ApoPharma Inc.

TWICE
DEFERIPRONE DELAYED RELEASE

Safety and acceptability of deferiprone delayed release tablets in patients with systemic iron overload
LA61-0218

CLINICAL STUDY PROTOCOL

IND Number:	45724
Investigational Product:	Deferiprone delayed release 1000 mg tablets
Development Phase:	Phase 2
Indication Studied:	Systemic iron overload
Study Design:	Multi-center open-label study in patients with transfusion-dependent blood disorders
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 1.0, 10 OCT 2018

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:	Safety and acceptability of deferiprone delayed release tablets in patients with systemic iron overload
Study Code:	LA61-0218
Version Number:	1.0
Version Date:	10 OCT 2018

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

Date (DD MMM YYYY)

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

Date (DD MMM YYYY)

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

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:	Safety and acceptability of deferiprone delayed release tablets in patients with systemic iron overload
Study Code:	LA61-0218
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Name of Principal Investigator:	
Name of Study Site:	
Location of Study Site: *(City, region/province/state, country)*	

Signature Date (DD MMM YYYY)

SYNOPSIS

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

Title of study:	Safety and acceptability of deferiprone delayed release tablets in patients with systemic iron overload
Study code:	LA61-0218
Phase of development:	Phase 2
Objectives:	**Primary objective:** To evaluate the safety of deferiprone delayed release (DR) tablets in two different dosage groups in patients with systemic iron overload. **Secondary objectives:** • To evaluate the tolerability of deferiprone DR tablets in two different dosage groups in patients with systemic iron overload • To evaluate the acceptability to patients of deferiprone DR
Study design:	Multi-center open-label study in patients with transfusion-dependent blood disorders who are currently taking deferiprone immediate release tablets (Ferriprox®) for the treatment of systemic iron overload. There will be two treatment groups, defined as "low dosage" (Group A) and "high dosage" (Group B). With Ferriprox, the recommended starting dosage is 75 milligrams per kilogram of body weight (mg/kg) per day and the recommended maximum is 100 mg/kg per day, but for most patients, the precise daily amount differs from either of these values since doses must be tailored to the individual patient's response and therapeutic goals and rounded to the nearest half-tablet. Study participants will be assigned to Group A or Group B depending on which end of the range their Ferriprox intake is closer to, with equal numbers of patients enrolled in each group: • **Group A, low dosage:** Patients currently taking Ferriprox tablets at a dosage that is closer to 75 mg/kg/day (n=15) • **Group B, high dosage:** Patients currently taking Ferriprox tablets at a dosage that is closer to 100 mg/kg/day (n=15) In each group, participants will be provided with deferiprone DR tablets to be taken twice daily (b.i.d.) for 28 days at a total daily dosage the matches the total amount of Ferriprox they have been taking three times daily (t.i.d.) as closely as possible. Individual doses will be rounded to the nearest 500 mg half-tablet. Doses are always to be taken with food. Following the last dose, patients will return to their regular chelation regimen.

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Study design (cont'd):	Screening will be conducted within 14 days prior to the start of dosing, and with the exception of hematology, laboratory results obtained at that time will be treated as the baseline values. Blood samples will be collected for the assessment of biochemistry (screening and Days 3, 7, 14, 21, and 28), hematology (screening, baseline, and Days 7, 14, 21, and 28), serology (screening only), and other safety parameters (screening and Day 28); and urine samples will be collected for urinalysis (screening and Day 28). For the Day 3, 7, 14, and 21 samples, patients may choose to visit a local laboratory instead of the study site; if this is done, they must use the same laboratory throughout the entire study. If deemed necessary, patients with ongoing adverse events may be asked after the last dose to provide further blood samples until resolution. On Day 28, patients will be asked for their views on the acceptability of the delayed release formulation vs. the immediate release (Ferriprox) tablets. Any patient who withdraws before completing treatment will be requested to return for an Early Termination visit, at which time the procedures scheduled for the Day 28 visit will be conducted. As this will be the first time that deferiprone DR is administered to patients with iron overload, as a precaution, enrollment will be conducted progressively in small groups, and safety results will be reviewed following the enrollment of a limited number of patients. Decisions regarding continuation will be based on the findings.
Duration of participation:	The duration of participation will be 28 days, excluding the screening period.
Criteria for evaluation:	<u>Safety</u> In recognition of the variability of levels of the liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in patients with iron overload, the criterion for deciding whether an individual patient's increases for each of these enzymes during the study constitute a safety concern will be set as follows: • For a patient whose level is within the normal range at baseline, the criterion will be reaching a value of 5 times the upper limit of normal (ULN) • For a patient whose level is above the ULN at baseline, the criterion will be reaching a value of 5 times the baseline value or 10 x ULN For each dosage group, the following will be determined: • The number and percentage of patients with increased post-dose levels of ALT and/or AST that meet either of the criteria defined above • Adverse events (AEs): Frequency, intensity, time to onset, duration, and relatedness to study drug

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Criteria for evaluation (cont'd):	• Serious adverse events (SAEs): Frequency, intensity, time to onset, duration, and relatedness to study drug • Number of discontinuations due to AEs <u>Acceptability</u> At the end of the treatment, patients will be asked to complete a questionnaire as to what their preference is between the two formulations (Ferriprox IR tablets vs. deferiprone DR tablets) with respect to scheduling, convenience of administration, and tolerability.
Number of patients:	A total of 30 patients will be enrolled in this study, 15 in each dosage group.
Diagnosis and main criteria for inclusion:	<u>Main inclusion criteria</u> • Male or female aged ≥ 18 years • Diagnosis of thalassemia syndrome, sickle cell disease, or other disorder requiring a regular regimen of red blood cell transfusions • On a stable regimen (≥3 months) of Ferriprox tablets for the treatment of systemic iron overload • A record of at least the last 12 measured ALT and AST levels prior to baseline <u>Main exclusion criteria</u> • ALT and/or AST value > 5 x ULN at screening • Active case of hepatitis B or C at screening
Investigational product:	Product: Deferiprone delayed release (DR) 1000 mg tablets Dose: All patients will receive deferiprone DR at approximately the same total daily dosage at which they were taking Ferriprox (Group A: closer to 75 mg/kg/day; Group B: closer to 100 mg/kg/day), approximately 12 hours apart, rounded to the nearest 500 mg half-tablet Mode of administration: Oral
Schedule of treatment and specimen collection:	<u>Schedule of Treatment</u> Patients will receive 28 days of b.i.d. dosing with deferiprone DR tablets. • Biochemistry: Screening and Days 3, 7, 14, 21, and 28 • Hematology: Screening, baseline, and Days 7, 14, 21, and 28 • Coagulation: Screening and Day 28 • Serology: Screening

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Schedule of treatment and specimen collection (cont'd):	• Urinalysis: Screening and Day 28 • Physical examination: Screening and Day 28 • Vital signs: Screening and Day 28 • Serum pregnancy test (if applicable): Screening and Day 28 • Adverse events: Throughout the study • Prior and concomitant medications: Throughout the study *Notes:* - With the exception of hematology, laboratory results obtained at screening will be treated as the baseline values. - There will be a window of ±1 day for assessments done at Days 3 and 7, and of ±2 days for assessments done at Days 14, 21, and 28. - The investigator may increase the frequency of safety evaluations if deemed appropriate for assessment of any clinically significant adverse event. In the case of increases in liver enzymes that meet the criteria for being considered a safety concern, the patient is to be followed until resolution of the event, beyond Day 28 if necessary. - If a patient withdraws from the study, the End of Study procedures are to be performed at an early termination visit. <u>Schedule of Evaluation of Acceptability</u> Questionnaire on patient preference for IR vs. DR formulation: Day 28
Statistical methods:	The Clopper-Pearson 95% confidence interval (CI) of the incidence of post-dose levels of ALT or AST that meet the criteria for being considered a safety concern will be calculated for each dosage group. Similarly, the Clopper-Pearson 95% CI of the incidence of gastrointestinal (GI) distress reported by patients during the study will also be calculated. Other AEs will be summarized by using frequency tables. The incidence of abnormal data for safety measures will be presented for each dosage group. The continuous and discrete variables for safety data will be summarized with descriptive statistics (mean, median, standard deviation, minimum, and maximum) and frequency tables, respectively, at each assessment. For each dosage group, frequency tables will be used to summarize the response to each question of the questionnaire on treatment acceptability between Ferriprox IR vs. deferiprone DR. Based on the responses to the question on overall preference for one formulation or the other, a one-sample proportion test will be used to test if the overall preference for deferiprone DR is greater than 0.5 for each dosage group.
Version and date of the protocol:	Version 1.0, 10 OCT 2018

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LIST OF IN-TEXT TABLES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
b.i.d.	twice daily
CS	clinically significant
CI	confidence interval
C_{max}	maximum observed plasma concentration over a dosing interval
CRO	contract research organization
eCRF	electronic case report form
DR	delayed release
EDC	electronic data capture
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IR	immediate release
IRB	Institutional Review Board
ME	medical event
MedDRA	Medical Dictionary for Regulatory Activities
NCS	not clinically significant
PK	pharmacokinetics
RBC	red blood cell
SAE	serious adverse event
t.i.d.	three times daily
ULN	upper limit of normal
WHO	World Health Organization

1 INTRODUCTION

1.1 Background

Beta thalassemia and certain other hereditary blood disorders are characterized by abnormal forms of hemoglobin that lead to excessive destruction of red blood cells and severe anemia, necessitating frequent and lifelong red blood cell (RBC) transfusions. As each RBC unit contains approximately 200 mg of iron and there is no natural mechanism for the excretion of extra iron, body iron accumulates rapidly in the absence of chelation treatment, with particular impact on the heart, endocrine glands, and liver. While iron plays an essential role in many metabolic pathways, free iron is toxic to cells, acting as a catalyst in the formation of free radicals and leading to morbidity and mortality. Accordingly, life-long iron chelation therapy is necessary for survival.

Deferiprone (3-hydroxy-1,2-dimethylpyridin-4-one) is a bidentate iron chelator that binds ferric iron tightly in a 3:1 (deferiprone:iron) molar ratio and has markedly lesser affinity for other cations. Deferiprone's small molecular size, lack of charge at physiological pH, and balanced octanol:water partition coefficient support cell permeability and rapid access to both extracellular and intracellular labile iron stores.[1]

Immediate-Release Deferiprone

Three commercial oral formulations of immediate release (IR) deferiprone are currently marketed by ApoPharma Inc. under the brand name Ferriprox®: 500 mg film-coated tablets, 1000 mg film-coated tablets, and a 100 mg/mL oral solution. In the European Union, all 3 formulations have been approved by the European Medicines Agency (EMA) for the treatment of iron overload in patients with thalassemia major for whom deferoxamine therapy is contraindicated or causes serious toxicity. In the United States, the Food and Drug Administration (FDA) has approved the 500 mg tablets and the 100 mg/mL oral solution for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate; and in Canada, all three formulations of Ferriprox were approved in 2015 by Health Canada for the same indication.

Ferriprox must be taken three times a day, at a total daily dosage of 75 up to 99 or 100 mg/kg (i.e., 3 equal doses of 25 to 33 mg/kg t.i.d.). However, post-marketing feedback from both clinicians and patients has indicated that the number of tablets per day, as well as the need to take a dose in the middle of the day, creates a situation where the choice is sometimes made to forgo the mid-day dose, particularly in the case of school-age children. The scale of this omission has not been formally assessed, but the frequency with which ApoPharma is asked if Ferriprox can be taken twice instead of three times daily supports the intuitive sense that mid-day dosing is a bona fide concern for a significant segment of the patient population.

Delayed-Release Deferiprone

In an effort to improve patient compliance, ApoPharma Inc. has developed a 1000 mg delayed release (DR) deferiprone tablet that would support twice-daily (b.i.d.) administration instead of the t.i.d. regimen required for the IR tablets. It contains an enteric coating to significantly decrease drug release in the stomach, and the composition of the core allows half-tablets to provide similar bioavailability of drug as that from a whole tablet. To date, the DR formulation has been assessed in four ApoPharma-sponsored trials in healthy volunteers: two that looked at pharmacokinetics (PK) and two that looked at tolerability, with one of the tolerability studies adding a special focus on the effect of this formulation on liver enzyme levels.

In the first PK study, **LA53-0116** (N=28), healthy volunteers received a single 1000 mg dose of deferiprone DR (equivalent to about 15 mg/kg for a subject weighing 70 kg) in the forms of a whole tablet under fed conditions, a whole tablet under fasting conditions, and two half-tablets under fed conditions. In the second, **LA45-0116** (N=36), healthy volunteers subjects received a total daily dosage of 3000 mg of deferiprone DR (equivalent to about 45 mg/kg for an average-weight subject), divided into 2 equal doses per day, for 3 consecutive days, under fed conditions. Both trials included a control treatment of the licensed Ferriprox IR tablets, administered as a single dose in the first trial and as a t.i.d. regimen in the second, and both involved a comparison of the safety and tolerability of the two formulations as well as of PK parameters. It was demonstrated that the extent of drug exposure (i.e., AUC) of the DR formulation was equivalent to that of the IR tablet after a single dose. There were no significant food effects on the pharmacokinetics of the DR formulation. There were also no differences in drug exposure between a whole tablet and two half-tablets of the DR formulation. At steady state, the PK profile of the two dose administrations of DR over a 24-hour period under fed conditions demonstrated a peak (i.e., C_{max}) and extent of drug exposure that were equivalent to those of the three dose administrations of IR over a 24-hour period. With respect to safety, the DR tablet at this dosage was found to be safe and well tolerated.

Study **LA58-0117**, with a planned sample size of 86, was a Phase I study that evaluated the gastrointestinal (GI) tolerance of deferiprone DR. Healthy subjects were randomized to receive the highest approved dosage (100 mg/kg daily) of either deferiprone DR or Ferriprox IR for 3 days, with dosing conducted in the fasting state in order to assess tolerability under the conditions most likely to induce GI distress, even though the 24-hour bioequivalence of DR and IR tablets had been demonstrated only in the fed state in study **LA45-0116**. Subjects randomized to deferiprone DR received 50 mg/kg b.i.d., while those randomized to Ferriprox received 33 mg/kg t.i.d. While the study was still in progress, it was observed that of the 19 participants at that time who had received the DR formulation, 31.6% experienced nausea and 26.3% experienced vomiting, compared to rates of 20.0% and 0.0%,

respectively, among the 20 subjects who had received Ferriprox. None of the events were deemed to be serious or severe, but in 2 cases they led to voluntary withdrawal. The study was terminated early as it was determined that sufficient information had been obtained on the GI tolerance of deferiprone DR in the fasting state. The subsequent study, **LA60-0118** (N=50), assessed the tolerability of deferiprone DR in healthy volunteers in the fed state, which is the condition under which iron-overloaded patients will be instructed to take it, as its 24-hour bioequivalence to Ferriprox IR tablets was demonstrated under fed conditions.

In both study LA58-0117 and the subsequent study LA60-0118, the dosage of deferiprone DR was set at 100 mg/kg/day (50 mg/kg b.i.d.), which is the maximum recommended dose that would be prescribed to patients for the treatment of systemic iron overload. While LA60-0118 was in progress, it was observed that half the subjects dosed to date had asymptomatic elevated levels of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), with approximately 20% reaching values of approximately 5 times the upper limit of normal (ULN) and 1 subject reaching 8 x ULN. Subjects remained asymptomatic, and liver enzyme levels returned to normal following the last dose. The protocol was amended to reduce the dosage for the remaining subjects to 75 mg/kg/day (37.5 mg/kg b.i.d.), which is the dose normally prescribed for the treatment of iron-overload at the start of therapy, in order to evaluate if there is a dose-related effect with regard to elevation of liver enzymes in healthy volunteers. That study is ongoing.

1.2 Rationale

According to pharmacokinetic bioequivalence criteria, adverse events that depend on C_{max} and/or AUC would be expected to be the same for two formulations that provide equivalent C_{max} and AUC over a 24-hour period. While transient liver enzyme elevations are a known adverse event at initiation of therapy with Ferriprox IR, particular attention will be paid to this effect in the current study given the rate of elevated liver enzymes seen in the Phase I study. While the reason for that happening is unclear, it is hypothesized that this effect will be less prominent in iron-overloaded individuals, since with them, unlike in healthy volunteers, deferiprone will rapidly bind to excess iron and will thus be less available for involvement in other biochemical reactions.

Previous clinical trials of deferiprone IR in patients with thalassemia have shown that ALT values in individual patients fluctuate, with declines from baseline of up to 369 U/L and increases from baseline of up to 564 U/L.[2] ALT levels of at least twice the upper limit of the reference range have been observed in up to 60% of patients treated with deferiprone.[3] In the majority of these patients, the increase is asymptomatic and returns to baseline levels without discontinuation or dose reduction of deferiprone. In ApoPharma clinical trials, elevations of liver enzymes led to discontinuation of deferiprone therapy in only 5 of 889 patients; 4 (0.4%) due to increased serum ALT levels and 1 (0.1%) due to an increase in both ALT and AST.

The current study will evaluate deferiprone DR in the target population of iron-overloaded patients. Participants must have been on Ferriprox IR tablets for at least 3 months at the time of enrollment, and will be switched to deferiprone DR tablets for 28 days at approximately the same daily dosage at which they have been taking Ferriprox IR. The study will thus be able to evaluate if switching from the IR to the DR formulation will have an impact on liver enzyme levels. Some increases are to be expected in this population, due to liver iron overload and frequent blood transfusions, and may be considered acceptable. In recognition of this, study participants' past record of liver enzyme levels will be taken into account when assessing safety concerns. With regard to other adverse effects, because of the higher than expected rates of gastrointestinal events that were observed in healthy volunteers (studies LA58-0117 and LA60-0118), attention will be paid to the occurrence of GI events as well.

Finally, in addition to the assessments of safety and tolerability, the study will allow for patients' input on the acceptability of this new formulation and of the change in dosing from t.i.d. to b.i.d.

1.3 Potential Risks and Benefits

The safety profile of two formulations is expected to be the same since they provide equivalent drug exposure over a 24-hour period. The elevations of ALT and AST that were seen in the Phase I subjects following b.i.d. dosing with deferiprone DR were not of clinical concern. However, it is possible that this formulation has a greater impact on liver enzymes than does t.i.d. dosing with the immediate-release formulation, at least in healthy volunteers. Whether this difference extends to patients with systemic iron overload is not yet known. Nevertheless, no other safety concerns were identified following a 3-day dosing period in healthy volunteers.

Comprehensive safety information on Ferriprox is provided in the Investigator's Brochure for that product.[4] In clinical trials, the most common adverse reactions were nausea, vomiting, and chromaturia (seen in more than 10% of patients) and increased ALT, arthralgia, and neutropenia (seen in more than 1% of patients); and the most serious adverse reaction was agranulocytosis, defined as an absolute neutrophil count (ANC) less than 0.5×10^9/L. Agranulocytosis has been reported in approximately 2% of patients taking Ferriprox, and less severe episodes of neutropenia (ANC $< 1.5 \times 10^9$/L but $> 0.5 \times 10^9$/L) have been reported in approximately 6.4% of patients. In clinical trials, all events of agranulocytosis or neutropenia resolved upon discontinuation of Ferriprox. Because of this known risk, participants in the present study will undergo safety monitoring that includes a weekly blood count to ensure early detection in case of a significant drop in ANC.

With respect to benefit, as bioequivalence of deferiprone DR tablets to Ferriprox IR tablets over a 24-hour period has been demonstrated, it is expected that study participants will achieve at least the same efficacy that they have been obtaining from Ferriprox. Furthermore,

given the recognized concerns associated with t.i.d. dosing, the opportunity to achieve the same control of iron overload through a less onerous regimen may be perceived as an advantage by some patients.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to evaluate the safety of deferiprone DR tablets in two different dosage groups in patients with systemic iron overload.

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

2.2 Secondary Objectives

- To evaluate the tolerability of deferiprone DR tablets in two different dosage groups in patients with systemic iron overload
- To evaluate the acceptability to patients of deferiprone DR

The endpoints for the secondary objectives provided in Section 9.1.2.

3 STUDY DESIGN

3.1 Description of Study Design

This is a multi-center open-label study in patients with transfusion-dependent blood disorders who are currently taking deferiprone immediate release tablets (Ferriprox) for the treatment of systemic iron overload. There will be two treatment groups, defined as “low dosage” (Group A) and “high dosage” (Group B). With Ferriprox, the recommended starting dosage is 75 milligrams per kilogram of body weight (mg/kg) per day and the recommended maximum is 100 mg/kg per day, but for many patients, the precise daily amount differs from either of these values since doses must be tailored to the individual patient’s response and therapeutic goals and rounded to the nearest half-tablet. Study participants will be assigned to Group A or Group B depending on which end of the range their Ferriprox intake is closer to, with equal numbers of patients enrolled in each group:

- Group A, low dosage: Patients currently taking Ferriprox tablets at a dosage that is closer to 75 mg/kg/day (n=15)
- Group B, high dosage: Patients currently taking Ferriprox tablets at a dosage that is closer to 100 mg/kg/day (n=15)

In each group, participants will be provided with deferiprone DR tablets to be taken twice daily (b.i.d.) for 28 days at a total daily dosage the matches the total amount of Ferriprox they have been taking three times daily (t.i.d.) as closely as possible. Individual doses will be rounded to the nearest 500 mg half-tablet. Doses are always to be taken with food. Following the last dose, patients will return to their regular chelation regimen.

Screening will be conducted within 14 days prior to the start of dosing, and with the exception of hematology, laboratory results obtained at that time will be treated as the baseline values. Blood samples will be collected for the assessment of biochemistry (screening and Days 3, 7, 14, 21, and 28), hematology (screening, baseline, and Days 7, 14, 21, and 28), serology (screening only), and other safety parameters (screening and Day 28); and urine samples will be collected for urinalysis (screening and Day 28). For the Day 3, 7, 14, and 21 samples, patients may choose to visit a local laboratory instead of the study site; if this is done, they must use the same laboratory throughout the entire study. If deemed necessary, patients with ongoing adverse events may be asked after the last dose to provide further blood samples for up to 30 days or until resolution. On Day 28, patients will be asked for their views on the acceptability of the delayed release formulation vs. the immediate release (Ferriprox) tablets.

Any patient who withdraws before completing treatment will be requested to return for an Early Termination visit, at which time the procedures scheduled for the Day 28 visit will be conducted.

As this will be the first time that deferiprone DR is administered to patients with iron overload, as a precaution, enrollment will be conducted progressively in small groups, and safety results will be reviewed following the enrollment of a limited number of patients. Decisions regarding continuation will be based on the findings. Details are provided in Section 3.1.1.

3.1.1 Precautions Regarding Enrollment

The process to be followed with respect to enrollment is described below.

3.1.1.1 Criteria for Safety Concerns

As a consequence of liver iron overload and frequent blood transfusions, patients in the target population may have fluctuations of AST and/or ALT that frequently exceed the reference ranges. In recognition of this variability, for each of these enzymes, the criteria for deciding whether an individual patient's increases during the current study is of concern will be set as follows:

- For a patient whose baseline level is within the normal range, the criterion will be reaching a value of 5 times the ULN during the study.

- For a patient whose baseline level is above the ULN, the criterion will be reaching a value of 5 times the baseline value during the study or 10 x ULN.

All cases of patients meeting either of the above criteria at any point during the study must be reported to ApoPharma by the investigator within 24 hours of occurrence, using the sponsor's SAE form.

If at any time during the study a patient's ALT and/or AST values reach a level of **10 x ULN**, do the following:

- If the patient is symptomatic and/or has any other clinically significant abnormal laboratory results, immediately withdraw the patient from the study.
- If the patient is asymptomatic and has no other clinically significant abnormal laboratory results, interrupt treatment and obtain a confirmatory count the next day.
    - If the value is confirmed to be ≥10 x ULN**:**
        - Stop treatment, withdraw the patient and complete all end of study assessments scheduled for Day 28
        - Document the event and report it within 24 hours to ApoPharma
        - Monitor the patient daily until the elevated value returns to a level that is regarded as not clinically significant
    - If the confirmatory value is found to be < 10 x ULN, resume treatment as per protocol, and monitor liver enzyme levels within 3 days of resuming therapy.

3.1.1.2 Rules for Enrollment

The rules that will be applied for enrolling patients in each group are described below, using the criteria provided in Section 3.1.1.1. Decisions will be made by a safety committee whose composition is described in Section 8.

Sites will enroll and start the dosing of patients in both groups. Once enrollment has reached **5 patients in either group**, enrollment will be paused, the safety data of those 5 patients will be reviewed by the safety committee after all 5 have completed at least one week of dosing, and further enrollment will depend on whether the findings are satisfactory or raise safety concerns.

If the first group to reach an N of 5 is **Group A** (low-dosage):

- If there are no safety concerns after one week of dosing, the safety committee will issue approval for enrollment of all remaining patients in Group A and enrollment in Group B up to 5 patients. (The criteria for enrollment in Group B are described below.)

- If 2 or more of the first 5 patients in Group A reach the criteria defined in Section 3.1.1.1, the committee will issue approval for enrollment of just 5 more patients in Group A, and enrollment in Group B will be put on hold. Dosing of the first 5 Group A patients will continue, and the committee will review the data of the 10 Group A patients once all of them have completed at least 1 week of dosing.
    - At this point, if there are no safety concerns, the committee will issue approval for enrollment of the final 5 patients in Group A and for enrollment of Group B to resume, as per the criteria described for that group.
    - If 4 or more of the 10 patients in Group A who have been dosed to date reach the criteria defined in Section 3.1.1.1, enrollment of additional patients in both groups will be put on hold, and the following processes are to be conducted:
        - Any patients who have reached the criterion and are symptomatic and/or have other associated abnormal laboratory values are to be withdrawn from the study.
        - Patients who did not reach the criterion and for whom there are no other safety concerns should continue dosing.
        - Patients who did reach the criterion but are asymptomatic and do not have any other associated abnormal laboratory values should continue dosing, but must have their enzyme levels monitored every 2 days:
            - If just one patient experiences a confirmed elevation of ALT and/or AST ≥10 x ULN, that patient is to be withdrawn from the study, but enrollment of the final 5 Group A patients may proceed.
            - If two or more patients experience a confirmed elevation of ALT and/or AST ≥10 x ULN, treatment is to be interrupted for all patients, and the safety committee must promptly meet to review all available safety data and recommend whether or not the study should continue.

If the first group to reach an N of 5 is **Group B** (high-dosage):

- If there are no safety concerns after one week of dosing, enroll all remaining patients in the study.
- If 2 or more of the first 5 patients in Group B reach the criteria defined in Section 3.1.1.1, the committee will issue approval for enrollment of just 5 more patients in Group B. Dosing of the first 5 Group B patients will continue, and the committee will review the data of the 10 patients once all of them have completed at least 1 week of dosing. (Enrollment may continue in the meantime in Group A, provided the stopping criteria defined for that group are not met.)
    - At this point, if there are no safety concerns, the committee will issue approval for enrollment of the final 5 patients in Group B.
    - If 4 or more of the 10 patients in Group B who have been dosed to date reach the criteria defined in Section 3.1.1.1, enrollment of additional patients in Group B will be put on hold, and as the processes described below are to be conducted. (Enrollment may continue in the meantime in Group A, provided the stopping criteria defined for that group are not met.)
        - Any patients who have reached the criterion and are symptomatic and/or have other associated abnormal laboratory values are to be withdrawn from the study.
        - Patients who did not reach the criterion and for whom there are no other safety concerns should continue dosing.
        - Patients who did reach the criterion but are asymptomatic and do not have any other associated abnormal laboratory values should continue dosing but must have their enzyme levels monitored every 2 days:
            - If just one patient experiences a confirmed elevation of ALT and/or AST ≥10 x ULN, that patient is to be withdrawn from the study, but enrollment of the final Group B patients may proceed.
            - If two or more patients experience a confirmed elevation of ALT and/or AST ≥10 x ULN, treatment is to be interrupted for all patients, and the safety committee must promptly meet to review all available safety data and recommend whether or not the study should continue

Repeat assessments to confirm laboratory results may be performed. The decision on whether to put the study on hold or terminate it will be made by the safety committee.

If a confirmed elevation of ALT and/or AST **> 10 x ULN** is experienced by **two subjects in the same dosage group**, a review of the data must immediately take place to decide whether or not the study should continue. The investigator must report any occurrence of this to the sponsor within 24 hours of occurrence, using the sponsor's SAE form.

3.2 Rationale for Study Design

Study population: To date, four Phase I trials have been or are currently being conducted to assess the safety, tolerability, and pharmacokinetics of deferiprone delayed release tablets in healthy volunteers. This study will be the first to look at the DR formulation in the population for which it is intended. It is possible that the rates of adverse events that were seen in healthy subjects would occur at different rates in patients, due to the different action of an iron chelator in iron-overloaded vs. non-iron-loaded recipients.

Dosages: Patients with systemic iron overload are usually prescribed deferiprone at a dosage ranging from 75 mg/kg/day to 100 mg/kg/day. Dosages within both the upper half and the lower half of this range will be investigated, to determine if there is a dose effect on the adverse events that were seen in healthy subjects (due to tailoring of dosages to individual patient needs and to rounding, most potential subjects will not be on a dosage of Ferriprox that is exactly 75 mg/kg/day or exactly 100 mg/kg/day). In all cases, the total daily dosage of deferiprone DR will be made to match that of Ferriprox IR as closely as possible. Since dosages will be rounded to the nearest 500 mg and body weights of participants will differ, some variability is unavoidable.

Safety Precautions: The findings from the first 5 participants to be enrolled in either dosage group will be assessed before enrollment can continue. Details are provided in Section 3.1.1. As a further precaution, alert events have been defined that will mandate extra monitoring or termination from the study in any patient in whom they are observed. Information on alert events is provided in Section 4.5.1.

Endpoints: The endpoints are safety and acceptability. No endpoints for efficacy have been included, as bioequivalence of deferiprone DR tablets to Ferriprox IR tablets over a 24-hour period has already been demonstrated.

3.3 Rationale for Selection of Doses

For Ferriprox, dosages of 75 mg/kg/day and 100 mg/kg/day represent the most common starting dose and the maximum recommended dose, respectively, of the therapeutic dose range approved for patients with systemic iron overload. The dosage groups in this study will be within either the upper half or the lower half of this range.

The Phase I studies LA58-0118 and LA60-0118, conducted in healthy volunteers, both evaluated the maximum recommended dose of deferiprone (100 mg/kg/day) without the titration that is

normally recommended for initiation of treatment in patients with iron overload. In both studies, following receipt of deferiprone DR, there were higher than expected percentages of subjects with GI events and elevated liver enzymes. It is possible that starting the dosing directly at 100 mg/kg/day with no titration may have been a factor in the occurrence of both types of events. It is also known that healthy volunteers are more adversely impacted by an iron chelator in ways that iron-overloaded patients would not be. That is, these events may prove to be less prominent in the latter since with them, deferiprone will rapidly bind to excess iron and will thus be less available for involvement in other biochemical reactions. As the maximum recommended dosage of deferiprone is essential in some patients, it is important to assess dosages at the high end of the range in the target population, with safety measures in place to ensure that participants are not placed at undue risk. In the case of liver enzymes, increases in ALT and AST are commonly observed in patients with transfusion-dependent thalassemia, irrespective of deferiprone therapy, and thus the clinical significance of any increase needs to be evaluated in individual patients based on their medical history.

Comparison of the low and high dosages will allow for assessment of a dose effect of deferiprone. In healthy volunteers, in contrast to the elevated ALT and AST levels seen at 100 mg/kg/day, no such concerns were observed in the earlier study LA45-0116, which employed a fixed dosage of 1500 mg b.i.d., the equivalent of about 20 mg/kg in an average-weight (70 kg) person. There would be no purpose in assessing a sub-therapeutic dosage in patients, but it will be of interest to see if there are fewer or less severe liver enzyme elevations in the lower dosage group.

4 STUDY POPULATION

4.1 Number of Patients

A total of 30 patients will be enrolled in this study, 15 in each dosing dosage group.

4.2 Inclusion Criteria

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

1. Male or female aged ≥ 18 years.
2. Diagnosis of thalassemia syndrome, sickle cell disease, or other disorder requiring a regular regimen of red blood cell transfusions.
3. On a stable regimen (≥3 months) of Ferriprox tablets for the treatment of systemic iron overload.
4. Absolute neutrophil count ≥1.5 x 10^9/L at screening.
5. A record of at least 12 measured ALT and AST levels.

6. A female volunteer must meet one of the following criteria:
   - If of childbearing potential, have a negative pregnancy test result at screening. In addition, she must:
     a. Agree to use an effective method of contraception according to local requirements, during the study and afterwards, OR
     b. Have undergone a tubal ligation (supporting evidence required), OR
     c. Abstain from heterosexual intercourse, OR
     d. Have a male sexual partner who has been sterilized (supporting evidence required)
   - Be of non-childbearing potential, defined as surgically sterile, having undergone complete hysterectomy or bilateral oophorectomy (supporting evidence required) or being in a menopausal state (at least 1 year without menses)
7. Fertile heterosexual males and/or their partners must agree to use an effective method of contraception during the study and afterwards.
8. All patients and/or their authorized legal representatives must provide signed and dated written informed consent prior to the first study intervention, and patients must be able to adhere to study restrictions, appointments, and evaluation schedules.

4.3 Exclusion Criteria

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

1. Receipt of any iron chelator other than Ferriprox (i.e., combination therapy) in the last 3 months, or planning to receive it at any time during the period of the study.
2. ALT and/or AST value > 5 times the upper limit of normal (ULN) at screening
3. Active case of hepatitis B or C at screening.
4. Positive for HIV at screening.
5. A serious, unstable illness, as judged by the Investigator, during the past 3 months before screening/baseline visit including but not limited to: hepatic, renal, gastroenterologic, respiratory, cardiovascular, endocrinologic, neurologic, or immunologic disease.
6. Evidence of abnormal kidney function at screening (creatinine levels >2 x ULN).
7. Myocardial infarction, cardiac arrest or cardiac failure within 1 year before screening/ baseline visit.
8. Bowel disease causing malabsorption.
9. History of allergy or sensitivity to the study product or related compounds or to other components of the formulation.

10. Receipt of any investigational products within the past 30 days or 5 half-lives (whichever is longer) preceding the first dose of study medication.
11. Participation in any investigational clinical study, other than observational, within the past 30 days; or plans to participate in such a study at any time from the day of enrollment until 30 days post-treatment in the current study.
12. History of drug or alcohol abuse within the last 6 months.
13. Presence of any medical, psychological, or psychiatric condition which in the opinion of the investigator would cause participation in the study to be unwise.
14. Pregnant, breastfeeding, or planning to become pregnant during the study period.
15. Identified as an investigator or other site staff directly affiliated with this study, or an immediate family member (spouse, parent, child, or sibling, whether biological or legally adopted) of either of the above.

4.4 Enrolment Violations

The criteria for enrolment must be followed explicitly. If there is inadvertent enrolment of 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 7.1.4)
- A confirmed ALT or AST value >10 x ULN (see Sections 4.5.1.1 and 7.1.1.8.1)
- A confirmed ANC value < 0.5 x 10^9 (see Sections 4.5.1.2 and 7.1.1.8.2)
- Occurrence of any adverse event characterized as life-threatening or disabling that is not associated with the patient's condition
- 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 until resolution.

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

4.5.1 Alert Events and Individual Stopping Rules

Certain events are defined in this study as alerts, meaning that any occurrence must be carefully monitored, and in some cases may mandate withdrawal of a patient or even early termination of the study.

4.5.1.1 Elevated Liver Enzymes

A patient who reaches an ALT and/or AST value ≥10 x ULN at any time during the study is to be **immediately** withdrawn if he or she is additionally symptomatic and/or has any other clinically significant abnormal laboratory results. If there are no other signs of concern, a confirmatory count is to be obtained the next day. If the value is confirmed, the patient is to be withdrawn; if it is not, the patient is to be closely monitored. Details are provided in Section 3.1.1.1.

4.5.1.2 Neutropenia

A sudden drop in absolute neutrophil count (ANC) is a reaction that has been associated with deferiprone treatment and is considered an adverse event of special interest. ANC values will be monitored throughout the study. For a case of mild, moderate, or severe neutropenia to be confirmed, there must be 2 consecutive counts of ANC, a maximum of 3 days apart,

that are both less than a specific value. If at any time, a patient's confirmed ANC level is found to be below < 1.5 x 10^9/L, the investigator is to do the following:

- *Mild neutropenia:* If the confirmed ANC is < 1.5 x 10^9/L but ≥1.0 x 10^9/L, continue treatment without interruption, but monitor ANC every 2 days until resolution.
- *Moderate neutropenia:* If the confirmed ANC is < 1.0 x 10^9/L but ≥ 0.5 x 10^9/L, interrupt treatment and monitor ANC every 2 days until resolution. The patient should re-initiate treatment once the event is resolved. If ANC is still < 1.5 x 10^9/L after 14 days, withdraw patient from the study and monitor until resolution of the event.
- *Severe neutropenia / agranulocytosis:* If a single ANC is < 0.5 x 10^9/L, immediately interrupt treatment without waiting for confirmation of the count and obtain a second measurement the following day. If the second ANC is still < 0.5 x 10^9/L, permanently withdraw the patient from the study and follow the procedures for the management of agranulocytosis.

Details on the management of each category of neutropenia are provided in Section 7.1.1.8.2.

4.5.1.3 Infection

If a patient reports any symptoms indicative of infection such as fever, sore throat, or flu-like symptoms, interrupt treatment immediately and obtain an ANC measurement, and monitor ANC more frequently; every 2 days if it is below <1.5 x 10^9/L but ≥ 0.5 x 10^9/L. Therapy can be re-initiated once all symptoms have been resolved and it is deemed safe by the investigator. (If ANC is found to be above 1.5 x 10^9/L, treatment can be continued if the investigator assesses the patient and considers continuation to be safe. Treatment should be interrupted in any case of fever of 38.5°C or greater.)

4.5.2 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 #5) 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

A male patient must inform the investigator if his female partner becomes pregnant during the trial or within 1 month following the last dose of study medication. As with the pregnancy of a female 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.

4.5.3 Replacement of Patients Who Withdraw

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

4.6 Prior and Concomitant Therapies

To be considered for enrollment, patients cannot be taking any iron chelator other than Ferriprox. Those who are on a combination regimen of Ferriprox and another product are not eligible.

In addition, during the trial, they may not take any other investigational product, or any drugs that are known to cause agranulocytosis. Medications that are being taken on a stable regimen and that are considered necessary for the subject'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 taken from 3 months prior to screening up to the end of the study (Day 28 or early termination) must be reviewed by the investigator and recorded in the source document and in the appropriate section of the eCRF.

4.7 Rescue Medication

Patients will be assigned to Group A or Group B based on the total daily dosage of Ferriprox they have been taking for the last 3 months (i.e., closer to 75 mg/kg/day or closer to 100 mg/kg/day) and must remain on their assigned dosage for the duration of the study. If it is determined during the study that a change in dosage or the addition of another chelator is required to control iron load, that patient will be withdrawn from the trial.

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

Study Procedure	Screening Day -14 to -1	Baseline Day 0	Day 3 (±1 day)	Day 7 (±1 day)	Day 14 (±2 days)	Day 21 (±2 days)	Day 28 (±2 days) or early termination [1]
Informed consent	X						
Demography	X						
Medical history [2]	X						
Medication history	X	X					
Eligibility criteria	X	V					
Biochemistry [3]	X		X	X	X	X	X
Hematology [4]	X	X		X	X	X	X
Coagulation [5]	X						X
Serology [6]	X						
Urinalysis [7]	X						X
Physical examination [8]	X						X
Vital signs	X						X
Serum pregnancy test [9]	X						X
Dispense study medication		X					
Dosing		Twice-daily from Day 1 to Day 28					
Collect study medication containers							X
Treatment compliance							X
Medical events	X	X					
Adverse events/ serious adverse events			Throughout the study				
Concomitant medications			Throughout the study				
Acceptability questionnaire							X

V: Verify

1. If deemed necessary, patients with ongoing adverse events may be asked after the last dose to provide further blood samples until resolution
2. Medical history is to include a record of at least 10 measured ALT and AST levels
3. Biochemistry: Total protein, gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), sodium, potassium, chloride, glucose, bilirubin (total, direct, and indirect), alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, blood urea nitrogen, calcium, creatinine, uric acid, alkaline phosphatase, amylase, serum ferritin, and blood iron
4. Hematology: Hemoglobin, total WBC count, ANC, MCV, and platelet count
5. Coagulation: Prothrombin Time (PT), Partial Thromboplastin Time (PTT), and International Normalized Ratio (INR)
6. Serology: HIV Ag/Ab Combo, hepatitis B (HBsAg (B)), and hepatitis C (anti-HCV (C))
7. Urinalysis: Color, appearance, specific gravity, pH, leukocyte, protein, glucose, ketones, bilirubin, blood, nitrite, urobilinogen. Microscopic examination must be performed if dipstick test is outside the reference range for leukocyte, blood, nitrite or protein. (Note: for patients with sickle cell disease, samples are to be sent for microscopy if there is blood in the urine or three or more “plus signs” for protein.)
8. At screening, a full physical examination will be performed, including measurement of weight. At Day 28 (or early termination), only a symptom-oriented examination will be performed.
9. Pregnancy testing (females only): Beta-HCG qualitative serum pregnancy test

5.1 Visit Procedures

Details on the procedures to be carried out at each study day are provided below. For details of the safety assessments, see Section 7.1.

Note: The procedures at screening, baseline, and Day 28 must be conducted at the study site. The procedures on all other study days may be handled via a telephone call (for collection of information on adverse events and concomitant medications) and at a local laboratory (for collection of blood samples for safety assessments). If a patient chooses to go to a local laboratory, the same one must be used throughout the entire study.

Screening Visit (Day -14 to Day -1)

- Explain the study to the prospective participant, and obtain written informed consent
- Collect demographic information
- Collect medical history
- Collect history of the last 12 or more ALT and AST results
- Collect information on prior and concomitant medications including current chelation therapy
- Collect blood samples for assessment of the following:
    - Biochemistry
    - Hematology
    - Coagulation
    - Serology
    - Pregnancy testing (women of childbearing potential only)
- Collect a urine sample for urinalysis. Microscopic examination must be performed if dipstick test is outside the reference range for leukocyte, blood, nitrite or protein. (Note: for patients with sickle cell disease, samples are to be sent for microscopy if there is blood in the urine or three or more "plus signs" for protein.)
- Perform a physical examination (to be completed by the principal investigator or a qualified delegate), including weight
- Measure vital signs (heart rate, blood pressure, and body temperature)
- Record any medical events that have occurred after the consent form was signed

Patients who are found to be eligible will complete the procedures below.

Baseline Visit (Day 0)

- Verify that the patient has met all inclusion/exclusion criteria
- Collect information on prior and concomitant medications
- Collect a blood sample for hematology
- Collect any medical events that have occurred since the previous visit
- Conduct contraceptive counseling if applicable
- Dispense an appropriate supply of deferiprone DR tablets at the specified dosage (see Section 6.1.1), along with instructions on how to take them. The first dose is to be taken the next day, in the morning. Patients are to be instructed to always take the medication with food.
- Provide patient with an emergency card with contact information, and explain that it is to be carried at all times
- Instruct patient to do the following:
  - Keep a record of all dosing, any concomitant medications that are taken, and any health problems that occur
  - In the event of any symptoms indicative of infection such as fever, sore throat, or flu-like symptoms, immediately interrupt therapy and contact the clinic
  - At the final visit, bring back the completed notes plus all medication containers, whether empty, partly used, or unopened
  - In the event of a decision to withdraw from the study before completion, return to the clinic for an Early Termination Visit as soon as possible, and no later than one month following the last dose of study medication

Day 3 (±1 day)

- Collect a blood sample for assessment of biochemistry (site visit or local laboratory)
- Collect information on concomitant medications (site visit or telephone call)
- Collect information on any adverse events that have occurred since the previous visit (site visit or telephone call)
- Remind the patient to keep a record of all dosing, any concomitant medications that are taken, and any health problems that occur

Days 7, 14, and 21 (±1 day for Day 7, ±2 days for the remainder)

- Collect blood samples for assessment of the following (site visit or local laboratory):
  - Biochemistry
  - Hematology
- Collect information on any adverse events that have occurred since the previous contact (site visit or telephone call)
- Collect information on concomitant medications (site visit or telephone call)
- Remind the patient to do the following:
  - Keep a record of all dosing, any concomitant medications that are taken, and any health problems that occur
  - Day 21 only: Bring back the completed notes plus all medication containers, whether empty, partly used, or unopened

Day 28 (±2 days) or Early Termination

- Collect blood samples for assessment of the following:
  - Biochemistry
  - Hematology
  - Coagulation
  - Pregnancy testing (women of childbearing potential only)
- Collect a urine sample for urinalysis. Microscopic examination must be performed if dipstick test is outside the reference range for leukocyte, blood, nitrite or protein. (Note: for patients with sickle cell disease, samples are to be sent for microscopy if there is blood in the urine or three or more "plus signs" for protein.)
- Perform a symptom-oriented physical examination (to be completed by the principal investigator or a qualified delegate)
- Measure vital signs (heart rate, blood pressure, and body temperature).
- Review information that has been noted by the patient about doses taken, concomitant medications, and adverse events
- Collect medication containers
- Verify treatment compliance through tablet count and review of information in the patient's notes
- Collect information on any adverse events that have occurred since the previous contact

- Collect information on concomitant medications
- Administer questionnaire on the acceptability of deferiprone DR vs. that of Ferriprox

If deemed necessary, patients with ongoing laboratory-related events may be asked after the last dose to provide further blood samples until resolution.

5.2 Method of Assignment to Treatment

All patients must have been on a stable regimen of Ferriprox IR tablets for at least the past 3 months, and will be assigned to take deferiprone DR at approximately the same daily dosage that they are currently on. Those who are presently on Ferriprox at a dosage closer to 75 mg/kg/day will be assigned to Group A, and those who are presently on Ferriprox at a dosage closer to 100 mg/kg/day will be assigned to Group B. In both cases, the total dosage of deferiprone DR will be as close as possible to that of Ferriprox, but divided b.i.d. instead of t.i.d.

5.3 Blinding Procedures

Not applicable. This study is open label.

5.4 Allocation of Patient Numbers

After provision of informed consent, each patient will be assigned a unique ID number, and will be identified in all study data by this number rather than by name. The ID number will consist of 6 digits, where the first 3 digits represent the site code (001 for site #1, 002 for site #2, etc.) and the next 3 digits are assigned sequentially for each individual enrolled at that site. For example, if site #1 enrolls 8 patients, the ID numbers will be 001001 to 001008. The assigned ID numbers of patients who are screening failures or who withdraw from the study will not be reused.

5.5 Treatment Compliance

Compliance will be determined as follows: 1) the patient will keep a daily record of the number of tablets taken, and 2) at Day 28, the investigator or a delegate will inspect the medication containers, whether empty, partly used, or unopened, and will check the number of tablets remaining. Compliance will be calculated by the number of tablets taken divided by the number of tablets prescribed. Any discrepancies must be discussed with the patient and documented in the source documents. Reasons for non-compliance with the treatment will be recorded in the source document and in the eCRFs. The investigator should discuss treatment compliance with the patient at each visit or during each telephone call.

If the number of returned tablets is less than it should be but the patient reports having taken the correct amount of medication, the site will report compliance as 100% in the eCRF, and will provide the reason for the apparent over-compliance (e.g., tablets were accidentally spoiled and could not be ingested), along with the actual percentage. Both under-compliance < 80% and over-compliance >120% will be reported as a protocol deviation, unless under-compliance is due to treatment interruption because of infection or neutropenia or other extenuating circumstances (see Section 7.1.1.8).

6 STUDY TREATMENTS

All patients will be treated with deferiprone delayed release 1000 mg tablets at approximately the same total daily dosage that they had been prescribed for Ferriprox .

6.1 Investigational Product

Deferiprone delayed release (DR) 1000 mg is a white to off-white, capsule-shaped, beveled edge, biconvex coated tablet, engraved with “FPX” score “DR” on one side and “APO” score “1000” on the other side. The tablets are manufactured by Apotex Inc., and will be supplied to the clinical site by ApoPharma Inc.

6.1.1 Dosage Form and Mode of Administration

Deferiprone DR tablets are to be taken twice a day, approximately 12 hours apart. The route of administration is oral. All patients will take approximately the same total daily dosage that they were taking three times a day with Ferriprox IR, whether that dosage was closer to 75 mg/kg/day (Group A) or closer to 100 mg/kg/day (Group B). The dosage for each subject will be rounded to the nearest multiple of 500 mg. The tablets are scored in a way that they can be split into two halves that maintain the release characteristics of the whole tablets.

6.1.2 Precautions for Use

The tablets are to be kept in a tightly closed bottle in order to protect them from moisture. The bottles are to be kept out of the sight and reach of children.

6.2 Packaging and Labeling

The tablets are packaged in 75 cc opaque, white, round high-density polyethylene (HDPE) bottles with induction seals and child-resistant caps. The bottles contain 50 tablets and a desiccant bag, and will bear a label whose content is in accordance with all applicable regulatory requirements.

6.3 Shipping and Storage

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

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

6.4 Product Accountability

It is the responsibility of the investigator to ensure that all study drug received at the study center is inventoried and accounted for throughout the study. Records of receipt, storage and administration of the study drug supplied must be maintained, and drug accountability will be performed. 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.

6.5 Replacement Doses

Patients who report that their medication has been lost or damaged will need to return to the study site to receive replacement tablets. Requests for replacement must be made in writing to the sponsor by the qualified staff member. All information related to the lost or damaged medication and the replacement medication is to be recorded in the drug accountability forms and patient source data.

6.6 Disposition of Unused Product

All investigational product (IP) that is unused for any other reasons will be returned to the sponsor or discarded by the site according to internal procedures, if approved, in writing, by the sponsor. Destruction certificates for the completed destructions (or proof that IP was sent for destruction) will be obtained. The destruction may take place only after written approval by the sponsor.

7 MEASUREMENTS AND EVALUATIONS

7.1 Safety Measurements

7.1.1 Medical Events, Adverse Events, and Serious Adverse Events

7.1.1.1 Definition of Medical Events and Adverse Events

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

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

AEs include:

- Exacerbation of a pre-existing illness, including acute episodes/crisis of a chronic underlying condition
- An increase in frequency or intensity of a pre-existing episodic event or condition
- A condition detected or diagnosed after study treatment administration, even though it may have been present prior to the start of the study
- A continuous persistent disease or symptom present at baseline that worsens following the start of the study
- Accidents (e.g., involving a motor vehicle)
- Reasons for changes in concomitant medication (type of drug and/or dose)
- Medical, nursing, or pharmacy consultation
- Admission to hospital and surgical operations
- Abnormalities in laboratory findings (e.g., clinical chemistry, hematology, urinalysis), ECG, or other assessments (e.g., vital signs) that are not part of a larger medical condition already recorded as an AE and which are judged by the investigator to be clinically significant. The investigator should exercise medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

AEs do not include:

- A pre-existing disease or condition present or detected at the start of the study that does not worsen
- Hospital admissions or surgical procedures that had been planned prior to enrolment into the study
- The disease or disorder being studied, or a sign or symptom associated with that disease or disorder, unless it has worsened
- An overdose of either the study treatment or concurrent medication without any signs or symptoms

7.1.1.2 Monitoring and Documenting of Medical Events and Adverse Events

Prior to enrolling a patient, study site personnel will note the occurrence and nature of any medical condition(s) in the source documents and the appropriate section of the eCRF. During the study, they will note any change in the condition(s), and the occurrence and nature of any MEs/AEs. MEs will be collected from the time the ICF is signed until the first dose of study drug, and AEs will be collected from the time the treatment starts until 30 days after the last dose.

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

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

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

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

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

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

The investigator will evaluate all AEs/MEs for their relationship to the investigational product (Section 7.1.1.3), intensity (Section 7.1.1.4), and seriousness (Section 7.1.1.5), 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.

7.1.1.3 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.

7.1.1.4 Assessment of Intensity

Intensity refers to the degree of discomfort or impairment associated with an event. The intensity of MEs/AEs is to be reported on the eCRF. To maximize consistency in assessment, the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) scale is to be used.

7.1.1.5 Serious Adverse Events

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

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability or incapacity
- A congenital anomaly in the offspring of a patient who received the study treatment
- An important medical event that does not result in death, is not life-threatening, and does not necessitate hospitalization but which in the investigator's judgment may jeopardize the patient and may necessitate medical or surgical intervention to prevent one of those outcomes. Examples include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or treatment-related substance abuse.

Clarifications:

- "Life-threatening" means that the patient was, in the view of the investigator, at immediate risk of death from the event as it occurred. This definition does not include an event that, had it occurred in a more severe form, might have caused death.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen during the study is not considered an AE.
- Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization, the event is considered an SAE.
- "Inpatient" hospitalization means the patient has been formally admitted to a hospital for medical reasons. This may or may not be overnight. It does not include presentation at a casualty or emergency room unless the event meets one of the other criteria for being an SAE.

- With regard to the criteria for an important medical event, medical and scientific judgment should be used in deciding whether prompt reporting is appropriate in this situation.

7.1.1.6 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. In the case of an SAE that is fatal or life-threatening, 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.

7.1.1.7 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.

7.1.1.8 Adverse Events of Special Interest

7.1.1.8.1 Elevated Liver Enzymes

Due to the rate of elevated levels of ALT and AST seen in healthy volunteers in study LA60-0118, particular attention will be paid to these measures in the current study to determine if their rates are higher than expected in patients with systemic iron overload. Investigators are to review all laboratory reports promptly, and are to report any increases in ALT or AST that meet the criteria described in Section 3.1.1 to the sponsor within 24 hours of occurrence, using the sponsor's SAE form.

7.1.1.8.2 Neutropenia

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

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 / agranulocytosis:	A confirmed ANC < 0.5 x 10^9/L

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

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

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

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

Mild and moderate neutropenia:

A patient who develops mild neutropenia is to continue treatment without interruption, but ANC is to be monitored every 2 days until resolution.

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

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

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

Severe neutropenia/agranulocytosis:

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

- Provide protective isolation; if clinically indicated, admit patient to hospital and obtain vital signs every 4 hours
- Examine the patient the same day, if possible, including drug history and physical examination
- Notify ApoPharma Inc. using the SAE form.

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

- If possible, consider obtaining bone marrow aspirate for:
    - Histology
    - Progenitor culture
    - Frozen storage (1 mL sample)
- If possible, consider obtaining bone marrow biopsy (minimum length 3 mm)
- Perform septic work-up including chest X-ray, blood, urine, and throat cultures
- Obtain q4h temperatures from patient (monitored by family at home if patient is not in the hospital)
- If warranted, administer granulocyte stimulating factors, such as G-CSF 10 μg/kg, on an in-patient basis if possible, beginning the same day that the ANC is confirmed as $< 0.5 \times 10^9$/L; administer daily until ANC is $> 1.5 \times 10^9$/L on 2 consecutive days
- If ANC $< 0.5 \times 10^9$/L for 7 days, repeat bone marrow biopsy and aspirate weekly during the period of agranulocytosis, if warranted

7.1.1.8.3 Infections

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

7.1.2 Laboratory Measurements

Samples for laboratory safety assessments will be taken at the time points indicated below.

Biochemistry: Total protein, gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), sodium, potassium, chloride, glucose, bilirubin (total, direct, and indirect), alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, blood urea nitrogen, calcium, creatinine, uric acid, alkaline phosphatase, amylase, serum ferritin, and blood iron	Screening and Days 3, 7, 14, 21, and 28

Hematology: Hemoglobin, total WBC count, ANC, MCV, and platelet count	Screening, baseline, and Days 7, 14, 21, and 28
Coagulation: Prothrombin Time (PT), Partial Thromboplastin Time (PTT), and International Normalized Ratio (INR)	Screening and Day 2
Serology: HIV Ag/Ab Combo, hepatitis B (HBsAg (B)), and hepatitis C (anti-HCV (C))	Screening
Urinalysis: Color, appearance, specific gravity, pH, leukocyte, protein, glucose, ketones, bilirubin, blood, nitrite, urobilinogen. Microscopic examination must be performed if dipstick test is outside the reference range for leukocyte, blood, nitrite or protein. (Note: For patients with sickle cell disease, samples are to be sent for microscopy if there is blood in the urine or three or more "plus signs" for protein.)	Screening and Day 28
Pregnancy testing: Beta-HCG qualitative serum pregnancy test	Screening and Day 28

Notes:

- With the exception of hematology, laboratory results obtained at screening will be treated as the baseline values.
- There will be a window of ±1 day for assessments done at Days 3 and 7, and of ±2 days for assessments done at Days 14, 21, and 28.
- The investigator may increase the frequency of safety evaluations if deemed appropriate for assessment of any clinically significant adverse event. In the case of increases in liver enzymes that meet the criteria for being considered a safety concern, the patient is to be followed until resolution of the event, beyond Day 28 if necessary.
- If a patient withdraws from the study, the End of Study procedures are to be performed at an early termination visit.

Investigators must document their review of each laboratory report 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 marked by the investigator as either "CS" (clinically significant) or "NCS" (not clinically significant). Any that are marked as CS must be further explained and documented as an AE.

7.1.3 Other Safety Measurements

7.1.3.1 Physical Examinations

Physical examination will consist of an examination of head, ears, eyes, nose, throat and neck, respiratory system, cardiovascular system, gastrointestinal system, musculoskeletal system, neurological systems (central and peripheral), and skin, nails, hair, and scalp. A complete examination will be performed at screening, and a symptom-oriented examination will be performed at Day 28. Any abnormalities noted prior to the first dose of study medication will be recorded as either medical history or a medical event (depending on time of occurrence), while any that are noted at the end of the study will be recorded as AEs.

Body weight (without shoes) will be measured at screening only.

7.1.3.2 Vital Signs

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

Vital signs will be measured at screening and Day 28. Clinically significant out-of-range values for vital signs will be reported as AEs (see Section 7.1.1.1).

7.1.3.3 Concomitant Medications

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

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

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

Information on concurrent medications will be obtained at every site visit or telephone contact.

7.1.4 Procedures in Case of Pregnancy

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

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

Any SAE occurring as a result of a post-study pregnancy that the investigator believes may have been caused by the study product or by a protocol procedure will be reported to the sponsor as described in Section 7.1.1.6.

7.2 Acceptability Measurements

On Day 28, following completion of study treatment, patients will be asked what their preference is between the two formulations (Ferriprox IR vs. deferiprone DR) with respect to scheduling, ease of administration, and tolerability. The questionnaire is provided in Appendix 1.

8 STUDY COMMITTEES

A safety committee will be set up that is composed of representatives from ApoPharma Inc. (the Vice President of Medical Affairs, the Director of Medical Safety, and the Director of Clinical Research) and the principal investigators. Other experts may be included as needed. This committee will review the available safety data at specified time points, with a particular emphasis on the number of patients with ALT and/or AST levels that meet the criteria described in Section 3.1.1.1, to confirm if enrollment may continue.

9 STATISTICAL ANALYSIS

SAS Windows version 9.3 or higher will be used for statistical analysis. The safety population, defined in Section 9.3.1, will be the primary population for this study.

The continuous and discrete variables for safety data will be summarized with descriptive statistics (mean, median, standard deviation, minimum, and maximum) and frequency tables, respectively, at each assessment.

9.1 Endpoints

9.1.1 Primary Endpoint

The primary endpoint is the incidence of any post-dose occurrence of increases in ALT and/or ALT levels that meet one of the criteria for being considered a safety concern. The safety criteria are:

- For a patient whose baseline level is within the normal range, the criterion will be reaching a value of 5 times the ULN during the study.
- For a patient whose baseline level is above the ULN, the criterion will be reaching a value of 5 times the baseline value during the study or >10 x ULN.

9.1.2 Secondary Endpoints

Secondary endpoints are as follows:

- The assessment of tolerability will be based on the incidence of gastrointestinal (GI) distress reported by patients during the study.
- The assessment of acceptability will be based on the number of patients who indicate that they prefer the DR formulation over Ferriprox IR after considering their preference with respect to scheduling, ease of administration, and tolerability.

9.2 Determination of Sample Size and Study Power

This is the first study of the safety, tolerability, and acceptability of deferiprone DR tablets in patients with systemic iron overload. No formal power calculation can be performed. It is believed that the data that will be obtained in this study will be adequate to evaluate the effect of the DR formulation on liver enzymes.

9.3 Study Populations

9.3.1 Safety Population

The primary analysis population used in this study will be the safety population, which will include all patients who received at least one dose of deferiprone DR tablets.

9.3.2 Per Protocol Population

The per protocol population, which includes all patients who completed the study without major study deviations, will be the secondary population for the assessment of the primary endpoint.

9.4 Data Analysis Plan

9.4.1 Planned Analyses

9.4.1.1 Patient Disposition and Drug Exposure

The number of patients who were exposed to the study medication, who completed the study, and who withdrew from the study will be presented, along with reasons for withdrawals.

9.4.1.2 Patient Characteristics

Patients characteristics including demographics will be summarized with descriptive statistics for continuous variables and with frequency tables for categorical variables. Medical history will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA). Prior and concomitant medications will be summarized using the WHO Drug Dictionary (WHO-DD).

9.4.1.3 Analysis of Safety

The Clopper-Pearson 95% confidence interval (CI) of the incidence of post-dose levels of ALT or AST that meet the criterion for being considered a safety concern will be calculated for each dosage group. Similarly, the Clopper-Pearson 95% CI of the incidence of GI distress reported by patients during the study will also be calculated. Other AEs will be summarized by using frequency tables. The incidence of abnormal data for safety measures will be presented for each dosage group.

9.4.1.4 Analysis of Acceptability

For each dosage group, frequency tables will be used to summarize the response to each question of the questionnaire in Appendix 1 on treatment acceptability between Ferriprox IR vs. deferiprone DR. Based on the response to the question on overall preference for one

formulation or the other (Question #4), a one-sample proportion test will be used to test if the overall preference of deferiprone DR is greater than 0.5 for each dosage group.

9.4.2 Interim Analyses

No interim analysis is planned.

9.5 Criteria for Evaluability of Patient Data

All patients who received at least one dose of study product will be eligible for evaluation of safety.

10 DATA MANAGEMENT CONSIDERATIONS

10.1 Data Management

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

Clinical data management activities will be performed by the sponsor in accordance with applicable standards and data cleaning procedures of the sponsor. An audit trail of all data processing will be stored in the database. The study biostatistician will be notified when all 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 EDC system. These eCRFs may be used for electronic submission data archiving or data review. A copy of the final patient-specific eCRFs will be sent to the clinical study sites after database freeze.

11 MONITORING, AUDITS, AND INSPECTIONS

11.1 Source Documents

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

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

11.2 Monitoring

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

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

11.3 Audits and Inspections

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

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

An inspection by any regulatory authority may occur at any time during or after completion of the study. If an investigator is contacted by a regulatory authority for the purpose of conducting an inspection or to discuss any compliance issues, he/she is required to contact ApoPharma Clinical Research immediately.

11.4 Site Closure

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

- Return all study data and equipment to the sponsor
- Complete data clarifications and/or resolutions
- Ensure that drug accountability is completed and that unused medication is either destroyed or returned to the sponsor, as instructed
- Review site study records for completeness

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

applicable regulations, the investigator must inform the IRB/IEC promptly and provide the reason for the suspension or termination.

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

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

11.5 Retention of Records

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, including signed ICFs that contain patients' names and IDs, 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 Study 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, co-investigator, and institution's representative 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. Otherwise, matters of confidentiality will be governed by the Clinical Study Agreement.

16 DISPUTE RESOLUTION

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 Study Agreement.

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 Study 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 Study Agreement.

19 REFERENCES

1. United States Prescribing Information for Ferriprox 500 mg Tablets, February 2015.

2. Cohen AR, Galanello R, Piga A, DiPalma A, Vullo C, Tricta F. Safety profile of the oral iron chelator deferiprone: a multicentre study. BrJ Haematol. 2000;108:305-12.

3. Al-Refaie FN, Hershko C, Hoffbrand AV, Kosaryan M, Olivieri NF, Töndury P, et al. Results of long-term deferiprone (L1) therapy: A report by the international study group on oral iron chelators. British Journal of Haematology. 1995;91:224-9.

4. ApoPharma Inc. Investigator's Brochure for Ferriprox® (deferiprone) for transfusional iron overload, Edition 12.0, Release date 11 May 2018.

APPENDIX 1: QUESTIONNAIRE ON TREATMENT ACCEPTABILITY

Patient Number: _____

Site Number: _____

Date: _____

1. What is your preference between deferiprone delayed release (DR) tablets and Ferriprox tablets with respect to the dosing schedule (twice a day vs. three times a day)?

○	○	○	○	○
Much prefer deferiprone DR	Somewhat prefer deferiprone DR	No preference	Somewhat prefer Ferriprox	Much prefer Ferriprox

2. What is your preference between deferiprone DR and Ferriprox with respect to taking the tablets (ease of swallowing, feel of tablet, aftertaste, or any other factors)?

○	○	○	○	○
Much prefer deferiprone DR	Somewhat prefer deferiprone DR	No preference	Somewhat prefer Ferriprox	Much prefer Ferriprox

3. What is your preference between deferiprone DR and Ferriprox with respect to any side effects (upset stomach, joint pain, or any other problems)?

○	○	○	○	○
Much prefer deferiprone DR	Somewhat prefer deferiprone DR	No preference	Somewhat prefer Ferriprox	Much prefer Ferriprox

4. After considering the above factors, if you had the choice of which formulation to take in future, which one would you prefer?

○	○
Deferiprone DR	Ferriprox