ApoPharma Inc.

Long-term Safety and Efficacy Study of Ferriprox® for the Treatment of Transfusional Iron Overload in Patients with Sickle Cell Disease or Other Anemias

LA38-EXT

CLINICAL STUDY PROTOCOL (U.S. ONLY)

EudraCT Number:	2014-005685-30
IND Number	IND 045724
Investigational Product:	Deferiprone
Development Phase:	Phase IV
Indication Studied:	Transfusional iron overload in patients with sickle cell disease or other anemias
Study Design:	Multi-center, 2-year prospective, single-arm, open-label extension study
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
Sponsor's Representative:	Fernando Tricta, MD Vice President, Medical Affairs Tel: 1-416-401-7332 Fax: 1-416-401-3867
Version and Date of Protocol:	Version 3.1, 01 MAY 2017

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SIGNATURE PAGES

Sponsor

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

Study Title:	Long-term Safety and Efficacy Study of Ferriprox® for the Treatment of Transfusional Iron Overload in Patients With Sickle Cell Disease Or Other Anemias
Study Code:	LA38-EXT
Version Number:	3.1
Version Date:	01 MAY 2017

Caroline Fradette, PhD
Director of Clinical Research, ApoPharma Inc.

03 May 2017
Date (DD MMM YYYY)

Anna Rozova, MD
Director of Medical Safety, ApoPharma Inc.

03 May 2017
Date (DD MMM YYYY)

Yu Chung Tsang, PhD
Chief Scientific Officer, Biopharmaceutics & Biostatistics, Apotex Inc.

04 MAY 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:	Long-term Safety and Efficacy Study of Ferriprox® for the Treatment of Transfusional Iron Overload in Patients With Sickle Cell Disease Or Other Anemias
Study Code:	LA38- EXT
Version Number:	3.1
Version Date:	01 MAY 2017
Name of Principal Investigator:	
Name of Study Site:	
Location of Study Site: *(City, region/province/state, country)*	

Signature

Date (DD MMM YYYY)

SYNOPSIS

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

Title of study:	Long-term safety and efficacy study of Ferriprox® for the treatment of transfusional iron overload in patients with sickle cell disease or other anemias
Study code:	LA38-EXT
Phase of development:	Phase IV
Objectives:	**Primary:** To evaluate the long-term safety and tolerability of deferiprone in iron-overloaded patients with sickle cell disease or other anemias **Secondary:** To evaluate the efficacy of deferiprone in the treatment of iron overload in patients with sickle cell disease or other anemias who have received deferiprone for up to 3 years
Study design:	LA38-EXT is a 2-year prospective, multi-center, single-arm, open-label extension of study LA38-0411. All patients who complete the earlier study will be offered the opportunity to continue in the extension study, with the final visit of LA38-0411 being Visit 1 of LA38-EXT. Patients who had been treated with deferiprone during LA38-0411 (Group 1) will continue to receive deferiprone for an additional 2 years, while those who had been treated with deferoxamine (Group 2) will be switched to deferiprone. Dosage will be 25–33 mg/kg three times a day (t.i.d.). All patients will visit the site quarterly for assessments of safety and efficacy for up to 2 years. Patients in Group 1 will additionally have blood counts monitored monthly, while those in Group 2 will have them monitored weekly for the first 6 months, biweekly for the next 6 months, and monthly thereafter.
Duration of participation:	The duration of participation in the extension study for each patient (i.e., first visit to last visit) will be approximately 2 years.
Criteria for evaluation:	**Safety:** • Adverse events (AEs): Frequency, severity, time to onset, duration, and relatedness to study product • Serious adverse events (SAEs): Frequency, severity, time to onset, duration, and relatedness to study product • Number of discontinuations due to AEs **Efficacy:** The time points for the efficacy assessments are defined below. Since the baseline measures are by definition those taken prior to the start of deferiprone

Criteria for evaluation (cont'd):	therapy, "baseline" is defined differently for the two groups, as follows: • **Group 1:** For patients who received deferiprone in LA38-0411, the baseline visit of that study will be treated as the baseline visit of LA38-EXT as well. Thus, Week 0 of the extension study will be Year 1 (i.e., the completion of one year of deferiprone treatment), Week 52 will be Year 2, and Week 104 will be Year 3. • **Group 2:** For patients who received deferoxamine in LA38-0411, the start of the extension study (Week 0) will be treated as the baseline visit. For this group, therefore, Week 52 will be Year 1, and Week 104 will be Year 2. Efficacy endpoints are provided below. For Group 1, the change from baseline to Year 1 is derived from study LA38-0411. For Group 2, there is no Year 3 of deferiprone treatment. • The change from baseline to Year 1 (both groups; Group 1 data are from LA38-0411), from baseline to Year 2 (both groups), and from baseline to Year 3 (Group 1 only) in liver iron concentration (LIC), as measured by magnetic resonance imaging (MRI) • The change from baseline to Year 1 (both groups; Group 1 data are from LA38-0411), from baseline to Year 2 (both groups), and (Group 1 only) from baseline to Year 3 in cardiac MRI T2* • The change from baseline to Year 1 (both groups; Group 1 data are from LA38-0411 data), from baseline to Year 2 (both groups), and from baseline to Year 3 (Group 1 only) in serum ferritin • Responder analysis, defined as the percentage of patients who show a ≥20% decline from baseline in LIC or serum ferritin or a ≥20% increase from baseline in cardiac MRI T2* at Year 1 (both groups; Group 1 data are from LA38-0411), at Year 2 (both groups), and at Year 3 (Group 1 only)
Number of patients:	In the LA38-0411 study, a planned total of 300 patients will be randomized to receive 1 year of treatment with either deferiprone or deferoxamine. All patients who complete that study will be invited to enroll in the extension study.
Main criterion for inclusion:	Completed study LA38-0411
Investigational product:	Product: Ferriprox® (deferiprone) 500 mg tablets or deferiprone 80 mg/mL oral solution Dose: 25–33 mg/kg t.i.d. Mode of administration: Oral
Schedule of treatment and specimen collection:	All patients will be scheduled to take deferiprone daily, 3 times a day, for up to 2 years. Safety and efficacy assessments will be conducted at the following time points: • Hematology: o Group 1: Monthly up to Visit 9 (End of Study) or the Early

Schedule of treatment and specimen collection (cont'd):	Termination visit o Group 2: Weekly up to Visit 3 (Week 26), then biweekly up to Visit 5 (Week 52), then monthly up to Visit 9 (End of Study) or the Early Termination visit • Biochemistry: Visit 1 and semi-annually up to Visit 9 or the Early Termination visit • Serology: Visits 1 and 9 • Serum ferritin: Visit 1 and quarterly up to Visit 9 or the Early Termination visit • Liver MRI scan: annually, at Visits 1, 5, and 9 or Early Termination visit • Cardiac MRI T2* scan: annually, at Visits 1, 5, and 9 or Early Termination visit
Statistical methods:	<u>Safety Analysis</u> The incidences of AEs and SAEs reported from the start of deferiprone therapy for all patients will be tabulated. For patients continuing on deferiprone, this time period will be from the start of LA38-0411 to the completion of LA38-EXT; while for those switching to deferiprone, it will be from the start of LA38-EXT to the completion of LA38-EXT. AEs will be summarized by worst severity and by relationship to the study medication. Time to onset and duration of all SAEs, of AEs of special interest such as neutropenia, agranulocytosis, increased ALT, and arthralgia, and of additional AEs that will be determined at the end of LA38-0411, will be analyzed as follows: 1) the mean time to the first onset and the mean time to the last recurrence will be calculated, and 2) the mean duration for the first episode and the mean duration for any recurrent episodes, excluding the first episode, will be calculated for all SAEs and such AEs. The percentage of discontinuations due to AEs will be calculated, and the AEs leading to discontinuation will be summarized in a frequency table. Laboratory data (hematology and chemistry) will be summarized using descriptive statistics for continuous variables and frequency tables for discrete variables. The incidences of out-of-range data that are seen for two consecutive measures will be tabulated, and the changes from baseline to the end of study will be presented in shift tables. <u>Efficacy Analysis</u> Changes in LIC, in cardiac MRI T2*, and in serum ferritin from baseline to Year 1(both groups; Group 1 data are from LA38-041), from baseline to Year 2 (both groups), and from baseline to Year 3 (Group 1 only) will be summarized with descriptive statistics, and will be tested against no change using a one-sample t-test. The changes in these 3 efficacy measures from the start of deferiprone therapy to the last visit of LA38-EXT in all patients, irrespective of whether deferiprone therapy was initiated in LA38-0411 or in LA38-EXT, will also be tested using a one-sample t-test. In addition, the percentages of responders will be tabulated for Year 1 (both groups; Group 1 data are from LA38-0411), for Year 2 (both groups), and for Year 3 (Group 1 only) of

	deferiprone therapy. Additional statistical analysis may be performed if deemed necessary. Details will be provided in the statistical analysis plan.
Version and date of the protocol:	Version 3.1, 01 MAY 2017

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
AF	assent form
ANCOVA	analysis of covariance
CS	clinically significant
CI	confidence interval
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
eCRF	electronic case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Hb	hemoglobin
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
NCS	not clinically significant
OCRDC	Oracle Clinical Remote Data Capture
PDR	Patient Data Report
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SCD	sickle cell disease
TEAE	treatment-emergent adverse event
t.i.d.	three times daily
ULN	upper limit of normal
WHO	World Health Organization

1 INTRODUCTION

1.1 Background

Pursuant to the Accelerated Approval of Ferriprox by the FDA in October 2011, ApoPharma Inc. committed to conduct a confirmatory trial of Ferriprox (deferiprone) in transfused patients, focusing primarily on those with sickle cell disease (SCD). Study LA38-0411, currently in progress, is a 52-week, prospective, multi-center, 2-arm, randomized, parallel, open-label trial comparing deferiprone therapy to deferoxamine therapy. Once patients in that trial have completed the last study visit (Week 52), they will be invited to enroll in LA38-EXT, a 2-year extension study in which all participants will receive deferiprone.

1.1.1 Sickle Cell Disease

SCD is an inherited hemoglobinopathy determined by combinations of 2 abnormal alleles of the beta globin gene, among which at least one carries the beta6 glu-val mutation.[(1)] The disease is clinically silent until expression of the gamma genes is substituted by expression of the beta genes, at between 3 and 9 months of age. There is a varied phenotypic expression as a result of diverse genetic and environmental factors.

Hemoglobin is the iron-containing oxygen-transport metalloprotein in red blood cells (RBCs) responsible for tissue oxygenation. Normal RBCs contain mainly hemoglobin A, while individuals with sickle cell conditions have the genetic variation hemoglobin S (HbS). RBCs that contain mostly HbS do not survive as long as normal RBCs; typically about 16 days, compared to about 120 days for normal cells.[(1)] RBCs containing HbS can become crescent (sickle) shaped, leading to loss of their mobility and flexibility.[(2)] As a result, they have difficulty passing through small blood vessels. This in turn leads to blood-cell agglomeration, impeding the circulation of blood and delivery of oxygen to vital tissues and organs.[(2)] Tissue that does not receive a normal blood flow eventually becomes ischemic.[(3)] The anemia and blockage of blood flow result in a variety of problems, such as sickle cell crisis (severe pain), susceptibility to infection, priapism, skin ulcers, acute chest syndrome, acute splenic sequestration, pulmonary disease, renal and hepatic dysfunction, and cerebrovascular disease, ultimately causing premature death.[(3,4)] Abnormal cardiac findings, with the notable development of a progressive proliferative systemic vasculopathy, pulmonary hypertension, and left ventricular diastolic dysfunction, are also present in most patients with SCD and are primarily the result of chronic anemia, cardiac chamber dilation, and compensatory increase in left and right ventricular mass.[(5,6)]

Some SCD patients undergo transfusions to improve blood rheology by replacing sickled RBCs with normal RBCs. Blood transfusions have been indicated for the prevention and treatment of vaso-occlusive complications such as painful crisis, stroke, acute chest syndrome, acute multi-organ failure, acute splenic sequestration, and medical intervention (preoperative preparation).[7]However, while chronic blood transfusions can reduce the incidence of sickle cell–induced morbidity and mortality, repeated transfusions result in progressive accumulation of iron in the blood.[8] Excess iron accumulates in organs, particularly the liver and endocrine glands, generating iron-induced morbidity and eventually causing premature death if left untreated.[9] A study in transfusion-dependent patients with SCD demonstrated increased iron deposition, with mean liver iron of 13.68 mg/g dry weight (range of 2.9 to 26.19 mg/g dry weight) and peak mean serum ferritin of 4614 ± 1989 µg/L over a transfusion period of 57 ± 35 months (range 12 to 146 months).[10]

In the sickle cell centers of the Cardeza Foundation and Thomas Jefferson University Hospital, approximately 50% of the patients with SCD admitted to the hospital received an average of 10 units of RBCs per year; of these, 17% to 37% developed iron overload. Compared to the non-iron-overloaded group, the iron-overloaded patients with serum ferritin level >1,500 µg/L and transferrin saturation >50% had a higher incidence of painful episodes per year (64% vs. 38%), organ failure (71% vs. 19%), and mortality (64% vs. 5%). Patients who died had significantly higher mean levels of serum ferritin than those who survived (2379 versus 597 µg/L, $p<0.05$). The results of this study indicate that iron overload is a determinant of morbidity and mortality in adult patients with SCD.[9]Results from a natural history study demonstrated that the unadjusted death rate of transfused patients with SCD (7.0/100 person years) was even higher than in patients with thalassemia (2.2/100 person years).[11] Iron metabolism and trafficking in patients with SCD have some distinctive characteristics. The high levels of inflammatory cytokines in SCD may enhance macrophage/reticuloendothelial cell iron and/or renal cell iron retention. This makes tissues that retain iron different in SCD, and thus the organs that fail due to excess iron load in patients with SCD are somewhat different from those of patients with thalassemia.[12] Indeed, unlike thalassemia patients, cardiac iron overload is not frequently observed in patients with SCD.[13] Nonetheless, cardiac siderosis does occur in some SCD patients who have been transfused for more than 10 years.[14] Care for SCD now commonly uses transfusion, which potentially results in iron overload and necessitates chelation.[12]

1.1.2 Ferriprox®

Ferriprox (deferiprone; active ingredient 3-hydroxy-1,2-dimethylpyridin-4-one) is a bidentate iron chelator that preferentially binds trivalent iron (Fe3+) in a 3:1 (deferiprone : iron) complex.

Its effectiveness has been assessed by urinary iron excretion, sequential measurements of serum ferritin levels, iron concentration in the liver and in the heart, and clinical outcomes such as the ability to prevent iron-induced cardiac disease and prolong survival in transfused patients with thalassemia. Ferriprox was first approved in 1999 by the European Medicines Agency (EMA), and is currently approved in more than 60 countries. In the USA, it was approved in 2011 by the Food and Drug Administration (FDA) for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate.

1.2 Rationale

ApoPharma Inc. is currently conducting a 12-month trial, study LA38-0411, to assess the safety and efficacy of deferiprone in patients with SCD or other anemias that necessitate regular blood transfusions (excluding thalassemia syndromes, MDS, myelofibrosis, Diamond Blackfan anemia, and primary bone marrow failure). In that study, a planned 300 participants will be randomized in a 2:1 ratio to receive either deferiprone or deferoxamine. Assessments include weekly, biweekly, or monthly monitoring of absolute neutrophil count (ANC); monthly assessments of adverse events, hematology, biochemistry, and vital signs; quarterly assessments of serum ferritin; and semi-annual serology, ECG, liver iron concentration (LIC) as measured by MRI, cardiac MRI T2*, and quality-of-life questionnaires.

Patients who complete study LA38-0411will be invited to enroll in the current study, LA38-EXT, in which all participants will receive deferiprone. Participants will thus receive deferiprone for a total of either 2 years or 3 years, depending on which treatment was assigned in the earlier study. The long-term data obtained will provide additional information on the safety and efficacy of deferiprone in patients with sickle cell disease or other anemias.

1.3 Potential Risks and Benefits

The safety profile of deferiprone in patients with thalassemia has been extensively characterized. Apart from chromaturia, which is due to iron excretion and is harmless, the most commonly reported adverse events seen in clinical trials have been nausea, vomiting, abdominal pain, increased alanine aminotransferase, arthralgia, and neutropenia. Comprehensive safety information is provided in the US full prescribing information (USPI) and the Investigator's Brochure.

The most significant serious adverse event (SAE) associated with deferiprone use is agranulocytosis, defined as a confirmed absolute neutrophil count less than 0.5×10^9/L. In

pooled clinical trials, the incidence of agranulocytosis was approximately 2% of patients. The mechanism of deferiprone-associated agranulocytosis is unknown. Agranulocytosis and neutropenia usually resolve upon discontinuation of deferiprone, but there have been some post-marketing reports of agranulocytosis leading to death.

Because of the awareness of this risk, weekly monitoring for neutrophil count was proposed in the first marketing authorization application for deferiprone and has been in effect since. However, a recent review of both clinical and post-marketing data accumulated over the last two decades confirmed that deferiprone-induced agranulocytosis is not dose-related within the therapeutic range, and its occurrence peaks at 5 months after initiation of therapy, declining in frequency after this period.[15] It was concluded that weekly monitoring is a prudent approach but that it does not preclude agranulocytosis from occurring and it could even provide false security, as agranulocytosis could occur shortly after the finding of a normal neutrophil count. The relevance of weekly monitoring of the neutrophil count appears to decrease even further after the first six months of therapy, when agranulocytosis occurs less often. Based upon analysis of data collected over the past 20 years, it appears that patient education may be the key to minimizing risks associated with agranulocytosis during deferiprone therapy. A better approach to minimizing the risks in patients receiving long-term deferiprone therapy is for ANC monitoring to be done weekly only at the beginning of the treatment and to emphasize the importance of educating patients on the need to immediately stop deferiprone and to maintain ANC monitoring upon signs of infection. Based on the conclusions of this review, the frequency of monitoring in this study is reduced: patients who have already been on deferiprone for 12 months in the earlier study, LA38-0411, will now only need to undergo hematology testing monthly, while those who had been on deferoxamine and are now receiving deferiprone for the first time will have their neutrophil count monitored weekly for the first 6 months, biweekly for the next 6 months, and monthly thereafter. Neutropenia management directives (as per Section 7.2.1.8) must be followed at the first sign of neutropenia. Treatment with deferiprone should not be initiated in patients with a history of recurrent neutropenia or an episode of agranulocytosis.

The most common adverse reactions (adverse events assessed as at least possibly related to deferiprone use) seen among the 712 patients treated with deferiprone in ApoPharma clinical trials carried out for the indication of systemic iron overload are listed in the table below. For detailed information on adverse events (AEs) associated with deferiprone, see the Investigator's Brochure. [16]

Adverse drug reactions occurring in ≥ 1% of 712 deferiprone-treated patients

System Organ Class Preferred Term	Patients n (%)
Blood and lymphatic system disorders	
Neutropenia	49 (6.9)
Agranulocytosis	15 (2.1)
Gastrointestinal disorders	
Nausea	89 (12.5)
Vomiting	69 (9.7)
Abdominal pain upper	39 (5.5)
Abdominal pain	23 (3.2)
Diarrhoea	21 (2.9)
Dyspepsia	13 (1.8)
Abdominal discomfort	10 (1.4)
Investigations	
Alanine aminotransferase increased	54 (7.6)
Neutrophil count decreased	50 (7.0)
Weight increased	12 (1.7)
Aspartate aminotransferase increased	11 (1.5)
Metabolism and nutrition disorders	
Increased appetite	26 (3.7)
Decreased appetite	8 (1.1)
Musculoskeletal and connective tissue disorders	
Arthralgia	75 (10.5)
Back pain	13 (1.8)
Pain in extremity	12 (1.7)
Arthropathy	9 (1.3)
Nervous system disorders	
Headache	17 (2.4)
Renal and urinary disorders	
Chromaturia	95 (13.3)

Data cut-off date: 31 August 2014

Currently, deferoxamine and deferasirox are the only iron chelators licensed for use in patients with sickle cell disease. The benefit to participants in this trial is that they will have the option of being treated with a third chelator.

2 STUDY OBJECTIVES

2.1 Primary Objective

To evaluate the long-term safety and tolerability of deferiprone in iron-overloaded patients with sickle cell disease or other anemias. The endpoints for the primary objective are provided in Section 9.1.1.

2.2 Secondary Objective

To evaluate the efficacy of deferiprone in the treatment of iron overload in patients with sickle cell disease or other anemias who have received deferiprone for up to 3 years.

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

3 STUDY DESIGN

3.1 Description of Study Design

LA38-EXT is a 2-year prospective, multi-center, single-arm, open-label extension of study LA38-0411. All patients who complete the earlier study will be offered the opportunity to continue in the extension study, with the final visit of LA38-0411 being Visit 1 of LA38-EXT. Patients who had been treated with deferiprone during LA38-0411 (Group 1) will continue to receive deferiprone for an additional 2 years, while those who had been treated with deferoxamine (Group 2) will be switched to deferiprone. Dosage will be 25–33 mg/kg three times a day (t.i.d.).

Patients will have blood counts monitored regularly (monthly throughout the study for patients in Group 1; weekly for the first 6 months, biweekly for the next 6 months, and monthly thereafter for patients in Group 2), and will visit the site quarterly for assessments of safety and efficacy for up to 2 years. The schedule of study procedures is shown in Table 5.1, and details are provided in Section 5.1.

3.2 Rationale for Study Design

This single-arm, open-label extension study design has been primarily chosen to gather information on the safety and efficacy of deferiprone in iron-overloaded patients with SCD or other anemias who have been treated with this chelator for up to 3 years.

3.3 Rationale for Selection of Doses

The dosage of deferiprone for each patient will be between 25 and 33 mg/kg t.i.d., for a total daily dose of 75 to 99 mg/kg. This is the approved therapeutic dose range, and the same as

that being used in study LA38-0411.

Dosing will be as follows:

- Patients who were treated with deferiprone in LA38-0411 will continue on the same dosing regimen in LA38-EXT, unless there has been less than 10% improvement in the last 6 months in at least one of the measures indicative of iron overload (serum ferritin, LIC, or cardiac MRI T2*), in which case the dose can be increased up to 33 mg/kg t.i.d. for patients who were receiving lower doses. If a patient who is already at that dose level is not showing improvement but has consented to participate in the extension study, he/she must remain at 33 mg/kg t.i.d. since that is the maximum permitted.

- For patients who were treated with deferoxamine in LA38-0411, the initial dose of deferiprone will be 15 mg/kg t.i.d. through Week 1, increasing to 20 mg/kg t.i.d. at Week 2 and then to 25 mg/kg t.i.d. at Week 3. It may be further increased to up to a limit of 33 mg/kg t.i.d. if any of the following is true:
  - Transfusional iron input > 0.3 mg/kg/day in the 3 months prior to Visit 1
  - Serum ferritin ≥2500 µg/L at Visit 1
  - LIC ≥15 mg/g dry weight at Visit 1
  - Cardiac T2* ≤ 20 ms at Visit 1

  Since the Visit 1 results for the above parameters may not be immediately available, the dosage beyond Week 3 cannot be confirmed at the time when the first supply of drug is dispensed. Details of how dispensing is to be handled at Visit 1 are provided in Section 5.1.

- For any patient, the dose can be increased up to a limit of 33 mg/kg t.i.d. if any of the following is true:
  - At any time during the trial if mean daily transfusional iron input increases to more than 0.3 mg/kg body weight for at least 3 consecutive months
  - If in the past 6 months there has been less than 10% improvement in at least one of the measures indicative of iron overload (serum ferritin, LIC, or cardiac MRI T2*)

- For any patient, the dose can be decreased at any time during the trial based on assessment of safety markers for adverse reactions that are possibly dose dependent (e.g., gastrointestinal upset, increases in serum liver enzyme levels, and arthropathies).

4 STUDY POPULATION

4.1 Number of Patients

A total of 300 patients are planned to be enrolled in study LA38-0411, and all patients who complete that study will be invited to enroll in the extension study.

4.2 Inclusion Criteria

Patients will be eligible to enroll in study LA38-EXT if they meet **all** the following criteria:

1. Completed study LA38-0411
2. Females of childbearing potential must have a negative pregnancy test result at Visit 1. In addition, if applicable, they must:
    - Use an effective method of contraception according to local requirements, during the study and within 30 days following their last dose of study medication, OR
    - Have had a tubal ligation (supporting evidence required), OR
    - Have had a hysterectomy (supporting evidence required), OR
    - Participate in a non-heterosexual lifestyle, OR
    - Have a male sexual partner who has been sterilized (supporting evidence required)
3. Fertile heterosexual males and/or their partners must agree to use an effective method of contraception during the study and for 30 days following the last dose of study medication
4. All patients and/or their authorized legal representatives must provide signed and dated written informed consent prior to the first study intervention, and assent will be obtained from patients who are considered to be minors. Patients must be able to adhere to study restrictions, appointments, and evaluation schedules.

4.3 Exclusion Criteria

Patients will be excluded from enrollment in study LA38-EXT if they meet **any** of the following criteria:

1. Plan to participate in another clinical trial at any time from the day of enrollment until 30 days post-treatment in the current study
2. For only those patients who were treated with deferoxamine in study LA38-0411 (Group 2): Presence of any medical condition (including clinically significant laboratory abnormalities, such as ALT $\geq$ 5 x ULN or creatinine $\geq$ 2 x ULN), psychological condition, or psychiatric condition which in the opinion of the investigator would cause participation in the study to be unwise.

3. Pregnant, breastfeeding, or planning to become pregnant during the study period.
4. Treatment failure after 1 year on deferiprone which in the investigator's judgment indicates the need for the patient to be started on a different iron chelator

4.4 Enrolment Violations

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

4.5 Patient Withdrawal

Patients have the right to withdraw from the study at any time and for any reason without consequence to future care by the investigator or study center.

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

- Medical or safety reasons considered significant by the patient and/or the investigator
- Requirement for concomitant medication that might interfere with the evaluation of study treatment or may be contraindicated
- Receipt of a rescue medication
- Occurrence of other illnesses that might affect the patient's further participation in the study or evaluation of study treatment
- A protocol deviation that might interfere with study assessments, as judged by the investigator
- Repetitive patient non-compliance with the protocol or with instructions of the investigator
- Participation in another clinical trial at any time during the conduct of this study
- Any other situation where, in the opinion of the investigator, continuation of the study would not be in the best interest of the patient

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

- Pregnant or planning to become pregnant (see Section 7.2.4, Procedures in Case of Pregnancy)

- Occurrence of any adverse event characterized as life-threatening or disabling that is not associated with the patient's condition
- A confirmed ANC < 0.5 x 10^9/L. (For the potential withdrawal of patients with ANC between 0.5 and 1.5 x 10^9/L, see Section 7.2.1.8.)

- Non-compliance with blood counts:
  - Group 1: Missing 2 consecutive monthly blood counts will result in automatic withdrawal. If a patient misses one of the scheduled quarterly visits at which hematology testing would normally be done, an unscheduled visit for hematology testing must be completed within 10 days of the missed visit.
  - Group 2: For the first 6 months, if a patient misses a weekly blood count visit, then missing a further 3 of the next 5 visits (i.e., a total of 4 out of 6) will result in automatic withdrawal. For the next 6 months, missing 3 consecutive biweekly blood counts will result in automatic withdrawal. For the remainder of the study, missing 2 consecutive monthly blood counts will result in automatic withdrawal. As with Group 1 patients, if a patient misses one of the scheduled quarterly visits, an unscheduled visit for hematology testing must be completed within 10 days of the missed visit.
- Termination of the study by the sponsor

Patients who decide to withdraw participation in the study should always be contacted, if possible, in order to ask about the reason for withdrawal, whether any adverse events (AEs) occurred, and use of concomitant medications. A withdrawn patient should return for an Early Termination Visit and a follow-up visit. All investigational product and materials should be returned. If any AEs occurred, the investigator must attempt to follow up the outcome for 30 days post-termination.

If a patient withdraws or is withdrawn before completing the study, the date and reason for the withdrawal must be entered on the source document and on the appropriate page of the case report form (CRF), and all other appropriate CRF 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 prior to study entry and prior to first administration of the study drug, and must agree to use an approved method of contraception (as defined in inclusion criterion # 2 throughout the course of the trial. 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

Male patients must inform the investigator if their 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 subject, 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

Not applicable. The only individuals eligible for enrollment are those who completed treatment in study LA38-0411.

4.5.3 Treatment Interruptions

Study medication will be interrupted for ANY of the following reasons:

Infection, fever, or decrease in ANC:

- If the patient develops an 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). Patients should be advised to report immediately to their physician any symptoms indicative of infection such as fever, sore throat, and flu-like symptoms. They will be provided with a thermometer, and instructed to seek immediate medical attention at a hospital or clinic if they experience fever (temperature >38.0° C/100.4°F). Body temperature may be measured at the mouth, axilla, or ear. Patients/legal guardians will be provided with an emergency services card with contact information, and will be advised to carry this card at all times. In presence of confirmed fever and/or infection, they will be required to have their neutrophil counts tested as soon as possible and no later than 24 hours after the symptoms of infection are detected. Therapy with deferiprone can be re-initiated once all symptoms have been resolved and it is deemed safe by the investigator.
- If temperature is >38.0°C/100.4°F and ANC is $\leq 0.5 \times 10^9$/L, the following must be done:
    - Commence therapy with antibiotics immediately (treatment should depend on the site of the suspected infection and on local antibiotic policy)
    - Perform a chest x-ray, and collect blood and other relevant cultures (if possible, collect culture samples before initiating antibiotics)

- If the patient develops moderate neutropenia while on deferiprone, therapy must be interrupted immediately and neutrophil count must be obtained and monitored every 2 days. Therapy with deferiprone can be re-initiated once two successive ANCs are >1.5 x 10^9/L and it is deemed safe by the investigator. The patient will be withdrawn from the study if the ANC remains <1.5 x 10^9/L by the end of a 2-week period (14 days).

For definitions of and further detail on the management of neutropenia, see Section 7.2.1.8.1.

Increase in ALT:

If a patient whose ALT level was normal at baseline is confirmed to have serum ALT levels ≥ 5 x ULN on 2 consecutive assessments, deferiprone treatment may be interrupted based on investigator judgment.

4.6 Prior and Concomitant Therapies

All medications taken from 3 months prior to Week 0 up to the end of the study (Week 104 or early termination) will be recorded and reviewed by the investigator. For medications that were ongoing at the final visit of LA38-0411, the site is to update the status if necessary during LA38-EXT (e.g., note if use of the medication stops).

Medications considered necessary for the patient's welfare may continue to be taken at the discretion of the investigator. All medications (including study product, herbal medications, and over-the-counter medications) and nutritional supplements must be recorded in the source document and the appropriate section of the eCRF. Patients must not take any other investigational product, or any drugs that are known to cause neutropenia or agranulocytosis, with the exception of hydroxyurea. See Appendix 2 for a list of prohibited drugs.

4.7 Rescue Medication

Rescue medication (deferoxamine, or a combination of 2 iron chelators: deferiprone, deferoxamine, or deferasirox) for the treatment of iron overload will not be allowed during the study. Should symptoms become intolerable for a patient, dose adjustment should be attempted. If the treatment is unsuccessful, the investigator may decide to withdraw the patient from the study in order to optimize treatment.

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

Procedure	Visit 1 [1]	Blood Draws [2]	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9 or Early Termination
Week:	0		13	26	39	52	65	78	91	104
Informed consent/assent	X									
Eligibility criteria	X									
Prior and concomitant medications	X		X	X	X	X	X	X	X	X
Transfusion information (if applicable) [3]	X	X	X	X	X	X	X	X	X	X
Serum pregnancy testing (if applicable) [4]	X		X	X	X	X	X	X	X	X
Physical examination	X					X				X
Vital signs (including weight and height) [5]	X		X	X	X	X	X	X	X	X
12-lead ECG	X					X				X
Contraceptive counseling	X		X	X	X	X	X	X	X	X
Serology	X									X
Hematology	X	X	X	X	X	X	X	X	X	X
Biochemistry [6]	X			X		X		X		X
Serum ferritin	X		X	X	X	X	X	X	X	X
Urinalysis	X					X				X
Liver MRI	X					X				X
Cardiac MRI T2*	X					X				X

Procedure	Visit 1 [1]	Blood Draws [2]	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9 or Early Termination
Week:	0		13	26	39	52	65	78	91	104
Dose calculation/verify and adjust dose level	X		X	X	X	X	X	X	X	
Collect used and unused study medication			X	X	X	X	X	X	X	X
Dispense study medication	X		X	X	X	X	X	X	X	
Dispense patient diary card	X		X	X	X	X	X	X	X	
Review and collect diary card			X	X	X	X	X	X	X	X
Adverse events	X		X	X	X	X	X	X	X	X

[1] Visit 1 of study LA38-EXT is also the final visit of study LA38-0411. It serves as the baseline visit for those patients who received deferoxamine in LA38-0411 and will now be receiving deferiprone for the first time. (For patients who received deferiprone in LA38-0411, the measures obtained at the baseline visit of the LA38-0411 study will be used as the baseline measures for LA38-EXT as well.)

[2] For Group 1, hematology testing is to be done monthly throughout the study. For Group 2, it is to be done weekly up to Visit 3 (Week 26), biweekly up to Visit 5 (Week 52), and monthly thereafter. At the quarterly site visits, this testing will be done as part of the routine procedures, and at the other time points it can be done at a local laboratory instead of at the site.

[3] Record volume of blood that the patient received during the transfusion, and the mean hematocrit of the packed red blood cell units transfused

[5] Females of childbearing potential only

[5] Height will be measured only at Visits 1, 5, and 9

[6] At Visits 1, 3, 5, 7, and 9, the blood sample must be drawn following a 10-hour fast

5.1 Visit Procedures

All transfusions must be performed during a study visit or during the weekly, biweekly, or monthly blood assessments conducted at the study site for the entire study duration, except for those patients who require an emergency transfusion. Data on all transfusions performed during the trial, including the type of transfusion (simple, exchange, partial exchange), volume of blood received, and the mean hematocrit of the packed red blood cell units transfused (data obtained from the site's blood bank) must be recorded in the eCRF and source documents. Iron input per transfusion will be calculated based on the information collected throughout the study.

Visit 1

Note: 1) Many of the procedures listed below are already scheduled as end-of-study procedures for study LA38-0411. 2) For patients who will be receiving deferiprone for the first time, the data obtained at this visit will be treated as the baseline measures.

- Explain the extension study to the patient and/or authorized legal representative, and obtain written informed consent/assent. (This step may also be done prior to Visit 1; i.e., before the end of study LA38-0411.)
- Ask patient or legal guardian if he/she would agree for a blood sample for genetic testing to be collected should an event of agranulocytosis occur, and if yes, obtain consent/assent. (As such a sample would only be obtained after detection of agranulocytosis, the decision about this consent could be deferred until then.)
- Determine patient's eligibility
- Collect and review new information about concomitant medications
- Obtain the results of the following tests and procedures which were done as part of the end-of-study visit in LA38-0411:
    - Hematology and biochemistry (**Note:** blood sample must be drawn following a 10-hour fast)
    - Serology
    - Serum ferritin
    - Pregnancy testing
    - Urinalysis
    - Physical examination
    - Vital signs, weight, and height
    - 12-lead ECG

  - MRI scan of the liver, for LIC calculation
  - Cardiac MRI T2*

- If the patient is receiving a blood transfusion during this visit or has received a blood transfusion since the last visit, record the type of transfusion (simple, exchange, partial exchange), the volume of blood patient received, and the mean hematocrit of the packed red blood cell units transfused (data obtained from the site's blood bank)
- Conduct contraceptive counseling for sexually active patients
- Verify or determine dosage of study medication
  - For patients who received deferiprone in LA38-0411 (Group 1), the dosage will be the same as at the completion of that study, unless the LIC, MRI T2*, and serum ferritin results obtained at this visit indicate the need for an increase, as per the criteria listed in Section 3.3.
  - For patients who received deferoxamine in LA38-0411 (Group 2), the initial dose of deferiprone will be 15 mg/kg t.i.d. through Week 1, increasing to 20 mg/kg t.i.d. at Week 2 and then to 25 mg/kg t.i.d. at Week 3. Based on the LIC, MRI T2*, and serum ferritin results obtained at this visit, the dose will either remain at 25 mg/kg t.i.d. or be further increased up to a limit of 33 mg/kg t.i.d., as per the criteria listed in Section 3.3.
- Dispense a 3-month supply of study medication, instruct patient how to take it. However, because there might be a delay in obtaining the Visit 1 results that are needed for dose determination, it may not be possible to provide the appropriate 3-month supply at this time. In that case, do one of the following, based on patient preference:
  - Dispense a 3-month quantity that is sufficient to meet the requirements of the highest possible dosage (for Group 1, this will only be done in cases where the investigator suspects that an increase in dosage may be necessary); instruct the patient to start on whatever dosage is currently verified; then, once the Visit 1 results are available, call to let the patient know what dosage to continue taking. A written confirmation of the dosage to be administered will be provided to the patient as well.

    OR:
  - Dispense only a 3-week supply (for Group 1, the dosage will be the same that it was in LA38-0411; for Group 2, it will be based on the required 3-week titration); and have the patient return to the site once the Visit 1 results are available, to obtain the remainder.

- Provide the patient or authorized legal representative with a diary card in which to keep daily track of study drug taken, adverse events, and any medication used to treat them; and explain how to complete it if necessary
- Remind the patient/authorized legal representative of the following:
    - To visit the site or a local laboratory for the weekly (Group 2) or monthly (Group 1) blood draws
    - To return the completed diary card at the next quarterly visit
    - To return all medication containers at the next quarterly visit, whether empty or unused
    - To interrupt therapy immediately if an infection develops, and to immediately report any symptoms indicative of infection such as fever, sore throat, or flu-like symptoms. In presence of confirmed fever and/or infection, they will be required to have their neutrophil counts tested as soon as possible and no later than 24 hours after the symptoms of infection are detected.
    - If patient decides to leave the study before completion, to return to the clinic for an Early Termination Visit as soon as possible, and no later than 1 month following the last dose of study medication
- Provide patient or authorized legal representative with an emergency card, and advise her/him to carry this card at all times
- Schedule next study visit

<u>Regular Blood Draws</u>

Notes:

- These blood draws can be conducted either at a local laboratory or at the study site.
- For patients in Group 1, the blood draws will be done monthly. For patients in Group 2, they will be done weekly for the first 6 months (up to Week 26), biweekly for the next 6 months (up to Week 52), and monthly thereafter. In all cases, the window is ± 3 days.

- Collect blood sample for hematology. Hematology results should be reviewed by the investigator as soon as they are received from the laboratory (within 24 hours if possible).
- If the patient receives a blood transfusion (either at one of these visits or at any other time during the study) , record the type of transfusion (simple, exchange, partial

exchange; and if exchange or partial exchange, what was the volume of blood removed and the average mean hematocrit of the packed red blood cells removed), volume of blood that the patient received during the transfusions, and the mean hematocrit of the packed red blood cell units transfused (data obtained from the site's blood bank).

Visit 2 (Week 13 ±7 days)

- Review patient diary card, and file it with the source documents
- Document information on adverse events, use of concomitant medications, and treatment compliance
- Collect blood samples for the following assessments:
  - Hematology
  - Serum ferritin

Pregnancy
  - testing for all females of childbearing potential. A negative result is required for study continuation.
- Measure vital signs and weight
- If the patient receives a blood transfusion at this visit (or at any other time during the study), record the type of transfusion (simple, exchange, partial exchange), volume of blood received, and the mean hematocrit of the packed red blood cell units transfused (data obtained from the site's blood bank)
- Conduct contraceptive counseling for sexually active patients
- Collect and account for the medication dispensed at the previous visit
- Give patient a new diary card, along with a reminder if necessary about how to complete it
- Verify or adjust dosage of study medication
- Dispense the next 3-month supply of study medication, along with instructions if necessary on how to take it
- Remind the patient/authorized legal representative of the following:
  - To visit the site or a local laboratory for the weekly (Group 2) or monthly (Group 1) blood draws
  - To return the completed diary card at the next quarterly visit
  - To return all medication containers at the next quarterly visit, whether empty or unused

- To interrupt therapy immediately if an infection develops, and to immediately report any symptoms indicative of infection such as fever, sore throat, or flu-like symptoms. In presence of confirmed fever and/or infection, they will be required to have their neutrophil counts tested as soon as possible and no later than 24 hours after the symptoms of infection are detected.
- If patient decides to leave study before completion, to return to the clinic for an Early Termination Visit as soon as possible, and no later than 1 month following the last dose of study medication

Visit 3 (Week 26 ±7 days)

- Review patient diary card, and file it with the source documents
- Document information on adverse events, use of concomitant medications, and treatment compliance
- Collect blood samples for the following assessments:
  - Hematology and biochemistry (**Note:** blood sample must be drawn following a 10-hour fast)
  - Serum ferritin
  - Pregnancy testing for all females of childbearing potential. A negative result is required for study continuation.
- Measure vital signs and weight
- If the patient receives a blood transfusion at this visit (or at any other time during the study), record the type of transfusion (simple, exchange, partial exchange), volume of blood received, and the mean hematocrit of the packed red blood cell units transfused (data obtained from the site's blood bank)
- Conduct contraceptive counseling for sexually active patients
- Collect and account for the medication dispensed at the previous visit
- Give patient a new diary card, along with a reminder if necessary about how to complete it
- Verify or adjust dosage of study medication
- Dispense the next 3-month supply of study medication, along with instructions if necessary on how to take it
- Remind the patient/authorized legal representative of the following:
  - To visit the site or a local laboratory for the biweekly (Group 2) or monthly (Group 1) blood draws

- To return the completed diary card at the next quarterly visit
- To return all medication containers at the next quarterly visit, whether empty or unused
- To interrupt therapy immediately if an infection develops, and to immediately report any symptoms indicative of infection such as fever, sore throat, or flu-like symptoms In presence of confirmed fever and/or infection, they will be required to have their neutrophil counts tested as soon as possible and no later than 24 hours after the symptoms of infection are detected.
- If patient decides to leave study before completion, to return to the clinic for an Early Termination Visit as soon as possible, and no later than 1 month following the last dose of study medication

Visit 4 (Week 39 ±7 days)

- Review patient diary card, and file it with the source documents
- Document information on adverse events, use of concomitant medications, and treatment compliance
- Collect blood samples for the following assessments:
  - Hematology
  - Serum ferritin
  - Pregnancy testing for all females of childbearing potential. A negative result is required for study continuation.
- Measure vital signs and weight
- If the patient receives a blood transfusion at this visit (or at any other time during the study), record the type of transfusion (simple, exchange, partial exchange), volume of blood received, and the mean hematocrit of the packed red blood cell units transfused (data obtained from the site's blood bank)
- Conduct contraceptive counseling for sexually active patients
- Collect and account for the medication dispensed at the previous visit
- Give patient a new diary card, along with a reminder if necessary about how to complete it
- Verify or adjust dosage of study medication
- Dispense the next 3-month supply of study medication, along with instructions if necessary on how to take it

- Remind the patient/authorized legal representative of the following:
    - To visit the site or a local laboratory for the biweekly (Group 2) or monthly (Group 1) blood draws
    - To return the completed diary card at the next quarterly visit
    - To return all medication containers at the next quarterly visit, whether empty or unused
    - To interrupt therapy immediately if an infection develops, and to immediately report any symptoms indicative of infection such as fever, sore throat, or flu-like symptoms. In presence of confirmed fever and/or infection, they will be required to have their neutrophil counts tested as soon as possible and no later than 24 hours after the symptoms of infection are detected.
    - If patient decides to leave study before completion, to return to the clinic for an Early Termination Visit as soon as possible, and no later than 1 month following the last dose of study medication

Visit 5 (Week 52 ±7 days)

- Review patient diary card, and file it with the source documents
- Document information on adverse events, use of concomitant medications, and treatment compliance
- Collect blood samples for the following assessments:
    - Hematology and biochemistry (**Note:** blood sample must be drawn following a 10-hour fast)
    - Serum ferritin
    - Pregnancy testing for all females of childbearing potential. A negative result is required for study continuation.
- Collect urine for urinalysis
- Measure vital signs, weight, and height
- Perform a physical examination (to be completed by the investigator or a qualified delegate)
- Administer a 12-lead ECG
- Perform an MRI scan of the liver, and arrange for the results to be transmitted to a central laboratory for interpretation and LIC calculation

- Perform a cardiac MRI T2*, and arrange for the results to be transmitted to a central laboratory for interpretation
- If the patient receives a blood transfusion at this visit (or at any other time during the study), record the type of transfusion (simple, exchange, partial exchange), volume of blood received, and the mean hematocrit of the packed red blood cell units transfused (data obtained from the site's blood bank)
- Conduct contraceptive counseling for sexually active patients
- Collect and account for the medication dispensed at the previous visit
- Give patient a new diary card, along with a reminder if necessary about how to complete it
- Verify or adjust dosage of study medication
- Dispense the next 3-month supply of study medication, along with instructions if necessary on how to take it
- Remind the patient/authorized legal representative of the following:
    - To visit the site or a local laboratory for the monthly blood draws
    - To return the completed diary card at the next quarterly visit
    - To return all empty and unused medication containers at the next quarterly visit
    - To interrupt therapy immediately if an infection develops, and to immediately report any symptoms indicative of infection such as fever, sore throat, or flu-like symptoms. In presence of confirmed fever and/or infection, they will be required to have their neutrophil counts tested as soon as possible and no later than 24 hours after the symptoms of infection are detected.
    - If patient decides to leave study before completion, to return to the clinic for an Early Termination Visit as soon as possible, and no later than 1 month following the last dose of study medication
- Schedule next study visit

<u>Visit 6 (Week 65 ±7 days)</u>

- Review patient diary card, and file it with the source documents
- Document information on adverse events, use of concomitant medications, and treatment compliance
- Collect blood samples for the following assessments:

  - Hematology
  - Serum ferritin
  - Pregnancy testing for all females of childbearing potential. A negative result is required for study continuation.
- Measure vital signs and weight
- If the patient receives a blood transfusion at this visit (or at any other time during the study), record the type of transfusion (simple, exchange, partial exchange), volume of blood received, and the mean hematocrit of the packed red blood cell units transfused (data obtained from the site's blood bank)
- Conduct contraceptive counseling for sexually active patients
- Collect and account for the medication dispensed at the previous visit
- Give patient a new diary card, along with a reminder if necessary about how to complete it
- Verify or adjust dosage of study medication
- Dispense the next 3-month supply of study medication, along with instructions if necessary on how to take it
- Remind the patient/authorized legal representative of the following:
  - To visit the site or a local laboratory for the monthly blood draws
  - To return the completed diary card at the next quarterly visit
  - To return all medication containers at the next quarterly visit, whether empty or unused
  - To interrupt therapy immediately if an infection develops, and to immediately report any symptoms indicative of infection such as fever, sore throat, or flu-like symptoms. In presence of confirmed fever and/or infection, they will be required to have their neutrophil counts tested as soon as possible and no later than 24 hours after the symptoms of infection are detected.
  - If patient decides to leave study before completion, to return to the clinic for an Early Termination Visit as soon as possible, and no later than 1 month following the last dose of study medication

<u>Visit 7 (Week 78 ±7 days)</u>

- Review patient diary card, and file it with the source documents

- Document information on adverse events, use of concomitant medications, and treatment compliance
- Collect blood samples for the following assessments:
  - Hematology and biochemistry (**Note:** blood sample must be drawn following a 10-hour fast)
  - Serum ferritin
  - Pregnancy testing for all females of childbearing potential. A negative result is required for study continuation.
- Measure vital signs and weight
- If the patient receives a blood transfusion at this visit (or at any other time during the study), record the type of transfusion (simple, exchange, partial exchange), volume of blood received, and the mean hematocrit of the packed red blood cell units transfused (data obtained from the site's blood bank)
- Conduct contraceptive counseling for sexually active patients
- Collect and account for the medication dispensed at the previous visit
- Give patient a new diary card, along with a reminder if necessary about how to complete it
- Verify or adjust dosage of study medication
- Dispense the next 3-month supply of study medication, along with instructions if necessary on how to take it
- Remind the patient/authorized legal representative of the following:
  - To visit the site or a local laboratory for the monthly blood draws
  - To return the completed diary card at the next quarterly visit
  - To return all medication containers at the next quarterly visit, whether empty or unused
  - To interrupt therapy immediately if an infection develops, and to immediately report any symptoms indicative of infection such as fever, sore throat, or flu-like symptoms. In presence of confirmed fever and/or infection, they will be required to have their neutrophil counts tested as soon as possible and no later than 24 hours after the symptoms of infection are detected.
  - If patient decides to leave study before completion, to return to the clinic for an Early Termination Visit as soon as possible, and no later than 1 month following the last dose of study medication

Visit 8 (Week 91 ±7 days)

- Review patient diary card, and file it with the source documents
- Document information on adverse events, use of concomitant medications, and treatment compliance
- Collect blood samples for the following assessments:
  - Hematology
  - Serum ferritin
  - Pregnancy testing for all females of childbearing potential. A negative result is required for study continuation.
- Measure vital signs and weight
- If the patient receives a blood transfusion at this visit (or at any other time during the study), record the type of transfusion (simple, exchange, partial exchange), volume of blood received, and the mean hematocrit of the packed red blood cell units transfused (data obtained from the site's blood bank)
- Conduct contraceptive counseling for sexually active patients
- Collect and account for the medication dispensed at the previous visit
- Give patient a new diary card, along with a reminder if necessary about how to complete it
- Verify or adjust dosage of study medication
- Dispense the next 3-month supply of study medication, along with instructions if necessary on how to take it
- Remind the patient/authorized legal representative of the following:
  - To visit the site or a local laboratory for the monthly blood draws
  - To return the completed diary card at the next quarterly visit
  - To return all medication containers at the next quarterly visit, whether empty or unused
  - To interrupt therapy immediately if an infection develops, and to immediately report any symptoms indicative of infection such as fever, sore throat, or flu-like symptoms. In presence of confirmed fever and/or infection, they will be required to have their neutrophil counts tested as soon as possible and no later than 24 hours after the symptoms of infection are detected.

- If patient decides to leave study before completion, to return to the clinic for an Early Termination Visit as soon as possible, and no later than 1 month following the last dose of study medication

Visit 9 (Week 104 ±7 days) or Early Termination Visit

- Review patient diary card, and file it with the source documents
- Document information on adverse events, use of concomitant medications, and treatment compliance
- Collect blood samples for the following assessments:
  - Hematology and biochemistry (**Note:** blood sample must be drawn following a 10-hour fast)
  - Serology
  - Serum ferritin
  - Pregnancy testing for all females of childbearing potential. A negative result is required for study continuation.
- Collect urine for urinalysis
- Measure vital signs, weight, and height
- Perform a physical examination (to be completed by the investigator or a qualified delegate)
- Administer a 12-lead ECG
- Perform an MRI scan of the liver, and arrange for the results to be transmitted to a central laboratory for interpretation and LIC calculation
- Perform a cardiac MRI T2*, and arrange for the results to be transmitted to a central laboratory for interpretation
- If the patient receives a blood transfusion at this visit (or at any other time during the study), record the type of transfusion (simple, exchange, partial exchange), volume of blood received, and the mean hematocrit of the packed red blood cell units transfused (data obtained from the site's blood bank)
- Conduct contraceptive counseling for sexually active patients
- Collect and account for the medication dispensed at the previous visit
- Instruct patient to inform the site if he/she experiences any SAEs in the 30 days following the last dose. If any are reported, follow up on any continuing AEs or SAEs

until resolution, until the condition stabilizes, until the event is otherwise explained, or until the patient is lost to follow-up.

5.2 Method of Assignment to Treatment

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

5.3 Blinding Procedures

Not applicable.

5.4 Allocation of Patient Numbers

All participants in study LA38-0411 will have been assigned a unique 6-digit number, where the first 3 digits represent the site code and the last 3 were sequentially assigned to each patient who signed the ICF. These assigned numbers will be maintained when patients continue on to study LA38-EXT.

Patients will be identified in all study data by this number rather than by name.

5.5 Treatment Compliance

Patients will be provided with a diary card in which they will daily record the number of Ferriprox tablets or volume of deferiprone oral solution taken. Compliance will be evaluated quarterly by the investigator or delegate by monthly pill counts or volume of drug returned. 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.

Compliance reported in the eCRF will be based on the patient's diary and on the return of used and unused medication containers. If compliance is greater than 100% and the patient reports taking all doses as prescribed, compliance will be reported as 100% in the eCRF. 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

All patients in the extension study will receive deferiprone.

6.1 Investigational Product

Deferiprone is manufactured by Apotex Inc., and will be supplied to the clinical sites by ApoPharma Inc.

6.1.1 Dosage Form and Mode of Administration

Deferiprone is provided as 500 mg film-coated scored tablets or 80 mg/mL oral solution. The tablets are marketed under the brand name Ferriprox®. Both forms are taken orally, 3 times a day.

6.1.2 Precautions for Use

Deferiprone can be taken with or without food, as per the investigator's recommendation.

6.2 Reference Product

Not applicable. All participants in study LA38-EXT will receive deferiprone.

6.3 Packaging and Labeling

Ferriprox tablets will be supplied in bottles of 100 tablets each, high-density polyethylene (HDPE) bottles with child-resistant closure. Deferiprone oral solution will be supplied in 250 mL bottles with child-resistant closure.

Both the tablet containers and oral solution containers will be provided with labels whose content is in accordance with all applicable regulatory requirements. The label will include protocol number, expiry date, lot/batch number, investigational statement, storage temperature, dosage, direction for use, visit number, date dispensed, and name and address of the sponsor.

6.4 Shipping and Storage

The study medication at each site will be kept in a secure location under adequate storage conditions, as per label requirements, with access to authorized individuals only. 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. The site must report temperature deviations immediately to the sponsor, and quarantine the product until the sponsor deems it acceptable for use.

6.5 Product Accountability

Each site must maintain a record of inventory and a record of dispensing for the investigational product.Investigational product accountability lies with the investigator at all

times. The investigator must maintain an updated Site Investigational Drug Inventory Record at the study site. This log will include 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 study center is inventoried and accounted for throughout the study. Records of receipt, storage and administration of the study drug supplied must be maintained, and the drug accountability will be verified by the sponsor or sponsor's designee during on-site monitoring visits. At the conclusion of the study, a final inventory must be performed by the investigator or delegate. The sponsor will be responsible for determining the specific conditions for destruction of unused product.

6.6 Replacement Doses

Patients will be dispensed study medication at the start of the extension study and quarterly thereafter. Dispensing of study medication must be done by appropriately qualified staff (e.g., physician, pharmacist, or nurse).

Patients reporting that their medication has been lost or misplaced will be asked to attend the study site to receive replacement medication. Requests for replacement must be made in

writing by the appropriate clinical site member (pharmacist/physician/investigator) to the sponsor's Project Leader, Clinical Research, who will approve the request. All information related to the lost/misplaced medication and the replacement medication must be recorded in the drug accountability forms.

6.7 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, which must include the issuance of appropriate signed destruction certificates including mode of destruction and complete drug accountability of destroyed materials.

6.8 Other Study Supplies

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

7 MEASUREMENTS AND EVALUATIONS

7.1 Efficacy Measurements

7.1.1 Liver Iron Concentration

The liver contains 70% or more of total body iron,[17] justifying the use of liver iron concentration (LIC) as a measure of body iron load.[18,19,20,21] In the absence of effective iron chelation therapy, transfusion-dependent patients experience a progressive increase in LIC.[22]Although liver iron concentrations may differ from the concentrations of iron in other organs, it has been reported that patients with LIC greater than 7 mg iron/g liver (dry weight; dw) are at increased risk of iron-induced toxicity such as cardiac disease, hepatic fibrosis, diabetes mellitus and death.[19,23,24]The current goal for chelation therapy in transfusion-dependent patients is to maintain an "optimal" body iron burden corresponding to hepatic storage concentrations of less than 7 mg/g dw.[19]

MRI scans for liver iron will be performed at Visit 1, Visit 5, and Visit 9 (or early termination), and will be transmitted to a central laboratory for interpretation and LIC calculation.

7.1.2 Cardiac MRI T2*

Myocardial MRI T2* can be used to monitor the myocardial iron load resulting from chronic transfusions, with low T2* levels reflecting a high cardiac iron concentration and high T2* values reflecting low cardiac iron. This technique has been calibrated with cardiac iron concentration in post mortem hearts.[25] Studies in non-iron-overloaded patients reveal that

none have a cardiac T2* <20 ms, a value that is now widely used clinically as the threshold for cardiac iron overload.[26]The ability of cardiac MRI T2* to identify patients at risk of iron-induced cardiac disease and premature death has been reported,[27] and its predictive value has been prospectively evaluated in 652 transfusion-dependent thalassemia patients from 21 UK centers who had cardiac MRI T2* assessment and who had their cardiac status followed over time.[27] The results of this study demonstrate that the lower the cardiac MRI T2* value, i.e., the higher the cardiac iron load, the higher is the risk of developing iron-induced cardiac failure within the subsequent 12 months.

MRI scans for the assessment of cardiac MRI T2* will be performed at Visit 1, Visit 5, and Visit 9 (or early termination), and will be transmitted to a central laboratory for interpretation.

7.1.3 Serum Ferritin

The most commonly used method for the assessment of body iron burden is the measurement of serum ferritin concentration.[28,29,30,31,32,33,34] Ferritin is the major storage protein for iron. It is present in low concentrations in the plasma and is a reflection of total body iron. In transfusion-dependent patients, due to continual transfusional iron input and the lack of a natural excretory pathway for excess iron, a progressive increase in serum ferritin concentration occurs in the absence of effective iron chelation therapy. Sequential measurement of serum ferritin concentration remains the most common method for assessment of body iron burden, and in clinical practice it is the standard for identifying trends in iron status within individuals and across populations. Serum ferritin is therefore a useful index of changes in iron load status. For decades, a serum ferritin level above 2,500 µg/L has been considered an important indicator of the relative risk of death.[23,24,35]

Serum ferritin will be assessed at the start of the extension study and quarterly thereafter.

7.2 Safety Measurements

7.2.1 Adverse Events and Serious Adverse Events

7.2.1.1 Definition of Adverse Events

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

AEs include:

- Exacerbation of a pre-existing illness, including acute episodes/crisis of a chronic underlying condition
- An increase in frequency or intensity of a pre-existing episodic event or condition
- A condition detected or diagnosed after study treatment administration, even though it may have been present prior to the start of the study
- A continuous persistent disease or symptom present at baseline that worsens following the start of the study
- Accidents (e.g., involving a motor vehicle)
- Reasons for changes in concomitant medication (type of drug and/or dose)
- Medical, nursing, or pharmacy consultation
- Admission to hospital and surgical operations
- Abnormalities in laboratory findings (e.g., 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 Adverse Events

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

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

- How are you feeling / How does your child seem to be feeling?
- Have you/ has your child had any medical problems since the last visit?
- Have you / has your child taken any new medications, other than those provided in this study, since the last visit?

Based on the patient's response to these questions, the investigator or delegate should ask additional questions relevant to the specific complaint, such as:

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

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

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

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

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

7.2.1.3 Assessment of Causality

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

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

7.2.1.4 Assessment of Intensity

Intensity refers to the degree of discomfort or impairment associated with an event. The intensity of AEs is to be reported on the CRF 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 adverse 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 adverse event, medical and scientific judgment should be used in deciding whether prompt reporting is appropriate in this situation.

7.2.1.6 Reporting of Serious Adverse Events

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

Patients will be instructed to report SAEs to the investigator **within 24 hours**, by telephone. In turn, the investigator must report all SAEs to the sponsor **within 24 hours** of 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 well as to the sponsor. If any SAE that is considered at least possibly related to the study medication and is unexpected occurs at one site, the sponsor will promptly inform all other sites of this, and all investigators must then report this event to their own IRBs/IECs, following the same timelines as above or following local IRB/IEC policy, whichever takes precedence.

7.2.1.7 Follow-up and Documentation of SAEs

SAEs that occur during the study and up to 30 days after the last dose of study drug must be documented in the patient's medical record and on the SAE report form. The investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis rather than the individual signs/symptoms should be documented as the SAE.

All SAEs must be followed until resolution, the condition stabilizes, the event is otherwise explained, or the patient is lost to follow-up. The investigator is responsible for ensuring that follow-up includes any supplemental investigations that may be indicated, in order to elucidate the nature and/or causality of the SAE as completely as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. The sponsor may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations.

If a patient dies during participation in the study or during a specified follow-up period, the sponsor should be sent a copy of any post-mortem findings, including histopathology.

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

The 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

Patients 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:

- Mild: A confirmed ANC < 1.5 x 10^9/L but ≥1.0 x 10^9/L
- Moderate: A confirmed ANC < 1.0 x 10^9/L but ≥ 0.5 x 10^9/L
- Severe: A confirmed ANC < 0.5 x 10^9/L. Severe neutropenia is also referred to as agranulocytosis.

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 both counts are below 1.5 x 10^9/L but are not in the same severity category, a third count will be required to determine the severity.

The management of different severities of neutropenia is described below. In addition to having ANC monitored, patients or authorized legal guardians will be advised to immediately report any symptoms indicative of infection such as fever, sore throat, and flu-like symptoms; and will be provided with an emergency services card with contact information which they are advised to carry with them at all times. In presence of confirmed fever and/or infection, they will be required to have their neutrophil counts tested as soon as possible and no later than 24 hours after the symptoms of infection are detected.

Mild neutropenia: The patient should continue deferiprone treatment, and ANC will be monitored every 2 days until resolution of the event, defined as 2 consecutive ANC ≥ 1.5 x 10^9/L. If ANC is still < 1.5 x 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. by fax

If a patient with mild neutropenia develops an infection, deferiprone therapy must be interrupted immediately, and neutrophil count will continue to be monitored every 2 days

until resolution. Therapy can be re-initiated once all symptoms have been resolved and it is deemed safe by the investigator.

Moderate neutropenia: Patient will immediately interrupt treatment, and ANC will be monitored every 2 days until resolution of the event. If ANC is still < 1.5 x 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
- 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
- If possible, obtain viral studies (CMV, parvovirus, hepatitis A/B/C), serum ALT, BUN, creatinine, and 10 mL serum split into two 5-mL aliquots for frozen storage, for future analysis
- Notify ApoPharma Inc. by fax

Severe neutropenia/agranulocytosis: Patient will immediately discontinue treatment and will be permanently withdrawn from the study, and ANC will be monitored daily until resolution of the event. 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
- If possible, obtain viral studies (CMV, parvovirus, hepatitis A/B/C), serum ALT, BUN, creatinine, and 10 mL serum split into two 5-mL aliquots for frozen storage
- With the patient's consent, collect a blood sample to attempt to identify genetic or other biomarkers related to agranulocytosis (refer to the operations manual for further instructions)
- 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, as an inpatient if possible, beginning the same day that the ANC is confirmed as < 0.5 x 10^9/L; administer daily until ANC is > 1.5 x 10^9/L on 2 consecutive days
- If ANC < 0.5 x 10^9/L for 7 days, repeat bone marrow biopsy and aspirate weekly during the period of agranulocytosis, if warranted
- Notify ApoPharma Inc. by fax

7.2.1.8.2 Infections

If the patient develops fever or any type 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 x 10^9/L). Patients should be advised to report immediately to their physician any symptoms indicative of infection such as fever, sore throat, and flu-like symptoms. Patients will be provided with an emergency services card with contact information, and the patient/legal guardian will be advised to carry this card at all times. In presence of confirmed fever and/or infection, they will be required to have their neutrophil counts tested as soon as possible and no later than 24 hours after the symptoms of infection are detected. Therapy with deferiprone can be re-initiated once all symptoms have been resolved and it is deemed safe by the investigator.

7.2.2 Laboratory Measurements

Analyses will be performed at a central laboratory, with the exception of the weekly, biweekly, or monthly hematology assessments which may be performed at a local laboratory. 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 values 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** (for Group 1, monthly throughout the study; for Group 2, weekly for the first 6 months, biweekly for the next 6 months, and monthly thereafter): hemoglobin, total WBC count, ANC, and platelet count
- **Biochemistry** (semi-annually; Visits 1, 3, 5, 7, and 9): total protein, GGT, lactate dehydrogenase (LDH), sodium, potassium, chloride, fasting glucose, total and direct bilirubin (indirect bilirubin will be calculated by the sponsor), AST, ALT, albumin, blood urea nitrogen, calcium, creatinine, uric acid, alkaline phosphatase, and amylase
- **Serology** (Visits 1 and 9): Hepatitis B and C and HIV testing
- **Urinalysis** (annually; Visits 1, 5, and 9): 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.
- **Pregnancy** (quarterly; Visits 1–9): serum pregnancy test

7.2.3 Other Safety Measurements

7.2.3.1 Physical Examination

At Visits 1, 5, and 9, the investigator or a qualified delegate will perform a physical examination of the following organs and systems: head, ears, eyes, nose, throat and neck, respiratory system, cardiovascular system, gastrointestinal system, musculoskeletal system, central and peripheral nervous system, skin, thyroid, and general constitution.

7.2.3.2 Vital Signs

Temperature, heart rate, respiration rate, and systolic and diastolic blood pressure will be measured at each visit.

Weight will be measured at each visit, and height will be measured at Visits 1, 5, and 9.

7.2.3.3 Electrocardiogram

A standard 12-lead ECG will be performed at Visits 1, 5, and 9. As a minimum, the following parameters will be assessed: HR, PR, QRS, QT, QTcF, QTcB. The results will be interpreted by the investigator, and the overall interpretation will be documented.

7.2.3.4 Concomitant Medications

Information about prior and concomitant medications will be collected at each visit. The following must be recorded in the source documents and eCRFs:

- Any medications that the patient continues to take during the trial
- Any medications that the patient starts to take during the trial

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

7.2.4 Procedures in Case of Pregnancy

If a patient becomes pregnant during the course of the study, she will be immediately withdrawn. The pregnancy will be immediately reported to the sponsor, and information about the pregnancy is to be recorded on the appropriate form and in the patient's CRF. 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 CRF. If the partner provides consent for follow-up of the pregnancy, she will be followed until the delivery of the child, and information on the delivery status of the mother and child will be forwarded to the sponsor no later than 8 weeks following the delivery date.

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

8 STUDY COMMITTEES

A Data Safety Monitoring Board (DSMB) will be set up to oversee the safety of the patients enrolled in the study.

9 STATISTICAL ANALYSIS

9.1 Endpoints

9.1.1 Primary Endpoints

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

9.1.2 Secondary Endpoints

The time points for the efficacy assessments are defined below. Since the baseline measures are by definition those taken prior to the start of deferiprone therapy, "baseline" is defined differently for the two groups, as follows:

- **Group 1:** For patients who received deferiprone in LA38-0411, the baseline visit of that study will be treated as the baseline visit of LA38-EXT as well. Thus, Week 0 of the extension study will be Year 1 (i.e., the completion of one year of deferiprone treatment), Week 52 will be Year 2, and Week 104 will be Year 3.
- **Group 2:** For patients who received deferoxamine in LA38-0411, the start of the extension study (Week 0) will be treated as the baseline visit. For this group, therefore, Week 52 will be Year 1, and Week 104 will be Year 2.

Efficacy endpoints are provided below. For Group 1, the change from baseline to Year 1 is derived from study LA38-0411. For Group 2, there is no Year 3 of deferiprone treatment.

- The change from baseline to Year 1 (both groups; Group 1 data are from LA38-0411), from baseline to Year 2 (both groups), and from baseline to Year 3 (Group 1 only) in liver iron concentration (LIC), as measured by magnetic resonance imaging (MRI)
- The change from baseline to Year 1 (both groups; Group 1 data are from LA38-0411), from baseline to Year 2 (both groups), and (Group 1 only) from baseline to Year 3 in cardiac MRI T2*
- The change from baseline to Year 1 (both groups; Group 1 data are from LA38-0411 data), from baseline to Year 2 (both groups), and from baseline to Year 3 (Group 1 only) in serum ferritin
- Responder analysis, defined as the percentage of patients who show a ≥20% decline from baseline in LIC or serum ferritin or a ≥20% increase from baseline in cardiac MRI T2* at

Year 1 (both groups; Group 1 data are from LA38-0411), at Year 2 (both groups), and at Year 3 (Group 1 only)

9.2 Determination of Sample Size and Study Power

A planned total of 300 patients will be randomized in the LA38-0411 study to receive 1 year of either deferiprone or deferoxamine, and all patients who complete that study will be invited to enroll in the extension study.

9.3 Study Populations

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

9.3.1 Intent-to-Treat Population

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

9.3.2 Per Protocol Population

The Per-Protocol (PP) population will include all enrolled 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, patients with major protocol violations will be reviewed and excluded, where appropriate, from the PP population. Major protocol violations will include (but not be limited to) the following:

- Patients who were not compliant with the treatment (<80% compliance)
- Patients who took iron chelator medications other than the assigned study medication during the course of the study

9.3.3 Safety Population

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

9.4 Data Analysis Plan

A separate detailed statistical analysis plan (SAP) will be prepared and approved before database lock. Any changes in the planned statistical methods after database lock will be documented in the final clinical study report.

9.4.1 Planned Analyses

9.4.1.1 Patient Disposition and Drug Exposure

Patient disposition will be summarized and presented, including the number and percentages of patients who were enrolled, received at least one dose of study medication, completed the study, and withdrew (including reasons for withdrawals). For each patient, the number of doses taken will be computed from the study drug dispensing and accountability eCRFs obtained at each visit. The extent of exposure to the study medication, the number of doses, and the total dose taken during the study will be summarized with descriptive statistics.

9.4.1.2 Patient Characteristics

Baseline characteristics for continuous variables will be summarized with descriptive statistics such as mean, standard deviation, minimum, median and maximum values. Baseline characteristics for discrete variables will be summarized with frequency tables.

9.4.1.3 Analysis of Efficacy

Changes in LIC, in cardiac MRI T2*, and in serum ferritin from baseline to Year 1(both groups; Group 1 data are from LA38-041), from baseline to Year 2 (both groups), and from baseline to Year 3 (Group 1 only) will be summarized with descriptive statistics, and will be tested against no change using a one-sample t-test. The changes in these 3 efficacy measures from the start of deferiprone therapy to the last visit of LA38-EXT in all patients, irrespective of whether deferiprone therapy was initiated in LA38-0411 or in LA38-EXT, will also be tested using a one-sample t-test. In addition, the percentages of responders will be tabulated for Year 1 (both groups; Group 1 data are from LA38-0411), for Year 2 (both groups), and for Year 3 (Group 1 only) of deferiprone therapy.

9.4.1.4 Analysis of Safety

The incidences of AEs and SAEs reported from the start of deferiprone therapy for all patients will be tabulated. For patients continuing on deferiprone, this time period will be from the start of LA38-0411 to the completion of LA38-EXT; for those switching to deferiprone, it will be from the start of LA38-EXT to the completion of LA38-EXT. AEs will be summarized by worst severity and by relationship to the study medication. Time to onset and duration of all SAEs, of AEs of special interest such as neutropenia, agranulocytosis, increased ALT, and arthralgia, and of additional AEs that will be determined at the end of LA38-0411, will be analyzed as follows: 1) the mean time to the first onset and the mean time to the last recurrence will be calculated, and 2) the mean duration for the first episode and the mean duration for any recurrent episodes, excluding the first episode, will be calculated for all SAEs and such AEs.

The percentage of discontinuations due to AEs will be calculated, and the AEs leading to discontinuation will be summarized in a frequency table.

Laboratory data (hematology and chemistry) will be summarized using descriptive statistics for continuous variables and frequency tables for discrete variables. The incidences of out-of-range data that are seen for two consecutive measures will be tabulated, and the changes from baseline to the end of study will be presented in shift tables.

9.4.2 Interim Analyses

There will be no interim analysis.

9.5 Criteria for Evaluability of Patient Data

All patients who were enrolled and treated with the study drug, including those who withdrew early, will be eligible for inclusion in the safety and efficacy analyses.

10 DATA MANAGEMENT CONSIDERATIONS

10.1 Data Management

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

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

Integrity of the database will be assured by limiting access through username/password combination and account control. Authorized access to the database will be provided to those

individuals with an inspection/auditing function (Regulatory Authorities/Quality Assurance); "read only" access will be provided to avoid unintentional corruption of the database.

The database will be backed up daily.

10.2 Case Report Forms

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

11 MONITORING, AUDITS, AND INSPECTIONS

11.1 Source Documents

The investigator or delegate will maintain adequately detailed source documents supporting significant source data for each patient. Source data are defined as all information in original records and/or certified copies of original records of clinical findings, observations, or other activities in a clinical study that are necessary for the reconstruction and evaluation of the study: e.g., medical history, physical examination, laboratory results, and x-ray or ultrasound results. The investigator will also retain all printouts/reports of tests or procedures performed as a requirement of the study. All source data that is printed on thermal paper, including laboratory printouts and ECGs scans, must be photocopied, initialed, and dated as authentic equivalents to the thermal paper documents to enable extended retention time.

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

11.2 Monitoring

Monitoring of the investigational sites will be conducted by the sponsor or contracted to a qualified 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

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

12 ETHICAL CONSIDERATIONS

12.1 Informed Consent

Prior to entering a patient into the study, the investigator or a designate must obtain written informed consent from the patient and/or where applicable the patient's legally authorized representative, according to the sponsor's procedures and as described in the Declaration of Helsinki, the Federal Food, Drug and Cosmetic Act, and U.S. applicable Code of Federal Regulations Title 21, Part 50. The investigator will ensure that the patient and/or legal representative is given full and adequate verbal and written information about the nature, purpose, and possible risks and benefits of the study, and is given ample opportunity to ask questions and to discuss the study with family members. The investigator must make a conscientious effort to be fully satisfied that the patient and/or legal representative has truly understood that for which the consent has been given. The patient and/or the legal representative must be notified that he/she is free to discontinue participation in the study at any time, and that such withdrawal will not affect present or future care. In the case of a minor or an incapacitated adult who is capable of forming an opinion and assessing the study information, the investigator must ensure that this individual's decision to not participate or to withdraw from the study will be respected even if consent is given by the legal representative.

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

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

12.2 Institutional Review Board/Independent Ethics Committee

It is the investigator's responsibility to ensure that the protocol is reviewed and approved by a properly constituted IRB or IEC (according to ICH GCP guidelines, Section 3.2). The IRB/IEC must also review and approve the site's ICF and any other written information that will be provided to patients, prior to any 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:
   - 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 INDEMNIFICATION

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

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

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

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

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

17 OWNERSHIP

All data 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.

18 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
Study monitoring	ApoPharma Inc.	200 Barmac Drive Toronto, Ontario Canada M9L 2Z7 Tel: +1-416-749-9300 Toll-free: 1-800-268-4623 Fax: +1-416-401-3867
Laboratory measures	Eurofins Global Central Laboratory	2430 New Holland Pike Building D, Suite 100 Lancaster, PA 17601 USA Tel: +1-717-656-2300 Fax: +1-717-556-0367 Email: clinicaltrials@eurofins.com Web: pharma.eurofins.com
Imaging Laboratories	BioMed Informatics, LLC	2801 Townsgate Road, Suite 212 Westlake Village, California 91361 USA Tel: +1-818-584-3560 Fax: +1-818-475-1986 Email: aaker@biomed-informatics.com
	CMR Core Lab Technologist	Royal Brompton Hospital Sydney Street, London SW3 6NP United Kingdom Tel: 011-44-20-7351-8768 Fax: 011-44-20-7351-881 Email: g.smith@rbh.nthames.nhs.uk

APPENDIX 2: LIST OF PROHIBITED DRUGS

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

- Any investigational drug
- Chloramphenicol (CHLOROMYCETIN)
- Clozapine (CLOZARIL), doxepin HCl (SINEQUAN), amitriptyline HCl/ perphenazine (ETRAFON), and other tricyclic antidepressants
- Clomipramine hydrochloride (ANAFRANIL)
- Propranolol hydrochloride (INDERAL)
- Bepredil (VASCOR)
- Aminoglutethimide (CYTADREN)
- Interferon (INTRON A)
- Para-aminophenol or pyrazolone derivatives
- Phenytoin (DILANTIN), carbamazepine
- Chlordiazepoxide (LIBRIUM) and other benzodiazepines
- Phenylbutazone
- Mefenamic acid (PONSTAN)
- Metoclopramide HCl (REGLAN)
- Chlorpromazine, prochlorperazine, and other phenothiazines
- Procainamide
- Levamisole (ERGAMISOLE)
- Diclofenac sodium (VOLTAREN)
- Trimethoprim/sulfamethoxazole (BACTRIM/SEPTRA)
- Aminopyrine