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

TIRCON2012V1-EXT

CLINICAL STUDY PROTOCOL

EudraCT Number:	2014-001427-79
IND Number:	104880
Investigational Product:	Deferiprone
Development Phase:	III
Indication Studied:	Pantothenate kinase-associated neurodegeneration (PKAN)
Study Design:	Multi-center, single-arm, open-label, 18-month extension of an earlier 18-month study assessing the safety and efficacy of deferiprone in patients with PKAN
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Version and Date of Protocol:	Version 2.0, 20 AUG 2014

SIGNATURE PAGES

Sponsor

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

Study Title:	Long-term safety and efficacy study of deferiprone in patients with pantothenate kinase-associated neurodegeneration (PKAN)
Study Code:	TIRCON2012V1-EXT
Version Number:	2.0
Version Date:	20 AUG 2014

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Principal Investigator

I, the undersigned, hereby declare that I agree to assume responsibility for the proper conduct of the study at this site; and that I will conduct the study in compliance with this protocol, with any future amendments, and with any other written study conduct procedures provided, reviewed, and approved by the sponsor or its delegate.

Study Title:	Long-term safety and efficacy study of deferiprone in patients with pantothenate kinase-associated neurodegeneration (PKAN)
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Name of Principal Investigator:	
Name of Study Site:	
Location of Study Site: *(City, region/province/ state, country)*	

Signature

Date (DD MMM YYYY)

SYNOPSIS

Name of Sponsor: ApoPharma Inc. **Name of Finished Product:** Deferiprone **Name of Active Ingredient:** 3-hydroxy-1,2-dimethylpyridin-4-one	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

Title of study:	Long-term safety and efficacy study of deferiprone in patients with pantothenate kinase-associated neurodegeneration (PKAN)
Study code:	TIRCON2012V1-EXT
Phase of development:	Phase III
Objectives:	**Primary:** To evaluate the long-term safety and tolerability of deferiprone in patients with PKAN. **Secondary:** • To evaluate the change in severity of dystonia over time in patients with PKAN treated with deferiprone. • To evaluate global improvement over time in patients with PKAN treated with deferiprone
Study design:	Study TIRCON2012V1-EXT is an 18-month, multi-center, single-arm, open-label extension of study TIRCON2012V1. In the initial study, patients with a diagnosis of PKAN are being randomized in a 2:1 ratio to receive 18 months of treatment with either deferiprone or placebo, respectively. All participants who complete TIRCON2012V1 will be offered the opportunity to continue in the extension study, with the final visit (Week 78) of the initial study being considered Visit 1 of the extension study. (A 4-week follow-up visit that is planned for the end of study TIRCON2012V1 will be cancelled for individuals who choose to continue.) Patients who were randomized to receive deferiprone in study TIRCON2012V1 will continue to receive deferiprone in the extension study, while those who were randomized to receive placebo will be switched to deferiprone. Since the initial study will still be in progress at the time that the first patients enter the extension study, patients and study staff will remain blinded as to which product was received for the previous 18 months. In order to minimize the possible gastrointestinal upset that could result from starting deferiprone at too high a dose (and which might alert the former placebo recipients to the change in product), the dosing regimen will be titrated weekly for the first 3 weeks. All patients, including those who were on deferiprone initially, will receive 5 mg/kg deferiprone twice a day (b.i.d.) for the first week. If this dose is tolerated and there are no signs of toxicity, the dose will be increased to 10 mg/kg b.i.d. for the next week; and if that dose is tolerated, it will be increased the following week to 15 mg/kg b.i.d. for the remainder of the study. Individual dosages may be adjusted downward if necessary at any time for reasons of safety or tolerability.

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Study design (cont'd):	Patients will have their hematology blood counts monitored weekly, and will undergo safety and efficacy assessments at 6 months (Visit 2), 12 months (Visit 3), and 18 months (Visit 4).
Duration of participation:	The duration of participation in the extension study for each patient will be approximately 18 months.
Criteria for evaluation:	**Safety:** • Adverse events (AEs): Frequency, severity, time to onset, duration, and relatedness to study product • Serious adverse events (SAEs): Frequency, severity, time to onset, duration, and relatedness to study product • Number of discontinuations due to AEs • Hematology assessments • Blood chemistry assessments • ECG assessments **Efficacy:** <u>All patients:</u> • Change in the Barry-Albright Dystonia Scale (BAD) total score from baseline (defined as prior to the start of deferiprone therapy) to Visit 4, as assessed by central evaluation of videotapes • Proportion of patients with improved or unchanged BAD scale total score between baseline and Visit 4 (responder analysis) • Change from baseline to Visit 4 in BAD scale score per body region (eyes, mouth, neck, trunk, and each upper and lower extremity), as assessed by central evaluation of videotapes • Change in score on the Patient Global Impression of Improvement (PGI-I) from Visit 1 to Visit 4 • Proportion of patients showing an improvement on PGI-I at Visit 4 (responder analysis) The time points for assessment of these efficacy endpoints are defined as follows: • For patients who received deferiprone in the earlier study, the baseline visit of that study will be treated as the baseline visit of TIRCON2012V1-EXT as well. Thus, Visit 1 of the extension study (Week 0) will be Year 1.5, and Visit 4 (Week 78) will be Year 3. • For patients who received placebo in the earlier study, Visit 1 of the extension study (Week 0) will be the baseline visit. Thus, Visit 4 (Week 78) will be Year 1.5.

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Criteria for evaluation (cont'd):	<u>Only patients who received placebo in initial study:</u> For this group only, for each measure, the change seen between the start and completion of study TIRCON2012V1 (i.e., following 18 months on placebo) will be compared against the change seen between the start and completion of study TIRCON2012V1-EXT (i.e., following 18 months on deferiprone) as follows: • Comparison of change in BAD total score from baseline to completion of the initial study vs. change in BAD total score from baseline to completion of the extension study • Comparison of the proportion of patients with improved or unchanged BAD total score between baseline and completion of the initial study vs. the proportion with improved or unchanged BAD total score from baseline to completion of the extension study (responder analysis) • Comparison of the change in BAD score per body region between baseline and completion of the initial study vs. change in BAD score per body region between baseline and completion of the extension study • Comparison of change in PGI-I score from baseline to completion of the initial study vs. change in PGI-I score from baseline to completion of the extension study • Comparison of the proportion of patients showing an improvement on PGI-I at completion of the initial study vs. the proportion showing an improvement at completion of the extension study (responder analysis)
Number of patients:	A planned total of 90 patients will be enrolled in the TIRCON2012V1 study. All patients who complete that study will be invited to enroll in the extension study.
Main criterion for inclusion:	Completed study TIRCON2012V1
Investigational product:	Product: Deferiprone oral solution (80 mg/mL) Dose: Up to 15 mg/kg b.i.d. (based on tolerability) Mode of administration: Oral

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Schedule of treatment and specimen collection:	All patients will be scheduled to take deferiprone daily, 2 times a day, for up to 18 months. Safety and efficacy assessments will be conducted at the following time points: • Hematology: Weekly up to Visit 4 (End of Study) or early termination • Blood chemistry: Visits 1, 2, 3, and 4 or early termination • ECG: Visits 1 and 4 or early termination • BAD: Visits 1, 2, 3, and 4 or early termination • PGI-I: Visits 2, 3, and 4 or early termination * * The PGI-I will be conducted at Visit 1 as well, but its data on that day will be applicable only to the initial study (for which this is the last visit), not to the extension study.
Statistical methods:	<u>Safety Analysis</u> The incidences of AEs and SAEs reported during deferiprone therapy for all patients, from the start of TIRCON2012V1 to the completion of TIRCON2012V1-EXT, will be tabulated. Similar tables will be produced for the severity of AEs and for their relationship to the study medication. Time to onset and duration of all AEs with an incidence of >5%, and of any AEs of special interest (e.g., worsening of dystonia), will be summarized with descriptive statistics. The percentage of discontinuations due to AEs will be calculated, and the AEs leading to discontinuation will be summarized in a frequency table by preferred term. Laboratory data (hematology and blood chemistry) will be summarized using descriptive statistics for continuous variables and frequency tables for discrete variables. The incidences of out-of-range data will be tabulated, and the changes from baseline to the end of study will be examined using shift tables. <u>Efficacy Analysis</u> For the efficacy measures of BAD (total score and by body region) and PGI-I, the change from baseline to each of the measurement time points will be determined and summarized using descriptive statistics. A paired t-test will be used to assess the statistical significance of the changes in these efficacy outcomes from baseline to Visit 4. For the BAD total score and for PGI-I, the proportions of patients determined to be responders at Visit 4 will be calculated and presented along with 95% confidence intervals.

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Statistical methods (cont'd):	For patients who received placebo in study TIRCON2012V1, a paired t-test will be used to compare the change in BAD (total score and by body region) and PGI-I between the start and completion of the initial study and between the start and completion of the extension study. For the BAD total score and for PGI-I, McNemar's test will be used to compare the proportion of responders in the initial study with the proportion of responders in the extension study.
Version and date of protocol:	Version 2.0, 20 AUG 2014

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
BAD	Barry Albright Dystonia
b.i.d.	*bis in die* (twice daily dosing)
CBC	complete blood count
CRA	clinical research associate
CRF	case report form
CS	clinically significant
DBS	Deep Brain Stimulation
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	intent-to-treat
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed-effect model repeated measure
NBIA	neurodegeneration with brain iron accumulation
NCS	not clinically significant
PGI-I	Patient Global Impression of Improvement
PKAN	pantothenate kinase-associated neurodegeneration

Abbreviation	Definition
PP	per protocol
PRN	*pro re nata* (as needed)
QA	Quality Assurance
RDC	remote data capture
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
WHO	World Health Organization

1 INTRODUCTION

1.1 Background

1.1.1 Background of the Disease

Pantothenate kinase-associated neurodegeneration (PKAN) is a rare disorder characterized by progressive dystonia, parkinsonism, spasticity, and brain iron accumulation (1, 2). Clinically, the disease manifests as rigidity, dystonia, and chorea (3). PKAN is the most prevalent form of a group of progressive extrapyramidal disorders associated with iron accumulation in the brain, collectively called **neurodegeneration with brain iron accumulation** (NBIA) (4). With the advent of molecular genetic testing, it has become apparent that there are several genetically distinct disorders classified as NBIA, of which PKAN accounts for approximately 50% of cases (5).

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 (5). 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 (6). 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 (7). 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 (3). 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 also as retinopathy, deterioration of cognition or hearing, or peripheral nerve changes.

Historically, PKAN has been described as either classical or atypical. The majority of cases are classical and therefore relatively homogeneous in their phenotype (3). Classical PKAN usually develops before 6 years of age (average age at onset of symptoms is 3.5 years) (3, 5). Most patients with the classical form of PKAN lose the ability to walk independently 10–15 years after the beginning of symptoms, and many require a wheelchair by their mid-teens; in some cases, earlier. Individuals with classical PKAN are also more likely to have eye problems, with approximately two-thirds suffering from 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 (5).

In contrast, 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 progresses more slowly 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.

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 (2, 8, 9).

1.1.2 Background of the Investigational Product

Deferiprone (3-hydroxy-1,2-dimethylpyridin-4-one) is an oral bidentate iron chelator that preferentially binds trivalent iron cations (Fe3+) in a 3:1 (deferiprone:iron) complex. Ferriprox® is the ApoPharma formulation of deferiprone. It 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, and iron concentration in the liver and in the heart; and by clinical outcomes such as its ability to prevent iron-induced cardiac disease and prolong survival. The results of ApoPharma-sponsored clinical studies and of independent trials demonstrate that therapy with Ferriprox® is associated with good compliance and with stabilization or decline of body iron load.

Ferriprox® was first approved in 1999 by the European Medicines Agency (EMA) for the treatment of systemic iron overload in patients with thalassemia major, 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 three times per day for a total of 75 mg/kg/day, and the maximum dose is 33 mg/kg three times per day for a total of 99 mg/kg/day.

1.1.3 Rationale for Deferiprone in the Treatment of PKAN

While iron is essential for normal physiological function, excessive amounts of it 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 (10, 11).

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 impairments 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 (12). In patients with Friedreich's Ataxia, another neurodegenerative condition involving regional iron deposition in the brain, deferiprone has been shown to be able to reduce localized elevated levels of brain iron, as evidenced by MRI scans (13).

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, such as transferrin, for transport to other compartments inside or outside the cells (12).

Deferiprone appears to fulfill at least some of the criteria required for a reversed siderophore:

- Ability to cross the blood brain barrier (14, 15)
- Ability to gain access to cells (16) and effectively scavenge intracellular labile iron pools (17), exiting cells bound to the iron as an iron-chelate

- Ability to selectively bind iron in the various intracellular labile iron pools (18) and thereby reduce iron-dependent free radical formation (14, 15, 19, 20, 21, 22)
- Ability to spare extracellular transferrin-bound iron and potentially transfer chelated iron to apotransferrin (13, 18, 23, 24)
- Ability to donate iron for metabolic reutilization (18)

Because of its low molecular weight and favorable physicochemical properties, deferiprone has been shown to readily cross the blood-brain barrier in animal studies (25), and there is indirect evidence to suggest that it does so in humans as well (13). 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 the urine and feces. 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. Targeting the site of iron accumulation within the brain and removing excess iron may potentially slow or halt the debilitation that accompanies PKAN.

1.2 Rationale

ApoPharma Inc. is currently conducting an 18-month trial, TIRCON2012V1, to assess the safety and efficacy of deferiprone in patients with PKAN. In that study, a planned 90 participants are being randomized in a 2:1 ratio to receive either deferiprone oral solution or placebo. Patients are scheduled to undergo weekly monitoring of absolute neutrophil count (ANC) and to undergo safety and efficacy assessments at Months 1.5, 3, 6, 12, and 18.

Patients who complete TIRCON2012V1will be invited to enroll in the current study, in which all participants will receive deferiprone. Participants will thus receive deferiprone for a total of either 1.5 years or 3 years, depending on which treatment was assigned in the earlier study. The long-term data obtained will enable a better understanding of the use of deferiprone in this patient population.

1.3 Potential Risks and Benefits

Risks:

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

pooled clinical trials, agranulocytosis has been seen in about 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 it leading to death.

The most common adverse reactions reported during clinical trials have been chromaturia, nausea, vomiting, abdominal pain, alanine aminotransferase increased, arthralgia, and neutropenia (26).

Benefits:

The findings of preclinical research and case studies suggest that deferiprone has the potential to access pathologically relevant brain iron and to produce clinical benefit in patients with PKAN.

2 STUDY OBJECTIVES

2.1 Primary Objective

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

The endpoints for the primary objective are provided in Section 9.1.1.

2.2 Secondary Objectives

- To evaluate the change in severity of dystonia over time in patients with PKAN treated with deferiprone.
- To evaluate global improvement over time in patients with PKAN treated with deferiprone

The endpoints for the secondary objectives are provided in Section 9.1.2.

3 STUDY DESIGN

3.1 Description of Study Design

Study TIRCON2012V1-EXT is an 18-month, multi-center, single-arm, open-label extension of study TIRCON2012V1, which began in 2012 and is currently in progress. In the initial study, patients with a diagnosis of PKAN are being randomized in a 2:1 ratio to receive 18 months of treatment with either deferiprone or placebo, respectively. All participants who complete TIRCON2012V1 will be offered the opportunity to continue in the extension study, with the final visit of the initial study being considered Visit 1 of the extension study. (The 4-week follow-up visit that is planned at the end of study TIRCON2012V1 will be cancelled for individuals who choose to continue.) Patients who had been randomized to

receive deferiprone in study TIRCON2012V1 will continue to receive deferiprone in the extension study, while those who had been randomized to receive placebo will be switched to deferiprone. Since the initial study will still be in progress at the time that the first patients enter the extension study, patients and study staff will remain blinded until the initial study is over as to which product was received for the previous 18 months.

Patients will have their hematology blood counts monitored weekly, and will return to the study site at 6 months (Visit 2), 12 months (Visit 3), and 18 months (Visit 4) for assessments of safety and efficacy. Due to the difficulties that travel may pose for patients with PKAN, participants will have the option of arranging for the Visit 2 and Visit 3 assessments to be done locally instead. Details are provided in Section 5.1.

3.2 Rationale for Study Design

This single-arm, open-label extension study design has been primarily chosen to gather data on multiple patient-years of exposure to deferiprone in order to understand and gain confidence in its safety and efficacy profile in patients with PKAN.

3.3 Rationale for Selection of Doses

The dosage of deferiprone for each patient will be the same as that being used in study TIRCON2012V1: up to 15 mg/kg twice a day (b.i.d.), for a total daily dose of 30 mg/kg.

In order to minimize the possible gastrointestinal upset that could result from starting deferiprone at too high a dose (and which might alert the former placebo recipients to the change in product), the dosing regimen will be titrated weekly for the first 3 weeks. All patients, including those who were on deferiprone initially, will receive 5 mg/kg deferiprone twice a day (b.i.d.) for the first week. If this dose is tolerated and there are no signs of toxicity, the dose will be increased to 10 mg/kg b.i.d. for the next week; and if that dose is tolerated, it will be increased the following week to 15 mg/kg b.i.d. for the remainder of the study. Individual dosages may be adjusted downward if necessary at any time for reasons of safety or tolerability.

4 STUDY POPULATION

4.1 Number of Patients

A planned total of 90 patients will be enrolled in the TIRCON2012V1 study. All patients who complete that study will be invited to enroll in the extension study.

4.2 Inclusion Criteria

Patients will be eligible to enroll in the study if they meet **all** the following criteria:

1. Completed study TIRCON2012V1
2. Sexually active females of childbearing potential, including those who are peri-menopausal (defined as less than 2 years since last menstrual period) must have a negative pregnancy test result at Visit 1 (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, they must meet at least one of the following criteria:

   - Use an effective method of contraception during the study and within 30 days following their last dose of study medication, OR
   - Participate in a non-heterosexual lifestyle, OR
   - Have a male sexual partner who has been sterilized (supporting evidence required)

   Approved methods of contraception will consist of the following or must follow local requirements:

   - Oral contraceptive used in conjunction with condom, diaphragm, or spermicide
   - Hormonal implant used in conjunction with condom, diaphragm, or spermicide
   - Injectable contraceptive used in conjunction with condom, diaphragm, or spermicide
   - Diaphragm or condom used with spermicide

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

   Female patients who meet any of the following criteria are not of childbearing potential and therefore do not need to practice contraception:

   - Post-menopausal (last menstrual period > 2 years ago)
   - Had a tubal ligation (supporting evidence required)
   - Had a hysterectomy or oophorectomy (supporting evidence required)
3. Fertile heterosexual males and/or their partners must agree to use an effective method of contraception during the study and for 30 days following the last dose of study medication
4. Patients and/or their authorized legal representatives must provide signed and dated written informed consent prior to the first study intervention, and patients must be able to adhere to study restrictions, appointments, and evaluation schedules. Patients who are minors must sign an assent form as per local regulatory requirements.

4.3 Exclusion Criteria

1. Withdrew from the study TIRCON2012V1 for reasons of safety
2. Plan to participate in another clinical trial at any time from the day of enrolment until 30 days post-treatment in the current study
3. Presence of any medical, psychological, or psychiatric condition which in the opinion of the investigator would cause participation in the study to be unwise.
4. Pregnant, breastfeeding, or planning to become pregnant during the study period.

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, the investigator should consider withdrawing these individuals from the study.

4.5 Patient Withdrawal

Patients have 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.

A patient may be withdrawn from the study at any time, at the discretion of the investigator, for any of the following reasons:

- Medical or safety reasons considered significant by the patient and/or the investigator
- Requirement for concomitant medication that might interfere with the evaluation of study treatment or may be contraindicated
- Occurrence of other illnesses that might affect the patient's further participation in the study or evaluation of study treatment
- A protocol deviation that might interfere with study assessments, as judged by the investigator
- Repetitive patient non-compliance with the protocol or with instructions of the investigator
- Participation in another clinical trial at any time during the conduct of 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 7.2.4, Procedures in Case of Pregnancy)

- Occurrence of any adverse event characterized as life-threatening or disabling that is not associated with the patient's primary diagnosis and that is assessed as at least possibly related to study drug by the investigator or the sponsor
- Non-compliance with weekly hematology blood counts (3 or more consecutively missed visits will result in automatic withdrawal)
- Termination of the study by the sponsor
- Occurrence of moderate neutropenia or severe neutropenia/agranulocytosis (see Section 7.2.1.8, Adverse Events of Special Interest)

Patients who decide to withdraw participation in the study should always be contacted, if possible, in order to ask about the reason for withdrawal, whether any adverse events (AEs) occurred, and use of concomitant medications. A withdrawn patient should return for an Early Termination Visit. 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.

If a patient withdraws or is withdrawn before completing the study, the date and reason for the withdrawal must be entered on the source document and on the appropriate page of the electronic case report form (eCRF), and all other appropriate eCRF pages must be completed.

4.5.1 Follow-up of Patient Withdrawal Due to 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 to 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 inclusion criterion #2) throughout the course of the trial and for 30 days following receipt of the last dose of study medication.

If a patient does become pregnant, the investigator must do the following upon becoming aware of the pregnancy:

- Ensure that the study medication is stopped immediately
- Inform the sponsor via the pregnancy report form
- Follow the pregnancy closely, and provide reports to the sponsor until delivery or other resolution
- Male patients must inform the investigator if their female partner becomes pregnant during the trial or within 30 days following the last dose of study medication. As

with the pregnancy of a female subject, the site must inform the sponsor and, if the partner consents, will follow the pregnancy and provide the sponsor with a report on its outcome.

4.5.2 Replacement of Patients Who Withdraw

Not applicable. The only individuals eligible for enrolment are those who completed treatment in study TIRCON2012V1.

4.5.3 Treatment Interruptions

As in the initial study, patients will be provided with a card containing contact information for emergency services which they are to carry at all times, and will be advised to promptly report any symptoms indicative of infection such as fever or flu-like symptoms. Treatment will be interrupted under the following circumstances:

- If a patient develops an infection, therapy will be interrupted based on the investigator's judgment. If ANC <1.5 x 10^9/L., neutrophil count must be obtained and monitored more frequently.
- If a patient develops a fever (defined as ≥38.5 ºC or 101.3 ºF), therapy must be interrupted immediately, and a CBC and differential count must be obtained.

Therapy with study medication can be re-initiated once all symptoms have been resolved and it is deemed safe by the investigator. See Section 7.2.1.8, Adverse Events of Special Interest.

4.6 Prior and Concomitant Therapies

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, patients must not receive any other investigational product or any drugs that are known to cause neutropenia or agranulocytosis. A list of prohibited drugs is provided in Appendix 2.

4.7 Rescue Medication

Rescue medication is defined as a newly prescribed medication or a change in dosage of a currently prescribed medication that has the potential to have an effect on dystonia symptoms and is provided because of a worsening of the patient's condition.

The use of rescue medication should be limited to circumstances judged as absolutely necessary by the investigator. Any use of a rescue medication must be documented, including

the reason. If a patient uses rescue medication for more than 2 events, the investigator should notify the sponsor to discuss the patient's continued participation in the study.

Rescue medications for dystonia include, but are not limited to, the list of drugs provided in Appendix 3.

5 STUDY PROCEDURES

The procedures and assessments to be conducted at each study visit are summarized in Table 5.1 and are detailed in the section that follows.

Table 5.1 Table of study procedures

Procedure	Visit 1 [1]	Weekly Blood Draws	Telephone Contact	Visit 2	Visit 3	Visit 4 or Early Termination
Week:	0	1 to 78	1 and 2	26	52	78
Informed consent/assent	X					
Confirmation of eligibility	X					
Review of medical history	X					X
Serum pregnancy testing[2]	X			X	X	X
Physical examination	X			X	X	X
Vital signs (including weight and height)[3]	X			X	X	X
12-lead ECG	X					X
Contraceptive counseling	X			X	X	X
Hematology	X	X		X	X	X
Blood chemistry	X			X	X	X
Urinalysis	X			X	X	X
BAD	X			X	X	X
PGI-I				X	X	X

Procedure	Visit 1 [1]	Weekly Blood Draws	Telephone Contact	Visit 2	Visit 3	Visit 4 or Early Termination
Week:	0	1 to 78	1 and 2	26	52	78
Dose calculation/verify and adjust dose level	X			X	X	
Dispense study medication	X			X	X	
Remind patient to adjust dosage [4]			X			
Collect used and unused study medication				X	X	X
Prior and concomitant medications	Throughout the study					
Adverse events and serious adverse events	Throughout the study					

[1] Visit 1 is the final visit (Month 18) of study TIRCON2012V1. It serves as the screening visit for TIRCON2012V1-EXT for all patients, and as the baseline for those patients who received placebo in TIRCON2012V1 and will now be receiving deferiprone for the first time. (For patients who received deferiprone in TIRCON2012V1, the measures obtained at the baseline visit of the TIRCON2012V1 study will be used as the baseline measures for TIRCON2012V1-EXT as well.)

[2] Sexually active females of childbearing potential only (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).

[3] Height will be measured only at Visits 1 and 4

[4] All patients, including those who were on deferiprone initially, will receive 5 mg/kg deferiprone b.i.d. for the first week. If the medication is tolerated and there are no signs of toxicity, the dose will be increased at Week 1 to 10 mg/kg b.i.d., and will be increased again at Week 2 to 15 mg/kg b.i.d. for the remainder of the study. Patients will receive a telephone call at these times to remind them to implement the increase in dosage, provided there are no safety concerns in doing so.

5.1 Visit Procedures

Visit 1 (Week 0)

This visit is the Month 18 visit of TIRCON2012V1: i.e., for patients who choose to continue on, the last visit of the initial study is considered the first of the extension study. For patients who had been on placebo and will now be receiving deferiprone for the first time, the data obtained at this visit will be treated as the baseline measures for TIRCON2012V1-EXT.

The following procedures will be done:

- Explain the extension study to the patient and/or authorized legal representative, and obtain written informed consent/assent
- Confirm eligibility criteria
- Review medical history
- Collect information about concomitant medications
- Ask patient about the use of any of the medications listed in Appendix 3 or any other medication that has the potential to affect dystonia symptoms (e.g., spasticity, muscular rigidity, and parkinsonism), as follows:
    - If patient has been on a regular dosing regimen of any of these medications since the start of study TIRCON2012V1, verify that the regimen has been stable
    - If patient has been taking any of these medications on a PRN (as needed) basis since the start of study TIRCON2012V1, verify that treatment was interrupted prior to the current visit according to the following timelines:

Medication	Treatment interruption period prior to current visit
Baclofen	30 days
Trihexyphenidyl	30 days
Clonazepam	30 days
Tizanidine	30 days
Botox	60 days
Tetrabenazine	90 days

- If patient has a DBS system or Baclofen pump in place, verify that the DBS stimulation parameters or pump settings have been stable, as confirmed by the investigator

- Collect blood samples for the following assessments:
  - Hematology
  - Blood chemistry
  - 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 a urine sample for urinalysis
- Measure vital signs, weight, and height
- Perform a 12-lead ECG
- Conduct contraceptive counseling for sexually active patients
- The following must be performed by a qualified investigator or a qualified delegate:
  - Conduct a physical examination
  - Record administration of the BAD in a standardized manner on videotape, and transmit tape to the evaluation center
- Verify dosage of study medication
- Dispense a 6-month supply of study medication
- Remind the patient/authorized legal representative to do the following:
  - Return all study medication containers at the next visit, whether empty or unused
  - Keep careful track of adverse events and medication(s) used
  - Interrupt therapy immediately in the event of fever (temperature ≥38.5 ºC/101.3 ºF), and promptly report any symptoms indicative of infection such as fever or flu-like symptoms
  - If patient is on a regular dosing regimen of any of the medications listed in Appendix 3 or of any other medication that has the potential to affect dystonia symptoms, to stay on the same 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.
  - If patient is being treated with any such medications on a PRN basis, to use them only under circumstances judged as absolutely necessary by the investigator, and to interrupt treatment prior to the next study visit according to the following timelines:

Medication	Treatment interruption period prior to current visit
Baclofen	30 days
Trihexyphenidyl	30 days
Clonazepam	30 days
Tizanidine	30 days
Botox	60 days
Tetrabenazine	90 days

- If patient has a DBS system or Baclofen pump in place, to make every effort 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.
- If leaving the study before completion, to return to the clinic for an Early Termination Visit as soon as possible and no later than 30 days following the last dose of study medication

- Provide patient with card containing contact information for emergency services, and advise that this card should be carried at all times

- Schedule next study visit

Weekly Blood Draws (every 7 ± 3 days)

Note: These blood draws can be conducted either at a local laboratory or at the study site.

- Collect blood sample for hematology assessment. The results are to be reviewed by the investigator in a timely manner when they are received from the laboratory.

Telephone Contact (Week 1 ±2 days and Week 2 ±2 days)

A study staff member will contact the patient and/or legal representative by telephone at Week 1 and Week 2 with the following queries and reminders, and will document the responses:

- Ask if treatment is proceeding satisfactorily. If the patient appears to be having difficulty, the telephone calls should be repeated as frequently as necessary.
- Remind the patient to increase the dosage of study medication at Week 1 from 5 mg/kg to 10 mg/kg, and at Week 2 from 10 mg/kg to 15 mg/kg, provided there are no safety concerns in doing so

- Remind the patient that if treatment is stopped early, to return to the clinic for an Early Termination Visit as soon as possible and no later than 1 month following treatment discontinuation
- Remind patient to interrupt therapy immediately in the event of fever (temperature ≥38.5 ºC/101.3 ºF), and to promptly report any symptoms indicative of infection such as fever or flu-like symptoms
- Ask if the patient has experienced any AEs or SAEs or has taken any concomitant medications. If yes, document these as specified in Sections 7.2.1.2, 7.2.1.6, and 7.2.3.4.
- Reconfirm the next study visit
- Document the date and time of the contact; the person contacted (patient, parent, legal representative); and the name and signature of the staff member who conducted the call

Visit 2 (Week 26 ± 14 days) and **Visit 3** (Week 52 ± 14 days)

The following procedures will be done:

- Collect information about concomitant medications
- Query patient about the use of any of the medications listed in Appendix 3 or any other medication that has the potential to affect dystonia symptoms, as follows:
  - If patient has been on a regular dosing regimen of any of these medications since the start of study TIRCON2012V1, verify that the regimen has been stable
  - If patient has been taking any of these medications on a PRN basis since the start of study TIRCON2012V1, verify that treatment was interrupted prior to the current visit according to the following timelines:

Medication	Treatment interruption period prior to current visit
Baclofen	30 days
Trihexyphenidyl	30 days
Clonazepam	30 days
Tizanidine	30 days
Botox	60 days
Tetrabenazine	90 days

- If patient has a DBS system or Baclofen pump in place, verify that the DBS stimulation parameters or pump settings have been stable, as confirmed by the investigator

- Collect blood samples for the following assessments:
  - Hematology
  - Blood chemistry
  - 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 a urine sample for urinalysis
- Measure vital signs and weight
- Conduct contraceptive counseling for sexually active patients
- The following must be performed by a qualified investigator or a qualified delegate:
  - Conduct a physical examination
  - Record administration of the BAD in a standardized manner on videotape, and transmit tape to the evaluation center
  - Administer the Patient Global Impression of Improvement
- Verify dosage of study medication
- Dispense a 6-month supply of study medication
- Collect any empty containers or unused medication from the previous 6 months, and perform drug accountability
- Remind the patient/authorized legal representative to do the following:
  - Return all study medication containers at the next visit, whether empty or unused
  - Keep careful track of adverse events and medication used
  - Interrupt therapy immediately if an infection develops, and immediately report any symptoms indicative of infection such as fever, or flu-like symptoms
  - If patient is on a regular dosing regimen of any of the medications listed in Appendix 3 or of any other medication that has the potential to affect dystonia symptoms, to stay on the same 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.
  - If patient is being treated with any such medication on a PRN basis, to use them only under circumstances judged as absolutely necessary by the investigator, and to interrupt treatment prior to the next study visit according to the following timelines:

Medication	Treatment interruption period prior to next visit
Baclofen	30 days
Trihexyphenidyl	30 days
Clonazepam	30 days
Tizanidine	30 days
Botox	60 days
Tetrabenazine	90 days

  - If patient has a DBS system or Baclofen pump in place, to make every effort 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.
  - If patient decides to leave the study before completion, return to the clinic for an Early Termination Visit as soon as possible and no later than 1 month following the last dose of study medication
- Schedule next study visit

Due to the difficulties that travel may pose for patients with PKAN, participants will have the option of arranging for the Visit 2 and Visit 3 assessments to be done locally instead, as follows:

- *At patient's home, via telephone:* Collection of information on concomitant medications, use of medications with potential to affect dystonia symptoms, and stability of DBS stimulation parameters or pump settings; conducting of contraceptive counseling; administration of the PGI-I; verification of dosage of study medication; reminders to patient as detailed above
- *At a local doctor's office:* Physical examination; measurement of weight; measurement of vital signs.
- *At a local laboratory:* Blood and urine samples for safety tests; blood sample for pregnancy test if applicable.
- *At patient's home, via videoconferencing:* Video recording for BAD assessment. Patients and their family members who will not be travelling to the site for Visits 2 and 3 will be provided with recording equipment and trained in how to operate it. On the day of the assessment, the study doctor will connect to the patient's home via videoconferencing, and will direct the patient what to do while the family member (or other appropriate individual) records it. Instructions will be provided on how to upload the video for transmission to the site and to the central assessors.

- *Via courier:* From patient to site: Return of used and unused study medication containers from the past 6 months. From site to patient: Provision of study medication for the next 6 months.

Visit 4 (Week 78 ± 14 days) / Early Termination Visit

The following procedures will be done:

- Review medical history
- Collect information about concomitant medications
- Query patient about the use of any of the medications listed in Appendix 3 or any other medication that has the potential to affect dystonia symptoms, as follows:
  - If patient has been on a regular dosing regimen of any of these medications since the start of study TIRCON2012V1, verify that the regimen has been stable
  - If patient has been taking any of these medications on a PRN basis since the start of study TIRCON2012V1, verify that treatment was interrupted prior to the current visit according to the following timelines:

Medication	Treatment interruption period prior to current visit
Baclofen	30 days
Trihexyphenidyl	30 days
Clonazepam	30 days
Tizanidine	30 days
Botox	60 days
Tetrabenazine	90 days

- Collect blood samples for the following assessments:
  - Hematology
  - Blood chemistry
  - 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 a urine sample for urinalysis
- Measure vital signs, weight, and height
- Perform a 12-lead ECG

- Conduct contraceptive counseling for sexually active patients
- The following must be performed by a qualified investigator or a qualified delegate:
  - Conduct a physical examination
  - Record administration of the BAD in a standardized manner on videotape, and transmit tape to the evaluation center
  - Administer the Patient Global Impression of Improvement
- Collect any empty containers or unused medication from the previous 6 months, and perform drug accountability
- Instruct the patient/authorized legal representative to report any AEs that occur in the next 14 days and any SAEs that occur in the next 30 days

Any ongoing AE or SAE is to be followed until one of the following outcomes:

- AE/SAE is resolved
- Patient's condition stabilizes
- AE/SAE is otherwise explained
- Patient is lost to follow-up

5.2 Method of Assignment to Treatment

Not applicable. All patients in the extension study will receive deferiprone.

5.3 Blinding Procedures

This study is open-label, with all participants receiving deferiprone. However, patients, study staff, and members of the ApoPharma study team will remain blinded during the extension study with regard to whether the patients had received deferiprone or placebo in the initial study. The blind will be broken once the initial study is completed.

5.4 Allocation of Patient Numbers

All patients who signed the ICF for study TIRCON2012V1 will have been assigned a unique 6-digit number, where the first 3 digits represent the site code and the last 3 are sequentially assigned to each patient. These assigned numbers will be maintained for patients who continue on to study TIRCON2012V1-EXT.

5.5 Treatment Compliance

At each visit, patients will be instructed to bring empty and unused containers of study medication back to the study site. Compliance will be evaluated by calculating the volume of medication dispensed and the volume of unused drug supply remaining in the bottle.

6 STUDY TREATMENTS

All patients in the extension study will receive deferiprone.

6.1 Investigational Product

Deferiprone (3-hydroxy-1,2-dimethylpyridin-4-one) is manufactured by Apotex Inc. The drug will be supplied to the clinical sites by ApoPharma Inc.

6.1.1 Dosage Form and Mode of Administration

Deferiprone will be provided as an 80 mg/mL oral solution. It is to be taken orally, twice a day, and can be taken with or without food, as per the investigator's recommendation.

6.1.2 Precautions for Use

Bottles should not be stored in direct light. The contents of a bottle must be used within 8 weeks of opening.

6.2 Reference Product

Not applicable. All participants in study TIRCON2012V1-EXT will receive deferiprone.

6.3 Packaging and Labeling

Deferiprone 80 mg/mL oral solution will be supplied in 500 mL amber-colored bottles with child-resistant closure and a tamper-evident seal. The containers will be provided with labels whose content is in accordance with all applicable regulatory requirements. The label will include protocol number, expiry date, lot/batch number, investigational statement, storage temperature, dosage, direction for use, visit number, date dispensed, and name and address of the study sponsor.

6.4 Shipping and Storage

A "Product Receipt Form and Temperature Verification Log" will be provided to the study sites by the sponsor with each shipment of investigational product. The investigator or a designate is to sign and date this receipt form to acknowledge receiving the entire product shipment in good condition, and to record the time at which the "TempTale 4" (Sensitech Inc.) temperature-monitoring device was removed and stopped. The site will fax a copy of this receipt form to the sponsor and retain the original in its Investigator Trial File.

The study medication is to be stored in a secure location (a locked room or cabinet), under the control of the investigator and with access to authorized individuals only, at room temperature (15–30 ºC [59–86 ºF]). The sites will use a digital temperature monitoring device and a temperature log to facilitate daily recording of the temperature of the storage facility.

6.5 Product Accountability

It is the responsibility of the investigator to ensure that all study drug received at the study center is inventoried and accounted for throughout the study. Records of receipt, storage and administration of the study drug supplied must be maintained, and the drug accountability will be verified by the sponsor or sponsor's designee during on-site monitoring visits. At the conclusion of the study, a final inventory must be performed by the investigator or delegate. The sponsor will be responsible for determining the specific conditions for destruction of unused product.

The investigator must maintain logs of the quantity of product received from the sponsor and of the quantity dispensed to each patient, as follows:

Site Investigational Drug Inventory Record:

- 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

Patient Investigational Drug Dispensing Record:

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

6.6 Replacement Doses

Patients will be dispensed a 6-month supply of study medication at Visit 1 (Week 0), Visit 2 (Week 26), and Visit 3 (Week 52). Dispensing must be done by appropriately qualified staff (physician, pharmacist, or nurse).

If a patient reports that medication has been lost or accidentally destroyed, the appropriate site staff member must make a request for replacement medication, in writing, to the Clinical Research Associate (CRA), who will review and forward the request to the sponsor. All information related to the replacement medication is to be recorded in the drug accountability forms.

6.7 Disposition of Unused Product

It is the responsibility of the investigator to ensure that all study drug received at the study center is inventoried and accounted for throughout the study. Records of receipt, storage and administration of the study drug supplied must be maintained, and the drug accountability will be verified by the sponsor or sponsor's designee during on-site monitoring visits. At the conclusion of the study, a final inventory must be performed by the investigator or delegate. The sponsor will be responsible for determining the specific conditions for destruction of unused product.

7 MEASUREMENTS AND EVALUATIONS

7.1 Efficacy Measurements

7.1.1 Barry-Albright Dystonia Scale

Dystonia is a neurological movement disorder in which sustained muscle contractions cause twisting and repetitive movements or abnormal postures. The Barry-Albright Dystonia (BAD) scale is a reliable and responsive measure for rating the degree to which dystonia interferes with function (27). A 5-point ordinal scale is used to rate the severity of dystonia in 8 body regions: eyes, mouth, neck, trunk, and each upper and each lower extremity. The individual scores are then summed to provide a total score that ranges from 0 to 32; the higher the score, the more severe the dystonia. See Appendix 4.

For study TIRCON2012V1, a protocol was prepared by a group of experts to define a standardized way to administer and read the BAD scale, including a provocation test to better capture episodic or non-continuous symptoms. The administration of the BAD scale by the investigator or delegate is videotaped, and the videotape is sent to a central evaluator for objective assessment. The results will be sent back to the site, and will be entered by the study site staff into the eCRF.

In study TIRCON2012V1-EXT, the BAD scale will be administered at Visits 1, 2, 3, and 4 (or early termination visit).

7.1.2 Patient 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. Patients are asked at each post–Week 0 visit to rate their overall condition since Visit 1 of the extension study on a 7-point rating scale: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse. In cases where the patient cannot complete the scale by him/herself, the parent or legal representative will complete the scale. See Appendix 5.

The PGI-I will be administered at Visits 2, 3, and 4 (or early termination).

7.2 Safety Measurements

7.2.1 Adverse Events and Serious Adverse Events

7.2.1.1 Definition of Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient who is administered a pharmaceutical or other therapeutic product in a clinical study, not necessarily having a causal relationship with the product. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a product, whether or not considered related to that product.

AEs include:

- Exacerbation of a pre-existing illness, including acute episodes/crisis of a chronic underlying condition
- 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
- Accidents (e.g., involving a motor vehicle)
- Reasons for changes in concomitant medication (type of drug and/or dose)
- Medical, nursing, or pharmacy consultation
- Admission to hospital and surgical operations
- Abnormalities in laboratory findings (e.g., blood chemistry, hematology, urinalysis), ECG, or other assessments (e.g., vital signs) that are not part of a larger medical condition already recorded as an AE and which are judged by the investigator to be clinically significant. The investigator should exercise medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

AEs do not include:

- A pre-existing disease or condition present or detected at the start of the study that does not worsen
- Hospital admissions or surgical procedures that had been planned prior to enrolment into the study

- The disease or disorder being studied, or a sign or symptom associated with that disease or disorder, unless it has worsened
- An overdose of either the study treatment or concurrent medication without any signs or symptoms

Note: A case of overdose that is not associated with an AE is to be documented as a protocol deviation and promptly reported to the Medical Monitor.

7.2.1.2 Monitoring and Documenting of Adverse Events

AEs will be collected until 14 days after the last dose, and SAEs will be collected until 30 days after the last dose.

AEs and SAEs that are related to the underlying medical condition for which the patient enrolled in the clinical trial will be recorded separately from others.

Patients will be instructed to report any AEs to the investigator or a delegate. In addition, the investigator will solicit information about the occurrence of AEs through open-ended, non-leading verbal questions such as:

- How are you feeling?
- Have you had any medical problems since the last visit?
- Have you taken any new medications, other than those provided in this study, since the last visit?

Based on the patient's response to these questions, the investigator or delegate 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?

The patient should also be questioned about any previously reported AEs that have not resolved.

The investigator will evaluate all AEs for their relationship to the investigational product (Section 7.2.1.3), intensity (Section 7.2.1.4), and seriousness (Section 7.2.1.5), and will document any measures taken to address the event. There should be an attempt to establish a diagnosis of the AE based on signs, symptoms, and/or other clinical information. Wherever possible, a diagnosis should be documented, rather than the individual signs/symptoms. All information is to be clearly recorded in the source documents.

If the dosage of study drug is reduced or treatment is discontinued as a result of an AE, the circumstances leading to such reduction or discontinuation must be clearly documented.

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

7.2.1.3 Assessment of Causality

The relationship of an AE to the study drug should be determined by the investigator after thorough consideration of all available facts, including 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):

- Not related: Temporal relationship to study drug administration is missing or implausible, or there is no evident cause.
- Possibly related: Reasonable time sequence to administration of study drug, but event could also be explained by concurrent disease or other drugs or chemicals.
- Probably related: Reasonable time sequence to administration of study drug, and unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required.
- Definitely related: Plausible time relationship to study drug administration, and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory re-challenge procedure if necessary.

7.2.1.4 Assessment of Intensity

Intensity refers to the degree of discomfort or impairment associated with an event. The intensity of AEs is to be reported on the eCRF as mild, moderate, or severe, according to the definitions provided below. In addition, to maximize consistency in assessment, it is

recommended that the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) scale be used.

Intensity	**Corresponding NCI CTCAE Grade**
Mild: awareness of a sign or symptom but easily tolerated	1
Moderate: discomfort sufficient to cause interference with normal daily activities	2
Severe: resulting in inability to do work or perform normal daily activities	3–5

7.2.1.5 Serious Adverse Events

An SAE is an adverse event occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability or incapacity
- A congenital anomaly in the offspring of a patient who received the study treatment
- An important medical event that does not result in death, is not life-threatening, and does not necessitate hospitalization but which in the investigator's judgment may jeopardize the patient and may necessitate medical or surgical intervention to prevent one of those outcomes. Examples 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.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen during the study is not considered an AE.

- Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization, the event is considered an SAE.
- "Inpatient" hospitalization 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 an SAE.
- With regard to the criteria for an important medical event, medical and scientific judgment should be used in deciding whether prompt reporting is appropriate in this situation.

7.2.1.6 Reporting of Serious Adverse Events

All SAEs occurring up to 30 days following completion of or discontinuation from the study must be reported to the sponsor, regardless of whether they are suspected of having a causal relationship with the study drug. Any SAEs for which the investigator does suspect a causal relationship must be reported to the sponsor regardless of the time elapsed since the last dose of the study drug.

Patients will be instructed to report SAEs to the investigator **within 24 hours**, by telephone. In turn, the investigator must report all SAEs to the sponsor **within 24 hours** of notification by the patient, using the sponsor's SAE form. The sponsor will provide the contact information for reporting SAEs. An assessment of causality must be provided at the time of the initial report. The investigator or delegate must then complete and submit a follow-up SAE form to the sponsor **within 5 calendar days**, and must submit further follow-up forms if additional relevant follow-up information becomes available.

The sponsor will submit reports of SAEs to the appropriate regulatory agencies, in line with local regulatory requirements and timelines.

Investigators must report all SAEs to their IRB/IEC as well as to the sponsor. If any SAE that is considered at least possibly related to the study medication and is unexpected occurs at one site, the sponsor will promptly inform all other sites of this, and all investigators must then report this event to their own IRBs/IECs, following the same timelines as above or following local IRB/IEC policy, whichever takes precedence.

7.2.1.7 Follow-up and Documentation of SAEs

SAEs that occur during the study and up to 30 days after the last dose of study drug must be documented in the patient's medical record and on the SAE report form. 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 rather than the individual signs/symptoms should be documented as the SAE.

All SAEs must be followed until resolution, the condition stabilizes, the event is otherwise explained, or the patient is lost to follow-up. The investigator is responsible for ensuring that

follow-up includes any supplemental investigations that may be indicated, in order to elucidate the nature and/or causality of the SAE as completely as possible. 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 specified follow-up period, the sponsor should be sent a copy of any post-mortem findings, including histopathology.

New or updated information is to be recorded on the originally completed SAE report form, with all changes signed and dated by the investigator.

The CRA will verify the original SAE report form against the source documents at the monitoring visit.

7.2.1.8 Adverse Events of Special Interest

An important AE that has a known association with deferiprone is **neutropenia**, defined as an absolute neutrophil count (ANC) less than 1.5×10^9/L. The severity of neutropenia is categorized as follows:

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.

"Confirmed" means that the ANC has been found to be within the specified range on 2 consecutive measurements a maximum of 3 days apart. If both consecutive counts are below 1.5×10^9/L but are not within the same range, a third count is required to determine the severity category. Neutropenia is considered to be resolved when ANC is $\geq 1.5 \times 10^9$/L on 2 consecutive counts.

Management of Neutropenia

Patients will be scheduled for weekly hematology testing throughout the study, and the results will be forwarded to the investigator. If an ANC $< 1.5 \times 10^9$/L is detected, the patient and, if possible, the primary care physician, are to be promptly notified. In addition, since both fever and infection can be associated with neutropenia, patients will be instructed to do the following:

- In the event of a temperature ≥38.5 ºC/101.3 ºF, they are to immediately discontinue treatment and contact the investigator at the 24-hour number provided. The investigator will request that CBC and differential count be obtained.
- If they develop any symptoms of infection, they are to promptly report this to the investigator at the 24-hour number provided. The investigator will then determine whether or not treatment should be interrupted.

The management of neutropenia depends on its severity, as described below.

Mild neutropenia:

- Instruct patient to interrupt deferiprone immediately.
- Repeat the ANC count daily until resolution.
- If possible, arrange for patient to be seen by a physician the same day for a physical examination, assessment of AEs, and a review of concomitant medications/therapies. If this is not possible, contact patient by phone to obtain information on AEs and medications.
- Advise patient to enter protective isolation, if possible.
- Notify the sponsor of the event by submitting the SAE form.
- If patient is not febrile and does not have an infection, deferiprone therapy can be re-initiated once 2 consecutive ANCs are ≥1.5 x 10^9/L and it is deemed safe by the investigator. If patient is febrile and/or has an infection, therapy cannot be re-initiated until all symptoms have resolved.

Moderate neutropenia:

- Instruct patient to discontinue deferiprone immediately, and withdraw him/her from the study. If this occurs, arrange for the patient to return to the site for an early termination visit.
- Repeat the ANC count daily until resolution.
- If possible, arrange for patient to be seen the same day by a physician for a physical examination, assessment of AEs, and a review of concomitant medications/therapies. If this is not possible, contact patient by phone to obtain information on AEs and medications.
- If clinically indicated, arrange for patient to be admitted to hospital and undergo q4h measurement of vital signs. Otherwise, advise him/her to enter protective isolation and

have a family member obtain q4h temperature.If patient has fever ≥38.5ºC/101.3 ºF, arrange for him/her to be seen by a physician within 4 hours and to undergo an evaluation, including at least a blood culture. Antibiotics are to be initiated prior to obtaining the culture results, and are to be maintained until the patient becomes afebrile, the neutropenia has resolved, and blood cultures have been negative for a minimum of 72 hours. The antibiotics chosen should be based on local microbial prevalence and antibiotic sensitivity patterns. Broad spectrum antibiotics should be used in order to cover both gram negative and gram positive organisms.

- If possible, obtain blood sample for viral studies (CMV, parvovirus, and hepatitis A/B/C); serum ALT, BUN, and creatinine; and 10 mL of serum split into two 5 mL aliquots for frozen storage.
- Notify the sponsor of the event by submitting the SAE form.

Severe neutropenia/agranulocytosis:

- Instruct patient to discontinue deferiprone immediately, and withdraw him/her from the study.
- Repeat the ANC count daily until resolution.
- If possible, arrange for patient to be seen the same day by a physician for a physical examination, assessment of AEs, and a review of concomitant medications/therapies. If this is not possible, contact patient by phone to obtain information on AEs and medications.
- If possible, arrange for patient to be admitted to hospital and to have vital signs monitored q4h. Otherwise, advise him/her to enter protective isolation and have a family member obtain q4h temperature.
- If patient has fever ≥38.5ºC/101.3 ºF, arrange for him/her to be seen by a physician within 4 hours and to undergo an evaluation, including at least a blood culture. Antibiotics are to be initiated prior to obtaining the culture results, and are to be maintained until the patient becomes afebrile, the neutropenia has resolved, and blood cultures have been negative for a minimum of 72 hours. The antibiotics chosen should be based on local microbial prevalence and antibiotic sensitivity patterns. Broad spectrum antibiotics should be used in order to cover both gram negative and gram positive organisms.
- Contact the treating physician at the hospital and arrange or request for the following to be done, if possible:

- If possible, obtain blood sample for viral studies (CMV, parvovirus, and hepatitis A/B/C); serum ALT, BUN, and creatinine; and 10 mL of serum split into two 5 mL aliquots for frozen storage.
- Collect a blood sample for use in attempting to identify genetic or other biomarkers related to agranulocytosis (separate patient consent needs to be obtained).
- Obtain bone marrow aspirate for:
  - Histology
  - Progenitor culture
  - Frozen storage (1 mL sample)
- Obtain bone marrow biopsy (minimum length 3 mm).
- Perform septic work-up including chest x-ray and blood, urine, and throat cultures.
- If warranted, administer granulocyte stimulating factor, such as G-CSF 10 μg/kg, beginning the day that the ANC is confirmed as $< 0.5 \times 10^9$/L and continuing daily until ANC is $\geq 1.5 \times 10^9$/L on 2 consecutive days.
- If ANC $< 0.5 \times 10^9$/L for 7 days, repeat bone marrow biopsy and aspirate weekly during the period of agranulocytosis, if warranted.

- Notify the sponsor of the event by submitting the SAE form.

7.2.2 Laboratory Measurements

Samples for laboratory safety assessments will be taken at the time points indicated below. If a patient withdraws from the study, the End of Study procedures are to be performed at an early termination visit.

Hematology: Complete blood count (CBC), including total WBC, ANC, platelet count, and hemoglobin	Weekly
Blood chemistry: Serum ferritin, total protein, GGT, LDH, sodium, potassium, chloride, glucose, total, bilirubin, AST, ALT, albumin, blood urea nitrogen, calcium, creatinine, uric acid, alkaline phosphatase, and amylase	Visits 1, 2, 3, and 4
Urinalysis: pH, specific gravity, glucose, protein, ketones, and blood. If indicated by the dipstick, sediment microscopy will be performed.	Visits 1, 2, 3, and 4
Pregnancy testing: Serum pregnancy tests will be performed for all sexually active females of childbearing potential (unless the investigator determines there is no reasonable risk of pregnancy because of significant incapacity)	Visits 1, 2, 3, and 4

The investigator must review and interpret each laboratory report, and document the review by signing or initialing and dating the report. Any laboratory values that fall outside a clinically accepted range, or values that differ significantly from previous values, must be marked by the investigator as either "CS" (clinically significant) or "NCS" (not clinically significant). Any that are marked as CS must be further explained and documented as an AE.

7.2.3 Other Safety Measurements

7.2.3.1 Physical Examinations

Physical examination will consist of an examination of head, ears, eyes, nose, throat and neck, respiratory system, cardiovascular system, gastrointestinal system, musculoskeletal system, neurological systems (central and peripheral), skin, thyroid, and general constitution. Physical examination will be performed at each study visit.

Body weight (without shoes) will be measured at each visit. Height will be measured at Visits 1 and 4 only.

7.2.3.2 Vital Signs

Resting heart rate, resting blood pressure, respiration rate, and body temperature will be taken. Blood pressure should always be measured in the sitting position, after a minimum 3-minute resting period, and using the same arm each time if possible. Systolic and diastolic blood pressures are to be recorded from one measurement.

Vital signs will be measured at each site visit. Clinically significant out-of-range values for vital signs will be reported as AEs (see Section 7.2.1.1).

7.2.3.3 Electrocardiogram

A standard 12-lead ECG will be performed at Visit 1 and Visit 4. At a minimum, the following parameters will be assessed: HR, PR, QRS, QT, QTcF, and QTcB. The individual parameters and the overall interpretation will also be documented.

7.2.3.4 Concomitant Medications/Therapies

Information about concomitant medications/therapies will be collected at each study visit, and the following information will be recorded in the source documents and eCRFs:

- All medications and therapies taken for dystonia symptoms, including DBS (including information about frequency of change and reason for change in dosage and settings)
- Any other medications that the patient starts to take or continues to take during the trial
- The name, dose, route, frequency, indication, and start and stop dates of all medications
- Whether or not the medication was used to treat an adverse event

7.2.4 Procedures in Case of Pregnancy

If a patient becomes pregnant during the course of the study, she will be immediately withdrawn. The pregnancy will be immediately reported to the sponsor, and information about the pregnancy is to be recorded on the appropriate form and in the patient's eCRF. The patient will be followed to determine the outcome, and any premature termination of the pregnancy will be reported. Upon delivery, the child will be examined for any adverse symptoms or congenital anomalies. Follow-up information on the status of the mother and child will be forwarded to the sponsor no later than 8 weeks following the delivery.

If the partner of a male patient becomes pregnant during the course of the study, or if the fetus may have been exposed to the patient's study products either through maternal exposure or through transmission via semen following paternal exposure, the pregnancy must be reported to the sponsor, and information about the pregnancy must be recorded on the appropriate form and in the patient's eCRF. If the partner provides consent for follow-up of the pregnancy, she will be followed until the delivery of the child, and information on the delivery status of the mother and child will be forwarded to the sponsor no later than 8 weeks following the delivery date.

Any SAE occurring as a result of a post-study pregnancy that the investigator believes may have been caused by the study product or by a protocol procedure will be reported to the sponsor as described in Section 7.2.1.6.

8 STUDY COMMITTEES

Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) was established prior to the start of study TIRCON2012V1 to monitor patient safety, and will be maintained during the extension study. The DSMB is responsible for overseeing the conduct of the trial, and is empowered to

recommend stopping the trial if, in its members' judgment, continuation is not ethically acceptable on the grounds of safety.

The following will trigger an evaluation by the DSMB for recommending stopping the study at any time point:

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
2. Occurrence of serious adverse events that:
    - Are not associated with exacerbation of a pre-existing condition, and
    - Are deemed to be at least possibly related to the study medication by either the investigator or the sponsor, and
    - Affect at least 2 patients

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

The operating model and the frequency of the interim safety review meetings are laid out in the DSMB charter.

The DSMB will be notified of any changes to the protocol or the study conduct, and will be included in the review of any substantive changes to the protocol that could affect patient safety prior to the submission of these changes to the IRB/IEC for implementation approval.

All DSMB meeting minutes and board composition will be submitted to the regulatory authorities with the final clinical study report.

Extension Study Scientific Steering Committee

This committee was established to provide scientific guidance and to maintain control over the study data and its dissemination. Details of the committee are provided in Appendix 6.

9 STATISTICAL ANALYSIS

9.1 Endpoints

9.1.1 Primary Endpoints

- Adverse events (AEs): Frequency, severity, time to onset, duration, and relatedness to study product

- Serious adverse events (SAEs): Frequency, severity, time to onset, duration, and relatedness to study product
- Number of discontinuations due to AEs
- Hematology assessments
- Blood chemistry assessments
- ECG assessments

9.1.2 Secondary Endpoints

All patients:

- Change in the BAD total score from baseline (defined as prior to the start of deferiprone therapy) to Visit 4, as assessed by central evaluation of videotapes
- Proportion of patients with improved or unchanged BAD scale total score between baseline and Visit 4 (responder analysis)
- Change from baseline to Visit 4 in BAD scale score per body region (eyes, mouth, neck, trunk, and each upper and lower extremity), as assessed by central evaluation of videotapes
- Change in score on the PGI-I from baseline to Visit 4
- Proportion of patients showing an improvement on PGI-I at Visit 4 (responder analysis)

The time points for these efficacy endpoints are defined as follows:

- For patients who received deferiprone in the earlier study, the baseline visit of that study will be treated as the baseline visit of TIRCON2012V1-EXT as well. Thus, Visit 1 of the extension study (Week 0) will be Year 1.5, and Visit 4 (Week 78) will be Year 3.
- For patients who received placebo in the earlier study, Visit 1 of the extension study (Week 0) will be the baseline visit. Thus, Visit 4 (Week 78) will be Year 1.5.

Patients who received placebo in initial study:

For this group only, for each measure, the changes seen between the start and completion of study TIRCON2012V1 (i.e., following 18 months on placebo) will be compared against the changes seen between the start and completion of study TIRCON2012V1-EXT (i.e., following 18 months on deferiprone), as follows:

- Comparison of change in BAD total score from baseline to completion of the initial study vs. change in BAD total score from baseline to completion of the extension study
- Comparison of the proportion of patients with improved or unchanged BAD scale total score between baseline and completion of the initial study vs. the proportion with improved or unchanged BAD scale total score from baseline to completion of the extension study (responder analysis)
- Comparison of the change in BAD score per body region between baseline and completion of the initial study vs. change in BAD score per body region between baseline and completion of the extension study
- Comparison of change in PGI-I score from baseline to completion of the initial study vs. change in PGI-I score from baseline to completion of the extension study
- Comparison of the proportion of patients showing an improvement on PGI-I at completion of the initial study vs. the proportion showing an improvement at completion of the extension study (responder analysis)

9.2 Determination of Sample Size and Study Power

A planned total of 90 patients will be enrolled in the TIRCON2012V1 study, and all patients who complete that study will be invited to enroll in the extension study.

9.3 Study Populations

The following study populations will be used for analysis: Intent-to-Treat (ITT), Per-Protocol (PP), and Safety. The ITT population will represent the primary analysis population for the evaluation of efficacy endpoints, and the PP population will be the secondary efficacy analysis population. The safety population will be used for the analysis of safety endpoints.

9.3.1 Intent-to-Treat Population

The ITT population will include all enrolled patients who received at least one dose of study drug and have a baseline and at least one post-baseline efficacy assessment.

9.3.2 Per Protocol Population

The PP population will include all enrolled patients who complete the study, have no major protocol deviations, and have an efficacy assessment at the end of the study. Prior to database lock, protocol deviations will be reviewed for their seriousness, and patients with major deviations will be excluded from the PP population.

9.3.3 Safety Population

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

9.4 Data Analysis Plan

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

9.4.1 Planned Analyses

9.4.1.1 Patient Disposition and Drug Exposure

Patient disposition will be summarized and presented, including the number and percentages of patients who were enrolled, completed the study, and withdrew (including reasons for withdrawals).

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

9.4.1.2 Patient Characteristics

Baseline characteristics for continuous variables will be summarized by mean, standard deviation, minimum, median, and maximum values; and baseline characteristics for discrete variables will be summarized with frequency and percentages.

9.4.1.3 Analysis of Efficacy

For the efficacy measures of BAD (total score and by body region) and PGI-I, the change from baseline to each of the measurement time points will be determined and summarized using descriptive statistics. A paired t-test will be used to assess the statistical significance of the changes in these efficacy outcomes from baseline to the end of study (Visit 4). For the BAD total score and for PGI-I, the proportions of patients determined to be responders at the end of study (Visit 4) will be calculated and presented along with 95% confidence intervals.

For patients who received placebo in study TIRCON2012V1, a paired t-test will be used to compare the change in BAD (total score and by body region) and PGI-I between the start and completion of the initial study and between the start and completion of the extension study. The incidence of changes in DBS settings and outcome impacting medication use as well as the frequency of PRN drug or rescue medication use will be compared between the initial

study and the extension study. If statistically significant imbalances are detected, they will be adjusted accordingly for the comparison of changes in BAD and PGI-I between the initial study and the extension study by using a modeling approach that is consistent with the planned analysis of the 2 efficacy measures in the initial study. The modeling approach will be detailed in the SAP. For the BAD total score and for PGI-I, McNemar's test will be used to compare the proportion of responders in the initial study with the proportion of responders in the extension study.

Additional statistical analyses may be performed if deemed necessary. Details will be provided in the SAP.

9.4.1.4 Analysis of Safety

All safety data reported and collected during deferiprone therapy for all patients will be presented in listings and summary tables to give an overview of the safety findings. For patients continuing on deferiprone in the extension study, this time period will be from the start of TIRCON2012V1 to the completion of TIRCON2012V1-EXT; for those who received placebo in the initial study and are switching to deferiprone in the extension study, it will be from the start to the completion of the extension study.

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 MedDRA (Medical Dictionary for Regulatory Activities) and will be summarized by MedDRA System Organ Class (SOC) and Preferred Term. Adverse events will be defined as: 1) AEs that occurred or worsened (increased in intensity 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. Events that occur within 14 days after treatment discontinuation will also be considered AEs. Serious adverse events that occur within 30 days after treatment discontinuation will be included in the database.

Adverse events 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 SOC (and preferred term within an SOC). AEs will also be presented by intensity (mild, moderate, severe), by seriousness (serious, non-serious), and by relationship to study medication (at least possibly related, not related). The number and percentage of patients who are withdrawn from the study due to AEs will be calculated, and the AEs involved will be summarized in a frequency table. Time to onset and duration of all AEs with an incidence of >5%, and of any AEs of special interest (e.g., worsening of dystonia), will be summarized with descriptive statistics.

Patients who have experienced the same AE multiple times will be counted only once for the corresponding preferred term. Similarly, if a patient experiences multiple AEs within the same SOC, that patient will be counted only once for that SOC. AEs will be tabulated by presenting SOCs alphabetically and, within each SOC, presenting the preferred terms in decreasing order of the total number of patients who experienced each type of AE. In summaries presenting the incidence of AEs by intensity, seriousness, and relation to study medication, a patient with multiple events coded to a given preferred term or SOC will be counted only once for that preferred term or SOC according to the most severe event, the most serious event, or the event with the closest relationship to study medication.

Listings of SAEs, of withdrawals due to AEs, and of deaths will be provided separately and described in patient narratives.

ECG:

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

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, and height, at baseline and each relevant visit. Data will also be presented graphically for examination of possible trends.

Biochemistry and Hematology:

Descriptive statistics for each clinical laboratory test will be presented for each scheduled visit. 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 3 categories at baseline versus end of study will be presented. Continuous data will also be presented graphically for examination of possible trends.

Clinically significant laboratory values will be reported in the AE 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.

9.4.2 Interim Analyses

No interim analysis is planned.

10 DATA MANAGEMENT CONSIDERATIONS

10.1 Data Management

The sponsor's Clinical Data Management group will be responsible for the processing, coding and validating/cleaning of clinical study data. Subject 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 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. The data will be coded using the MedDRA (Medical Dictionary for Regulatory Activities) and WHODD (World Health Organization Drug Dictionary) dictionaries. An electronic signature will be required of the investigator on the eCRFs, 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 subject 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.

10.2 Case Report Forms

Electronic CRFs may be generated and/or printed at any time using the sponsor's RDC system. These eCRFs may be used for electronic submission data archiving or data review. A copy of the final patient-specific eCRFs will be sent to the clinical study sites after database freeze.

11 MONITORING, AUDITS, AND INSPECTIONS

11.1 Source Documents

The investigator or delegate 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 study that are necessary for the reconstruction and evaluation of the study: e.g., medical history, physical examination, laboratory results, and x-ray or ultrasound results. The investigator will also retain all printouts/reports of tests or procedures performed as a requirement of the study. All source data that is printed on thermal paper, including laboratory printouts and ECGs scans, must be photocopied, initialed, and dated as authentic equivalents to the thermal paper documents to enable extended retention time.

The source documents must be available at the time of an audit; a site visit from the sponsor, sponsor representatives, or IRB/IEC; and a regulatory authority inspection.

11.2 Monitoring

Monitoring of the investigational sites will be conducted by the sponsor or contracted to a qualified contract research organization (CRO). The sponsor will determine the extent, nature, and frequency of on-site visits that are needed to ensure that the study is being conducted in accordance with the approved protocol (and any amendments), GCP, and all applicable regulatory requirements. At site visits, the monitor will, as required, assess the progress of the study; check that the study data chosen for verification are authentic, accurate, and complete; verify that the safety and rights of patients are being protected; compare original documents with data entered into the study database; and identify any issues and address their resolution.

The investigator agrees to allow the monitor(s) direct access to all relevant documents, and to allocate his/her time and the time of staff to discuss findings, corrective actions and any relevant issues. In addition to contacts during the study, the monitor may also contact the site prior to the start of the study to discuss the protocol and data collection procedures with site personnel.

11.3 Audits and Inspections

In accordance with the principles of ICH E6 Guideline for Good Clinical Practice, the study site may be inspected by regulatory authorities and/or audited by ApoPharma Quality Assurance (QA) or their designates. The investigator and relevant clinical support staff will be required to be actively involved in audits and inspections, including staff interviews, and to make all necessary documentation and data available upon request.

During the course of the study and/or after it has been completed, one or more investigator site audits may be undertaken by auditors from ApoPharma QA or delegates. The purpose of these audits is to determine whether or not the study is being/has been conducted and monitored in compliance with recognized ICH E6 Guideline for Good Clinical Practice, protocol and approved amendment requirements, applicable local SOPs, and local laws and regulations. It is the responsibility of the investigator and site staff to promptly address, by coordinating with ApoPharma Clinical Research, any deficiencies stemming out of regulatory inspections and ApoPharma QA or delegate audits, and to ensure that agreed-upon corrective and preventive actions are implemented as soon as possible.

An inspection by any regulatory authority 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 ApoPharma Clinical Research immediately.

11.4 Site Closure

Upon completion of the study, the investigator must conduct the following activities, when applicable:

- Return all study data and equipment to the sponsor
- Complete data clarifications and/or resolutions
- Perform accountability, reconciliation, and final disposition of used and unused study drug, ensuring that unused medication is either destroyed or returned to the sponsor, as instructed
- Review site study records for completeness

The sponsor reserves the right to temporarily suspend or prematurely discontinue this study at any time and for any reason. If such action is taken, the sponsor will discuss this with the investigator (including the reasons for taking such action) at that time. The sponsor will promptly inform all other investigators conducting the study if the study is suspended or terminated for safety reasons, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IRB/IEC promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must be returned to the sponsor. In addition, the site must conduct final disposition of all unused study medication in accordance with the study procedures.

Financial compensation to investigators and/or institutions will be in accordance with the agreement established between the investigator and the sponsor.

11.5 Retention of Records

In accordance with applicable regulatory requirements, following closure of the study, the investigator will maintain a copy of all site study records in a safe and secure location. The sponsor will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements.

12 ETHICAL CONSIDERATIONS

12.1 Informed Consent

Prior to entering a patient into the study, the investigator or a designate must obtain written informed consent from the patient and/or where applicable the patient's legally authorized representative, according to the sponsor's procedures and as described in the Declaration of Helsinki, the Federal Food, Drug and Cosmetic Act, and U.S. applicable Code of Federal

Regulations Title 21, Part 50. The investigator will ensure that the patient and/or legal representative is given full and adequate verbal and written information about the nature, purpose, and possible risks and benefits of the study, and is given ample opportunity to ask questions and to discuss the study with family members. The investigator must make a conscientious effort to be fully satisfied that the patient and/or legal representative has truly understood that for which the consent has been given. The patient and/or the legal representative must be notified that he/she is free to discontinue participation in the study at any time, and that such withdrawal will not affect present or future care. In the case of a minor or an incapacitated adult who is capable of forming an opinion and assessing the study information, the investigator must ensure that this individual's decision to not participate or to withdraw from the study will be respected even if consent is given by the legal representative.

The sponsor will provide a model version of the informed consent form to the sites as a separate document. Each site may then revise this version according to the requirements of its individual IRB/IEC.

The patient and/or legal representative will sign and date the consent form prior to the first study intervention, and will be provided with a copy of the signed and dated ICF. Should a protocol amendment be made, the ICF may need to be revised to reflect the changes to the protocol. The investigator must then ensure that the revised ICF is signed by all patients currently enrolled as well as those subsequently entered in the study.

12.2 Institutional Review Board/Independent Ethics Committee

It is the investigator's responsibility to ensure that the protocol is reviewed and approved by a properly constituted IRB or IEC (according to ICH GCP guidelines, Section 3.2). The IRB/IEC must also review and approve the site's ICF and any other written information that will be provided to patients, prior to any enrolment and the release of any advertisements for patient recruitment. Prior to the start of the study, the investigator or designee must forward copies of the IRB/IEC approval and the approved ICF materials to the sponsor.

If it is necessary to amend either the protocol or the ICF during the study, the investigator will be responsible for ensuring that the IRB/IEC reviews these amended documents, and that once their approval is obtained, that any new patients are enrolled under the amended protocol. Copies of the amended ICF and of the IRB/IEC's approval of it must be forwarded to the sponsor as soon as they are available.

12.3 Patient Confidentiality

To ensure that patients' identities remain unknown to the sponsor, all data will be identified by patient ID.

The investigator must inform patients of the possibility that representatives from regulatory authorities and/or the sponsor may require access to hospital or clinic records for verification of data pertinent to the study, including medical history.

The investigator is responsible for keeping a list of all patients entered, including patient code, patient ID, full name, and last known address.

13 REGULATORY REQUIREMENTS

13.1 Regulatory Obligations

This trial is to be conducted in accordance with the Declaration of Helsinki, the ICH Consolidated Guidelines for Good Clinical Practice (GCP), FDA regulations, and any local regulatory requirements. The trial will not begin at any given site until the site has provided the following documents to the sponsor or its delegate, as per the ICH Consolidated Guideline on GCP (Section 8.2):

1. Signed and dated IRB/IEC approval indicating review and approval of each the following documents:
   - Protocol and any amendments
   - Patient Informed Consent Form
   - Any written information to be provided to patients
   - Any advertisements for patient recruitment
   - Any compensation to patients
2. Membership of the IRB/IEC, to document that the committee is constituted in agreement with GCP
3. Regulatory authority approval of the protocol
4. Curriculum vitae of the investigator, sub-investigator(s), study coordinator, and pharmacist if applicable (updated within the last 2 years)
5. For any laboratory evaluations performed at locations other than the study central laboratory:

- Accreditation, certification, established quality control, or external quality assessment of the laboratory
- Normal ranges or values for all laboratory test or procedures conducted during the trial

6. Financial Disclosure Forms (where applicable)

7. Regulatory Authority statement of investigator forms (e.g., FDA form 1572 where applicable)

8. Signed Clinical Trial Agreement

13.2 Amendments to the Protocol

No amendments to this protocol will be made without consultation with and the agreement of the sponsor. Any amendment to the trial that seems indicated as the trial progresses must be discussed between the investigator and sponsor concurrently. If agreement is reached concerning the need for an amendment, this amendment will be produced in writing by the sponsor and will be made a formal part of the protocol.

The investigator is responsible for ensuring that changes in the approved research project, during the period for which IRB/IEC approval has already been given, are not initiated without review and approval of the IRB/IEC except where necessary to eliminate apparent immediate hazards to the patients.

14 EARLY STUDY TERMINATION

The sponsor reserves the right to discontinue this study at any time; or, an investigator may terminate it at his/her respective site following consultation with the sponsor. On discontinuance of the study, in its entirety or at a specific site, the investigator(s) will inform the study patients, the relevant clinical study staff, and the respective IRB/IEC of the discontinuance; provide them with the reasons for the discontinuance; and advise them in writing of any potential risks to the health of the study patients. It is the sponsor's responsibility to report discontinuance of the study to regulatory agencies, to provide them with the reasons for the discontinuance, and to advise them in writing of any potential risks to the health of the study patients.

15 CONFIDENTIALITY

The confidentiality agreement signed by each investigator for the initial study concerning the protection of the sponsor's confidential and proprietary information will apply to the

extension study as well. Other than for study recruitment purposes and progress reports required by the regulatory agencies, the information contained in this document and all future information relating to this study is privileged, confidential, and proprietary, and may not be used or disclosed without the expressed written consent of the sponsor or unless otherwise required by law (in which case the requirement to make such disclosure shall be communicated to the sponsor in advance and in writing). All information provided to the investigator by the sponsor is to be considered strictly confidential unless otherwise specified.

16 INDEMNIFICATION

Indemnification will be made in accordance with the terms and conditions set forth in the Clinical Trial Agreement agreed upon with the sponsor or its delegate.

During the course of the clinical study, patients may not participate in any other study.

Any deterioration in a patient's health during or directly after the clinical study must be reported to the investigator at once.

Should the patient receive any medical care not pertaining to the study in question, this must be reported to the investigator.

Any legal dispute that may arise in respect of the interpretation of this protocol will be settled definitively in accordance with the applicable law in accordance with the terms and conditions set forth in the Clinical Trial Agreement agreed upon with the sponsor or its delegate.

17 OWNERSHIP

All data generated during the study (other than patients' medical records) are the property of the sponsor and the Extension Study Scientific Steering Committee (see Appendix 6), and all inventions discovered in the course of conducting the study are the exclusive property of the sponsor. The sponsor retains exclusive property of all "Background", as defined in the TIRCON FP7 Grant Agreement No. 277984 and the TIRCON Consortium Agreement, and this "Background" will continue to apply for the TIRCON2012V1-EXT study. Details are provided in the Clinical Trial Agreement that was completed by the sponsor and the investigator and/or site.

18 PUBLICATION

Data derived from the study are the property of the sponsor and the Extension Study Scientific Steering Committee, both of which will be responsible for the primary publication of the data.

Investigators may publish or otherwise disclose (e.g., present at a conference or use for instructional purposes) data from the trial solely in accordance with the terms and conditions described in the Clinical Trial Agreement.

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APPENDIX 1: CLINICAL STUDY ADMINISTRATIVE STRUCTURE

Function	Name of Organization	Address and Contact Information
Study monitoring	TheraGenesis GmbH	Bruehlstrasse 50 D-76297 Stutensee Germany Tel: +49-7249-952-063 Main contact: Erik Hesse
Centralized BAD score evaluation	Klinikum der Universitaet Muenchen Friedrich-Baur Institute, Department of Neurology, University of Munich	Dr. Boriana Buechner Ziemssenstr. 1, 80336 Munich, Germany Tel: +49-89-4400-5-7443 Fax: +49-89-4400-5-7402 Email: Boriana.Buechner@med.uni-muenchen.de

APPENDIX 2: LIST OF PROHIBITED DRUGS

Use of the following medications is precluded by protocol TIRCON2012V1-EXT. 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. Aminoglutethimide (CYTADREN)
8. Interferon (INTRON A)
9. Para-aminophenol, with the following exception: paracetamol/acetaminophen (TYLENOL) may be used with caution *
10. Pyrazolone derivatives
11. Phenytoin (DILANTIN), Carbamazepine
12. Chlordiazepoxide (LIBRIUM) and other benzodiazepines
13. Phenylbutazone
14. Mefenamic Acid (PONSTAN)
15. Metoclopramide HCl (REGLAN)
16. Chlorpromazine, prochlorperazine and other phenothiazines
17. Procainamide
18. Levamisole (ERGAMISOLE)
19. Diclofenac Sodium (VOLTAREN)
20. Hydroxyurea (HYDREA)
21. Trimethoprim/sulfamethoxazole (BACTRIM/SEPTRA)
22. Aminopyrine

* In years of experience with Ferriprox for a different indication (thalassemia), no safety concerns have been reported that are related to concomitant use of this drug, and there are no restrictions on this drug in the Ferriprox prescribing information. Hence, paracetamol/acetaminophen may be taken by PKAN patients in this study under close supervision.

APPENDIX 3: LIST OF RESCUE MEDICATIONS

Rescue medication is defined as a newly prescribed medication or a change in dosage of a currently prescribed medication that has the potential to have an effect on dystonia symptoms and is provided because of a worsening of the patient's condition.

The use of rescue medication should be limited to circumstances judged as absolutely necessary by the investigator. Any use of a rescue medication must be documented, including the reason. If a patient uses rescue medication for more than 2 events, the investigator should notify the sponsor to discuss the patient's continued participation in the study.

Rescue medications for dystonia include, but are not limited to, the following:

- Baclofen
- Trihexyphenidyl
- Clonazepam
- Tizanidine
- Tetrabenazine
- Botox

APPENDIX 4: BARRY-ALBRIGHT DYSTONIA SCALE

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.

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: _____**

APPENDIX 5: PATIENT 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. 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

APPENDIX 6: SCIENTIFIC STEERING COMMITTEE

Composition of the Committee

The Extension Study Scientific Steering Committee includes the following members:

Michael Spino, PhD	President, ApoPharma Inc.
Fernando Tricta, MD	Vice President of Medical Affairs, ApoPharma Inc.
Elliott Vichinsky, MD	UCSF Benioff Children's Hospital Oakland Oakland, California, USA
Thomas Klopstock, MD	Klinikum der Universität München Munich, Germany
Nardo Nardocci, MD	Foundation Neurological Institute C. Besta Milan, Italy
Patrick Chinnery, MD	Newcastle University Institute of Human Genetics Newcastle Upon Tyne, United Kingdom

Responsibilities

- Provide scientific advice and guidance
- Maintain exclusive ownership of the TIRCON2012V1-EXT study data
- Oversee primary publication of the TIRCON2012V1-EXT study results
- Review and approve all publications, abstracts, presentations, or manuscripts that contain TIRCON2012V1-EXT study data

Signatures

Michael Spino ApoPharma Inc.	Date (DD MMM YYYY)
Fernando Tricta ApoPharma Inc.	Date (DD MMM YYYY)
Elliott Vichinsky Principal Investigator	Date (DD MMM YYYY)
Thomas Klopstock Principal Investigator	Date (DD MMM YYYY)
Nardo Nardocci Principal Investigator	Date (DD MMM YYYY)
Patrick Chinnery Principal Investigator	Date (DD MMM YYYY)