ApoPharma Inc.

A Dose-Ranging Study of the Efficacy, Safety, and Pharmacokinetics of Deferiprone Delayed Release Tablets in Patients with Parkinson's Disease

LA48-0215

CLINICAL STUDY PROTOCOL

IND Number:	126655
EudraCT Number:	2015-004344-19
Investigational Product:	Deferiprone delayed release formulation
Development Phase:	Phase 2
Indication Studied:	Parkinson's disease
Study Design:	Multi-center, randomized, double-blind, placebo-controlled, dose-ranging study in patients with Parkinson's disease
Sponsor:	ApoPharma Inc. 200 Barmac Drive Toronto, Ontario M9L 2Z7, Canada Telephone: +1-416-749-9300 Toll-Free: 1-800-268-4623 (North America only) Fax: +1-416-401-3867
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Version and Date of Protocol:	Version 4.0, 20 MAR 2017

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:	A dose-ranging study of the efficacy, safety, and pharmacokinetics of deferiprone delayed release tablets in patients with Parkinson's disease
Study Code:	LA48-0215
Version Number:	4.0
Version Date:	20 MAR 2017

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20 Mar 2017
Date (DD MMM YYYY)

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21 Mar 2017.
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22 MAR 2017
Date (DD MMM YYYY)

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:	A dose-ranging study of the efficacy, safety, and pharmacokinetics of deferiprone delayed release tablets in patients with Parkinson's disease
Study Code:	LA48-0215
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Version Date:	20 MAR 2017
Name of Principal Investigator:	
Name of Study Site:	
Location of Study Site: *(City, region/province/state, country)*	

Signature _____ Date (DD MMM YYYY) _____

SYNOPSIS

Title of study:	A dose-ranging study of the efficacy, safety, and pharmacokinetics of deferiprone delayed release tablets in patients with Parkinson's disease
Study code:	LA48-0215
Phase of development:	Phase 2
Objectives:	Primary objective • To evaluate the efficacy of four different dosages of deferiprone delayed release (deferiprone-DR) tablets in patients with Parkinson's disease Secondary objectives • To evaluate the safety and tolerability of deferiprone-DR tablets in patients with Parkinson's disease • To evaluate the pharmacokinetics of deferiprone-DR tablets in a subset of study participants • To evaluate the relationship between the pharmacokinetics and pharmacodynamics of deferiprone-DR tablets Exploratory objectives • To determine whether the efficacy responses to deferiprone differ depending on the genotype of certain enzymes that are implicated in Parkinson's disease • To determine whether the efficacy responses to deferiprone are correlated with ceruloplasmin levels or ceruloplasmin ferroxidase activities
Study design:	Multi-center, randomized, double-blind, placebo-controlled, dose-ranging study in 140 patients who have been diagnosed with typical Parkinson's disease up to 3 years prior to the screening visit and are currently taking antiparkinsonian medication. Screening will be conducted within 30 days prior to the start of dosing. At baseline, eligible participants will be randomized to one of four dosage cohorts, and within each cohort will be further randomized in a 4:1 ratio to receive either active product or placebo. The assigned study product will be taken twice-daily (b.i.d.), at least 8 hours apart, for 9 months. Dosages are as follows: • Cohort 1: 300 mg deferiprone-DR tablets (n=28) or placebo (n=7) • Cohort 2: 600 mg deferiprone-DR tablets (n=28) or placebo (n=7) • Cohort 3: 900 mg deferiprone-DR tablets (n=28) or placebo (n=7) • Cohort 4: 1200 mg deferiprone-DR tablets (n=28) or placebo (n=7) Patients will return to the site at Months 1, 2, 3, 4, 5, 6, and 9, and will receive a follow-up telephone call at Month 10. Safety parameters will be assessed at each site visit and at the follow-up call. For safety reasons, all patients will additionally have their absolute neutrophil count monitored weekly after the start of dosing, at either the study site or a local laboratory (or possibly at home, by a visiting study nurse). Efficacy measures will be assessed at baseline and Months 3, 6, and 9; and sparse pharmacokinetics (PK) sampling will be done on all patients at baseline and Month 3. In addition, an optional subset of 16 patients will undergo extensive

Study design (cont'd):	blood sampling for PK analysis at Month 1, and an optional subset of 18 patients will each provide one sample of cerebrospinal fluid (CSF) for drug level assessment at Month 3. Any patient who withdraws before completing treatment will be requested to return for an Early Termination visit, at which time the procedures normally scheduled for the Month 9 visit will be conducted.
Duration of participation:	The duration of participation in the study for each patient, including the screening period and the follow-up telephone call, will be approximately 11 months.
Criteria for evaluation:	Efficacy Criteria *Primary efficacy criterion:* Change from baseline to Month 9 in the motor examination subscale (Part III) of the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) *Secondary efficacy criteria:* • Change from baseline to Month 9 in the following measures: o Total score on the MDS-UPDRS o Scores on the individual subscales Part I (non-motor experiences of daily living), Part II (motor experiences of daily living), and Part IV (motor complications) of the MDS-UPDRS o Combined scores from Parts II and III of the MDS-UPDRS o Overall cognitive function, as assessed by the Montreal Cognitive Assessment (MoCA) test o Pharmacodynamics measures of the following oxidative stress biomarkers: total antioxidant status, lipid peroxidation (malondialdehyde), protein carbonyls, 8-OHdG, glutathione, superoxide dismutase o Pharmacodynamics measures of the following inflammatory factor biomarkers: TNF alpha and IL-6 • Time elapsed until the need for rescue medication *Exploratory efficacy criteria:* Mechanism of action (MOA) biomarkers to evaluate the following: • Whether specific genotypes of the following enzymes which play a role in Parkinson's disease affect the potential disease-modifying action of deferiprone: o D544E polymorphisms of the glycoprotein ceruloplasmin o V158M polymorphisms of the enzyme catechol O-methyltransferase (the only analysis will be determination at baseline of the COMT genotype) • Whether the degree of change from baseline in ceruloplasmin levels and ceruloplasmin ferroxidase activity is correlated with the efficacy of deferiprone

Criteria for evaluation (cont'd):	Safety Criteria • Adverse events (AEs): Frequency, intensity, time to onset, duration, and relatedness to study drug • Serious adverse events (SAEs): Frequency, intensity, time to onset, duration, and relatedness to study drug • Number of discontinuations due to AEs • Laboratory measures (hematology, blood chemistry, and urinalysis) • ECG • Vital signs • Physical examination • Assessment of suicidality (based on the Columbia Suicide Severity Rating Scale) Pharmacokinetics Criteria The following PK parameters will be determined for deferiprone and its 3-*O*-glucuronide metabolite in the subset of patients who undergo extensive PK sampling: • C_{max} • T_{max} • AUC_{0-t} • $AUC_{0-\infty}$ • λ_Z • $T_{½}$ $T_{½}$ and $AUC_{0-\infty}$ will be determined only in patients in whom the log-linear terminal phase can be clearly defined. Pharmacokinetics/Pharmacodynamics Criteria Possible relationships between pharmacokinetic findings and efficacy biomarkers and endpoints will be evaluated.
Number of patients:	A planned total of 140 patients will be enrolled: 112 to receive one of the 4 dosages of deferiprone, and 28 to receive placebo.
Diagnosis and main criteria for inclusion:	Main inclusion criteria • Male or female aged ≥18 to < 80 years • Body weight ≥60 kg but ≤100 kg • Parkinson's disease diagnosed according to UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria and based on the presence of at least two of the three cardinal features of the disease (rest tremor, bradykinesia, and rigidity). If rest tremor is not present, patient must have unilateral onset of symptoms. • Absolute neutrophil count (ANC) ≥1.5 x 10^9/L (≥1.0 x 10^9/L for Black population) at screening

Diagnosis and main criteria for inclusion (cont'd)	• On a stable dose for at least 3 months prior to the screening visit of any of the following treatments at an L-dopa equivalent daily dose of up to 600 mg: o Dopaminergic agonist alone o L-dopa alone o Combination therapy with dopaminergic agonist and L-dopa o Rasagiline • At an early stage of the disease, without motor fluctuations and/or L-dopa–induced dyskinesia <u>Main exclusion criteria</u> • Diagnosis of Parkinson's disease more than 3 years prior to screening visit • Hoehn and Yahr stage ≥ 3 • Atypical or secondary Parkinsonism without dopa-sensitivity (e.g., vascular parkinsonism, supranuclear palsy, multisystem atrophy) • Progressing Axis I psychiatric disorders (psychosis, hallucinations, compulsive disorders, substance addiction, bipolar disorder, severe depression, anxiety) as assessed in a semi-structured interview in accordance with the Diagnostic and Statistical Manual of Mental Disorders • Not stabilized in terms of the current antiparkinsonian therapeutic regimen: already requires dose adaptation and/or is likely to require any change in dopamine therapy over the duration of the trial • Current treatment with bromocriptine • Current treatment with any antiparkinsonian drug other than those listed in the inclusion criteria • Current treatment with coenzyme Q10 or idebenone. (Patients who are on these medications but stop taking them at least 2 weeks prior to baseline may be enrolled.) • Current use of a Deep Brain Stimulation (DBS) system. (Patients who previously had a DBS system but have had it removed may be enrolled.)
Investigational product:	Product: Deferiprone delayed release 600 mg bisectable tablets Dose: 300 mg, 600 mg, 900 mg, or 1200 mg b.i.d., for a total daily dosage of 600 mg, 1200 mg, 1800 mg, or 2400 mg Mode of administration: Oral
Reference product:	Product: Placebo Dose: Number of tablets matching that required for a 300, 600, 900, or 1200 mg dose of active product Mode of administration: Oral

<table>
<tr>
<td>Schedule of treatment and assessments:</td>
<td>
<u>Treatment</u>

All patients will take the assigned study medication at specified times twice daily, at least 8 hours apart, for 9 months.

<u>Efficacy assessments</u>

• The MDS-UPDRS and MoCA will be completed at baseline and Months 3, 6, and 9
• Blood samples for the assessment of pharmacodynamics biomarkers and of the MOA biomarkers of total antioxidant status protein carbonyls, glutathione, and super-oxide dismutase will be collected at baseline and Months 3, 6, and 9
• Urine samples for the assessment of the oxidative stress biomarkers 8-OHdG and lipid peroxidation (malondialdehyde) will be collected at baseline and Months 3, 6, and 9

Note: The MDS-UPDRS and MoCA are to be administered early in the morning, at approximately the same time (± 1 hour) at each visit, and by the same qualified investigator.

<u>Safety assessments</u>

• Hematology: Screening and weekly after the start of dosing up to Month 9
• Blood chemistry: Screening and Months 1, 2, 3, 4, 5, 6, and 9
• Urinalysis: Screening and Months 3, 6, and 9
• ECG: Screening and Month 9
• Vital signs: Each site visit up to Month 9
• Physical examination: Screening, baseline, and Months 2, 4, 6, and 9
• Assessment of suicidality: Baseline and each visit thereafter up to Month 9
• Adverse events: Collected throughout the study, from baseline (post–Dose 1) to Month 10

<u>Pharmacokinetics assessments</u>

Blood and CSF samples for the assay of deferiprone and its 3-O-glucuronide metabolite will be collected at the following time points:

<table>
<tr><td>CSF samples (subset of 18 patients only)</td><td>Month 3: A total of 18 samples from 18 patients: 6 of the samples to be collected pre-dose, 6 to be collected at 2 hours post-dose (± 15 minutes), and 6 to be collected at 4 hours post-dose (± 15 minutes).
The time of sample collection for each patient will be assigned prior to the Month 3 visit.</td></tr>
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<table>
<tr><td>Schedule of treatment and assessments (cont'd):</td><td>
<table>
<tr><td>Sparse collection of blood samples (all patients)</td><td>Baseline and Month 3: Three samples collected at each visit: 1 collected pre-dose, 1 collected at 2 hours post-dose (± 45 minutes), and 1 collected at 4 hours post-dose (± 45 minutes), with a minimum of 1 hour between samples.
Note: For the subset of patients who have agreed to provide a CSF sample at Month 3, the applicable blood sample at Month 3 (either pre-dose, 2 hours post-dose, or 4 hours post-dose) is to be taken within ± 15 minutes of the CSF sample.</td></tr>
<tr><td>Extensive collection of blood samples (subset of 16 patients only)</td><td>Month 1: 18 samples from each patient: Pre-dose and at 0.25, 0.5, 0.75, 1.0, 1.33, 1.66, 2.0, 2.33, 2.66, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, and 12.0 hours post-dose</td></tr>
</table>
</td></tr>
<tr><td>Statistical methods:</td><td>Data from all patients who were randomized to receive placebo will be combined into one group for the statistical analyses. Thus, there will be 5 treatment groups in the efficacy and safety analyses: placebo and 300 mg, 600 mg, 900 mg, and 1200 mg deferiprone.

<u>Efficacy Analysis</u>
The data on the change from baseline to each follow-up visit will be summarized, by treatment group and overall, using descriptive statistics for each continuous efficacy endpoint. Frequency and proportion will be presented for each discrete efficacy endpoint. Analysis of variance (ANOVA) will be used to compare means, and Fisher's exact test will be used to compare proportions.

An analysis of covariance (ANCOVA) approach will be used for assessing the deferiprone effect on change from baseline to study end for all efficacy variables except time elapsed until rescue medication, with baseline value as a covariate, and treatment group and visit as the main factors in the model. Each deferiprone group will be compared to the placebo group to assess the treatment effect at each deferiprone dose level. Regression analysis will be employed to assess the dose-response relationship. If a statistically significant relationship exists between deferiprone dose and an efficacy outcome, the dose-response relationship will be assessed through pairwise comparison of each dose level to the next lower dose level: 1200 mg vs. 900 mg, 900 mg vs. 600 mg, and 600 mg vs. 300 mg. A time to event analysis will be performed to compare the time elapsed until the need for rescue medication among the treatment groups.

<u>Safety Analysis</u>
The safety data for continuous variables will be summarized using descriptive statistics, and the safety data for discrete variables will be tabulated with frequency tables.</td></tr>
</table>

Statistical methods (cont'd)	Pharmacokinetic/Pharmacodynamic Analysis The pharmacokinetics parameters will be summarized using descriptive statistics. The power model will be used for assessing dose proportionality of AUC. Relationships will be assessed between the appropriate PK parameters and pharmacodynamics biomarkers and efficacy endpoints.
Version and date of protocol:	Version 4.0, 20 MAR 2017

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LIST OF IN-TEXT TABLES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
ANC	absolute neutrophil count
ANOVA	analysis of variance
ANCOVA	analysis of covariance
C-SSRS	Columbia Suicide Severity Rating Scale
CS	clinically significant
CI	confidence interval
CRA	clinical research associate
CRO	contract research organization
COMT	catechol O-methyltransferase
CSF	cerebrospinal fluid
DBS	Deep Brain Stimulation
DR	delayed release
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
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
IVRS/IWRS	interactive voice/web response system

Abbreviation	Definition
MDS-UPDRS	Movement Disorder Society-Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MoCA	Montreal Cognitive Assessment
MOA	mechanism of action
NCS	not clinically significant
PD	Parkinson's disease
PK	pharmacokinetics
PT	preferred term
ROS	reactive oxygen species
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
WHO	World Health Organization

1 INTRODUCTION

1.1 Background of the Disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder that affects about 1% of the over-60 population. It is characterized by severe motor symptoms including uncontrollable tremor, postural imbalance, slowness of movement, rigidity, and psychiatric and cognitive disorders,[1] as well as by an elevated rate of mortality.[2]

The main hallmark of PD is loss of dopaminergic neurons in the substantia nigra; accordingly, pharmacological treatments have focused on restoring dopaminergic neurotransmission to relieve motor symptoms. However, these treatments have several major limitations. The dopaminergic medications that are currently available modulate the several steps involved in dopamine transmission, but they do not act directly on the activity of the presynaptic dopamine transporter that could directly impact the extracellular dopamine level. Moreover, in addition to the dopaminergic system, the noradrenergic, cholinergic, and neurotransmission glutamatergic systems are also impacted in PD, and these too may have involvement in a variety of motor and non-motor symptoms of PD. All of the treatments currently used in PD act on symptoms, not on the disease per se. Thus, there is an urgent need for disease-modifying treatments that could slow progression and reduce the occurrence of the disabling disorders seen in late-stage PD.

As with several other chronic neurological disorders, PD is associated with brain iron accumulation: specifically, an increase of iron in the substantia nigra is another hallmark of the disease.[3] While iron is essential for normal physiological function, an excessive amount of it or dysregulation of its metabolism is potentially toxic. Excessive "free" iron in tissues is believed to lead to generation of reactive oxygen species (ROS), including the extremely damaging hydroxyl radical, and to cause localized toxicity and oxidative neuronal destruction.[4,5] Determining the molecular mechanisms that underlie iron dysregulation and the neurodegeneration induced by ROS could lead to therapies that would restore brain iron homeostasis and reduce neurodegeneration. In PD, the regions of the brain with the highest iron accumulation include those that control motor output. Thus, motor impairment is thought to be due, at least in part, to the oxidative damage and necrosis that occurs as a result of long-term iron-induced damage.[6,7,8]

It is possible that if excess labile iron can be sequestered from vulnerable brain regions prior to cell death, oxidative neuronal loss may be prevented and thus, disease progression and the ensuing clinical symptoms of Parkinson's disease could be reduced. In conditions of iron overload, the accepted therapeutic strategy for the management of iron accumulation is administration of iron chelators, which both increases iron excretion and prevents the toxic

effects of iron excess. Although patients with PD do not have generalized iron overload, mismanagement of iron in the brain appears to lead to neurotoxicity and to localized deposition of excess iron. These deposits may contribute to or mark an aspect of disease pathology, or may reflect the tissues' attempt to render labile iron less harmful. In either case, removal of the excess iron may be a strategy for treating PD. The aim of chelation 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 for reuse.[6]

1.2 Background of the Investigational Product

Deferiprone (IUPAC name 3-hydroxy-1,2-dimethylpyridin-4-one) is an iron (III)-chelating agent. An immediate-release formulation of deferiprone, Ferriprox®, was first approved in 1999 by the European Medicines Agency for the treatment of systemic iron overload in patients with thalassemia major; and deferiprone is currently approved for that indication in over 60 countries.

Deferiprone appears to fulfill several criteria required of a chelator with clinical applicability in localized intracellular iron mismanagement in the brain:

- It has the ability to gain access to cells,[9] effectively bind to labile iron within a cell to create an iron-chelator complex,[10] and exit the cell in that form, thereby reducing the formation of iron-dependent free radicals [11,12,13]
- It spares extracellular transferrin-bound iron and potentially transfers chelated iron to transferrin [14,15,16,17]
- It can donate iron for metabolic reutilization [16]
- Because of its low molecular weight and favorable physicochemical properties, it has been shown in animal studies to readily cross the blood-brain barrier, [18] and there is indirect evidence to suggest that it does so in human as well [14]

Deferiprone has been investigated in several neurological disorders that are associated with localized iron accumulation or disturbance of iron homeostasis. In patients with PD, Friedreich's ataxia, and pantothenate kinase-associated neurodegeneration, deferiprone has been shown to reduce the characteristic regionally elevated levels of brain iron, as evidenced by MRI scans.[19,20,21]

1.3 Rationale

Based on reports in the literature that deferiprone can act to reduce iron within the substantia nigra as well as slow the progression of motor handicap symptoms associated with PD, [19,21] ApoPharma Inc. is proceeding with a clinical development plan to investigate the use of

deferiprone for this indication. The trials will use a new formulation of deferiprone that is currently under development: an enteric-coated 600 mg delayed release tablet, deferiprone-DR, which would support less frequent administration than the licensed immediate-release tablets and may be associated with better tolerability. In a Phase 1 study conducted in healthy volunteers, single doses of deferiprone-DR were found to be safe and well tolerated, and showed a similar extent of drug exposure but a 50% lower peak exposure when compared to the immediate-release formulation.[22]

The Phase 2 dose-ranging trial described in this protocol seeks to establish the dosages of deferiprone-DR in Parkinson's disease patients that would show clinical efficacy while maintaining an acceptable safety profile. A population of patients with relatively recent onset of the disease (<3 years since diagnosis) will be studied, as the goal is to sequester excess labile iron from vulnerable brain regions prior to cell death.

1.4 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 its use in that population is severe neutropenia or agranulocytosis, defined as a confirmed absolute neutrophil count (ANC) less than 0.5×10^9/L. In pooled clinical trials, agranulocytosis has been seen in about 2% 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. Accordingly, deferiprone recipients are required to undergo weekly hematology testing to ensure early detection of a drop in ANC. The most common non-serious adverse reactions reported during clinical trials have been chromaturia (due to iron excretion), nausea, vomiting, abdominal pain, increased alanine aminotransferase, arthralgia, and mild or moderate neutropenia (ANC less than 1.5×10^9/L).[23] The safety profile observed so far in patients with local iron overload has been found to be similar to that seen in the population with systemic iron overload, with respect to major risks. For detailed information on adverse events associated with deferiprone, see the Investigator's Brochure. [24]

Benefits: The findings of preclinical and clinical research suggest that deferiprone has the potential to access pathologically relevant brain iron and to produce clinical benefit in patients with Parkinson's disease. The currently available medications for PD act only on symptoms, not on the underlying cause of the disorder. This treatment may possibly act to prevent the cell death that gives rise to those symptoms.

2 STUDY OBJECTIVES

2.1 Primary Objective

To evaluate the efficacy of four different dosages of deferiprone delayed release tablets in patients with Parkinson's disease.

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

2.2 Secondary Objectives

- To evaluate the safety and tolerability of deferiprone delayed release tablets in patients with Parkinson's disease
- To evaluate the pharmacokinetics of deferiprone delayed release tablets in a subset of study participants
- To evaluate the relationship between the pharmacokinetics and pharmacodynamics of deferiprone delayed release tablets

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

2.3 Exploratory Objectives

- To determine whether the efficacy responses to deferiprone differ depending on the genotype of certain enzymes that are implicated in Parkinson's disease
- To determine whether the efficacy responses to deferiprone are correlated with ceruloplasmin levels or ceruloplasmin ferroxidase activities

The endpoints for the exploratory objectives are provided in Section 9.1.3.

3 STUDY DESIGN

3.1 Description of Study Design

This is a multi-center, randomized, double-blind, placebo-controlled, dose-ranging study in 140 patients who have been diagnosed with typical Parkinson's disease within the last 3 years and are currently taking antiparkinsonian medication. Screening will be conducted within 30 days prior to the start of dosing. At baseline, eligible participants will be randomized to one of four dosage cohorts, and within each cohort will be further randomized in a 4:1 ratio to receive either active product or placebo. The assigned study product will be taken twice-daily (b.i.d.), at least 8 hours apart, for 9 months. Dosages are as follows:

- Cohort 1: 300 mg deferiprone delayed release tablets (n=28) or placebo (n=7)
- Cohort 2: 600 mg deferiprone delayed release tablets (n=28) or placebo (n=7)
- Cohort 3: 900 mg deferiprone delayed release tablets (n=28) or placebo (n=7)
- Cohort 4: 1200 mg deferiprone delayed release tablets (n=28) or placebo (n=7)

Patients will return to the site at Months 1, 2, 3, 4, 5, 6, and 9, and will receive a follow-up telephone call at Month 10. Safety will be assessed at each site visit and at the follow-up call; efficacy measures will be assessed at baseline and Months 3, 6, and 9; and sparse pharmacokinetics (PK) sampling will be done on all patients at baseline and Month 3. In addition, an optional subset of 16 patients will undergo extensive blood sampling for PK analysis at Month 1, and an optional subset of 18 patients will each provide one sample of cerebrospinal fluid (CSF) for drug level analysis at Month 3. (No selection will be done to enroll these subsets: all patients will be asked if they are willing to provide either or both of these types of samples, and they will be enrolled as they come until the total number of subjects is reached for each subset.) For safety reasons, all patients will have their absolute neutrophil count monitored weekly after the start of dosing. This procedure may be done either at either the study site or a local laboratory, or, with sponsor approval, at the patient's home by a visiting study nurse.

Any patient who withdraws before completing treatment will be requested to return within one month for an Early Termination visit, at which time the procedures normally scheduled for the Month 9 visit will be conducted.

3.2 Rationale for Study Design

The study is placebo-controlled since improvement, stabilization, or even a lesser worsening of motor symptoms in the active treatment groups compared to the placebo group would indicate efficacy.

The rationale for enrolling patients who are currently on antiparkinsonian medications is because the MDS-UPDRS scores of such patients are expected to be higher than those of patients who are treatment-naïve and recently diagnosed. Since the primary endpoint of the study is the change from baseline in MDS-UPDRS score, and the N is relatively small, the presence of higher scores at the start of the study should more easily permit the detection of a significant change in score between the deferiprone-treated and the placebo-treated groups. Furthermore, this population matches those used in investigator-led studies that showed promising results. [19,21]

The selection of study duration is based on findings in the literature. An investigator-driven pilot study found a significant difference between deferiprone and placebo after 6 months,

indicating that this duration might be sufficient to assess a symptomatic effect.[19] However, in order to assess a delay in the progression of the disease, treatment of 9 months would be preferable. Indeed, in the only study to have successfully demonstrated such an effect in PD,[25,26] treatment of 9 months was chosen as being a balance between being sufficiently long to observe the best global effect, but sufficiently brief to avoid the need for any change in current antiparkinsonian treatment. Hence, the duration of treatment in study LA48-0215 will be 9 months.

3.3 Rationale for Selection of Doses

The objective of this study is to determine what dose of deferiprone is likely to provide the most favorable benefit/risk ratio for the treatment of patients with PD: i.e., the balance between being high enough to have an effect but low enough to avoid clinically important toxicity. Data from two investigator-driven studies suggest that 15 mg/kg b.i.d. is the dose most likely to provide the greatest benefit vs. risk, but relatively few patients were enrolled in those studies.[19,21] In the case of thalassemia patients with systemic iron overload, dosages of Ferriprox are defined in terms of mg per kg of body weight; however, the span of weight in that patient population varies 10-fold, as both children and adults are being treated. In the case of PD, body weight is likely to vary less than 4-fold for the vast majority of patients, and according to key opinion leaders in the PD field, the average body weight in patients with PD is about 80 kg. Using 4 fixed doses of 300, 600, 900, and 1200 mg b.i.d. (i.e., for total daily dosages of 600, 1200, 1800, and 2400 mg) and an inclusion criterion of body weight between 60 and 100 kg, the following doses in terms of mg/kg/day should be obtained:

Actual Dose Received (mg/kg/day) When Prescribed Fixed Doses				
Body weight (kg)	300 mg b.i.d.	600 mg b.i.d.	900 mg b.i.d.	1200 mg b.i.d.
60	10	20	30	40
70	9	17	26	34
80	**8**	**15**	**23**	**30**
90	6	13	20	27
100	6	12	18	24

4 STUDY POPULATION

4.1 Number of Patients

A total of 140 patients will be randomized.

4.2 Inclusion Criteria

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

1. Male or female aged ≥18 to < 80 years
2. Body weight ≥60 kg but ≤100 kg
3. Diagnosis of Parkinson's disease according to UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria and based on the presence of at least two of the three cardinal features of the disease (rest tremor, bradykinesia, and rigidity). If rest tremor is not present, patient must have unilateral onset of symptoms.
4. Absolute neutrophil count ≥1.5 x 10^9/L (≥1.0 x 10^9/L for Black population) at screening
5. On a stable dose for at least 3 months prior to the screening visit of any of the following treatments at an L-dopa equivalent daily dose of up to 600 mg:
    - Dopaminergic agonist alone
    - L-dopa alone
    - Combination therapy with dopaminergic agonist and L-dopa
    - Rasagiline
6. At an early stage of the disease, without motor fluctuations and/or L-dopa–induced dyskinesia
7. A female patient must meet one of the following criteria:
    - If of childbearing potential, have a negative pregnancy test result at screening. In addition, she must:
        a. Agree to use an effective method of contraception according to local requirements, during the study and for 30 days following the last dose of study medication, OR
        b. Have undergone a tubal ligation (supporting evidence required), OR
        c. Abstain from heterosexual intercourse, OR
        d. Have a male sexual partner who has been sterilized (supporting evidence required)
    - Be of non-childbearing potential, defined as surgically sterile, having undergone complete hysterectomy or bilateral oophorectomy (supporting evidence required) or

being in a menopausal state (being 50 years of age or older and at least 1 year without menses)

8. Fertile heterosexual males must agree to use an effective method of contraception during the study and for 30 days following their last dose of study medication
9. All 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

4.3 Exclusion Criteria

Individuals will be excluded from enrollment if they meet **any** of the following criteria:

1. Diagnosis of Parkinson's disease more than 3 years prior to screening visit
2. Hoehn and Yahr stage ≥ 3
3. Atypical or secondary Parkinsonism without dopa-sensitivity (e.g., vascular parkinsonism, supranuclear palsy, multisystem atrophy)
4. Progressing Axis I psychiatric disorders (psychosis, hallucinations, compulsive disorders, substance addiction, bipolar disorder, severe depression, anxiety) as assessed in a semi-structured interview in accordance with the Diagnostic and Statistical Manual of Mental Disorders
5. Not stabilized in terms of the current antiparkinsonian therapeutic regimen: already requires dose adaptation and/or is likely to require any change in dopamine therapy over the duration of the trial
6. Current treatment with bromocriptine
7. Current treatment with any antiparkinsonian drug other than those listed in inclusion criterion #5
8. Current treatment with coenzyme Q10 or idebenone. (Patients who are on these medications but stop taking them at least 2 weeks prior to baseline may be enrolled.)
9. Current use of a Deep Brain Stimulation (DBS) system. (Patients who previously had a DBS system but have had it removed may be enrolled.)
10. History of malignancy, with the exception of cancers that have been in remission for ≥5 years at the time of screening
11. Evidence of abnormal liver or kidney function at screening (serum ALT level > 5 times upper limit of normal or creatinine levels >2 times upper limit of normal)
12. A serious, unstable illness, as judged by the investigator, during the past 3 months before screening visit, including but not limited to hepatic, renal, gastro-enterologic, respiratory, cardiovascular, endocrinologic, or immunologic disease

13. Disorders associated with neutropenia (ANC < 1.5 x 10^9/L; < 1.0 x 10^9/L in Black population) or thrombocytopenia (platelet count < 50 x 10^9/L) in the 12 months preceding the initiation of the study medication. Exception: For patients whose neutropenia is attributed by the treating physician to episodes of infection or to drugs associated with a decline in the neutrophil count and in whom the ANC is back to a normal level at the screening visit.
14. Clinically significant abnormalities on 12-lead ECG, as judged by the investigator
15. Myocardial infarction, cardiac arrest, or cardiac failure within 1 year before screening visit
16. Bowel disease causing malabsorption
17. History of allergy or sensitivity to deferiprone or to other components of the formulation
18. Receipt of any investigational products within the past 30 days or 5 half-lives (whichever is longer) preceding the first dose of study medication
19. Participation in any investigational clinical study, other than observational, within the past 30 days; or plans to participate in such a study at any time from the day of screening until 30 days post-treatment in the current study
20. History of or current drug or alcohol use or dependence which in the opinion of the investigator would interfere with adherence to study requirements
21. Presence of any medical, psychological, or psychiatric condition which in the opinion of the investigator would cause participation in the study to be unwise
22. Pregnant, breastfeeding, or planning to become pregnant during the study period
23. Identified as an investigator or other site staff directly affiliated with this study, or an immediate family member (spouse, parent, child, or sibling, whether biological or legally adopted) of either of the above

4.4 Enrolment Violations

The criteria for enrolment must be followed explicitly. If there is inadvertent enrolment of a patient who does not meet the enrolment criteria, the investigator should consider withdrawing that individual 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 site.

A patient may be withdrawn from the study at any time 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
- 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 during the study period (see Section 7.2.4, Procedures in Case of Pregnancy)
- Occurrence of severe neutropenia/agranulocytosis (see Section 7.2.1.8.1, Neutropenia)
- Occurrence of any adverse event characterized as life-threatening or disabling that is not associated with the patient's condition
- Receipt of a rescue medication (see Section 4.7 for definition)
- Termination of the study by the sponsor

Patients who decide to withdraw from 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 within one month of withdrawal. All study 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 females of childbearing potential must have a negative serum pregnancy test at the screening visit and prior to first administration of the study drug, and must agree to use an approved method of contraception throughout the course of the trial and up to 1 month

following 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
- With the patient's consent, follow the pregnancy closely, and provide reports to the sponsor until delivery or other resolution

A male patient must inform the investigator if his female partner becomes pregnant during the trial or within 1 month following the last dose of study medication. As with the pregnancy of a female patient, the site must inform the sponsor and, if the partner consents, follow the pregnancy and provide the sponsor with a report on its outcome.

4.5.2 Replacement of Patients Who Withdraw

Patients who are withdrawn from the study will not be replaced.

4.5.3 Treatment Interruptions

Patients should be advised to immediately report any symptoms indicative of infection such as fever (≥38.5°C), sore throat, or flu-like symptoms. If a patient develops fever or any type of infection, deferiprone must be interrupted immediately and neutrophil count should be obtained and monitored more frequently; every 2 days if ANC $<1.5 \times 10^9$/L ($<1.0 \times 10^9$/L for black patients). Therapy with deferiprone can be re-initiated once all symptoms have resolved and it is deemed safe by the investigator.

4.6 Prior and Concomitant Therapies

Prior Therapies:

- Patients must have been on a stable dose for at least the past 3 months of any of the following treatments at an L-dopa equivalent daily dose of up to 600 mg:
    - Dopaminergic agonist alone
    - L-dopa alone
    - Combination therapy with dopaminergic agonist and L-dopa
    - Rasagiline
- If coenzyme Q10 or idebenone is being taken, it must be stopped at least 2 weeks prior to baseline
- If a Deep Brain Stimulation (DBS) system had been in place, it must have been removed at least 3 months prior to baseline

Concomitant Therapies:

- The regimen of antiparkinsonian medication that was in effect at the time of screening must remain stable throughout the trial

- During the trial, patients may not use a DBS system; may not take coenzyme Q10, idebenone, bromocriptine, or any antiparkinsonian drug other than those listed in inclusion criterion #5; and may not take any other investigational product or any drugs that are known to cause neutropenia or agranulocytosis. Other medications that are being taken on a stable regimen and that are considered necessary for the patient's welfare may continue to be taken, at the discretion of the investigator.

All medications (including herbal medications and over-the-counter medications) and nutritional supplements taken from 3 months prior to screening up to Month 10 or early termination must be reviewed by the investigator and recorded in the source document and in the appropriate section of the eCRF.

4.7 Rescue Medication

A patient whose regimen of antiparkinsonian medication is changed, including a change in dosage, must be withdrawn from the trial.

In order for rescue medication to be provided, the patient must a) request it and b) show a worsening of condition as evidenced by at least one of the following:

- An increase of ≥5 points on the MDS-UPDRS Part III score from baseline
- An increase of ≥8 points on the total MDS-UPDRS score from baseline

For patients who meet the above criteria, the reason for withdrawal will be defined as need for a rescue medication.

5 STUDY PROCEDURES

The procedures and assessments to be conducted at each study visit are shown in Table 5.1.

Table 5.1 Table of study procedures

	Day -30–0 (Screening)	Month 0, Day 0 (Baseline)	Month 1 ± 5 days	Month 2 ± 5 days	Month 3 ± 5 days	Month 4 ± 5 days	Month 5 ± 5 days	Month 6 ± 5 days	Month 9 ± 5 days or Early Termination	Month 10 +5 days Telephone Call
Informed consent	X									
Medical history	X									
Demographics	X									
Eligibility criteria	X	V								
Randomization		X								
MDS-UPDRS [1]		X			X			X	X	
MoCA [1]		X			X			X	X	
C-SSRS		X	X	X	X	X	X	X	X	
Hematology [2]	X [3]	Weekly (±3 days) after start of dosing until Month 9								
Blood chemistry [4]	X [3]		X	X	X	X	X	X	X	
Urinalysis [5]	X [3]				X			X	X	
Pregnancy testing [6]	X	X	X	X	X	X	X	X	X	
Physical examination [7]	X	X		X		X		X	X	
Vital signs (supine and standing) and body temperature [8]	X	X	X	X	X	X	X	X	X	
12-lead ECG	X [3]								X	
Contraceptive counseling	X	X	X	X	X	X	X	X	X	
Blood for PK analysis		X [9]	X [10]		X [11]					
Blood for biomarkers [12]		X			X			X	X	
Urine for biomarkers [13]		X			X			X	X	
CSF sampling [14]					X					

	Day -30–0 (Screening)	Month 0, Day 0 (Baseline)	Month 1 ± 5 days	Month 2 ± 5 days	Month 3 ± 5 days	Month 4 ± 5 days	Month 5 ± 5 days	Month 6 ± 5 days	Month 9 ± 5 days or Early Termination	Month 10 +5 days Telephone Call
Dispense study medication [15]		X		X		X		X		
Provide diary card		X	X	X	X	X	X	X		
Dosing [16]		Twice daily from baseline until Month 9								
Review and collect diary card			X	X	X	X	X	X	X	
Collect used and unused study medication containers				X		X		X	X	
Treatment compliance			X	X	X	X	X	X	X	
Prior & concomitant medications	X	X	X	X	X	X	X	X	X	X
Medical events		X								
Adverse events		Throughout the study after start of dosing								

Abbreviations

V: Verify; **ECG:** Electrocardiogram; **C-SSRS:** Columbia Suicide Severity Rating Scale; **MDS-UPDRS:** Movement Disorder Society - Unified Parkinson's Disease Rating Scale; **MoCA:** Montreal Cognitive Assessment; **PK:** Pharmacokinetics; **CSF:** cerebrospinal fluid

[1] The MDS-UPDRS and the MoCA are to be conducted early in the morning, at approximately the same time (± 1 hour) at each visit, and by the same qualified investigator at each visit.

[2] Hematology: Hemoglobin, total WBC count, ANC, MCV, and platelet count.

[3] If performed more than 14 days prior to Week 0 (baseline visit), must be repeated before Day 0.

[4] Blood chemistry: Total protein, GGT, lactate dehydrogenase (LDH), sodium, potassium, chloride, fasting glucose, bilirubin (total, direct, and indirect), AST, ALT, albumin, blood urea nitrogen, calcium, creatinine, uric acid, alkaline phosphatase, amylase, serum ferritin, blood iron, zinc, and copper.

[5] Urinalysis: pH, specific gravity, glucose, protein, ketones, blood, and (if indicated by the dipstick results), sediment microscopy. If there is blood in the urine or three or more "plus signs" for protein, samples must be sent for microscopy.

[6] Pregnancy testing: Females of childbearing potential only. Both urine and serum tests will be done at baseline; serum test only at all other time points.

[7] Physical examination: Weight (without shoes) will be measured only at screening and Month 9 (or early termination visit). Height will be measured only at screening.

[8] Vital signs: Orthostatic vital signs (pulse and blood pressure) will be measured in the supine followed by the standing position. At baseline, three sets of orthostatic measurements will be conducted, with 10–30 minute intervals between measurements. At all other time points, a single set of measurements will be performed.

[9] PK at baseline: All patients; pre-dose, at 2 hours post-dose (± 45 minutes), and at 4 hours post-dose (± 45 minutes) with a minimum of 1 hour between samples.

[10] PK at Month 1: A subset of 16 patients will provide samples pre-dose and at 0.25, 0.5, 0.75, 1.0, 1.33, 1.66, 2.0, 2.33, 2.66, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, and 12.0 hours post-dose.

[11] PK at Month 3: All patients; pre-dose, at 2 hours post-dose (± 45 minutes), and at 4 hours post-dose (± 45 minutes), with a minimum of 1 hour between samples. **Note:** For the subset of patients who have agreed to provide a CSF sample at Month 3, the applicable blood sample (either pre-dose, 2 hours post-dose, or 4 hours post-dose) is to be taken within ± 15 minutes of the CSF sample.

[12] Blood samples: The following biomarkers will be determined:

- Oxidative stress biomarkers: total antioxidant status, protein carbonyls, glutathione, and super oxide dismutase
- Inflammatory factor biomarkers: TNF alpha and IL-6
- Mechanism of action biomarkers: Determination of catechol *O*-methyltransferase and ceruloplasmin genotypes (baseline only) and of ceruloplasmin levels and ceruloplasmin ferroxidase activity

[13] Urine sample: The oxidative stress biomarkers of 8-OHdG and lipid peroxidation (malondialdehyde) will be assessed.

[14] CSF: Subset of 18 patients; 6 to provide a sample pre-dose, 6 to provide one at 2 hours post-dose (± 15 minutes), and 6 to provide one at 4 hours post-dose (± 15 minutes). The time of sample collection for each of the 18 subjects will be assigned prior to the Month 3 visit.

[15] Dispensing: A 2-month supply of study product will be provided at Months 0, 2, and 4, and a 3-month supply will be provided at Month 6

[16] Dosing: Deferiprone delayed release 600 mg tablets (assigned dose of 300 mg, 600 mg, 900 mg, or 1200 mg) b.i.d. or matching placebo tablets b.i.d, at least 8 hours apart

5.1 Visit Procedures

Note: Patients are to be instructed to fast before each site visit, including the screening visit. On most days the fast will be for at least 8 hours, and on days when pharmacokinetics testing is done, it must be for at least 10 hours.

Screening Visit (Day -30 to Day 0)

- Explain the study to the patient, and obtain written informed consent
- Collect demographic information
- Collect medical history
- Administer the Hoehn and Yahr scale to determine the patient's stage of PD (not required if supporting documentation from within the last 6 months is available)
- Conduct a semi-structured interview in accordance with the Diagnostic and Statistical Manual of Mental Disorders to determine the presence of Axis I psychiatric disorders (not required if supporting documentation from within the last 6 months is available)
- Collect information on prior and concomitant medications
- Perform a physical examination (to be completed by the investigator or a qualified delegate), including measurement of weight and height (without shoes)
- Measure orthostatic vital signs (pulse and blood pressure), first in the supine and then in the standing position, and body temperature
- Collect blood samples for the following assessments:
    - Hematology and blood chemistry (including fasting glucose)
    - Pregnancy testing for females of childbearing potential
- Collect a urine specimen for urinalysis
- Perform a 12-lead ECG
- Conduct contraceptive counseling if applicable
- Schedule baseline visit if all eligibility criteria are met

Baseline Visit (Month 0, Day 0)

Notes:

- Hematology, blood chemistry, urinalysis, and ECG testing must have been done within 14 days prior to the baseline visit. If more than 14 days have elapsed since the screening visit, those tests will need to be repeated prior to the baseline visit.

- As pharmacokinetics testing will be done at this visit, patients must be told beforehand to fast for 10 hours rather than 8. (They will be allowed to eat about 1.5 hours after dosing.)
- At this visit, it must be kept in mind that at Months 3, 6, and 9, the MDS-UPDRS and MoCA will need to be administered at approximately the same time of day as at baseline (early in the morning) and must be conducted by the same qualified investigator.

- Collect information on any medical events
- Collect information on concomitant medications
- Measure vital signs: three sets of orthostatic vital signs (pulse and blood pressure), first in the supine and then in the standing position, with a 10- to 30-minute interval between sets, and a single measurement of body temperature
- Perform a physical examination (to be completed by the investigator or a qualified delegate)
- Collect blood samples for the following pre-dose assessments:
  - Pharmacokinetics
  - Pharmacodynamics biomarkers (oxidative stress, inflammatory factors)
  - Mechanism of action biomarkers (determination of genotype for ceruloplasmin and COMT, ceruloplasmin levels, ceruloplasmin ferroxidase activity)
- Collect a urine sample for the pre-dose assessment of oxidative stress biomarkers
- Collect both a blood sample and a urine sample for pregnancy testing (females of childbearing potential only). A negative result on the urine test is required for the start of dosing, and a negative result on the serum test is required for study continuation.
- Complete the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) *
- Complete the Montreal Cognitive Assessment (MoCA) *
- Complete the Columbia Suicide Severity Rating Scale (C-SSRS)
- Verify eligibility
- Contact the Interactive Voice (or Web) Randomization System (IVRS/IWRS) to have the patient randomized to one of the four dosage cohorts and to receive either active product or placebo within that cohort
- Dispense a 2-month supply of study medication (see Section 6.5), along with instructions on how to take it

* Must be conducted by the qualified investigator, early in the morning

- Administer first dose of study medication
- Collect blood samples for post-dose PK testing at 2 hours post-dose (± 45 minutes) and at 4 hours post-dose (± 45 minutes), with a minimum of 1 hour between samples
- Conduct contraceptive counseling if applicable
- Provide patient with a diary card and explain how to complete it
- Provide patient with an emergency card with contact information, and explain that it is to be carried at all times
- Instruct patient to do the following:
    - Undergo a weekly blood draw, at either the study site or a local laboratory, or, with sponsor approval, at the patient's home by a visiting study nurse
    - In the event of any symptoms indicative of infection such as fever, sore throat, or flu-like symptoms, immediately interrupt therapy and contact the clinic
    - At the next visit, bring back the completed diary card plus all medication containers, whether empty, partly used, or unopened
    - In the event of a decision to withdraw from the study before completion, return to the clinic for an Early Termination Visit as soon as possible, and no later than one month following the last dose of study medication
- Schedule next study visit.

Weekly Blood Draws (every 7 ± 3 days except on weeks that include a study visit)

Patients must provide a weekly blood sample for hematology testing. The results should be reviewed by the investigator as soon as they are received, preferably within 24 hours.

Note: This procedure may be done either at a local laboratory or at the study site, or, with sponsor approval, at the patient's home by a visiting study nurse.

Month 1 (± 5 days)

Note: Since this visit will include pre-dose blood sampling for PK testing in a subset of patients, those individuals must be reminded beforehand to **not** take their morning dose that day before coming to the site, and to have fasted for at least 10 hours rather than 8. (They will be allowed to eat about 1.5 hours after dosing.) In addition, those who agreed to take part in the extensive PK testing need to be reminded that this visit will involve an all-day stay at the site.

- Collect blood samples for the following assessments:
  - Hematology and blood chemistry (including fasting glucose)
  - Pregnancy testing for all females of childbearing potential (a negative result is required for study continuation)
  - Subset of patients who have agreed to undergo extensive PK testing: Pre-dose PK sample
- Administer morning dose of study medication, and note the time at which it was given
- Subset of patients who have agreed to undergo extensive PK testing: Collect blood samples at 0.25, 0.5, 0.75, 1.0, 1.33, 1.66, 2.0, 2.33, 2.66, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, and 12.0 hours post-dose
- Complete the C-SSRS
- Verify treatment compliance through review of patient diary card and tablet count, and confirm that the patient has enough medication to last until the next visit
- Additionally review diary card for information on adverse events and use of concomitant medications, and file the diary card with the source documents
- Measure vital signs, first in the supine and then in the standing position (single measurement for each) and body temperature
- Conduct contraceptive counseling if applicable
- Give patient a new diary card, along with a reminder if necessary about how to complete it
- Remind patient to do the following:
  - Undergo a weekly blood draw, at either the study site or a local laboratory, or, with sponsor approval, at the patient's home by a visiting study nurse
  - In the event of any symptoms indicative of infection such as fever, sore throat, or flu-like symptoms, immediately interrupt therapy and contact the clinic
  - At the next visit, bring back the completed diary card plus all medication containers, whether empty, partly used, or unopened
  - In the event of a decision to withdraw from the study before completion, return to the clinic for an Early Termination Visit as soon as possible, and no later than one month following the last dose of study medication
- Schedule next study visit

<u>Month 2 (± 5 days)</u>

- Collect all medication containers, whether empty, partly used, or unopened, and account for the medication dispensed
- Calculate treatment compliance through review of diary card and tablet count

- Additionally review diary card for information on adverse events and use of concomitant medications, and file the diary card with the source documents
- Measure vital signs, first in the supine and then in the standing position (single measurement for each), and body temperature
- Perform a physical examination (to be completed by the investigator or a qualified delegate)
- Conduct contraceptive counseling if applicable
- Collect blood samples for the following assessments:
    - Hematology and blood chemistry (including fasting glucose)
    - Pregnancy testing for all females of childbearing potential (a negative result is required for study continuation)
- Complete the C-SSRS
- Dispense a 2-month supply of study medication (see Section 6.5), along with instructions if necessary on how to take it
- Give patient a new diary card, along with a reminder if necessary about how to complete it
- Remind patient to do the following:
    - Undergo a weekly blood draw, at either the study site or a local laboratory, or, with sponsor approval, at the patient's home by a visiting study nurse
    - In the event of any symptoms indicative of infection such as fever, sore throat, or flu-like symptoms, immediately interrupt therapy and contact the clinic
    - At the next visit, bring back the completed diary card plus all medication containers, whether empty, partly used, or unopened
    - In the event of a decision to withdraw from the study before completion, return to the clinic for an Early Termination Visit as soon as possible, and no later than one month following the last dose of study medication
- Schedule next study visit

Month 3 (± 5 days)

Notes:

- Since this visit will include pre-dose blood sampling for PK testing and pre-dose CSF sampling in subsets of patients, those individuals must be reminded beforehand to **not** take their morning dose that day before coming to the site, and to fast for at least 10 hours beforehand rather than 8. (They will be allowed to eat about 1.5 hours after dosing.)

- The MDS-UPDRS and the MoCA are to be conducted early in the morning, at approximately the same time (± 1 hour) that they were done at baseline, and must be conducted by the same qualified investigator who completed them at baseline.

- Collect blood samples for the following assessments:
  - Hematology and blood chemistry (including fasting glucose)
  - Pregnancy testing for all females of childbearing potential (a negative result is required for study continuation)
  - Pre-dose PK sample

  Note: For the subset of 6 patients who will also be contributing a pre-dose CSF sample, this blood sample is to be collected within ±15 minutes of the CSF sample.
- For the subset of 6 patients who agreed to undergo CSF sampling and were assigned the pre-dose time point, collect a single CSF sample
- Administer morning dose of study medication, and note the time at which it was given
- Complete the MDS-UPDRS [*]
- Complete the MoCA [*]
- Complete the C-SSRS
- Collect blood samples for the following, and note the time at which they are collected:
  - Pharmacodynamics biomarkers (oxidative stress, inflammatory factors)
  - Mechanism of action biomarkers (ceruloplasmin levels, ceruloplasmin ferroxidase activity)
- Collect a urine sample for the following, and note the time at which it is collected:
  - Assessment of oxidative stress biomarkers
  - Urinalysis
- Collect blood samples for post-dose PK testing at 2 hours post-dose (± 45 minutes), and at 4 hours post-dose (± 45 minutes), with a minimum of 1 hour between samples.

  Note: For the subsets of patients who will be contributing CSF samples at 2 hours or 4 hours post-dose, the applicable blood sample is to be collected within ±15 minutes of the CSF sample.

[*] Must be conducted by the same qualified investigator as before, early in the morning

- For the two subsets of patients (n=6 each) who were assigned to give a post-dose CSF sample, collect a single sample at either 2 hours (±15 minutes) or 4 hours (±15 minutes) post-dose
- Verify treatment compliance through review of patient diary card and tablet count, and confirm that the patient has enough medication to last until the next visit
- Additionally review diary card for information on adverse events and use of concomitant medications, and file the diary card with the source documents
- Measure vital signs, first in the supine and then in the standing position (single measurement for each), and body temperature
- Conduct contraceptive counseling if applicable
- Give patient a new diary card, along with a reminder if necessary about how to complete it
- Remind patient to do the following:
    - Undergo a weekly blood draw, at either the study site or a local laboratory, or, with sponsor approval, at the patient's home by a visiting study nurse
    - In the event of any symptoms indicative of infection such as fever, sore throat, or flu-like symptoms, immediately interrupt therapy and contact the clinic
    - At the next visit, bring back the completed diary card plus all medication containers, whether empty, partly used, or unopened
    - In the event of a decision to withdraw from the study before completion, return to the clinic for an Early Termination Visit as soon as possible, and no later than one month following the last dose of study medication
- Schedule next study visit

<u>Month 4 (± 5 days)</u>

- Collect all medication containers, whether empty, partly used, or unopened, and account for the medication dispensed
- Calculate treatment compliance through review of diary card and tablet count
- Additionally review diary card for information on adverse events and use of concomitant medications, and file the diary card with the source documents
- Measure vital signs, first in the supine and then in the standing position (single measurement for each), and body temperature
- Perform a physical examination (to be completed by the investigator or a qualified delegate)
- Conduct contraceptive counseling if applicable

- Collect blood samples for the following assessments:
  - Hematology and blood chemistry (including fasting glucose)
  - Pregnancy testing for all females of childbearing potential (a negative result is required for study continuation)
- Complete the C-SSRS
- Dispense a 2-month supply of study medication (see Section 6.5), along with instructions if necessary on how to take it
- Give patient a new diary card, along with a reminder if necessary about how to complete it
- Remind patient to do the following:
  - Undergo a weekly blood draw, at either the study site or a local laboratory, or, with sponsor approval, at the patient's home by a visiting study nurse
  - In the event of any symptoms indicative of infection such as fever, sore throat, or flu-like symptoms, immediately interrupt therapy and contact the clinic
  - At the next visit, bring back the completed diary card plus all medication containers, whether empty, partly used, or unopened
  - In the event of a decision to withdraw from the study before completion, return to the clinic for an Early Termination Visit as soon as possible, and no later than one month following the last dose of study medication
- Schedule next study visit

Month 5 (± 5 days)

- Verify treatment compliance through review of patient diary card and tablet count, and confirm that patient has enough medication to last until the next visit
- Additionally review diary card for information on adverse events and use of concomitant medications, and file the diary card with the source documents
- Measure vital signs, first in the supine and then in the standing position (single measurement for each), and body temperature
- Conduct contraceptive counseling if applicable
- Collect blood samples for the following assessments:
  - Hematology and blood chemistry (including fasting glucose)
  - Pregnancy testing for all females of childbearing potential (a negative result is required for study continuation)
- Complete the C-SSRS

- Give patient a new diary card, along with a reminder if necessary about how to complete it
- Remind patient to do the following:
    - Undergo a weekly blood draw, at either the study site or a local laboratory, or, with sponsor approval, at the patient's home by a visiting study nurse
    - In the event of any symptoms indicative of infection such as fever, sore throat, or flu-like symptoms, immediately interrupt therapy and contact the clinic
    - At the next visit, bring back the completed diary card plus all medication containers, whether empty, partly used, or unopened
    - In the event of a decision to withdraw from the study before completion, return to the clinic for an Early Termination Visit as soon as possible, and no later than one month following the last dose of study medication
- Schedule next study visit

Month 6 (± 5 days)

Notes:

- Patients are to be instructed beforehand that on the day of this visit, they are either to not take their morning dose before coming to the site, or if they do take it, to note the time and inform the investigator of it when they arrive.
- The MDS-UPDRS and the MoCA are to be conducted early in the morning, at approximately the same time (± 1 hour) that they were done at baseline, and must be conducted by the same qualified investigator who completed them at baseline.

- Collect all medication containers, whether empty, partly used, or unopened, and account for the medication dispensed
- Collect blood samples for the following assessments:
    - Hematology and blood chemistry (including fasting glucose)
    - Pregnancy testing for all females of childbearing potential (a negative result is required for study continuation)
- If patient did not yet take the day's morning dose, administer it at this time. If patient did take the dose before arriving, record the time at which it was taken.

- Complete the MDS-UPDRS [*]
- Complete the MoCA [*]
- Complete the C-SSRS
- Collect blood samples for the following, and note the time at which they are collected:
  - Pharmacodynamics biomarkers (oxidative stress, inflammatory factors)
  - Mechanism of action biomarkers (ceruloplasmin levels, ceruloplasmin ferroxidase activity)
- Collect a urine sample for the following, and note the time at which it is collected:
  - Assessment of oxidative stress biomarkers
  - Urinalysis
- Calculate treatment compliance through review of patient diary card and tablet count
- Additionally review diary card for information on adverse events and use of concomitant medications, and file the diary card with the source documents
- Measure vital signs, first in the supine and then in the standing position (single measurement for each), and body temperature
- Perform a physical examination (to be completed by the investigator or a qualified delegate)
- Conduct contraceptive counseling if applicable
- Dispense a 3-month supply of study medication (see Section 6.5), along with instructions if necessary on how to take it
- Give patient a new diary card, along with a reminder if necessary about how to complete it
- Remind patient to do the following:
  - Undergo a weekly blood draw, at either the study site or a local laboratory, or, with sponsor approval, at the patient's home by a visiting study nurse
  - In the event of any symptoms indicative of infection such as fever, sore throat, or flu-like symptoms, immediately interrupt therapy and contact the clinic
  - At the next visit, bring back the completed diary card plus all medication containers, whether empty, partly used, or unopened

[*] Must be conducted by the same qualified investigator as before, early in the morning

  - In the event of a decision to withdraw from the study before completion, return to the clinic for an Early Termination Visit as soon as possible, and no later than one month following the last dose of study medication

- Schedule next study visit

Month 9 (± 5 days) – End-of-study visit/Early termination visit

Notes:

- Patients are to be instructed beforehand that on the day of this visit, they are either to not take their morning dose before coming to the site, or if they do take it, to note the time and inform the investigator of it when they arrive.
- The MDS-UPDRS and the MoCA are to be conducted early in the morning, at approximately the same time (± 1 hour) that they were done at baseline, and must be conducted by the same qualified investigator who completed them at baseline.

- If patient did not yet take the day's morning dose, administer it at this time. If patient did take the dose before arriving, record the time at which it was taken.
- Complete the MDS-UPDRS*
- Complete the MoCA*
- Collect blood samples for the following, and note the time at which they are collected:
  - Hematology and blood chemistry (including fasting glucose)
  - Pregnancy testing for all females of childbearing potential
  - Pharmacodynamics biomarkers (oxidative stress, inflammatory factors)
  - Mechanism of action biomarkers (ceruloplasmin levels, ceruloplasmin ferroxidase activity)
- Collect a urine sample for the following, and note the time at which it is collected:
  - Assessment of oxidative stress biomarkers
  - Urinalysis
- Complete the C-SSRS
- Review patient diary card; collect and document information on adverse events, use of concomitant medications, and treatment compliance; and file the diary card with the source documents

* Must be conducted by the same qualified investigator as before, early in the morning

- Calculate treatment compliance through review of diary card and tablet count.
- Collect all containers of study medication, whether empty, partly used, or unopened, and account for the medication dispensed
- Measure vital signs, first in the supine and then in the standing position (single measurement for each), and body temperature
- Perform a physical examination,(to be completed by the investigator or a qualified delegate) including measurement of weight (without shoes)
- Perform a 12-lead ECG
- Conduct contraceptive counseling if applicable
- Schedule follow-up telephone call
- Advise patient to immediately report any symptoms indicative of infection such as fever, sore throat, and flu-like symptoms during the first week following completion of treatment. If infection is found to be present, the patient's ANC must be monitored in order to check for neutropenia.

Month 10 Follow-up Telephone Call (+ 5 days)

Call patient to collect information about any adverse events that may have occurred since the last visit and any concomitant medications that were taken. If this call is made earlier than 30 days after the last dose of study medication, ask the patient to inform the site if he/she experiences a serious adverse event (SAE) in the next couple of days.

5.2 Method of Assignment to Treatment

At baseline, 140 eligible participants will be randomized to one of four dosage cohorts (n=35 each), and within each cohort will be further randomized in a 4:1 ratio to receive either active product (n=28) or placebo (n=7). Thus, a total of 112 patients will receive one of the four dosages of deferiprone, and a total of 28 will receive placebo.

The sponsor will generate the randomization codes according to the study design. Once generated, the randomization codes will be final and will not be modifiable. An IVRS/IWRS will be used to perform the randomization in this study.

5.3 Blinding Procedures

The placebo tablets will have the same appearance as the deferiprone tablets. Within each cohort, all participants will take the same number of tablets at each dose: 1 half-tablet in Cohort 1; 1 tablet in Cohort 2; 1.5 tablets in Cohort 3; and 2 tablets in Cohort 4.

Sites will be provided with code-breaking instructions. In the event of an emergency, the randomization code may be broken only if knowledge of the respective treatment is necessary for adequate treatment of the emergency. The sponsor must be contacted within 24 hours in case of unblinding. Randomization information will be held by designated individual(s). The date and reason for breaking the blind must be documented.

5.4 Allocation of Patient Numbers

After provision of informed consent, each patient will be assigned a unique ID number and will be identified in all study data by this number. The ID number will consist of 6 digits, where the first digit represents the country code, the next 2 digits represent the site code (01 for site #1, 02 for site #2, etc.), and the next 3 digits (separated from the first 3 by a hyphen) are assigned sequentially for each individual screened at that site. For example, if site #1 from the country designated as "1" screens 8 patients, the ID numbers will be 101-001 through 101-008. The assigned ID numbers of patients who are screening failures or who withdraw from the study will not be reused.

5.5 Treatment Compliance

Compliance will be determined as follows: 1) the patient will use the daily diary card to record the number of tablets taken, and 2) at each visit, the investigator or delegate will inspect the medication containers whether empty, partly used, or unopened, and will check the number of tablets remaining. Compliance will be calculated by the number of tablets taken divided by the number of tablets prescribed as per the dosing frequency and length of treatment. Any discrepancies must be discussed with the patient and documented in the source documents. Reasons for non-compliance with the treatment will be recorded in the source document and in the eCRFs. The investigator should discuss treatment compliance with the patient at each visit.

If the number of returned tablets is less than it should be, but the patient reports having taken the correct amount of medication, the site will report compliance as 100% in the eCRF, and will provide the reason for the apparent over-compliance (e.g., tablets were accidentally spoiled and could not be ingested), along with the actual percentage. Both under-compliance < 80% and over-compliance >120% will be reported as a protocol deviation, unless under-compliance is due to treatment interruption because of infection or neutropenia or other extenuating circumstances (see Section 7.2.1.8).

6 STUDY TREATMENTS

Patients will receive either deferiprone delayed release tablets or placebo tablets.

6.1 Investigational Product

Deferiprone delayed release tablets are manufactured by Apotex Inc., and will be supplied to the clinical sites by ApoPharma Inc. The tablets are biconvex, capsule-shaped, white to off-white in color, enteric-coated, engraved with "APO 400" on one side, and scored on both sides. Each tablet contains 600 mg of deferiprone. Non-medicinal ingredients are hypromellose acetate succinate, magnesium oxide, magnesium stearate, colloidal silicon dioxide, triethyl citrate, sucrose, talc 500 mesh, methacrylic acid copolymer dispersion, and titanium dioxide.

6.1.1 Dosage Form and Mode of Administration

The tablets are scored in a way that they can be split into two halves that maintain the release characteristics of the whole tablets. Depending on the cohort, study participants will take either 1 half-tablet (300 mg), 1 tablet (600 mg), 1.5 tablets (900 mg), or 2 tablets (1200 mg) twice a day, at least 8 hours apart. Patients in Cohorts 1 and 3 will be instructed to cut their tablets on an as-needed basis, not all at once upon receipt of the medication. The route of administration is oral.

6.1.2 Precautions for Use

The tablets are to be stored at 15–30°C in a tightly closed bottle in order to protect them from moisture and light, and the bottle kept out of the reach and sight of children.

The study product can be taken with or without food.

6.2 Reference Product

Placebo tablets are identical in appearance to the deferiprone delayed release tablets. Within each cohort, the number of placebo tablets taken at each dose will match that of the corresponding active product : i.e., 1 half-tablet, 1 tablet, 1.5 tablets, or 2 tablets. Placebo tablets will be taken twice a day, at least 8 hours apart.

6.3 Packaging and Labeling

The study products will be supplied in high-density polyethylene (HDPE) bottles with child-resistant closure, containing 100 tablets each. Each bottle will contain a desiccant bag.

The bottles will be provided with a label 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 sponsor.

6.4 Shipping and Storage

The study medication at each site will be kept in a secure location (a locked room or cabinet) under adequate storage conditions, as per label requirements, under the control of the investigator and with access to authorized individuals only. Product is to be kept at room temperature (15–30 ºC / 59–86 ºF). The room must have a calibrated digital temperature-monitoring device, and site personnel must use a temperature log to facilitate daily recording of the temperature of the storage facility. Temperature deviations must be immediately reported to the sponsor for investigation and determination of impact on the study medication.

Each shipment of investigational product will include shipment documents, which the investigator or a designate must complete as per the provided instructions and retain the original copies in the Investigator Trial File.

6.5 Dispensing Procedures

Patients will be dispensed a 2-month supply of study medication at baseline, Month 2, and Month 4, and a 3-month supply at Month 6. Dispensing of study medication must be done by appropriately qualified staff (e.g., physician, pharmacist, or nurse).

Patients will be dispensed a sufficient amount of study medication, with an allowance for the visit windows of ±5 days. Each bottle of deferiprone-DR or placebo contains 100 tablets. Hence, the following quantities will be provided:

	Baseline, Month 2, and Month 4	**Month 6**
Cohort 1	1 bottle	2 bottles
Cohort 2	2 bottles	3 bottles
Cohort 3	3 bottles	4 bottles
Cohort 4	3 bottles	5 bottles

6.6 Product Accountability

The investigator must maintain an updated Site Investigational Drug Inventory Record at the study site. This log will include at a minimum:

- Name of sponsor

- Name of investigator
- Study identifier
- Date and quantity of investigational product received from sponsor
- Lot/batch number

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

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

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

It is the responsibility of the investigator to ensure that all study drug received at the site 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. The sponsor will be responsible for determining the specific conditions for destruction of unused product.

6.7 Replacement Doses

Patients who report that their medication has been lost or damaged will need to return to the study site to receive replacement tablets. Requests for replacement must be made in writing to the sponsor by the qualified staff member, and the study coordinator must contact the IVRS/IWRS again to ensure that the patient is provided with the correct product. All information related to the lost or damaged medication and the replacement medication is to be recorded in the drug accountability forms and patient source data.

6.8 Disposition of Unused Product

All investigational product that has been returned by the patient or that is unused for any other reasons will be returned to the sponsor or discarded by the site according to internal procedures, if approved, in writing, by the sponsor. The destruction procedures must include the issuance of appropriate signed destruction certificates including mode of destruction and

complete drug accountability of destroyed materials. The destruction may take place only after written approval by the sponsor.

6.9 Other Study Supplies

All required study supplies, including but not limited to diary cards and laboratory kits, will be provided by the sponsor to the sites.

7 MEASUREMENTS AND EVALUATIONS

7.1 Efficacy Measurements

Efficacy will be measured using 1) the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS), 2) the Montreal Cognitive Assessment (MoCA) test, 3) pharmacodynamic biomarkers, and 4) mechanism of action biomarkers.

7.1.1 Primary Efficacy Measurements

7.1.1.1 Motor Score on the Unified Parkinson's Disease Rating Scale

The MDS-UPDRS is the most recent version of the major rating scale used to assess the severity of symptoms of PD. It consists of 4 parts: Part I, non-motor experiences of daily living; Part II, motor experiences of daily living; Part III, motor examination; and Part IV, motor complications. Part I has two components: I-A concerns a number of behaviors that are assessed by the investigator using all pertinent information from patient and caregiver, and I-B is completed by the patient with or without the aid of the caregiver, but independently of the investigator. These sections can, however, be reviewed by the rater to ensure that all questions are answered clearly, and the rater can help explain any perceived ambiguities. Part II is designed to be a self-administered questionnaire, but can be reviewed by the investigator to ensure completeness and clarity. Part III has instructions for the rater to give or demonstrate to the patient; it is completed by the rater. Part IV has instructions for the rater and also instructions to be read to the patient. This part integrates patient-derived information with the rater's clinical observations and judgments, and is completed by the rater. Each time the MDS-UPDRS is completed, both individual subscale scores and a total score are generated. The MDS-UPDRS is to always be administered by the same qualified investigator, at approximately the same time (early in the morning).

The primary measurement for efficacy in this study is the score on the motor examination section (Part III). It will be obtained at baseline and Months 3, 6, and 9.

7.1.2 Secondary Efficacy Measurements

7.1.2.1 Total Score on the Unified Parkinson's Disease Rating Scale

The total score derived from all of the MDS-UPDRS subscale scores will be obtained at baseline and Months 3, 6, and 9.

7.1.2.2 Other Scores on the Unified Parkinson's Disease Rating Scale

The individual scores derived from the MDS-UPDRS Part I (non-motor experiences of daily living), Part II (motor experiences of daily living), and Part IV (motor complications) as well as the combined score from Parts II and III will be obtained at baseline and Months 3, 6, and 9.

7.1.2.3 Montreal Cognitive Assessment Test

The Montreal Cognitive Assessment (MoCA) test is a rapid screening instrument (administration time around 10 minutes) for the detection of mild cognitive dysfunction. It is used to assess the following cognitive domains: short-term memory recall, visuospatial abilities, executive functions, attention, concentration, working memory, language, and orientation to time and place. The full version of the scale will be used in this study.

The MoCA will be completed at baseline and Months 3, 6, and 9. It is always to be administered by the same qualified investigator, at approximately the same time (early in the morning).

7.1.2.4 Oxidative Stress Biomarkers

Free radicals, oxygen-containing molecules with one or more unpaired electrons, are highly reactive with other molecules and will appropriate their electrons in order to become stabilized; this triggers a chain of reactions as each target molecule in turn seeks to appropriate an electron from another, and can result in serious damage to cell components including lipids, proteins, and DNA. Antioxidants are molecules within cells that prevent these chain reactions by donating an electron to the free radicals without becoming destabilized themselves. When there is an imbalance between oxidants and antioxidants, i.e., when the production of free radicals surpasses a cell's ability to counteract or detoxify their harmful effects through neutralization by antioxidants, the result is oxidative stress. This condition is seen in various neurodegenerative disorders, including Parkinson's disease. Hence, measuring biomarkers that are indicators of oxidative stress may serve as a measure of progression or improvement of disease.

The oxidative stress biomarkers of total antioxidant status, protein carbonyls, glutathione, and super-oxide dismutase will be measured in a panel of blood/serum tests at baseline and Months 3, 6, and 9. The oxidative stress biomarkers of 8-OHdG and of malondialdehyde, which results from lipid peroxidation of polyunsaturated fatty acids, will be assessed in urine at these same time points.

7.1.2.5 Inflammatory Factor Biomarkers

Numerous studies have indicated the presence of an inflammatory process in PD. Hence, biomarkers of such processes may serve as a measure of worsening or improvement of disease.

The inflammatory factor biomarkers of TNF alpha and IL-6 will be measured in a panel of blood tests at baseline and Months 3, 6, and 9.

7.1.3 Exploratory Efficacy Measurements

Mechanism of Action (MOA) biomarkers will be examined to evaluate whether specific genotypes of enzymes that play a role in Parkinson's disease affect the potential disease-modifying action of deferiprone.

7.1.3.1 D544E (AT) Polymorphisms of Ceruloplasmin

Ceruloplasmin is a glycoprotein that plays a role in the oxidation of iron, oxidizing toxic ferrous iron (Fe2+) into ferric iron (Fe3+) and enabling iron transportation between blood and cells. The genotypes AT and AA determine whether an individual is a low or a high metabolizer of ceruloplasmin, respectively. Individuals with the AT genotype, who are low metabolizers, have lower ceruloplasmin ferroxidase activity, which may result in increased brain iron overload.

A blood sample for the determination of ceruloplasmin genotype will be taken at baseline.

7.1.3.2 Ceruloplasmin Levels and Ceruloplasmin Ferroxidase Activity

Blood samples for the measurement of ceruloplasmin levels and ceruloplasmin ferroxidase activity will be collected at baseline and Months 3, 6, and 9.

7.1.3.3 V158M Polymorphisms of Catechol O-methyltransferase

Catechol O-methyltransferase (COMT) is a metabolic enzyme that participates in the inactivation of dopamine and other neurotransmitters. The Val158Met (V158M) polymorphism of COMT is associated with Parkinson's disease.

A blood sample for the determination of the COMT genotype will be taken at baseline.

7.2 Safety Measurements

7.2.1 Medical Events, Adverse Events, and Serious Adverse Events

7.2.1.1 Definition of Medical Events and Adverse Events

Medical Event (ME): Any new untoward medical occurrence or worsening of a pre-existing condition in a clinical trial participant that occurs after signing the informed consent form (ICF) but before receiving the first dose of study drug.

Adverse Event (AE): 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., clinical 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

7.2.1.2 Monitoring and Documenting of Medical Events and Adverse Events

Prior to enrolling a patient, study site personnel will note the occurrence and nature of any medical condition(s) in the source documents and the appropriate section of the eCRF. During the study, they will note any change in the condition(s), and the occurrence and nature of any MEs/AEs. MEs will be collected from the time the ICF is signed until the first dose of study drug; non-serious AEs will be collected from the first dose until the final day of dosing; AEs that are still ongoing at the time of study termination will be followed until resolution or stabilization of the event or its sequelae; and serious AEs will be collected from the first dose until 30 days after the last dose of study medication.

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 MEs/AEs to the investigator or a delegate. In addition, the investigator will solicit information about the occurrence of MEs/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/MEs 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 MEs/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 the last dose of study medication 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 occurrence or notification by the patient, using the sponsor's SAE form. The sponsor will provide 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 per local policy, 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 a new SAE report form, indicated as follow-up, and signed and dated by the investigator.

The clinical research associate (CRA) will verify the original SAE report form against the source documents at the next monitoring visit.

7.2.1.8 Adverse Events of Special Interest

7.2.1.8.1 Neutropenia

Individuals taking deferiprone must be monitored for neutropenia, defined as a confirmed absolute neutrophil count (ANC) less than 1.5 x 10^9/L. Categories of neutropenia are as follows:

Category	Black Population	All Other Races
Mild	A confirmed ANC < 1.0 x 10^9/L but ≥ 0.65 x 10^9/L	A confirmed ANC < 1.5 x 10^9/L but ≥1.0 x 10^9/L
Moderate	A confirmed ANC < 0.65 x 10^9/L but ≥ 0.5 x 10^9/L	A confirmed ANC < 1.0 x 10^9/L but ≥ 0.5 x 10^9/L
Severe/agranulocytosis	A confirmed ANC < 0.5 x 10^9/L	

For a case of neutropenia to be confirmed, there must be 2 consecutive counts, a maximum of 3 days apart, that are both less than the specified value. If the 2 counts are not in the same severity category, a third count will be required to determine the severity. If a patient has just a single ANC value less than 1.5 x 10^9/L (< 1.0 x 10^9/L for a black patient), this is to be documented in the CRF as an AE of "decreased ANC", but is not to be defined as neutropenia. The investigator is to use judgment as to whether the decrease is clinically significant.

In addition to having ANC monitored, patients will be advised to immediately report any symptoms indicative of infection such as fever (≥ 38.5°C), sore throat, and flu-like symptoms at any time during treatment or during the first week following treatment. They will be

provided with an emergency services card with contact information, and advised to carry it with them at all times.

Depending of the severity of neutropenia, patients will either remain in or be withdrawn from the study. The management of different severities of neutropenia is described below.

Mild and moderate neutropenia:

A patient who develops either mild or moderate neutropenia is to interrupt treatment as soon as the neutropenia is confirmed, and ANC is to be monitored every 2 days until resolution.

The patient should re-initiate treatment once the event is resolved, defined as 2 consecutive ANC $\geq 1.5 \times 10^9$/L (ANC $\geq 1.0 \times 10^9$/L for a black patient). If ANC is still $< 1.5 \times 10^9$/L after 14 days, the investigator is to do the following:

- Withdraw patient from the study and monitor him/her until resolution of the event
- Advise patient regarding protective isolation
- Examine patient the same day (if possible), including drug history and physical examination
- Notify ApoPharma Inc. using the SAE form

Severe neutropenia/agranulocytosis:

A patient in whom a single ANC measurement $< 0.5 \times 10^9$/L is detected is to immediately stop treatment, without waiting for confirmation of the count, and a second measurement is to be done the following day. If the second ANC is still $< 0.5 \times 10^9$/L, the patient is to be permanently withdrawn from the study, and ANC is to be monitored daily until resolution. The following procedures should be done by the investigator or the treating physician, as appropriate:

- Provide protective isolation; if clinically indicated, admit patient to hospital and obtain vital signs every 4 hours
- Examine the patient the same day, if possible, including drug history and physical examination
- With the patient's consent, collect a blood sample to attempt to identify genetic or other biomarkers related to agranulocytosis
- Notify ApoPharma Inc. using the SAE form.

The following additional measures describe a suggested medical management and monitoring:

- If possible, consider obtaining bone marrow aspirate for:
    - Histology
    - Progenitor culture
    - Frozen storage (1 mL sample)
- If possible, consider obtaining bone marrow biopsy (minimum length 3 mm)
- Perform septic work-up including chest X-ray, blood, urine, and throat cultures
- Obtain q4h temperatures from patient (monitored by family at home if patient is not in the hospital)
- If warranted, administer granulocyte stimulating factors, such as G-CSF 10 µg/kg, on an in-patient basis if possible, beginning the same day that the ANC is confirmed as $< 0.5 \times 10^9$/L; administer daily until ANC is $> 1.5 \times 10^9$/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

7.2.1.8.2 Infections

If a patient develops fever (≥ 38.5°C) or any sign of infection during the study, deferiprone must be interrupted immediately, and neutrophil count should be obtained and monitored more frequently; every 2 days if ANC $<1.5 \times 10^9$/L (ANC $< 1.0 \times 10^9$/L for a black patient). Therapy with deferiprone can be re-initiated once all symptoms have been resolved and it is deemed safe by the investigator.

7.2.1.8.3 Decreased Serum Ferritin

As deferiprone is an iron chelator, treatment might decrease the levels of serum ferritin to a level that could fall below normal limits. The levels of serum ferritin will therefore be monitored during this study. A patient who is found to have low serum ferritin may be prescribed iron supplements, based on investigator judgment.

7.2.2 Laboratory Measurements

Analyses will be performed at a central laboratory, with the exception of the weekly hematology assessments which may be performed at a local laboratory or, with sponsor approval, at the patient's home by a visiting study nurse. Investigators must interpret each report promptly (preferably within 24 hours) and must document their review by signing or initialing and dating it. Any laboratory values that fall outside a clinically accepted range, or that differ significantly from previous values, must be assessed for clinical significance, and

must be marked by the investigator as either "CS" (clinically significant) or "NCS" (not clinically significant). Any clinically significant abnormalities or changes that are not part of a larger medical condition that is already recorded must be further explained on the laboratory report and documented as an adverse event in the eCRF.

The following laboratory tests will be performed:

Hematology: hemoglobin, total WBC count, ANC, MCV, and platelet count	Screening and weekly after start of dosing until Month 9
Blood chemistry: Total protein, GGT, lactate dehydrogenase (LDH), sodium, potassium, chloride, fasting glucose, bilirubin (total, direct, and indirect), AST, ALT, albumin, blood urea nitrogen, calcium, creatinine, uric acid, alkaline phosphatase, amylase, serum ferritin, blood iron, zinc, and copper	Screening and each visit after start of dosing until Month 9
Urinalysis: pH, specific gravity, glucose, protein, ketones, blood, and (if indicated by the dipstick results), sediment microscopy. If there is blood in the urine or three or more "plus signs" for protein, samples must be sent for microscopy.	Screening and Months 3, 6, and 9
Pregnancy testing (women of childbearing potential only): Both urine and serum tests at baseline; only serum test at each other time point	Each visit

7.2.3 Other Safety Measurements

7.2.3.1 Physical Examination

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), and skin, nails, hair, and scalp. Examinations will be performed at screening, baseline, and Months 2, 4, 6, and 9. Any clinically significant abnormalities noted prior to the screening visit will be recorded as medical history, any noted between screening and the first dose of study medication will be recorded as medical events, and any that are noted post–Dose 1 will be recorded as AEs.

Body weight (without shoes) will be measured at screening and Month 9. Height will be measured at screening only.

7.2.3.2 Vital Signs

Supine and standing heart rate, supine and then standing blood pressure, and body temperature will be taken. Blood pressure should always be measured 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. At the Day 0 visit (baseline), 3 sets of orthostatic vital signs (pulse and blood pressure), first in the supine and then in the standing position, are to be conducted prior to start of treatment, with 10- to 30-minute intervals between measurements. A single set of measurements is to be performed at all other time points.

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 screening and Month 9. At a minimum, the following parameters will be assessed: HR, PR, QRS, QT, QTcF, and QTcB. The results will be interpreted by the investigator, and the overall interpretation will be documented.

7.2.3.4 Columbia Suicide Severity Rating Scale

Current guidelines for clinical trials of investigational neurological drugs call for the prospective assessment of suicidal ideation and behavior, whereby the physician actively queries the patient rather than relying on the patient to report any occurrences spontaneously. The Columbia Suicide Severity Rating Scale (C-SSRS) is designed to track suicidal adverse events across a treatment trial. The scale assesses a range of ideation and behavior, as well as intensity of ideation. The Baseline/Screening version of the scale will be used at baseline, and the Since Last Visit version will be used at post-baseline visits.

The C-SSRS will be completed at each visit from baseline to Month 9 by the qualified investigator or delegate.

7.2.3.5 Concomitant Medications

The following information about prior and concomitant medications is to be recorded:

- All medications used within the 3 months prior to screening
- Any medications that the patient continues to take during the study
- Any medications that the patient starts to take during the study

The name, dose, route, frequency, indication, and stop and start dates of all medications used during the study must be noted in the source documents and eCRFs, as well as whether or not the medication was used to treat an AE.

Information on concurrent medications will be obtained at every site visit and at the follow-up telephone call.

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 is to 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.

7.3 Pharmacokinetics Measurements

7.3.1 Collection of Samples

Blood (5 mL at each time point) and cerebrospinal fluid (0.5–1.0 mL) for analyses of deferiprone and deferiprone 3-O-glucuronide will be collected. Details on sample collection will be provided in a separate laboratory manual.

All patients: At baseline and Month 3, a total of 3 blood samples will be collected: pre-dose, at 2 hours post-dose (± 45 minutes), and at 4 hours post-dose (± 45 minutes), with a minimum of 1 hour between samples.

Note: For the subset of 18 patients who have agreed to undergo CSF sampling, the post-dose blood samples at Month 3 will be taken at 2 hours (± 15 minutes) and 4 hours (± 15 minutes) post-dose, to be aligned with the timing of the CSF samples.

Subset of 16 patients: At Month 1, a total of 18 blood samples per patient will be collected: pre-dose and at 0.25, 0.5, 0.75, 1.0, 1.33, 1.66, 2.0, 2.33, 2.66, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, and 12.0 hours post-dose.

Subset of 18 patients: At Month 3, patients who agree to undergo a spinal tap will contribute one sample of CSF. Six of the 18 patients will provide this sample pre-dose, 6 will provide it at 2 hours post-dose (± 15 minutes), and 6 will provide it at 4 hours post-dose (± 15 minutes). The time of sample collection will be assigned prior to the Month 3 visit.

7.3.2 Processing of Samples

Details on the processing of blood and CSF samples will be provided in the laboratory manual.

8 STUDY COMMITTEES

An independent Data Safety Monitoring Board (DSMB) will be established to monitor the safety of patients during the course of the study. Members of the DSMB will be responsible for overseeing the conduct of the trial, and will be empowered to recommend stopping the trial if, in their judgment, continuation is not ethically acceptable on the grounds of safety.

Death or a life-threatening event in any study patient which is deemed by either the investigator or the sponsor to be at least possibly related to the study medication will trigger an evaluation by the DSMB for recommending stopping the study. Details will be provided in the DSMB charter. No study-stopping decision will be made without prior consultation with the sponsor.

The operating model and the frequency of the interim safety review meetings will be laid out in the DSMB charter. The DSMB will be constituted prior to the enrolment of any patients into the study, and its members will be notified of any changes to the protocol or the study conduct. The DSMB will be informed of any substantive changes to the protocol that could affect patient safety prior to their implementation.

9 STATISTICAL ANALYSIS

9.1 Endpoints

9.1.1 Primary Endpoint

The primary endpoint is the change from baseline to Month 9 in the motor examination subscale (Part III) of the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS).

9.1.2 Secondary Endpoints

- Change from baseline to Month 9 in the following measures:
    - Total score on the MDS-UPDRS
    - Scores on the individual subscales Part I (non-motor experiences of daily living), Part II (motor experiences of daily living), and Part IV (motor complications) of the MDS-UPDRS
    - Combined scores from Parts II and III of the MDS-UPDRS
    - Overall cognitive function, as assessed by the Montreal Cognitive Assessment (MoCA) test
    - Pharmacodynamics measures of the following oxidative stress biomarkers: total antioxidant status, lipid peroxidation (malondialdehyde), protein carbonyls, 8-OHdG, glutathione, superoxide dismutase
    - Pharmacodynamics measures of the following inflammatory factor biomarkers: TNF alpha and IL-6
- Time elapsed until the need for rescue medication

9.1.3 Exploratory Endpoints

The following Mechanism of Action (MOA) biomarkers will be examined to evaluate whether specific genotypes of enzymes that play a role in Parkinson's disease affect the potential disease-modifying action of deferiprone:

- D544E polymorphisms of the glycoprotein ceruloplasmin
- V158M polymorphisms of the enzyme catechol O-methyltransferase
- Ceruloplasmin levels (to be analyzed depending on the outcomes of the primary and/or secondary efficacy endpoints)
- Ceruloplasmin ferroxidase activity (to be analyzed depending on the outcomes of the primary and/or secondary efficacy endpoints)

9.1.4 Safety Endpoints

- Adverse events (AEs): Frequency, intensity, time to onset, duration, and relatedness to study drug
- Serious adverse events (SAEs): Frequency, intensity, time to onset, duration, and relatedness to study drug
- Number of discontinuations due to AEs
- Laboratory measures (hematology, blood chemistry, and urinalysis)

- ECG
- Change from baseline in vital signs (the average of the three sets of vital signs collected at the baseline visit will be considered the baseline value)
- Physical examination
- Assessment of suicidality (as per the Columbia Suicide Severity Rating Scale)

9.1.5 Pharmacokinetics Endpoints

The following PK parameters will be determined for deferiprone and its 3-O-glucuronide metabolite in the subset of patients who undergo extensive PK sampling:

- C_{max}
- T_{max}
- AUC_{0-t}
- $AUC_{0-\infty}$
- λ_Z
- $T_{½}$

The parameters of λ_Z, $T_{½}$, and $AUC_{0-\infty}$ will be determined only in patients in whom the log-linear terminal phase can clearly be defined. In addition, Cl_{tot}/F and V_D/F will also be determined for deferiprone.

9.2 Determination of Sample Size and Study Power

There is no formal sample size and power calculation. Based on preliminary data from other investigators, it is estimated that 28 subjects per dosage will be sufficient to provide meaningful assessment of each dosage for the study objectives.

9.3 Study Populations

Four study populations for analysis will be defined: Intent-to-Treat (ITT), Per-Protocol (PP), Safety, and Pharmacokinetics. All efficacy endpoints will be analyzed for the ITT population, which represents the primary analysis population. The primary efficacy endpoint will also be analyzed for the PP population, which represents the secondary analysis population.

9.3.1 Intent-to-Treat Population

The ITT population is defined as all randomized patients who received at least one dose of study drug and have a baseline and at least one post-baseline efficacy assessment. All efficacy endpoints will be analyzed for the ITT population.

9.3.2 Per Protocol Population

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

9.3.3 Safety Population

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

9.3.4 Pharmacokinetics Population

The Pharmacokinetics population will include all patients who have sufficient PK data to derive at least one PK parameter.

9.4 Data Analysis Plan

Separate statistical analysis plans (SAPs) will be prepared, one for the efficacy and safety analyses, and either one or two others for the pharmacokinetics and the pharmacokinetics/ pharmacodynamics analyses. The SAPs will detail the specifications given below, and will be approved prior to database lock. Any changes in the planned statistical methods will be documented in the final study report.

9.4.1 Planned Analyses

Data from all patients who were randomized to receive placebo will be combined into one group for the statistical analyses. Thus, there will be 5 treatment groups in the efficacy and safety analyses: placebo and 300 mg, 600 mg, 900 mg, and 1200 mg deferiprone.

9.4.1.1 Patient Disposition and Drug Exposure

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

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

9.4.1.2 Patient Characteristics

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

9.4.1.3 Analysis of Efficacy

The data on the change from baseline to each follow-up visit will be summarized by treatment group and overall, using descriptive statistics for each continuous efficacy endpoint. Frequency and proportion will be presented for each discrete efficacy endpoint. Analysis of variance (ANOVA) will be used to compare means, and Fisher's exact test will be used to compare proportions.

An analysis of covariance (ANCOVA) approach will be used for assessing the deferiprone effect on change from baseline to study end for all efficacy variables except time elapsed until rescue medication, with baseline value as a covariate, and treatment group and visit as the main factors in the model. Each deferiprone group will be compared to the placebo group to assess the treatment effect at each deferiprone dose level. Regression analysis will be employed to assess the dose-response relationship. If a statistically significant relationship exists between deferiprone dose and an efficacy outcome, the dose-response relationship will be assessed through pairwise comparison of each dose level to the next lower dose level: 1200 mg vs. 900 mg, 900 mg vs. 600 mg, and 600 mg vs. 300 mg.

For all efficacy data except time elapsed until rescue medication, missing data will be assumed to be missing at random (MAR), and a Mixed-Effect Model Repeated Measure (MMRM) model will be used as the primary analysis method to analyze the observed data. An appropriate sensitivity analysis will be performed to evaluate the robustness of the analysis results. Details will be provided in the SAP.

A time to event analysis will be performed to compare the time elapsed until the need for rescue medication among the treatment groups.

If efficacy is evidenced, exploratory analyses will be performed to study the role of MOA biomarkers on the efficacy endpoints. The appropriate analyses will be detailed in the SAP.

If the blinded review of the efficacy data performed before the breaking of the treatment codes indicates a severe non-normality of the data, an appropriate transformation (e.g., log transformation) will be applied to the data, or nonparametric statistical methods based on ranks will be employed, if warranted.

9.4.1.4 Analysis of Safety

All safety data collected will be presented in listings and summary tables to give an overview of the safety findings. For safety data analyses, no imputation of missing data will be performed; analyses will be based on observed cases.

Adverse Events

A summary table of adverse events (AEs) by treatment group 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
- Number of patients withdrawn
- Number of withdrawals due to AEs

Untoward medical occurrences, whether new events or worsening of severity or frequency of pre-existing conditions, will be coded using MedDRA (Medical Dictionary for Regulatory Activities), and will be summarized by treatment and by MedDRA system organ class (SOC) and preferred term (PT). An event will be considered an AE if 1) its start date is on or after the date of the first dose of study medication, 2) the start date is missing and the stop date is on or after the date of the first dose of study medication, or 3) both the start and the stop dates are missing. SAEs that begin within 30 days after the last dose of study medication, and both SAEs and non-serious AEs that are still ongoing for up to 30 days after the last dose, will be included in the database.

Adverse events will be summarized using the total number of events, 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 PT 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 of patients withdrawn and the reasons for withdrawal will also be presented.

To count the number of patients who experienced each AE, patients who experienced the same AE multiple times will only be counted once for the corresponding preferred term. Similarly, if a patient experiences multiple AEs within the same SOC, that patient will be counted only once for that SOC. AEs will be tabulated by presenting the SOCs alphabetically,

and within each SOC, the preferred term will be presented in decreasing order of the total number of patients who experienced each AE. In summaries presenting the incidence of AEs by severity, seriousness, and relation to study medication, a patient with multiple events coded to a given PT or SOC will be counted only once for that PT or SOC according to the most severe event, the most serious event, or the event with the closest relationship to study medication.

Listing of SAEs and listing of withdrawals due to AEs will be presented. Patient deaths will be listed separately, and will be described in narratives.

Vital Signs and Weight

Descriptive statistics (mean, median, standard deviation, minimum and maximum) will be presented at each visit for supine and standing heart rate, supine and standing blood pressure, body temperature, and weight. Data will also be presented graphically for examination of possible trends. Change from baseline in vital signs (at baseline, the values for orthostatic vital signs will be the average of the three sets collected) and weight will be assessed.

Electrocardiogram

The number and percentage of patients with normal and abnormal ECG results will be provided. Descriptive statistics will be presented for HR, PR, QRS, QT, QTcF, and QTcB.

Biochemistry, Hematology and Urinalysis

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 three categories at baseline versus end of treatment will be presented. Continuous data will also be presented graphically for examination of possible trends.

Clinically significant laboratory values will be reported in the adverse event analysis.

Concomitant Medications

Medications will be coded using the WHO Drug Dictionary. Medications taken during the course of the trial (on or after the first study drug dose and before or on the study termination date) will be considered as concomitant medications. Medications started after the study termination date will not be reported in tables, but will be presented in listings. Concomitant medications that were 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 certain 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.

Suicidality

Descriptive statistics will be presented for C-SSRS at each visit. Data will also be presented graphically for examination of possible trends.

9.4.1.5 Pharmacokinetics Analyses

The pharmacokinetics parameters will be summarized using descriptive statistics (arithmetic mean, SD, CV, median, minimum and maximum values). The power model will be used for assessing dose proportionality of AUC. Actual sampling times will be used for pharmacokinetic evaluations. Relationships will be assessed between the appropriate PK parameters and pharmacodynamics biomarkers through correlation analysis.

Additional pharmacokinetics analyses may be performed if deemed appropriate.

Detailed analyses on PK assessments and pharmacokinetics/pharmacodynamics assessments will be included in separate statistical analysis plans.

9.4.2 Interim Analyses

No interim analysis is planned.

9.5 Criteria for Evaluability of Patient Data

Statistical analysis will be based on the study populations defined in Section 9.3.

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. Patient data will be entered by the investigator or designee using the electronic Case Report Forms (eCRFs) provided by the sponsor. Clinical data will be entered and stored into a validated database. The eCRFs will be provided in the Electronic Data Capture (EDC) 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 current versions of 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 study monitor will verify the eCRFs on-line.

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

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

The database will be backed up daily.

10.2 Case Report Forms

Electronic CRFs may be generated and/or printed at any time using the sponsor's EDC 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 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
- Ensure that drug accountability is completed and 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

Following closure of the study, the investigator will maintain a copy of all site study records in a safe and secure location for at least 25 years or as specified in the Clinical Trial Agreement. 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 and other regulatory authority codes as applicable. 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 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 enrollment 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 IRB/IEC approval of the amended ICF is obtained before any additional patients are enrolled. 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, if available:
    - 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

Each investigator must sign a confidentiality agreement, in form and content satisfactory to the sponsor, concerning the protection of the sponsor's confidential and proprietary information disclosed to or obtained by the investigator during the course of the study. 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 OWNERSHIP

All data and records provided by the sponsor or its delegate or generated during the study (other than a patient's medical records) and all inventions discovered in the course of

conducting the study are the exclusive property of the sponsor. Details are provided in the Clinical Trial Agreement completed by the sponsor and the investigator and/or site.

17 PUBLICATION

Data derived from the study are the exclusive property of the sponsor, and the sponsor 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
Safety Analysis Laboratories	Eurofins Central Laboratory, LLC.	2430 New Holland Pike Building D, Suite 100 Lancaster PA 17601, USA Tel: +1 717 556 7350 Fax: +1 717 556 3888
	Eurofins Central Laboratory Breda	Eurofins Central Laboratory B.V. Bergschot 71 4817 PA Breda The Netherlands Tel: +31 76 57 37 373 Fax: +31 76 57 37 778
Pharmacokinetics and Biomarkers Analysis Laboratory	Algorithme Pharma Inc.	575, boul. Armand-Frappier Laval, Quebec Canada H7V 4B3 Tel: 1-450-973-6077 Fax: 1-450-973-2801
Genotyping Laboratory	PGXL Technologies	201 E. Jefferson St., Suite 309 Louisville, KY 40202, USA Tel: 1-502-569-1584 Toll-free: 1-877-564-2199 Email: info@pgxlab.com
Interactive Voice/Web Response System	ICON Clinical Research Ltd.	South County Business Park Leopardstown Dublin 18, Ireland Tel: +353 (1) 291 2000 Fax: +353 (1) 291 2700