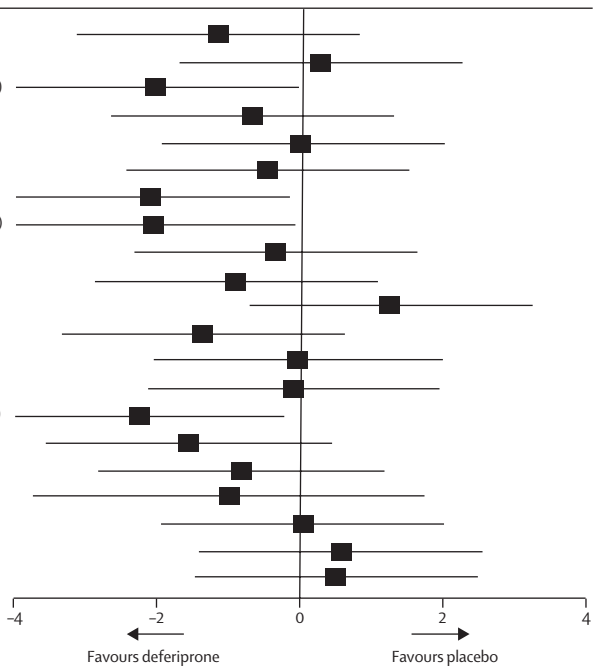

Figure 4: **Forest plot of all secondary endpoint outcomes**

Each square represents the estimated marginal mean difference between deferiprone and placebo for an endpoint. Mean and 95% CIs are standardised by the SE of the marginal mean difference. BAD=Barry-Albright Dystonia. FIM=Functional Independence Measure. PedsQL=Pediatric Quality of Life. PSQI=Pittsburgh Sleep Quality Index. UPDRS=Unified Parkinson's Disease Rating Scale. WeeFIM=paediatric Functional Independence Measure.

group (six [11%]), with the greatest difference between groups for botulinum toxin type A.

Compliance, as assessed by volume of medication taken versus volume prescribed, was very high at all timepoints, ranging from 95% to 99% volume taken in the placebo group and from 97% to 99% in the deferiprone group.

One patient in the placebo group had a baseline BAD score of 31 and one in the deferiprone group had the maximum score of 32 (table 1), 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 (appendix p 5). Patients in both treatment groups worsened over time (figure 2). In the main analysis, using the marginal means from the MMRM model, the scores of patients in the deferiprone group worsened by 2·48 points (SE 0·63) versus 3·99 points (0·82) in the placebo group (difference −1·51, 95% CI −3·19 to 0·16, p=0·076; table 2).

By contrast with the 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 (SE 0·4) for placebo and 4·6 [0·3] for deferiprone (difference −0·12, 95% CI −0·80 to 0·56, p=0·728), 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 (appendix p 7).

A predefined subgroup analysis that assessed separately patients with classic or atypical PKAN provided some evidence to show that deferiprone use in patients with atypical PKAN could be associated with slower progression of clinical symptoms (2·33 points [0·73]) than the use of placebo (4·52 points [0·91]; difference 2·19 points, 95% CI −4·00 to −0·38, p=0·019). In patients with classic PKAN, the difference of 0·81 points in favour of deferiprone was not supported by the evidence (p=0·570; table 2). In the responder analysis, 20 (36%) patients treated with deferiprone responded to therapy, compared with four (14%) patients treated with placebo (p=0·089).

Iron concentrations in the globus pallidus were measured via MRI-R2* imaging in a subset of patients at the start (16 in the placebo group and 24 in the deferiprone group) and end of the study (13 and 19 patients, respectively). In the placebo group, there was no change in mean iron concentration (mean R2* decrease of 0·5 Hz, SE 4·0, 95% CI −8·7 to −7·78), whereas in the deferiprone group, there was a significant decrease of 36·1 Hz (3·1, −42·5 to −29·7), difference −35·6 Hz (95% CI −44·8 to −26·3, p <0·0001; figure 3).

Of the 21 measures we examined, although more outcome measures seemed to favour deferiprone than placebo, there was weak evidence only in support of a

difference between groups for the WeeFIM cognition score (difference 6·30, p=0·032) and for BAD scores for specific body regions (neck –0·43, p=0·047; left lower extremity –0·28, p=0·039; and right lower extremity –0·25, p=0·044; figure 4). Detailed results on the WeeFIM assessments are provided in the appendix (p 8).

Overall, deferiprone was well tolerated. All but one patient experienced at least one adverse event (57 [98%] of patients receiving deferiprone and 30 [100%] of patients receiving placebo). Adverse events occurring in more than 10% of patients are shown in table 3. Incidence of these events was similar between the treatment groups, except for events directly related to treatment with deferiprone, such as anaemia. Six (10%) patients in the deferiprone group had mild anaemia (haemoglobin >11 g/dL) and six (10%) had moderate anaemia (haemoglobin 8·0–10·9 g/dL). A higher proportion of patients in the deferiprone group had mildly lower concentrations of serum ferritin than patients in the placebo group (19 [33%] *vs* five [17%], p=0·134) and had mild iron deficiency (nine [16%] *vs* three [10%], p=0·744; appendix p 10). Iron supplementation as needed was permitted on the basis of the investigator's assessment, and was taken by 23 (40%) of patients in the deferiprone group and by eight (27%) 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 incidence of mild neutropenia (five [9%] *vs* two [7%]).

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

BAD scores at the start of the extension study are shown in table 1 (at this timepoint, one patient on placebo–deferiprone had a score of 30 and one on deferiprone–deferiprone had the maximum score of 32). Figure 2 displays the change in BAD total scores for the 62 patients who provided evaluable efficacy data in both studies. In both groups, scores continued to increase (worsen) over time, but patients in the deferiprone–deferiprone group showed a similar rate of progression in both studies, whereas patients in the placebo–deferiprone group progressed more rapidly in the first study and slowed when they were switched to deferiprone. Over the 18 months of the extension study, there was no significant difference in the change in BAD score for patients who had received deferiprone from the start (1·9 points [SE 0·5] in the first 18 months *vs* 1·4 points [0·4] in the second 18 months, p=0·268), while patients in the placebo–deferiprone group worsened significantly more (4·4 points [1·1] when they were receiving placebo *vs* 1·4 points [0·9] when they were receiving deferiprone, p=0·021; appendix p 11).

	Placebo (n=30)	Deferiprone (n=58)	p value (Fisher's exact test)
Dystonia	14 (47%)	25 (43%)	0·823
Pyrexia	13 (43%)	16 (28%)	0·157
Serum ferritin decreased	5 (17%)	19 (33%)	0·134
Headache	9 (30%)	13 (22%)	0·448
Nasopharyngitis	6 (20%)	11 (19%)	1·00
Anaemia	0 (0%)	12 (21%)	0·007
Condition aggravated	9 (30%)	10 (17%)	0·183
Pain in extremity	4 (13%)	10 (17%)	0·764
Cough	5 (17%)	10 (17%)	1·00
Vomiting	8 (27%)	9 (16%)	0·258
Iron deficiency	3 (10%)	9 (16%)	0·744
Oropharyngeal pain	3 (10%)	9 (16%)	0·744
Upper respiratory tract infection	4 (13%)	8 (14%)	1·00
Arthralgia	1 (3%)	8 (14%)	0·158
Bronchitis	2 (7%)	7 (12%)	0·712
Laceration	3 (10%)	6 (10%)	1·00
Ear pain	3 (10%)	1 (2%)	0·113
Abdominal pain upper	5 (17%)	4 (7%)	0·264
Constipation	4 (13%)	2 (3%)	0·175
Diarrhoea	3 (10%)	4 (7%)	0·686
Gastrointestinal infection	3 (10%)	3 (5%)	0·406
Freezing phenomenon	3 (10%)	0	0·037

Table 3: **Summary of adverse events seen in at least 10% of randomised patients who received at least one dose of the study drug**

With respect to the PGI-I, as in the randomised study, patients did not detect a change in their condition after the additional 18 months of treatment, with mean scores of 4·1 [SE 0·2] in the deferiprone–deferiprone group and of 4·7 [0·3] in the placebo–deferiprone group.

For evaluation of safety throughout the whole study period, data were combined for all 68 patients. Overall, deferiprone was well tolerated for the 36-month period. There were two deaths, both secondary to pulmonary aspiration (one from pneumonia and multi-organ failure, the other to aspiration following the patient vomiting in his sleep). Neither of these patients had had neutropenia while the study was ongoing. The most common adverse event was dystonia, reported in 40 (59%) patients, followed by pyrexia in 23 (34%), headache in 20 (29%), and decrease of serum ferritin in 18 (27%).

To investigate whether a ceiling effect confounded the results of our study, we did an exploratory analysis and repeated the MMRM analysis excluding all patients with a baseline BAD score of less than 27 who would potentially be subject to a ceiling effect. In this analysis, patients treated with deferiprone showed a numerically lesser progression in BAD scores than patients treated with placebo, with the marginal mean difference being similar to that from the analysis of the intention-to-treat population (appendix p 5). Additional exploratory analysis

was done to compare response to treatment according to the tertiles of baseline BAD scores, showing weak evidence for a potential benefit of deferiprone versus placebo, although this benefit was not significant.

Discussion

The data from up to 3 years of deferiprone therapy in patients with PKAN show that its use was well tolerated, was associated with a reduction of excess iron in the brain, and was potentially associated with some slowing of disease progression. To our knowledge, our study is the largest randomised trial to date and provides the longest prospective follow-up of any population with NBIA. It yields valuable information about the impact of iron chelation on PKAN, but also on the disease's natural history through the detailed assessment of patients receiving placebo, indicating that the rate of disease progression is slower than previously estimated.[22] In our 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 less than we anticipated. Accordingly, the only way a significant group difference could have been achieved would have been for deferiprone 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. Thus, whether a treatment duration longer than 18 months might provide evidence for a treatment effect should be explored.

We did not exclude patients with high BAD scores for enrolment, which might have led 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. Randomisation resulted in proportionally more patients with high baseline BAD scores being assigned to receive deferiprone. Post-hoc exploratory MMRM analyses suggested that the intention-to-treat analysis had not been confounded by a possible ceiling effect in patients with high BAD scores, although it was not possible to distinguish whether deferiprone was truly beneficial in those patients. In conclusion, these analyses provided evidence suggesting that PKAN progression as measured by the BAD score slows with increasing baseline values and that this trend leads to a ceiling effect at very high baseline scores. Although this information is important for the design of future trials, it did not affect the principal outcome of our study. The potential benefit of deferiprone is also supported by the lower use of dystonia medications during the trial by patients taking deferiprone than by patients taking placebo, and by the results of the extension study. In patients who received deferiprone in both studies, disease progression continued at the same rate, whereas in those who switched from placebo to deferiprone, it slowed to match the rate seen in those who had received deferiprone in the first study. The fact that the rate of deterioration in the placebo–deferiprone group was less (p=0·021) during the 18 months of deferiprone 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 a drug to slow progression is introduced, the less the expected benefit. Participants in this study had been having PKAN symptoms for approximately 13 years at the time of enrolment, and it is probable that for many the disease progression was too advanced for a preventive drug to provide significant benefit. If brain iron contributes to the pathology seen in PKAN,[10] then early initiation of deferiprone in patients with less extensive iron-induced neurodegeneration would be expected to maximise its benefit in slowing disease progression. Support for this view was provided by our predefined subgroup analysis looking separately at patients with classic versus atypical PKAN. In atypical PKAN, symptoms appear later and the disease progresses more slowly than in classic PKAN.[2,7] Hence, although 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 lower. This difference might explain why patients with atypical PKAN seemed to have a better response than patients on placebo in the randomised portion of the study.

The low prevalence of PKAN (1 to 3 cases per million)[22] was responsible for the paucity of patients, and, considering the slower than predicted rate of disease progression, an increased number of patients could have compensated for inadequate power to reach the pre-set level of significance of p<0·05 in the 18-month study. As the conduct of studies larger than ours is improbable, any attempt at future clinical trials will probably 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 was weak (r=0·29), in which less than 10% of the variation in PGI-I scores could be explained by the change in BAD scores (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 probably inappropriate for this study. It might be a good tool for assessing the short-term effect of drugs that improve or reverse disease, but it was probably difficult for patients to judge whether their condition had worsened or improved over a period as long as 18 months, explaining why no net worsening was detected by this measure, even by those on placebo.

The most notable change observed was the large reduction of iron in the globus pallidus: a mean decrease of 36·1 Hz in patients in the deferiprone group compared with 0·50 Hz in the placebo group (p<0·0001). This

finding is consistent with reports of deferiprone-induced reductions in the concentrations of brain iron seen in Friedreich's ataxia,[17] Parkinson's disease,[18] and other NBIA disorders.[23] Importantly, the reduction in brain iron load induced by deferiprone was not associated with systemic iron depletion.

Freezing of gait, an event commonly observed in PKAN patients, was seen in three (10%) of 30 patients taking placebo, but in none of those taking deferiprone (p=0·037), although there were twice as many patients in the deferiprone group. 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 deferiprone. Further investigation of the mechanism through which deferiprone might decrease the clinical manifestations of PKAN is warranted.[24]

With respect to other secondary efficacy endpoints of the randomised study, although many of the group differences did not reach significance, patients who received deferiprone deteriorated less over 18 months of treatment than patients on placebo in most outcome measures. Responder analysis (the proportion of patients showing either improvement or stabilisation of their total BAD score) found that the response was not different between patients receiving deferiprone and those receiving placebo. Patients on deferiprone deteriorated less on their individual BAD scores for nearly all body regions, with group differences reaching significance (albeit marginal, as they would not be significant if multiplicity were considered) for neck, left lower extremity, and right lower extremity.

After the reduction of brain iron concentrations, the most substantial difference between treatments was seen on the WeeFIM measure, where actual improvement—not merely reduced worsening—was seen in cognition in patients on deferiprone, with the difference between treatment groups reaching significance (p=0·032). No significant group differences were seen on the other secondary measures. However, examination of all the secondary endpoints showed a pattern that suggested a beneficial effect of deferiprone across a broad range of functions.

The tolerability of deferiprone was evidenced by the near-total compliance and low number of dropouts in both studies. The two deaths were unrelated to study treatment, and adverse events, which were mainly mild, were similar between the treatment groups on most measures (table 3, appendix p 10). In general, the safety findings were consistent with those of other studies of deferiprone in patients with both brain iron overload[6,12,25,26] and systemic iron overload.[27] There were no occurrences of agranulocytosis, the most serious adverse event associated with deferiprone use, and there was no significant group difference in the frequency of patients having milder episodes of neutropenia, all of which resolved rapidly. There was a concern that the treatment of patients who did not have iron overload with an iron chelator might experience haematological events linked to a reduction of iron body stores, such as decreased serum ferritin, anaemia, and iron deficiency. However, although these events were seen in an increased percentage of patients taking deferiprone in the randomised trial, the incidence was low, the group difference was significant only for anaemia, none of the events was serious, and all could be managed by iron supplementation.

A major strength of the study related to the ability to actually enrol close to 10% of all estimated patients with PKAN in the USA and Europe. The major limitation in the study was the lack of adequate pre-existing natural history data in these patients to enable an informed power calculation for the primary outcome related to a change in BAD score. Consequently, it is possible that the slower-than-expected rate of worsening in the patients treated with placebo might have affected our ability to achieve a significant difference in the overall intention-to-treat 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. Although the clinical endpoints were not met for the intention-to-treat population in the randomised trial, planned subgroup analyses provided some evidence of slowing of disease progression in patients with atypical disease, and the results of the extension trial indicate potential slowing of progression by deferiprone in the overall population as well. This study will help to shape the design of future trials in this ultra-orphan disease.

Contributors

TKl and EV conceived the study and were the coordinating investigators. TKl, FT, CF, MS, SJH, PH, and EV designed the study protocol. LN, BK, and BB managed the trial. TKl, RH, PFC, NN, and EV were the site principal investigators, responsible for participant recruitment and data collection. IK, LN, GZ, HES, AB, CK, CN, FZi, and CA were site investigators and contributed to participant recruitment and data collection. TKm, PD, and ZY recruited participants and were responsible for local care in Poland, Czech Republic, and Turkey, respectively. SH and PH were rated videotapes for the BAD score examination of all patients from baseline and month 18. BB rated BAD videotapes for the extension trial. IW and AMB defined the MRI protocol, oversaw image quality assurance, and analysed all available MRI data from baseline and month 18. FZh did the statistical analysis. TKl wrote the first draft of the article. TKl, 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

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Data sharing

The Treat Iron-Related Childhood-Onset Neurodegeneration (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 by www.clinicalstudydatarequest.com.

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References

1 Hayflick SJ, Westaway SK, Levinson B, et al. Genetic, clinical, and radiographic delineation of Hallervorden-Spatz syndrome. *N Engl J Med* 2003; **348:** 33–40.

2 Zhou B, Westaway SK, Levinson B, Johnson MA, Gitschier J, Hayflick SJ. A novel pantothenate kinase gene (PANK2) is defective in Hallervorden-Spatz syndrome. *Nat Genet* 2001; **28:** 345–49.

3 Gregory A, Polster BJ, Hayflick SJ. Clinical and genetic delineation of neurodegeneration with brain iron accumulation. *J Med Genet* 2009; **46:** 73–80.

4 Gregory A, Hayflick SJ. Pantothenate kinase-associated neurodegeneration. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. Gene Reviews. Seattle, WA: University of Washington, Seattle, 1993.

5 Hayflick SJ. Hallervorden-Spatz Syndrome (PKAN). In: Kompoliti K and Metman LV, eds. Encyclopedia of Movement Disorders. Elsevier, 2010: 1–3.

6 Zorzi G, Zibordi F, Chiapparini L, et al. Iron-related MRI images in patients with pantothenate kinase-associated neurodegeneration (PKAN) treated with deferiprone: results of a phase 2 pilot trial. *Mov Disord* 2011; **26:** 1756–59.

7 Kurian MA, McNeill A, Lin JP, Maher ER. Childhood disorders of neurodegeneration with brain iron accumulation (NBIA). *Dev Med Child Neurol* 2011; **53:** 394–404.

8 Poulsen HE. Oxidative DNA modifications. *Exp Toxicol Pathol* 2005; **57** (suppl 1): 161–69.

9 Singh KK. Mitochondria damage checkpoint, aging, and cancer. *Ann NY Acad Sci* 2006; **1067:** 182–90.

10 Hayflick SJ, Hogarth P. As iron goes, so goes disease? *Haematologica* 2011; **96:** 1571–72.

11 Sohn YS, Breuer W, Munnich A, Cabantchik ZI. Redistribution of accumulated cell iron: a modality of chelation with therapeutic implications. *Blood* 2008; **111:** 1690–99.

12 Zuccarelli A, Sanna PMG, Bellu L, Solinas, Mulas G. Therapy with deferiprone in a case of pantothenate kinase-associated neurodegeneration (PKAN). 5 Congresso Nazionale Soste; Cagliari; Oct 16–18, 2008 (in Italian).

13 Abbruzzese G, Cossu G, Balocco M, et al. A pilot trial of deferiprone for neurodegeneration with brain iron accumulation. *Haematologica* 2011; **96:** 1708–11.

14 Pratini NR, Sweeters N, Vichinsky E, Neufeld JA. Treatment of classic pantothenate kinase-associated neurodegeneration with deferiprone and intrathecal baclofen. *Am J Phys Med Rehabil* 2013; **92:** 728–33.

15 Rohani M, Razmeh S, Shahidi GA, Alizadeh E, Orooji M. A pilot trial of deferiprone in pantothenate kinase-associated neurodegeneration patients. *Neurol Int* 2018; **9:** 7279.

16 Boddaert N, Quan Sang KH, Rotig A, et al. Selective iron chelation in Friedreich ataxia. Biological and clinical implications. *Blood* 2007; **110:** 401–08.

17 Pandolfo M, Arpa J, Delatycki MB, et al. Deferiprone in Friedreich's ataxia: a six-month randomized controlled trial. *Ann Neurol* 2014; **76:** 509–21

18 Devos D, Moreau C, Devedjian JC, et al. Targeting chelatable iron as a therapeutic modality in Parkinson's disease. *Antioxid Redox Signal* 2014; **21:** 195–210.

19 Dooling EC, Schoene WC, Richardson EP Jr. Hallervorden-Spatz syndrome. *Arch Neurol* 1974; **30:** 70–83.

20 Forni GL, Balocco M, Cremonesi L, Abbruzzese G, Parodi RC, Marchese R. Regression of symptoms after selective iron chelation therapy in a case of neurodegeneration with brain iron accumulation. *Mov Disord* 2008; **23:** 904–07.

21 Bellanti F, Danhof M, Della Pasqua O. Population pharmacokinetics of deferiprone in healthy subjects. *Br J Clin Pharmacol* 2014; 78: 1397–406.

22 Timmermann L, Pauls KA, Wieland K, et al. Dystonia in neurodegeneration with brain iron accumulation: outcome of bilateral pallidal stimulation. *Brain* 2010; **133:** 701–12.

23 Cossu G, Abbruzzese G, Matta G, et al. Efficacy and safety of deferiprone for the treatment of pantothenate kinase-associated neurodegeneration (PKAN) and neurodegeneration with brain iron accumulation (NBIA): results from a four years follow-up. *Parkinsonism Relat Disord* 2014; **20:** 651–54.

24 Liu Z, Shen HC, Lian TH, et al. Iron deposition in substantia nigra: abnormal iron metabolism, neuroinflammatory mechanism and clinical relevance. *Sci Rep* 2017; **7:** 14973.

25 Clinical study report: a six-month double-blind, randomized, placebo-controlled study investigating the safety and tolerability of deferiprone in patients with Friedreich's Ataxia (LA29–0207). ApoPharma Inc, 2011.

26 Dexter DT, Statton SA, Whitmore C, et al. Clinically available iron chelators induce neuroprotection in the 6-OHDA model of Parkinson's disease after peripheral administration. *J Neural Transm* 2011; **118:** 223–31.

27 Ceci A, Baiardi P, Felisi M, et al. The safety and effectiveness of deferiprone in a large-scale, 3-year study in Italian patients. *Br J Haematol* 2002; **118:** 330–36.