ApoPharma Inc.

Safety and efficacy of early-start deferiprone treatment in infants and young children newly diagnosed with transfusion-dependent beta thalassemia

LA55-0417

CLINICAL STUDY PROTOCOL

IND Number:	45724
EudraCT Number:	2017-002318-29
Investigational Product:	Deferiprone oral solution
Development Phase:	Phase 4
Indication Studied:	Transfusion-dependent beta-thalassemia
Study Design:	Multi-center, randomized, double-blind, placebo-controlled study in infants and young children
Sponsor:	ApoPharma Inc. 200 Barmac Drive Toronto, Ontario M9L 2Z7, Canada Telephone: +1-416-749-9300 Toll-Free: 1-800-268-4623 (North America only) Fax: +1-416-401-3867
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Version and Date of Protocol:	Version 4.0, 12 DEC 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 efficacy of early-start deferiprone treatment in infants and young children newly diagnosed with transfusion-dependent beta thalassemia
Study Code:	LA55-0417
Version Number:	Version 4.0
Version Date:	12 DEC 2018

Caroline Fradette, PhD Director of Clinical Research, ApoPharma Inc.	Date (DD MMM YYYY)
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Principal Investigator

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

Study Title:	Safety and efficacy of early-start deferiprone treatment in infants and young children newly diagnosed with transfusion-dependent beta thalassemia
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Name of Principal Investigator:	
Name of Study Site:	
Location of Study Site: *(City, region/province/state, country)*	

Signature _____ Date (DD MMM YYYY) _____

SYNOPSIS

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

Title of study:	Safety and efficacy of early-start deferiprone treatment in infants and young children newly diagnosed with transfusion-dependent beta thalassemia (START)
Study code:	LA55-0417
Phase of development:	Phase 4
Objectives:	**Primary:** To evaluate the effect of early treatment with deferiprone on lessening progressive iron overload in infants and young children with transfusion-dependent β-thalassemia **Secondary**: To evaluate the safety and tolerability of early treatment with deferiprone in infants and young children with transfusion-dependent β-thalassemia
Study design:	Multi-center, randomized, double-blind, placebo-controlled study in infants and young children newly diagnosed with transfusion-dependent β-thalassemia. Patients will have started on a red blood cell (RBC) transfusion regimen designed to maintain a hemoglobin level > 9 g/dL but will still have a serum ferritin level well below 1000 µg/L, which current treatment guidelines state to be the threshold that should be reached before iron chelation therapy can begin. Screening will be conducted within 14 days prior to the start of dosing. At baseline, eligible participants will be randomized in a 1:1 ratio to receive either deferiprone oral solution 80 mg/mL or matching placebo. Visits will be scheduled approximately monthly (every 30 ±10 days) for the determination of levels of serum ferritin (SF), labile plasma iron (LPI), and transferrin saturation (TSAT), and for assessments of safety that include determination of liver enzymes (ALT and AST) and growth measurements. Dosage will begin at 25 mg/kg/day, divided into 3 doses (t.i.d.), and will be increased to 50 mg/kg/day (divided t.i.d.) after 2 weeks. After that, it will be increased to 75 mg/kg/day (divided t.i.d.) for patients who meet either of the following criteria: • An SF value ≥ 800 µg/L (but still below 1000 µg/L) and/or an LPI value ≥ 0.6 µM and/or a TSAT value ≥ 60% at 2 consecutive visits, **or** • An increasing trend in any of the above 3 measures (SF, LPI, and/or TSAT) at 3 consecutive visits, regardless of value

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Study design (cont'd):	If a single occurrence of any of the following is detected at any time, treatment will be interrupted: • SF value below the lower reference range for the child's age • Mild neutropenia, defined as an absolute neutrophil count (ANC) $< 1.5 \times 10^9$/L but $\geq 1.0 \times 10^9$/L • Fever or other signs of infection, prior to confirmation that ANC is $\geq 1.5 \times 10^9$/L As these parameters are known to fluctuate, the assessment will be repeated as soon as possible to verify that treatment interruption is necessary. Treatment will be re-initiated after the abnormally low SF, LPI, TSAT, or ANC level has recovered, or when the fever or infection has resolved or has been determined to not be indicative of neutropenia. If moderate neutropenia (ANC $< 1.0 \times 10^9$/L) is confirmed, the patient will be withdrawn from the study. Patients will remain in the study for 12 months or until their SF level has been confirmed to be ≥1000 µg/L at 2 consecutive visits, whichever comes first. Those whose SF levels are still under 1000 µg/L at 12 months will be offered participation in an extension study, LA55-EXT, in which they will continue to receive their assigned study product for up to 2 more years. Those who are terminated early will not be eligible to enroll in the extension study.
Duration of participation:	The duration of participation in this study for each patient will be up to 12 months.
Criteria for evaluation:	**Efficacy:** *Primary efficacy endpoint:* The percentage of patients who still have a serum ferritin level < 1000 µg/L at Month 12. *Secondary efficacy endpoints:* • The percentage of patients whose serum ferritin level is still less than 1000 µg/L at each visit • The percentage of patients whose LPI value is still less than 0.6 µM at each visit • The percentage of patients in each treatment arm whose TSAT value is still less than 60% at each visit • Time to reach a serum ferritin level ≥ 1000 µg/L • Time to reach an LPI value ≥ 0.6 µM • Time to reach a TSAT value ≥ 60%

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Criteria for evaluation (cont'd):	**Safety:** • Adverse events (AEs): Frequency, intensity, time to onset, duration, and relatedness to study drug • Serious adverse events (SAEs): Frequency, intensity, time to onset, duration, and relatedness to study drug • Number of discontinuations due to AEs • Growth parameters: Weight, height, and height velocity, as classified using the Z-score system • Change in prolactin level from baseline to Month 12
Number of patients:	A planned total of 64 patients will be randomized in a 1:1 ratio to the two arms.
Diagnosis and main criteria for inclusion:	Main inclusion criteria • Male or female aged ≥ 6 months to < 10 years • Confirmed diagnosis of beta-thalassemia, as determined by high performance liquid chromatography (HPLC) or DNA testing • Started on a regular RBC transfusion regimen, with a minimum of 2 transfusions already completed • Screening level of serum ferritin greater than >200 µg/L but not more than 600 µg/L. Since SF level may be impacted by the presence of infection, it must additionally be verified that the child has had no signs of infection in the previous 7 days, including the day of screening, and that the level of C-reactive protein (CRP) is no greater than 20% higher than the normal range for the patient's age. If there are signs of infection and/or the CRP level is above this threshold, the SF level must be checked again a minimum of one week later. (Note: If an investigator has valid reason to believe that an out-of-range SF level may be attributable to infection even if this is not indicated by the CRP result, SF may be rechecked once more a minimum of one week later.) Main exclusion criteria • Prior use of iron chelation • Diagnosis of hepatitis B or C, or HIV infection • Evidence of abnormal liver or kidney function at screening (serum ALT level > 5 times upper limit of normal or creatinine levels >2 times upper limit of normal) • Disorders associated with neutropenia (ANC < 1.5 x 10^9/L) prior to the initiation of study medication

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Diagnosis and main criteria for inclusion (cont'd):	*Exception:* Patients whose neutropenia is attributed by the treating physician to episodes of infection or to drugs associated with a decline in the neutrophil count and in whom the ANC has returned to a normal level at the screening visit.
Investigational product:	**Product:** Deferiprone oral solution 80 mg/mL **Dose:** 25, 50, or 75 mg/kg/day, divided t.i.d. **Mode of administration:** Oral
Reference product:	**Product:** Placebo **Dose:** Volume of solution matching that required for a 25, 50, or 75 mg/kg/day dose of active product, divided t.i.d. **Mode of administration**: Oral
Schedule of treatment and specimen collection:	Treatment: All patients will be administered the assigned study product 3 times daily for the duration of the study. Efficacy assessments: Blood samples for the assessment of LPI, TSAT, and SF will be collected at screening/baseline and at each monthly visit until termination from the study. Safety assessments: • Hematology: Screening, baseline, weekly after the start of dosing up to Month 6, then biweekly until Month 12 or early termination from the study • Blood chemistry: Screening and Months 1, 3, 6, 9, and 12 or until early termination from the study • Prolactin: Baseline and Month 12 • Vital signs: Each visit • Physical examination: Screening and Months 1, 3, 6, 9, and 12 or until early termination from the study • Urinalysis: Screening and Month 12 or early termination from the study • Weight and height: Baseline and monthly until Month 12 or early termination from the study • Adverse events: Collected throughout the study, from baseline until Month 12 or early termination from the study

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Statistical methods:	Sample size: With 64 patients, there will be over 90% power to detect a statistically significant difference ($\alpha = 0.05$) between the two treatment groups in the percentage of patients who have a serum ferritin level < 1000 µg/L at Month 12 if the deferiprone arm and the placebo arm have an expected incidence of 70% and 20%, respectively. Efficacy evaluation: The percentage of patients who have not reached levels of LPI ≥ 0.6 µM, TSAT ≥ 60%, and SF ≥ 1000 µg/L will be compared between the two treatment groups at each monthly time point as well as at the end of study, using the Fisher's exact test. The effect of baseline value on each of the 3 endpoints will be examined in a covariate analysis. The Kaplan-Meier survival curve for the time to reach a serum ferritin level ≥ 1000 µg/L, an LPI value ≥ 0.6 µM, and a TSAT value ≥ 60% will be generated for the two treatment groups. The log-rank test will be used for comparing the two survival curves for each of the 3 endpoints. The trend analysis over time for LPI, TSAT, and SF measures will be performed to compare the rates of change in these measures between the two treatment groups. Safety evaluation: Descriptive statistics (mean, standard deviation, minimum, and maximum) will be produced for continuous variables, and frequency tables will be produced for discrete variables by treatment group. Summaries of adverse events and serious adverse events will be produced by treatment group. Shift tables will be generated for comparing the screening/baseline values and end of study values of the relevant measures. For weight and height, the change from baseline to last assessment will be compared between the two treatment groups using an ANCOVA model with baseline value as a covariate and treatment as the main factor. The rate of change in height will be assessed using regression analysis. For prolactin, a similar ANCOVA model will be used for the evaluation of change in prolactin from baseline to Month 12. The appropriate procedures in SAS will be used for the efficacy and safety analyses.
Version and date of the protocol	Version 4.0, 12 DEC 2018

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
ALT	alanine transaminase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
AST	aspartate transaminase
CS	clinically significant
CI	confidence interval
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
eCRF	electronic case report form
EDC	electronic data capture
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
HPLC	high performance liquid chromatography
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	intent-to-treat
LPI	labile plasma iron
MedDRA	Medical Dictionary for Regulatory Activities
NCS	not clinically significant
RBC	red blood cell
SAE	serious adverse event
SF	serum ferritin
TSAT	transferrin saturation
WHO	World Health Organization

1 INTRODUCTION

1.1 Background of the Disease

Beta thalassemia major is a hereditary blood disorder characterized by a genetic deficiency in the synthesis of beta-globin chains, resulting in an abnormal form of hemoglobin. This leads 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 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.

In young children with a diagnosis of β-thalassemia major, current practice is to start this therapy only after 10 to 20 RBC transfusions have been received or when serum ferritin levels rise above 1000 μg/L.[1] This delay is believed to be necessary in order to minimize the risk of toxicities due to excessive depletion of iron needed for normal biologic reactions. With the parenteral iron chelator deferoxamine, growth delays were commonly observed in children with mild iron overload who had started chelation at very young ages, and delaying the start of treatment was found to be effective in preventing that problem.[2] However, this delay may also increase the risk of iron accumulation in endocrine glands such as the pancreas, pituitary, and thyroid, where toxicities could manifest later in life.[3]

1.2 Background of the Investigational Product

Deferiprone (3-hydroxy-1,2-dimethylpyridin-4-one; brand name Ferriprox®) is a bidentate iron chelator that preferentially binds trivalent iron cations (Fe^{3+}) in a 3:1 (deferiprone:iron) complex. It was first approved in 1999 by the European Medicines Agency for the treatment of iron overload in transfusion-dependent patients with thalassemia major, and is currently approved for that indication in over 60 countries. The effectiveness of deferiprone in reducing body iron in the case of systemic iron overload has been assessed by urinary iron excretion, by sequential measurements of serum ferritin levels, and by iron concentrations in the liver and heart, while clinical outcomes include reduction of iron-induced cardiac disease and prolongation of survival.

Compared to deferoxamine, deferiprone has a lower physiological affinity for iron (pFe3+ log stability constants of 19.9 vs. 26.6 for deferoxamine), which reduces the risks of excessive iron depletion, particularly in conditions of only mild to moderate iron overload.[4,5] Data from clinical trials in young children with transfusion-dependent thalassemia and in

patients with local but not systemic iron overload support the safety profile for deferiprone in those conditions.[6,7] Further, deferiprone has been shown to be more effective than deferoxamine in promoting iron release from iron-loaded macrophages, which is the initial site of iron overload in transfusional iron overload, and to make it accessible to biologic receptors, where it can then be used for protein biosynthesis.[8,9,10,11,12] These characteristics of deferiprone support its use for initiation of chelation therapy in children with transfusion-dependent thalassemia at a lower threshold of iron load than what is used for initiation of therapy with deferoxamine.

1.3 Rationale

A recent investigator-led trial that explored whether early-start therapy with deferiprone could delay the progression of iron accumulation without inducing toxicity yielded promising results.[13] Recently diagnosed thalassemia patients aged approximately 12 months were randomized to either start receiving deferiprone at a low dose of 50 mg/kg/day or to wait until their serum ferritin levels reached the threshold of 1000 µg/L recommended by current guidelines. All the subjects who were not receiving chelation reached this threshold at about 6 months post-baseline, after receipt of about 10 transfusions; in comparison, for those on deferiprone, none had reached it by 6 months, only 10% had reached it by 9 months, and the remainder reached it only at 12 months, after 16 to 18 transfusions. Large group differences were seen for other indices of iron overload as well. With respect to safety, there were no unexpected, serious, or severe adverse events associated with deferiprone treatment.

The current trial has been designed to further evaluate the early use of deferiprone in young children with newly diagnosed transfusion-dependent thalassemia. The objectives are to determine whether such a regimen can postpone saturation of transferrin and thus the appearance of labile plasma iron (considered the main source of iron overload in endocrine glands and myocytes) while maintaining a good safety profile.[14] Participants in this trial will have already started on a transfusion regimen designed to maintain a hemoglobin level > 9 g/dL, but will still have a serum ferritin well below 1000 µg/L, which is the current standard for starting iron chelation therapy.

1.4 Potential Risks and Benefits

Risks: The safety profile of deferiprone in patients with systemic iron overload has been extensively characterized. The most serious adverse event associated with its use is severe neutropenia or agranulocytosis, defined as a confirmed absolute neutrophil count (ANC) less than 0.5×10^9/L. In pooled clinical trials, agranulocytosis has been seen in about 2% of patients. The most common non-serious adverse reactions reported during clinical trials have been nausea, vomiting, abdominal pain, increased alanine aminotransferase, arthralgia, and mild or moderate neutropenia (ANC less than 1.5×10^9/L).[15,16]

Table 1.1 displays the most common adverse drug reactions associated with deferiprone that have been reported in the pooled database of patients with systemic iron overload.

Table 1.1 Adverse drug reactions seen in ≥ 1% deferiprone-treated patients with systemic iron overload

System Organ Class **Preferred Term**	**N=860** **n (%)**
Blood and lymphatic system disorders	
Neutropenia	54 (6.3)
Agranulocytosis	18 (2.1)
Gastrointestinal disorders	
Nausea	96 (11.2)
Vomiting	85 (9.9)
Abdominal pain upper	46 (5.3)
Abdominal pain	42 (4.9)
Diarrhea	22 (2.6)
Dyspepsia	13 (1.5)
Abdominal discomfort	10 (1.2)
General disorders and administration site conditions	
Pyrexia	12 (1.4)
Investigations	
Alanine aminotransferase increased	65 (7.6)
Neutrophil count decreased	55 (6.4)
Aspartate aminotransferase increased	22 (2.6)
Transaminases increased	15 (1.7)
Weight increased	12 (1.4)
Metabolism and nutrition disorders	
Increased appetite	26 (3.0)
Musculoskeletal and connective tissue disorders	
Arthralgia	79 (9.2)
Pain in extremity	14 (1.6)
Back pain	13 (1.5)
Arthropathy	11 (1.3)
Nervous system disorders	
Headache	21 (2.4)

* Data cut-off date: 31 Aug 2016

Benefits: The findings of the investigator-led study indicate that deferiprone has the potential to prevent early accumulation of iron toxicity in very young children who are transfusion-dependent but not yet considered eligible to start conventional chelation therapy. Early-start chelation may possibly act to prevent accumulation of iron in organs and thereby avert long-term toxicity.

2 STUDY OBJECTIVES

2.1 Primary Objective

To evaluate the effect of early treatment with deferiprone on lessening progressive iron overload in infants and young children with transfusion-dependent β-thalassemia. The endpoints for the primary objective are provided in Section 9.1.1.

2.2 Secondary Objective

To evaluate the safety and tolerability of early treatment with deferiprone in infants and young children with transfusion-dependent β-thalassemia.

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

3 STUDY DESIGN

3.1 Description of Study Design

This is a multi-center, randomized, double-blind, placebo-controlled study in infants and young children newly diagnosed with transfusion-dependent β-thalassemia. Patients will have started on a red blood cell (RBC) transfusion regimen designed to maintain a hemoglobin level > 9 g/dL, but still have a serum ferritin level well below the threshold that current treatment guidelines state should be reached before iron chelation therapy can begin.

Screening will be conducted within 14 days prior to the start of dosing. At baseline, eligible participants will be randomized in a 1:1 ratio to receive either deferiprone oral solution 80 mg/mL or matching placebo. Visits will be scheduled approximately monthly (every 30 ±10 days) for the determination of levels of serum ferritin (SF), labile plasma iron (LPI), and transferrin saturation (TSAT), and for assessments of safety that include determination of liver enzymes (ALT and AST) and growth measurements.

Dosage will begin at 25 mg/kg/day, divided into 3 doses (t.i.d.), and will be increased to 50 mg/kg/day (divided t.i.d.) after 2 weeks. After that, it will be increased to 75 mg/kg/day (divided t.i.d.) for patients who meet either of the following criteria:

- An SF value ≥ 800 µg/L (but still below 1000 µg/L) and/or an LPI value ≥ 0.6 µM and/or a TSAT value ≥ 60% at 2 consecutive visits, or
- An increasing trend in any of the above 3 measures (SF, LPI, and/or TSAT) at 3 consecutive visits, regardless of value

If a single occurrence of any of the following is detected at any time, treatment will be interrupted:

- SF value below the lower reference range for the child's age
- Mild neutropenia, defined as an absolute neutrophil count (ANC) < 1.5 x 10^9/L but ≥ 1.0 x 10^9/L
- Fever or other signs of infection, prior to confirmation that ANC is ≥ 1.5 x 10^9/L

As these parameters are known to fluctuate, the assessment will be repeated as soon as possible to verify that treatment interruption is necessary. Treatment will be re-initiated after the abnormally low SF or ANC level has recovered, or when the fever or infection has resolved or has been determined to not be indicative of neutropenia.

If moderate neutropenia (ANC < 1.0 x 10^9/L) is confirmed, the patient will be withdrawn from the study.

Patients will remain in the study for 12 months or until their SF level is found to be ≥ 1000 µg/L at 2 consecutive visits, whichever comes first. Since SF level may be impacted by the presence of infection, it must additionally be verified that the child has had no signs of infection in the previous 7 days, including the day of the visit, and that the level of C-reactive protein (CRP) is no greater than 20% higher than the normal range for the patient's age. If there are signs of infection and/or the CRP level is above this threshold, the SF level must be checked again a minimum of one week later. (**Note:** If an investigator has valid reason to believe that an SF level ≥ 1000 µg/L may be attributable to infection even if this is not indicated by the CRP result, SF may be rechecked once more a minimum of one week later.)

Patients whose SF levels are still under 1000 µg/L at 12 months will be offered participation in an extension study, LA55-EXT, in which they will continue to receive their assigned study product for up to 2 more years. Those who are terminated early will not be eligible to enroll in the extension study.

3.2 Rationale for Study Design

The study is placebo-controlled in order to compare the current standard of care of no chelation vs. early-start chelation, on both safety and efficacy measures.

Apart from the use of placebo, the design is similar to that of the earlier investigator-led open-label study, in which the control group received no treatment.[13] The same parameters

that were used in that study to measure iron overload—serum ferritin, transferrin saturation, and labile plasma iron—are used here, with the difference of applying a criterion of 60% rather than 70% for transferrin saturation. The same criterion of discontinuing patients from the study when they reach a serum ferritin level ≥ 1000 µg/L at 2 consecutive visits is maintained, which ensures that patients who are ready to begin standard chelation therapy will not be delayed in doing so.

3.3 Rationale for Selection of Doses

The earlier study used a low dose of 50 mg/kg/day, divided t.i.d., but iron balance studies have shown that such a dose is insufficient to neutralize the transfusional iron load in most patients with transfusion-dependent thalassemia.[17,18] Here, dosing will start at an even lower level, 25 mg/kg/day, in order to minimize the gastrointestinal adverse events that are sometimes seen when deferiprone is first introduced, and will be raised to 50 mg/kg/day after 2 weeks. Once a patient reaches any of several criteria based on indices of iron overload, the dose will be further increased to a therapeutic level of 75 mg/kg/day, to see if this will act to delay reaching the threshold of serum ferritin ≥ 1000 µg/L for a longer time. Strict criteria for treatment interruptions will be in place throughout the study to ensure patients' safety.

4 STUDY POPULATION

4.1 Number of Patients

A planned total of 64 patients will be enrolled in the study, 32 in each arm.

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 ≥ 6 months to < 10 years
2. Confirmed diagnosis of beta-thalassemia, as determined by high performance liquid chromatography (HPLC) or DNA testing
3. Started on a regular RBC transfusion regimen, with a minimum of 2 transfusions already completed
4. Screening levels of serum ferritin greater than >200 µg/L but not more than 600 µg/L. . Since SF level may be impacted by the presence of infection, it must additionally be verified that the child has had no signs of infection in the previous 7 days, including the day of screening, and that the level of C-reactive protein (CRP) is no greater than 20% higher than the normal range for the patient's age. If there are signs of infection and/or the CRP level is above this threshold, the SF level must be checked again a minimum of

one week later. (**Note:** If an investigator has valid reason to believe that an out-of-range SF level may be attributable to infection even if this is not indicated by the CRP result, SF may be rechecked once more a minimum of one week later.)

5. Parent(s) or legal guardian (as per local requirements) must provide signed and dated written informed consent prior to the first study intervention, and must verify that patient will be able to adhere to study restrictions, appointments, and evaluation schedules. If applicable, patients who are old enough will additionally provide assent.

4.3 Exclusion Criteria

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

1. Prior use of iron chelation
2. Diagnosis of hepatitis B or C, or HIV infection
3. Evidence of abnormal liver or kidney function at screening (serum ALT level > 5 times upper limit of normal or creatinine levels >2 times upper limit of normal)
4. Disorders associated with neutropenia (ANC < 1.5 x 10^9/L) prior to the initiation of study medication

   Exception: Patients whose neutropenia is attributed by the treating physician to episodes of infection or to drugs associated with a decline in the neutrophil count and in whom the ANC has returned to a normal level at the screening visit.
6. 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, gastro-enterologic, respiratory, cardiovascular, endocrinologic, neurologic or immunologic disease.
7. History of allergy or sensitivity to any components of the study product or related compounds.
8. Receipt of any investigational products within the past 30 days or 5 half-lives (whichever is longer) preceding the first dose of study medication.
9. 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.
10. Presence of any medical condition which in the opinion of the investigator would cause participation in the study to be unwise.
11. Identified as a child, either biological or legally adopted, of an investigator or other site staff directly affiliated with this study.

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.

Exception: A patient who does not have DNA confirmation of a diagnosis of beta-thalassemia available at the time of screening may be enrolled on the basis of HPLC results (see inclusion criterion #2). If subsequent DNA results are found to not confirm the diagnosis, the patient will still be permitted to remain in the study if all other eligibility criteria are met.

4.5 Patient Withdrawal

Patients/parents have the right to withdraw/withdraw their child 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 parent/legal guardian (or patient, if applicable) and/or the investigator
- Requirement for concomitant medication that might interfere with the evaluation of study treatment or may be contraindicated
- Occurrence of other illnesses that might affect the patient's further participation in the study or evaluation of study treatment
- A protocol deviation that might interfere with study assessments, as judged by the investigator
- Repetitive 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:

- Attainment of a serum ferritin level ≥ 1000 µg/L at 2 consecutive visits (provided that the child has had no signs of infection in the previous 7 days and that CRP level is not greater than 20% higher than the normal range for the patient's age)
- Occurrence of moderate neutropenia or of severe neutropenia/agranulocytosis (see Section 7.2.1.8.1)
- Occurrence of any adverse event characterized as life-threatening or disabling that is not associated with the patient's condition

- Receipt of a rescue medication (see Section 4.7)
- Termination of the study by the sponsor

Parents/legal guardians who decide to withdraw their child from the study (or, in the case of a child who is able to communicate this, a patient who wishes to withdraw) should always be contacted, if possible, in order to ask about the reason for withdrawal, whether any adverse events (AEs) occurred, and use of concomitant medications. A withdrawn patient should return for an Early Termination visit. All investigational product and materials should be returned. If any AEs occurred, the investigator must attempt to follow up on the outcome until resolution or for 30 days post-termination, whichever comes first.

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 Replacement of Patients Who Withdraw

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

4.5.2 Treatment Interruptions

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

- If a patient develops fever (≥ 38.0°C) or any sign of infection during the study, deferiprone must be interrupted immediately, and neutrophil count should be obtained and monitored more frequently; every 2 days if ANC <1.5 x 10^9/L. Therapy with deferiprone can be re-initiated once all symptoms have been resolved, if the ANC is ≥1.5 x 10^9/L.
- Parents/guardians (and patients if applicable) are to be advised to immediately report any symptoms indicative of infection such as fever, sore throat, and flu-like symptoms. Participants will be provided with a thermometer, and will be instructed to seek immediate medical attention at a hospital or clinic if the patient experiences fever (temperature ≥38.0° C/100.4°F). Body temperature may be measured at the ear, axilla, or mouth. In presence of confirmed fever and/or infection, patients will be required to have their neutrophil counts tested as soon as possible and no later than 24 hours after the symptoms of infection are detected. Therapy with study drug can be re-initiated once all symptoms have been resolved and it is deemed safe by the investigator.
- If a patient develops mild neutropenia during the study (ANC <1.5 x 10^9/L but ≥1.0 x 10^9/L; see Section 7.2.1.8.1), therapy must be interrupted immediately, and neutrophil count must be obtained and monitored every 2 days. Therapy can be re-initiated once

two successive ANCs are ≥1.5 x 10^9/L and it is deemed safe by the investigator. If the ANC is still <1.5 x 10^9/L after 14 days, the patient will be withdrawn from the study.

- A patient who develops neutropenia that is defined as moderate (ANC <1.0 x 10^9/L) or severe (ANC <0.5 x 10^9/L) is to be immediately withdrawn from the study.

4.6 Prior and Concomitant Therapies

All medications taken during the 3 months prior to dosing up to the end of the study (Month 12 or early termination) will be recorded and reviewed by the investigator.

Medications considered necessary for the patient's welfare may be given at the discretion of the investigator. The administration of all medications (including study product, herbal medications, and over-the-counter medications) and nutritional supplements must be recorded in the source document and the appropriate sections of the electronic case report form (eCRF). During the study, patients must not receive any other investigational product or any drugs that are known to cause neutropenia or agranulocytosis.

4.7 Rescue Medication

Administration of any other iron chelator (deferoxamine, deferasirox, or a combination of two chelators) or an increase in deferiprone dosage above the limit specified in the protocol will not be allowed. Patients who need higher doses of deferiprone than what is permitted in this study or a different chelator to control their iron overload will be withdrawn, as per protocol.

5 STUDY PROCEDURES

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

Table 5.1 Table of study procedures

	Day -14 to 0 (Screening)	Month 0, Day 0 (Baseline)	Month 1 [1]	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12 or End of Study [2]
Informed consent/ assent	X													
Demographics	X													
Medical history	X													
Eligibility criteria	X	V												
Randomization		X												
Hematology [3]	X	X	Weekly (±3 days) after start of dosing up to Month 6						Biweekly (±3 days) until termination from the study					
Blood chemistry [4,5]	X		X		X			X			X			X
DNA testing (if applicable) [6]	X													
Urinalysis [5,7]	X													X
Serology [8]	X													
Physical examination [5]	X		X		X			X			X			X
Vital signs[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height[10]		X	X	X	X	X	X	X	X	X	X	X	X	X
Weight		X	X	X	X	X	X	X	X	X	X	X	X	X
Labile plasma iron [11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Transferrin saturation [11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum ferritin [11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prolactin [12]		X												X

	Day -14 to 0 (Screening)	Month 0, Day 0 (Baseline)	Month 1 [1]	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12 or End of Study [2]
Dispense study medication		X	X	X	X	X	X	X	X	X	X	X	X	
Provide diary card		X	X	X	X	X	X	X	X	X	X	X	X	
Dosing [13]		Three times daily from baseline until termination from the study												
Review and collect diary card			X	X	X	X	X	X	X	X	X	X	X	X
Collect study medication containers			X	X	X	X	X	X	X	X	X	X	X	X
Assess treatment compliance			X	X	X	X	X	X	X	X	X	X	X	X
Prior & concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical events	X	X												
Adverse events		Throughout the study after start of dosing												
Transfusion history	Throughout the study													

V: Verify

1 Visits will be scheduled every 30 days (± 10 days).

2 Patients will be terminated from the study at Month 12 or when they have been found to have a serum ferritin level ≥ 1000 µg/L at 2 consecutive visits, whichever comes first.

3 Hematology: Hemoglobin, total WBC count, ANC, MCV, and platelet count.

4 Blood chemistry: Total protein, GGT, glucose, bilirubin (total, direct, and indirect), AST, ALT, albumin, blood urea nitrogen, calcium, creatinine, total iron binding capacity, serum iron, zinc, and CRP.

5 The results obtained at screening for blood chemistry, physical examination, and urinalysis will be considered to be the baseline results. These tests will not be repeated at Day 0.

[6] A blood sample for DNA testing is to be taken only if DNA confirmation of a diagnosis of beta-thalassemia is not available at the time of screening.

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

[8] Hepatitis B, hepatitis C, and HIV.

[9] Heart rate, blood pressure, and body temperature. At the time of these measurements, the child must be calm and not crying.

[10] For infants not yet able to stand upright, stature will be measured as recumbent length.

[11] For TSAT and SF, the values obtained at the screening visit (not those obtained at baseline) will be used for the eligibility criteria.

[12] Blood samples for the assessment of prolactin will be taken pre-dose and at + 1.5 h +/- 5 minutes post-dose. The second set of samples will be taken only from patients who are still in the study at Month 12; they will not be taken from patients who are terminated before that time.

[13] Dosing: Deferiprone oral solution 80 mg/mL or matching placebo solution.

5.1 Visit Procedures

Details on the procedures to be carried out at each study visit are provided below.

Note: If possible, blood transfusions should be conducted on the same days as the study visits. Data on all transfusions performed during the trial period, including type of transfusion, volume of blood received, and the mean hematocrit of the packed red blood cell units transfused, must be recorded in the eCRF and source documents. Iron input per transfusion will be calculated based on the information collected throughout the study.

Screening Visit (Day -14 to Day 0)

- Explain the study to the parent/legal guardian (and patient if applicable), and obtain written informed consent, and assent from the patient if applicable
- Collect demographic information
- Collect medical history
- Check eligibility criteria

  Note: If DNA confirmation of the diagnosis of beta-thalassemia is not available at this time, the patient may be enrolled on the basis of HPLC results, and a blood sample will be taken for later DNA testing.
- Collect blood samples for assessment of the following:
  - Hematology
  - Blood chemistry
  - Serology
  - Labile plasma iron
  - Transferrin saturation
  - Serum ferritin
  - C-reactive protein
  - DNA testing if applicable

    Note: A patient whose SF level is outside of the specified range will not be enrolled; however, since SF levels may be impacted by the presence of infection, it must additionally be verified that the child has had no signs of infection in the previous 7 days, including the day of screening, and that the level of CRP is no greater than 20% higher than the normal range for the patient's age. If there are signs of infection and/or the CRP level is above this threshold, the SF level must be checked again a minimum of one week later. (If an investigator has valid reason to believe that an SF level ≥ 1000 µg/L

may be attributable to infection even if this is not indicated by the CRP result, SF may be rechecked once more a minimum of one week later.)

- Collect a urine specimen for urinalysis
- Perform a physical examination (to be completed by the investigator or a qualified delegate)
- Measure vital signs (heart rate, blood pressure, and body temperature)
- Obtain transfusion history
- Collect information on prior and concomitant medications
- Record any medical events that have occurred after the consent form was signed
- Schedule baseline visit if all eligibility criteria are met

Baseline Visit (Month 0, Day 0)

Notes:

- For blood chemistry, physical examination, and urinalysis, the results obtained at screening will be considered to be the baseline results, and these tests will not be repeated at Day 0.

- All of the post-baseline visits will need to be timed early enough in the day so that blood samples for the assessment of serum ferritin, LPI, and TSAT (as well as prolactin, at Month 12) will be drawn approximately 12 hours after the last dose of study drug and prior to administration of the next. Accordingly, the baseline visit must be scheduled early in the day as well, and the samples collected at approximately the same time at each visit, to ensure consistency across the study.

- Verify eligibility criteria

  Notes:

  - For TSAT and SF, the values obtained at the screening visit (not those obtained at baseline) will be used for the eligibility criteria.

  - In the case of a patient who did not have DNA confirmation of diagnosis available at screening but was enrolled based on HPLC results, if the results of the DNA testing done post-screening are found not to confirm beta thalassemia major, such a patient will be permitted to remain in the study if all other eligibility criteria are met.

- Contact the Interactive Voice (or Web) Randomization System (IVRS/IWRS) to have the patient randomized to receive either active product or placebo

- Collect pre-dose blood samples for assessment of the following:
    - Hematology
    - Prolactin (pre-dose sample)
    - Labile plasma iron
    - Transferrin saturation
    - Serum ferritin
    - C-reactive protein

      Notes:

      - Since SF level may be impacted by the presence of infection, it must additionally be verified that the child has had no signs of infection in the previous 7 days, including the day of the visit, and that the level of CRP is no greater than 20% higher than the normal range for the patient's age. If there are signs of infection and/or the CRP level is above this threshold, the SF level must be checked again a minimum of one week later. (If an investigator has valid reason to believe that an out-of-range SF level may be attributable to infection even if this is not indicated by the CRP result, SF may be rechecked once more a minimum of one week later.)
      - If a transfusion is scheduled on the day of the visit, the blood samples for SF, LPI, and TSAT must be collected before the transfusion is performed.
- Measure vital signs (heart rate, blood pressure, and body temperature)
- Measure weight and height

  Note: For infants not yet able to stand upright, stature will be measured as recumbent length.
- Review and update transfusion history
- Collect information on concomitant medications
- Collect information on any medical events that have occurred since the screening visit
- Calculate the amount of study medication required, based on a dosage of 25 mg/kg/day (divided t.i.d.) for the first 2 weeks and 50 mg/kg/day (divided t.i.d.) for the next 2 weeks (± 10 days)
- Dispense enough study medication to last until the next scheduled visit, with an allowance for the visit window of ± 10 days, and provide the parent/guardian (and patient, if applicable) with instructions on how to administer it

- Provide parent/guardian (or patient, if applicable) with a diary card and explain how to complete it
- Administer the first dose of study medication, and note the time at which it is given
- Collect a blood sample for the assessment of prolactin at 1.5 hours (± 5 min) post-dose
- Provide parent/guardian (and patient, if applicable) with an emergency card containing contact information, and explain that it is to be carried at all times
- Provide parent/guardian with a thermometer
- Instruct parent/guardian (and patient, if applicable) to do the following:
    - Bring the patient to either the study site or a local laboratory for a weekly blood draw
    - In the event of any symptoms indicative of infection such as fever, sore throat, or flu-like symptoms, immediately interrupt therapy and contact the clinic
    - At the next site visit, bring back the completed diary card plus all medication containers, whether empty, partly used, or unopened
    - In the event of a decision to withdraw from the study before completion, bring the patient to the clinic for an Early Termination Visit as soon as possible, and no later than one month following the last dose of study medication
- Schedule next study visit, and instruct the parent/guardian that: 1) on the preceding day, the evening dose of study medication must be administered at least 12 hours before the start of the visit, and 2) on the day of the visit, the morning dose must not be taken beforehand; it will be administered at the site.

From this day until study termination, the patient is to receive the assigned study medication 3 times daily. On days of study visits, the morning dose will be administered at the site.

Blood Draws for Hematology

Hematology testing is to be done weekly (every 7 ±3 days) after start of dosing up to Month 6, and then biweekly (every 14 ±3 days) until termination from the study. On weeks that include a site visit, this testing will be done as part of the regular study procedures. On other applicable weeks, it may be done either at the site or at a local laboratory. The results are to be reviewed by the investigator as soon as they are received, preferably within 24 hours.

Month 1 (± 10 days)

- Collect blood samples for the following assessments (at approximately the same time that this was done at baseline):
    - Hematology
    - Blood chemistry
    - Labile plasma iron
    - Transferrin saturation
    - Serum ferritin
    - C-reactive protein

      Notes:

        - Since SF level may be impacted by the presence of infection, it must additionally be verified that the child has had no signs of infection in the previous 7 days, including the day of the visit, and that the level of CRP is no greater than 20% higher than the normal range for the patient's age. If there are signs of infection and/or the CRP level is above this threshold, the SF level must be checked again a minimum of one week later. (If an investigator has valid reason to believe that an SF level ≥ 1000 µg/L may be attributable to infection even if this is not indicated by the CRP result, SF may be rechecked once more a minimum of one week later.)
        - If a transfusion is scheduled on the day of the visit, the blood samples for serum ferritin, LPI, and TSAT must be collected before the transfusion is performed.
- Perform a physical examination (to be completed by the investigator or a qualified delegate)
- Measure vital signs (heart rate, blood pressure, and body temperature)
- Measure weight and height/length
- Review and update transfusion history
- Ask the parent/guardian (and patient, if applicable) about any adverse events that have occurred and concomitant medications that have been taken since the last site visit
- Additionally review the diary card for information on adverse events and use of concomitant medications, and file the diary card with the source documents
- Collect study medication containers, and check them in order to calculate treatment compliance

- Dispense enough study medication to last until the next scheduled visit, with an allowance for the visit window of ± 10 days, along with a reminder if necessary on how to administer it
- Administer the morning dose of study medication
- Provide the parent/guardian (or patient, if applicable) with a new diary card, along with a reminder if necessary about how to complete it
- Instruct parent/guardian (and patient, if applicable) to do the following:
    - Bring the patient to either the study site or a local laboratory for a weekly blood draw
    - In the event of any symptoms indicative of infection such as fever, sore throat, or flu-like symptoms, immediately interrupt therapy and contact the clinic
    - At the next site visit, bring back the completed diary card plus all medication containers, whether empty, partly used, or unopened
    - In the event of a decision to withdraw from the study before completion, bring the patient to the clinic for an Early Termination visit as soon as possible, and no later than one month following the last dose of study medication
- Schedule next study visit, and instruct the parent/guardian that: 1) on the preceding day, the evening dose of study medication must be administered at least 12 hours before the start of the visit, and 2) on the day of the visit, the morning dose must not be taken beforehand; it will be administered at the site

Month 2 (± 10 days)

- Collect blood samples for the following assessments (at approximately the same time that this was done at baseline):
    - Hematology
    - Labile plasma iron
    - Transferrin saturation
    - Serum ferritin
    - C-reactive protein

      Notes:

        - A patient whose SF level is found to be ≥1000 µg/L at 2 consecutive visits is to be withdrawn; however, since SF level may be impacted by the presence of infection, it must additionally be verified that the child has had

no signs of infection in the previous 7 days, including the day of the visit, and that the level of CRP is no greater than 20% higher than the normal range for the patient's age. If there are signs of infection and/or the CRP level is above this threshold, an SF level ≥1000 µg/L must be checked again a minimum of a week later before the patient's study status can be determined. (If an investigator has valid reason to believe that an SF level ≥ 1000 µg/L may be attributable to infection even if this is not indicated by the CRP result, SF may be rechecked once more a minimum of one week later.)

- If a transfusion is scheduled on the day of the visit, the blood samples for serum ferritin, LPI, and TSAT must be collected before the transfusion is performed.

- Measure vital signs (heart rate, blood pressure, and body temperature)
- Measure weight and height/length
- Review and update transfusion history
- Ask about any adverse events that have occurred and concomitant medications that have been taken since the last site visit
- Additionally review the diary card for information on adverse events and use of concomitant medications, and file the diary card with the source documents
- Collect study medication containers, and check them in order to calculate treatment compliance
- Check the laboratory results from the previous 2 visits (baseline and Month 1) to verify whether the patient has had an SF value ≥ 800 µg/L (but still below 1000 µg/L) and/or an LPI value ≥ 0.6 µM and/or a TSAT value ≥ 60% at both these visits. If none of these criteria are met, the dosage is to remain at 50 mg/kg/day; if any of them are met, the dosage is to be increased to 75 mg/kg/day.
- Dispense enough study medication to last until the next scheduled visit, with an allowance for the visit window of ± 10 days, along with a reminder if necessary on how to administer it
- Administer the morning dose of study medication
- Provide parent/guardian (or patient, if applicable) with a new diary card, along with a reminder if necessary about how to complete it
- Instruct parent/guardian (or patient, if applicable) to do the following:

- Bring the patient to either the study site or a local laboratory for a weekly blood draw
- In the event of any symptoms indicative of infection such as fever, sore throat, or flu-like symptoms, immediately interrupt therapy and contact the clinic
- At the next site visit, bring back the completed diary card plus all medication containers, whether empty, partly used, or unopened
- In the event of a decision to withdraw from the study before completion, bring the patient to the clinic for an Early Termination visit as soon as possible, and no later than one month following the last dose of study medication

- Schedule next study visit, and instruct the parent/guardian that: 1) on the preceding day, the evening dose of study medication must be administered at least 12 hours before the start of the visit, and 2) on the day of the visit, the morning dose must not be taken beforehand; it will be administered at the site

As soon as the SF results from this visit are available, check to see if the SF level was ≥ 1000 µg/L (taking the factor of possible infection into account, as described above) at **both this and the previous visit**. If no, have the patient continue; if yes, immediately terminate the patient from the study and schedule an early termination visit.

Month 3 (± 10 days)

- Collect blood samples for the following assessments (at approximately the same time that this was done at baseline):
  - Hematology
  - Blood chemistry
  - Labile plasma iron
  - Transferrin saturation
  - Serum ferritin
  - C-reactive protein

    Notes:

    - A patient whose SF level is found to be ≥1000 µg/L at 2 consecutive visits is to be withdrawn; however, since SF level may be impacted by the presence of infection, it must additionally be verified that the child has had no signs of infection in the previous 7 days, including the day of the visit, and that the level of CRP is no greater than 20% higher than the normal range for the patient's age. If there are signs of infection and/or the CRP

level is above this threshold, an SF level ≥1000 µg/L must be checked again a minimum of a week later before the patient's study status can be determined. (If an investigator has valid reason to believe that an SF level ≥ 1000 µg/L may be attributable to infection even if this is not indicated by the CRP result, SF may be rechecked once more a minimum of one week later.)

- If a transfusion is scheduled on the day of the visit, the blood samples for serum ferritin, LPI, and TSAT must be collected before the transfusion is performed.

- Perform a physical examination (to be completed by the investigator or a qualified delegate)
- Measure vital signs (heart rate, blood pressure, and body temperature)
- Measure weight and height/length
- Review and update transfusion history
- Ask the parent/guardian (and patient, if applicable) about any adverse events that have occurred and concomitant medications that have been taken since the last site visit
- Additionally review the diary card for information on adverse events and use of concomitant medications, and file the diary card with the source documents
- Collect study medication containers, and check them in order to calculate treatment compliance
- Check the laboratory results from the previous 3 visits (baseline, Month 1, and Month 2) to verify whether:
  - The patient has had an SF value ≥ 800 µg/L (but still below 1000 µg/L) and/or an LPI value ≥ 0.6 µM and/or a TSAT value ≥ 60% at 2 consecutive visits, **or**
  - An increasing trend in any of the above 3 measures at 3 consecutive visits, regardless of value

  If none of these criteria are met, the dosage is to remain at 50 mg/kg/day; if any of them are met, the dosage is to be increased to 75 mg/kg/day.
- Dispense enough study medication to last until the next scheduled visit, with an allowance for the visit window of ± 10 days, along with a reminder if necessary on how to administer it
- Administer the morning dose of study medication
- Provide the parent/guardian (or patient, if applicable) with a new diary card, along with a reminder if necessary about how to complete it

- Instruct parent/guardian (and patient, if applicable) to do the following:
    - Bring the patient to either the study site or a local laboratory for a weekly blood draw
    - In the event of any symptoms indicative of infection such as fever, sore throat, or flu-like symptoms, immediately interrupt therapy and contact the clinic
    - At the next site visit, bring back the completed diary card plus all medication containers, whether empty, partly used, or unopened
    - In the event of a decision to withdraw from the study before completion, bring the patient to the clinic for an Early Termination visit as soon as possible, and no later than one month following the last dose of study medication
- Schedule next study visit, and instruct the parent/guardian that: 1) on the preceding day, the evening dose of study medication must be administered at least 12 hours before the start of the visit, and 2) on the day of the visit, the morning dose must not be taken beforehand; it will be administered at the site.

As soon as the SF results from this visit are available, check to see if the SF level was ≥ 1000 µg/L (taking the factor of possible infection into account, as described above) at **both this and the previous visit**. If no, have the patient continue; if yes, immediately terminate the patient from the study and schedule an early termination visit.

Month 4 and Month 5 (± 10 days)

- Collect blood samples for the following assessments (at approximately the same time that this was done at baseline):
    - Hematology
    - Labile plasma iron
    - Transferrin saturation
    - Serum ferritin
    - C-reactive protein

      Notes:

        - A patient whose SF level is found to be ≥1000 µg/L at 2 consecutive visits is to be withdrawn; however, since SF level may be impacted by the presence of infection, it must additionally be verified that the child has had no signs of infection in the previous 7 days, including the day of the visit, and that the level of CRP is no greater than 20% higher than the normal range for the patient's age. If there are signs of infection and/or the CRP

level is above this threshold, an SF level ≥1000 µg/L must be checked again a minimum of a week later before the patient's study status can be determined. (If an investigator has valid reason to believe that an SF level ≥ 1000 µg/L may be attributable to infection even if this is not indicated by the CRP result, SF may be rechecked once more a minimum of one week later.)

- If a transfusion is scheduled on the day of the visit, the blood samples for serum ferritin, LPI, and TSAT must be collected before the transfusion is performed.

- Measure vital signs (heart rate, blood pressure, and body temperature)
- Measure weight and height/length
- Review and update transfusion history
- Ask about any adverse events that have occurred and concomitant medications that have been taken since the last site visit
- Additionally review the diary card for information on adverse events and use of concomitant medications, and file the diary card with the source documents
- Collect study medication containers, and check them in order to calculate treatment compliance
- Check the laboratory results from the previous 3 visits (Months 1, 2, and 3 *or* Months 2, 3, and 4) to verify whether:
    - The patient has had an SF value ≥ 800 µg/L (but still below 1000 µg/L) and/or an LPI value ≥ 0.6 µM and/or a TSAT value ≥ 60% at 2 consecutive visits, **or**
    - An increasing trend in any of the above 3 measures at 3 consecutive visits, regardless of value

  If none of these criteria are met, the dosage is to remain at 50 mg/kg/day; if any of them are met, the dosage is to be increased to 75 mg/kg/day.
- Dispense enough study medication to last until the next scheduled visit, with an allowance for the visit window of ± 10 days, along with a reminder if necessary on how to administer it
- Administer the morning dose of study medication
- Provide parent/guardian (or patient, if applicable) with a new diary card, along with a reminder if necessary about how to complete it
- Instruct parent/guardian (or patient, if applicable) to do the following:

- Bring the patient to either the study site or a local laboratory for a weekly blood draw
- In the event of any symptoms indicative of infection such as fever, sore throat, or flu-like symptoms, immediately interrupt therapy and contact the clinic
- At the next site visit, bring back the completed diary card plus all medication containers, whether empty, partly used, or unopened
- In the event of a decision to withdraw from the study before completion, bring the patient to the clinic for an Early Termination visit as soon as possible, and no later than one month following the last dose of study medication

- Schedule next study visit, and instruct the parent/guardian that: 1) on the preceding day, the evening dose of study medication must be administered at least 12 hours before the start of the visit, and 2) on the day of the visit, the morning dose must not be taken beforehand; it will be administered at the site.

As soon as the SF results from this visit are available, check to see if the SF level was ≥ 1000 µg/L (taking the factor of possible infection into account, as described above) at **both this and the previous visit**. If no, have the patient continue; if yes, immediately terminate the patient from the study and schedule an early termination visit.

Month 6 (± 10 days)

- Collect blood samples for the following assessments (at approximately the same time that this was done at baseline):
  - Hematology
  - Blood chemistry
  - Labile plasma iron
  - Transferrin saturation
  - Serum ferritin
  - C-reactive protein

    Notes:

    - A patient whose SF level is found to be ≥1000 µg/L at 2 consecutive visits is to be withdrawn; however, since SF level may be impacted by the presence of infection, it must additionally be verified that the child has had no signs of infection in the previous 7 days, including the day of the visit, and that the level of CRP is no greater than 20% higher than the normal range for the patient's age. If there are signs of infection and/or the CRP

level is above this threshold, an SF level ≥1000 µg/L must be checked again a minimum of a week later before the patient's study status can be determined. (If an investigator has valid reason to believe that an SF level ≥ 1000 µg/L may be attributable to infection even if this is not indicated by the CRP result, SF may be rechecked once more a minimum of one week later.)

- If a transfusion is scheduled on the day of the visit, the blood samples for serum ferritin, LPI, and TSAT must be collected before the transfusion is performed.

- Perform a physical examination (to be completed by the investigator or a qualified delegate)
- Measure vital signs (heart rate, blood pressure, and body temperature)
- Measure weight and height/length
- Review and update transfusion history
- Ask the parent/guardian (and patient, if applicable) about any adverse events that have occurred and concomitant medications that have been taken since the last site visit
- Additionally review the diary card for information on adverse events and use of concomitant medications, and file the diary card with the source documents
- Collect study medication containers, and check them in order to calculate treatment compliance
- Check the laboratory results from the previous 3 visits (Months 3, 4, and 5) to verify whether:
    - The patient has had an SF value ≥ 800 µg/L (but still below 1000 µg/L) and/or an LPI value ≥ 0.6 µM and/or a TSAT value ≥ 60% at 2 consecutive visits, **or**
    - An increasing trend in any of the above 3 measures at 3 consecutive visits, regardless of value

  If none of these criteria are met, the dosage is to remain at 50 mg/kg/day; if any of them are met, the dosage is to be increased to 75 mg/kg/day.
- Dispense enough study medication to last until the next scheduled visit, with an allowance for the visit window of ± 10 days, along with a reminder if necessary on how to administer it
- Administer the morning dose of study medication

- Provide the parent/guardian (or patient, if applicable) with a new diary card, along with a reminder if necessary about how to complete it
- Instruct parent/guardian (and patient, if applicable) to do the following:
    - Bring the patient to either the study site or a local laboratory for a biweekly blood draw (as of Month 6, this is reduced from weekly)
    - In the event of any symptoms indicative of infection such as fever, sore throat, or flu-like symptoms, immediately interrupt therapy and contact the clinic
    - At the next site visit, bring back the completed diary card plus all medication containers, whether empty, partly used, or unopened
    - In the event of a decision to withdraw from the study before completion, bring the patient to the clinic for an Early Termination visit as soon as possible, and no later than one month following the last dose of study medication
- Schedule next study visit, and instruct the parent/guardian that: 1) on the preceding day, the evening dose of study medication must be administered at least 12 hours before the start of the visit, and 2) on the day of the visit, the morning dose must not be taken beforehand; it will be administered at the site.

As soon as the SF results from this visit are available, check to see if the SF level was ≥ 1000 µg/L (taking the factor of possible infection into account, as described above) at **both this and the previous visit**. If no, have the patient continue; if yes, immediately terminate the patient from the study and schedule an early termination visit.

Month 7 and Month 8 (± 10 days)

- Collect blood samples for the following assessments (at approximately the same time that this was done at baseline):
    - Hematology
    - Labile plasma iron
    - Transferrin saturation
    - Serum ferritin
    - C-reactive protein

      Notes:

      - A patient whose SF level is found to be ≥1000 µg/L at 2 consecutive visits is to be withdrawn; however, since SF level may be impacted by the presence of infection, it must additionally be verified that the child has had

no signs of infection in the previous 7 days, including the day of the visit, and that the level of CRP is no greater than 20% higher than the normal range for the patient's age. If there are signs of infection and/or the CRP level is above this threshold, an SF level ≥1000 µg/L must be checked again a minimum of a week later before the patient's study status can be determined. (If an investigator has valid reason to believe that an SF level ≥ 1000 µg/L may be attributable to infection even if this is not indicated by the CRP result, SF may be rechecked once more a minimum of one week later.)

- If a transfusion is scheduled on the day of the visit, the blood samples for serum ferritin, LPI, and TSAT must be collected before the transfusion is performed.

- Measure vital signs (heart rate, blood pressure, and body temperature)
- Measure weight and height/length
- Review and update transfusion history
- Ask the parent/guardian (and patient, if applicable) about any adverse events that have occurred and concomitant medications that have been taken since the last site visit
- Additionally review the diary card for information on adverse events and use of concomitant medications, and file the diary card with the source documents
- Collect study medication containers, and check them in order to calculate treatment compliance
- Check the laboratory results from the previous 3 visits (Months 4, 5, and 6 *or* Months 5, 6, and 7) to verify whether:
    - The patient has had an SF value ≥ 800 µg/L (but still below 1000 µg/L) and/or an LPI value ≥ 0.6 µM and/or a TSAT value ≥ 60% at 2 consecutive visits, **or**
    - An increasing trend in any of the above 3 measures at 3 consecutive visits, regardless of value

  If none of these criteria are met, the dosage is to remain at 50 mg/kg/day; if any of them are met, the dosage is to be increased to 75 mg/kg/day.
- Dispense enough study medication to last until the next scheduled visit, with an allowance for the visit window of ± 10 days, along with a reminder if necessary on how to administer it
- Administer the morning dose of study medication

- Provide the parent/guardian (or patient, if applicable) with a new diary card, along with a reminder if necessary about how to complete it
- Instruct parent/guardian (and patient, if applicable) to do the following:
    - Bring the patient to either the study site or a local laboratory for a biweekly blood draw
    - In the event of any symptoms indicative of infection such as fever, sore throat, or flu-like symptoms, immediately interrupt therapy and contact the clinic
    - At the next site visit, bring back the completed diary card plus all medication containers, whether empty, partly used, or unopened
    - In the event of a decision to withdraw from the study before completion, bring the patient to the clinic for an Early Termination visit as soon as possible, and no later than one month following the last dose of study medication
- Schedule next study visit, and instruct the parent/guardian that: 1) on the preceding day, the evening dose of study medication must be administered at least 12 hours before the start of the visit, and 2) on the day of the visit, the morning dose must not be taken beforehand; it will be administered at the site.

As soon as the SF results from this visit are available, check to see if the SF level was ≥ 1000 µg/L (taking the factor of possible infection into account, as described above) at **both this and the previous visit**. If no, have the patient continue; if yes, immediately terminate the patient from the study and schedule an early termination visit.

Month 9 (± 10 days)

- Collect blood samples for the following assessments (at approximately the same time that this was done at baseline):
    - Hematology
    - Blood chemistry
    - Labile plasma iron
    - Transferrin saturation
    - Serum ferritin
    - C-reactive protein

Notes:

- A patient whose SF level is found to be ≥1000 µg/L at 2 consecutive visits is to be withdrawn; however, since SF level may be impacted by the presence of infection, it must additionally be verified that the child has had no signs of infection in the previous 7 days, including the day of the visit, and that the level of CRP is no greater than 20% higher than the normal range for the patient's age. If there are signs of infection and/or the CRP level is above this threshold, an SF level ≥1000 µg/L must be checked again a minimum of a week later before the patient's study status can be determined. (If an investigator has valid reason to believe that an SF level ≥ 1000 µg/L may be attributable to infection even if this is not indicated by the CRP result, SF may be rechecked once more a minimum of one week later.)
- If a transfusion is scheduled on the day of the visit, the blood samples for serum ferritin, LPI, and TSAT must be collected before the transfusion is performed.

- Perform a physical examination (to be completed by the investigator or a qualified delegate)
- Measure vital signs (heart rate, blood pressure, and body temperature)
- Measure weight and height/length
- Review and update transfusion history
- Ask the parent/guardian (and patient, if applicable) about any adverse events that have occurred and concomitant medications that have been taken since the last site visit
- Additionally review the diary card for information on adverse events and use of concomitant medications, and file the diary card with the source documents
- Collect study medication containers, and check them in order to calculate treatment compliance
- Check the laboratory results from the previous 3 visits (Months 6, 7, and 8) to verify whether:
    - The patient has had an SF value ≥ 800 µg/L (but still below 1000 µg/L) and/or an LPI value ≥ 0.6 µM and/or a TSAT value ≥ 60% at 2 consecutive visits, **or**
    - An increasing trend in any of the above 3 measures at 3 consecutive visits, regardless of value

  If none of these criteria are met, the dosage is to remain at 50 mg/kg/day; if any of them are met, the dosage is to be increased to 75 mg/kg/day.

- Dispense enough study medication to last until the next scheduled visit, with an allowance for the visit window of ± 10 days, along with a reminder if necessary on how to administer it
- Administer the morning dose of study medication
- Provide the parent/guardian (or patient, if applicable) with a new diary card, along with a reminder if necessary about how to complete it
- Instruct parent/guardian (and patient, if applicable) to do the following:
    - Bring the patient to either the study site or a local laboratory for a biweekly blood draw
    - In the event of any symptoms indicative of infection such as fever, sore throat, or flu-like symptoms, immediately interrupt therapy and contact the clinic
    - At the next site visit, bring back the completed diary card plus all medication containers, whether empty, partly used, or unopened
    - In the event of a decision to withdraw from the study before completion, bring the patient to the clinic for an Early Termination visit as soon as possible, and no later than one month following the last dose of study medication
- Schedule next study visit, and instruct the parent/guardian that: 1) on the preceding day, the evening dose of study medication must be administered at least 12 hours before the start of the visit, and 2) on the day of the visit, the morning dose must not be taken beforehand; it will be administered at the site.

As soon as the SF results from this visit are available, check to see if the SF level was ≥ 1000 µg/L (taking the factor of possible infection into account, as described above) at **both this and the previous visit**. If no, have the patient continue; if yes, immediately terminate the patient from the study and schedule an early termination visit.

Months 10 and Month 11 (± 10 days)

- Collect blood samples for the following assessments (at approximately the same time that this was done at baseline):
    - Hematology
    - Labile plasma iron
    - Transferrin saturation
    - Serum ferritin
    - C-reactive protein

Notes:

- A patient whose SF level is found to be ≥1000 µg/L at 2 consecutive visits is to be withdrawn; however, since SF level may be impacted by the presence of infection, it must additionally be verified that the child has had no signs of infection in the previous 7 days, including the day of the visit, and that the level of CRP is no greater than 20% higher than the normal range for the patient's age. If there are signs of infection and/or the CRP level is above this threshold, an SF level ≥1000 µg/L must be checked again a minimum of a week later before the patient's study status can be determined. (If an investigator has valid reason to believe that an SF level ≥ 1000 µg/L may be attributable to infection even if this is not indicated by the CRP result, SF may be rechecked once more a minimum of one week later.)
- If a transfusion is scheduled on the day of the visit, the blood samples for serum ferritin, LPI, and TSAT must be collected before the transfusion is performed.

- Measure vital signs (heart rate, blood pressure, and body temperature)
- Measure weight and height/length
- Review and update transfusion history
- Ask the parent/guardian (and patient, if applicable) about any adverse events that have occurred and concomitant medications that have been taken since the last site visit
- Additionally review the diary card for information on adverse events and use of concomitant medications, and file the diary card with the source documents
- Collect study medication containers, and check them in order to calculate treatment compliance
- Check the laboratory results from the previous 3 visits (Months 7, 8, and 9 *or* Months 8, 9, and 10) to verify whether:
    - The patient has had an SF value ≥ 800 µg/L (but still below 1000 µg/L) and/or an LPI value ≥ 0.6 µM and/or a TSAT value ≥ 60% at 2 consecutive visits, **or**
    - An increasing trend in any of the above 3 measures at 3 consecutive visits, regardless of value

  If none of these criteria are met, the dosage is to remain at 50 mg/kg/day; if any of them are met, the dosage is to be increased to 75 mg/kg/day.

- Dispense enough study medication to last until the next scheduled visit, with an allowance for the visit window of ± 10 days, along with a reminder if necessary on how to administer it
- Administer the morning dose of study medication
- Provide the parent/guardian (or patient, if applicable) with a new diary card, along with a reminder if necessary about how to complete it
- Instruct parent/guardian (and patient, if applicable) to do the following:
    - Bring the patient to either the study site or a local laboratory for a biweekly blood draw
    - In the event of any symptoms indicative of infection such as fever, sore throat, or flu-like symptoms, immediately interrupt therapy and contact the clinic
    - At the next site visit, bring back the completed diary card plus all medication containers, whether empty, partly used, or unopened
    - In the event of a decision to withdraw from the study before completion, bring the patient to the clinic for an Early Termination visit as soon as possible, and no later than one month following the last dose of study medication
- Schedule next study visit, and instruct the parent/guardian that: 1) on the preceding day, the evening dose of study medication must be administered at least 12 hours before the start of the visit, and 2) on the day of the visit, the morning dose must not be taken beforehand; it will be administered at the site.

As soon as the SF results from this visit are available, check to see if the SF level was ≥ 1000 µg/L (taking the factor of possible infection into account, as described above) at **both this and the previous visit**. If no, have the patient continue; if yes, immediately terminate the patient from the study and schedule an early termination visit.

Month 12 (± 10 days) (End of Study Visit)

Note: A study staff member is to call the patient's home prior to this visit with a reminder to not administer the morning dose before coming to the site.

- Collect blood samples for the following assessments (at approximately the same time that this was done at baseline):
    - Hematology
    - Blood chemistry
    - Prolactin (pre-dose sample)

- Labile plasma iron
- Transferrin saturation
- Serum ferritin
- C-reactive protein

Notes:

- Since SF level may be impacted by the presence of infection, it must additionally be verified that the child has had no signs of infection in the previous 7 days, including the day of the visit, and that the level of CRP is no greater than 20% higher than the normal range for the patient's age. . If there are signs of infection and/or the CRP level is above this threshold, an SF level ≥ 1000 µg/L must be checked again a minimum of a week later. (If an investigator has valid reason to believe that an SF level ≥ 1000 µg/L may be attributable to infection even if this is not indicated by the CRP result, SF may be rechecked once more a minimum of one week later.)
- If a transfusion is scheduled on the day of the visit, the blood samples for serum ferritin, LPI, and TSAT must be collected before the transfusion is performed.

- Collect a urine specimen for urinalysis
- Perform a physical examination (to be completed by the investigator or a qualified delegate)
- Measure vital signs (heart rate, blood pressure, and body temperature)
- Measure weight and height/length
- Review and update transfusion history
- Ask about any adverse events that have occurred and concomitant medications that have been taken since the last site visit
- Additionally review the diary card for information on adverse events and use of concomitant medications, and file the diary card with the source documents
- Collect study medication containers, and check them to calculate treatment compliance
- Administer the final dose of study medication, ensuring that this is done at approximately the same time as at baseline, and note the exact time at which it is given
- Collect a blood sample for the assessment of prolactin at 1.5 hours (± 5 min) post-dose

Early termination visit (if applicable)

From Month 2 to Month 11, a patient who is determined to have had a serum ferritin level ≥1000 µg/L at 2 consecutive visits will be terminated from the study, and is to return for an early termination visit as soon as possible. The following procedures will be done:

- Collect blood samples for hematology and blood chemistry assessments
- Collect a urine specimen for urinalysis
- Perform a physical examination (to be completed by the investigator or a qualified delegate)
- Measure vital signs (heart rate, blood pressure, and body temperature)
- Measure weight and height/length
- Review and update transfusion history
- Ask about any adverse events that have occurred and concomitant medications that have been taken since the last site visit
- Additionally review the diary card for information on adverse events and use of concomitant medications, and file the diary card with the source documents
- Collect study medication containers, and check them to calculate treatment compliance

For patients who withdraw early for reasons other than reaching the serum ferritin threshold, the early termination visit will include all procedures done at the Month 12 visit except for measurement of prolactin.

Participation in the study is now complete. Patients whose SF level is still below 1000 µg/L at 12 months will be offered participation in an extension study, LA55-EXT, in which they will continue to receive their assigned study product for up to 2 more years. Patients who are terminated early because they have already reached the 1000 µg/L threshold will not be eligible to enroll in the extension study.

5.2 Method of Assignment to Treatment

A total of 64 participants will be randomized, 32 to receive placebo and 32 to receive deferiprone.

The sponsor will generate the randomization codes according to the study design. Once generated, the randomization codes will be final and will not be modifiable. An Interactive Voice (or Web) Response System (IVRS/IWRS) will be used to perform the randomization in this study.

5.3 Blinding Procedures

The placebo solution will have the same appearance and flavor as deferiprone oral solution, and will be administered at a volume matching that required for a 25, 50, or 75 mg/kg/day dose of active product.

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

5.4 Allocation of Patient Numbers

After provision of informed consent (and assent if applicable), 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 (separated from the first 3 by a hyphen) are assigned sequentially for each individual enrolled at that site. For example, if site #1 enrolls 8 patients, the ID numbers will be 001-001 to 001-008. The assigned ID numbers of patients who are screening failures or who withdraw from the study will not be reused.

5.5 Treatment Compliance

Compliance will be determined as follows: 1) participants will use the daily diary card to record the amount of study medication administered, and 2) at each visit, the investigator or delegate will collect the medication containers, whether empty, partly used, or unopened, and will check the volume of solution remaining by weighing the bottles. Compliance will be calculated by the volume of solution taken divided by the volume of solution prescribed as per the dosing frequency and length of treatment. Any discrepancies must be discussed with participants 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 at each visit.

If the volume of returned solution is less than it should be but the parent/guardian (or patient, as applicable) reports having administered or 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., solution was accidentally spilled), along with the actual percentage. Both under-compliance < 80% and over-compliance >120% will be reported as a protocol deviation, unless under-compliance is due to treatment interruption because of infection or neutropenia or other extenuating circumstances (see Section 7.2.1.8).

6 STUDY TREATMENTS

Patients will receive either deferiprone oral solution 80 mg/mL or matching placebo solution.

6.1 Investigational Product

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

The 80 mg/mL formulation used in this study is a clear reddish solution with a bubble gum–flavored aroma.

6.1.1 Dosage Form and Mode of Administration

Deferiprone oral solution is to be administered orally, using a syringe, three times a day. It can be given with or without food, as per the investigator's recommendation.

6.1.2 Precautions for Use

Deferiprone oral solution 80 mg/mL is to be stored at 15–30°C in the container in which it is supplied. Bottles should not be stored in direct light.

6.2 Reference Product

The placebo product will be matched to deferiprone oral solution for color and flavor, and will be provided in the same type of bottle and with the same label.

6.3 Packaging and Labeling

The product will be supplied in 250 mL amber-colored bottles with child-resistant closure and a tamper-evident seal. The containers will be provided with labels whose content is in accordance with all applicable regulatory requirements and includes details such as protocol number, expiry date, lot/batch number, investigational statement, storage temperature, dosage, direction for use, visit number, date dispensed, and name and address of the study sponsor.

6.4 Shipping and Storage

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 daily recordings of the storage facility temperature must be available. Temperature excursions must be immediately reported to the sponsor for investigation and determination of impact on the study medication.

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

6.5 Product Accountability

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

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

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

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

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

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

6.6 Replacement Doses

If medication has been lost or damaged, participants will need to return to the study site to receive replacement bottles. 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.

6.7 Disposition of Unused Product

All investigational product that has been returned by participants or that is unused for any other reasons will be returned to the sponsor or discarded by the site according to internal procedures, if approved, in writing, by the sponsor. The destruction procedures must include the issuance of appropriate signed destruction certificates including mode of destruction and complete drug accountability of destroyed materials. The destruction may take place only after written approval by the sponsor.

6.8 Other Study Supplies

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

7 MEASUREMENTS AND EVALUATIONS

7.1 Efficacy Measurements

Efficacy will be measured by monitoring levels of serum ferritin, transferrin saturation, and labile plasma iron.

7.1.1 Serum Ferritin

Ferritin is a protein that stores iron in a non-toxic form, transports it to areas where it is required, and releases it in a controlled manner, thereby acting as a buffer against iron deficiency and iron overload. It is mainly found in tissues, but small amounts are secreted into the serum, where it can serve as an indirect but easily measurable marker of the total amount of iron stored in the body. (Drawbacks of using it as a marker include lack of specificity, as disorders other than iron overload can cause large amounts of ferritin to be released into the circulation, and inter-patient variability.) Levels of serum ferritin above 1000 ng/mL are often considered to be associated with iron toxicity. In young children who have only recently begun an RBC transfusion regimen, it takes some time for this level to be reached, but in the absence of chelation it inevitably is reached.

Serum ferritin will be measured at each visit, and the time to reach a level ≥ 1000 µg/L will be compared between the treatment arms.

7.1.2 Transferrin Saturation

Transferrin is a protein that combines with ferritin and transports it where iron is required. When its capacity to bind incoming iron is exceeded, excess iron circulates as free non-transferrin-bound iron (NTBI), and is taken up by tissues where it can cause cell and organ damage. Transferrin saturation, defined as the percentage of the iron-binding sites of transferrin that are already occupied, is easily measured and hence serves as a marker for NTBI. High levels of transferrin saturation are associated with iron toxicity. As this measure is highly variable, the blood samples for its assessment will always be collected at approximately the same time of day and at approximately the same amount of time after the last dose of study medication, in an attempt to decrease variability as much as possible.

Transferrin saturation will be measured at each visit, and the time to reach a level ≥ 60% will be compared between the treatment arms.

7.1.3 Labile Plasma Iron

Labile plasma iron is a component of NTBI, and is the most toxic form of iron since it acts as a catalyst in the formation of harmful free hydroxyl radicals which can damage cellular DNA, proteins, and membrane lipids. High levels of this form of iron may be found in individuals with conditions of iron overload. As this measure is highly variable, the blood samples for its assessment will always be collected at approximately the same time of day and at approximately the same amount of time after the last dose of study medication, in an attempt to decrease variability as much as possible.

Labile plasma iron will be measured at each visit, and the time to reach a level ≥0.6 μM will be compared between the treatment arms.

7.2 Safety Measurements

7.2.1 Medical Events, Adverse Events, and Serious Adverse Events

7.2.1.1 Definition of Medical Events and Adverse Events

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

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

AEs include:

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

AEs do not include:

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

7.2.1.2 Monitoring and Documenting of Medical Events and Adverse Events

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

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

- How is your child feeling?
- Has your child had any medical problems since the last visit?
- Has your child taken any new medications, other than those provided in this study, since the last visit?

Based on the responses 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?

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

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

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

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

7.2.1.3 Assessment of Causality

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

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

7.2.1.4 Assessment of Intensity

Intensity refers to the degree of discomfort or impairment associated with an event. The intensity of MEs/AEs is to be reported on the CRF as mild, moderate, or severe, according to the definitions provided below. In addition, to maximize consistency in assessment, it is recommended that the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) scale be used.

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

7.2.1.5 Serious Adverse Events

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

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

Clarifications:

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

7.2.1.6 Reporting of Serious Adverse Events

All SAEs occurring up to 30 days following completion of or discontinuation from the study must be reported to the sponsor, regardless of whether they are suspected of having a causal

relationship with the study drug. Any SAEs for which the investigator does suspect a causal relationship must be reported to the sponsor regardless of the time elapsed since the last dose of the study drug.

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

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

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

7.2.1.7 Follow-up and Documentation of SAEs

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

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

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

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

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

7.2.1.8 Adverse Events of Special Interest

7.2.1.8.1 Neutropenia

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 neutropenia	A confirmed ANC < 1.5 x 10^9/L but ≥1.0 x 10^9/L
Moderate neutropenia	A confirmed ANC < 1.0 x 10^9/L but ≥ 0.5 x 10^9/L
Severe neutropenia / 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 CRF as an AE of "decreased ANC", but is not to be defined as neutropenia. The investigator is to use judgment as to whether the decrease is clinically significant.

In addition to having ANC monitored, participants will be advised to immediately report any symptoms indicative of infection such as fever (≥ 38.0°C), sore throat, and flu-like symptoms at any time during the study and for one week following the last dose. 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 neutropenia: A patient who develops mild 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 ≥ 1.5 x 10^9/L. If ANC is still < 1.5 x 10^9/L after 14 days, the investigator is to do the following:

- Withdraw patient from the study and monitor him/her until resolution of the event
- Provide advice regarding protective isolation
- Examine patient the same day (if possible), including drug history and physical examination

- Notify ApoPharma Inc. using the SAE form

Moderate neutropenia: A patient in whom a single ANC measurement <1.0 x 10^9/L but ≥ 0.5 x 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 within 48 hours. If the second ANC is still < 1.0 x 10^9/L, the investigator is to do the following:

- Withdraw patient permanently from the study and monitor ANC daily until resolution
- Provide advice 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 x 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 within 48 hours. If the second ANC is still < 0.5 x 10^9/L, the patient is to be permanently withdrawn from the study, and ANC is to be monitored daily until resolution. The following procedures should be done by the investigator or the treating physician, as appropriate:

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

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

- If possible, consider obtaining bone marrow aspirate for:
    - Histology
    - Progenitor culture
    - Frozen storage (1 mL sample)
- If possible, consider obtaining bone marrow biopsy (minimum length 3 mm)

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

7.2.1.8.2 Infections

If a patient develops fever (≥ 38.0°C) or any sign of infection during the study, study product must be interrupted immediately, and neutrophil count should be obtained and monitored more frequently; every 2 days if ANC $<1.5 \times 10^9$/L. Therapy can be re-initiated once all symptoms have been resolved, if the ANC is $\geq 1.5 \times 10^9$/L.

7.2.2 Laboratory Measurements

Analyses will be performed at a central laboratory, with the exception of the weekly or biweekly hematology assessments which may be performed at a local laboratory. Investigators must interpret each report promptly (preferably within 24 hours) and must document their review by signing or initialing and dating it. Any laboratory values that fall outside a clinically accepted range, or that differ significantly from previous values, must be assessed for clinical significance, and must be marked by the investigator as either "CS" (clinically significant) or "NCS" (not clinically significant). Any clinically significant abnormalities or changes that are not part of a larger medical condition that is already recorded must be further explained on the laboratory report and documented as an adverse event in the eCRF.

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

Hematology: Hemoglobin, total WBC count, ANC, MCV, and platelet count	Screening and weekly after start of dosing up to Month 6 visit, then biweekly until Month 12 or early termination from the study
Blood chemistry: Total protein, GGT, glucose, bilirubin (total, direct, and indirect), AST, ALT, albumin, blood urea nitrogen, calcium, creatinine, total iron binding capacity, serum iron, zinc, and C-reactive protein (CRP)	Screening and Months 1, 3, 6, 9, and 12 (or end of study)
Urinalysis: pH, specific gravity, glucose, protein, ketones, blood, and (if indicated by the dipstick results), sediment microscopy. If there is blood in the urine or three or more "plus signs" for protein, samples must be sent for microscopy.	Screening and Month 12 (or end of study)
Serology: Hepatitis B, hepatitis C, HIV	Screening
Other: Prolactin	Baseline and Month 12

7.2.3 Other Safety Measurements

7.2.3.1 Physical Examinations

Physical examination will consist of an examination of head, ears, eyes, nose, throat and neck, respiratory system, cardiovascular system, gastrointestinal system, musculoskeletal system, neurological systems (central and peripheral), and skin, nails, hair, and scalp. Physical examination will be performed at screening and at Months 1, 3, 6, 9, and 12 (or end of study). Any clinically significant abnormalities noted prior to the screening visit will be recorded as medical history, any noted between screening and the first dose of study medication will be recorded as medical events, and any that are noted post–Dose 1 will be recorded as AEs.

The growth parameters of body weight and height (or length, in infants not yet able to stand upright) which are separate safety endpoints, will be measured at each post-screening visit.

7.2.3.2 Vital Signs

Resting heart rate, resting blood pressure, and body temperature will be taken. ("Resting" implies that the child must be calm and not crying.) Blood pressure should always be measured after a minimum 3-minute resting period, and using the same arm each time if possible. Systolic and diastolic blood pressures are to be recorded from one measurement.

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

7.2.3.3 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 CRFs, 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.

8 STUDY COMMITTEES

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

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

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

9 STATISTICAL ANALYSIS

9.1 Endpoints

9.1.1 Primary Efficacy Endpoint

The primary endpoint is the percentage of patients who still have a serum ferritin level < 1000 μg/L at Month 12.

9.1.2 Secondary Efficacy Endpoints

The secondary endpoints are:

- The percentage of patients whose serum ferritin level is still less than 1000 μg/L at each visit
- The percentage of patients whose LPI value is still less than 0.6 μM at each visit
- The percentage of patients in each treatment arm whose TSAT value is still less than 60% at each visit
- Time to reach a serum ferritin level ≥ 1000 μg/L
- Time to reach an LPI value ≥ 0.6 μM
- Time to reach a TSAT value ≥ 60%

9.1.3 Safety Endpoints

- Adverse events (AEs): Frequency, intensity, time to onset, duration, and relatedness to study drug
- Serious adverse events (SAEs): Frequency, intensity, time to onset, duration, and relatedness to study drug
- Number of discontinuations due to AEs
- Growth parameters: Weight, height, and height velocity, as classified using the Z-score system
- Change in prolactin level from baseline to Month 12

9.2 Determination of Sample Size and Study Power

The sample size for this study is 64 patients, randomized in a 1:1 ratio to the two arms. With this number of patients, there will be over 90% power to detect a statistically significant difference ($\alpha = 0.05$) between the two treatment groups in the percentage of patients who have a serum ferritin level < 1000 μg/L at Month 12 if the deferiprone arm and the placebo arm have an expected incidence of 70% and 20%, respectively.

9.3 Study Populations

9.3.1 Intent-to-Treat Population

The intent-to-treat (ITT) population will be composed of patients who have been randomized, have received at least one dose of study medication, and have had at least one post-baseline measurement on the efficacy variables. All efficacy endpoints will be analyzed for the ITT population, which represents the primary analysis population.

9.3.2 Per Protocol Population

The per protocol (PP) population represents the secondary analysis population, and will be composed of patients who have completed the study and have an assessment for the primary efficacy measure at the end of the study. Patients with major protocol deviations will be excluded from the PP population. The primary efficacy endpoint will be analyzed for this population as well.

9.3.3 Safety Population

The safety population will be composed of subjects who have received at least one dose of study medication.

9.4 Data Analysis Plan

SAS Windows Version 9.3 or higher will be used for all statistical analyses.

9.4.1 Planned Analyses

9.4.1.1 Patient Disposition and Drug Exposure

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

9.4.1.2 Patient Characteristics

Subject characteristics at baseline, 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 Efficacy

The percentage of patients who have not reached levels of LPI ≥ 0.6 μM, TSAT ≥ 60% and SF ≥ 1000 μg/L will be compared between the two treatment groups at each monthly time point as well as at the end of study, using the Fisher's exact test. The effect of baseline value on each of the 3 endpoints will be examined in a covariate analysis. The Kaplan-Meier survival curve for the time to reach a serum ferritin level ≥ 1000 μg/L, an LPI value ≥ 0.6 μM, and a TSAT value ≥ 60% will be generated for the two treatment groups. The log-rank test will be used for comparing the two survival curves for each of the 3 endpoints. The trend analysis over time for LPI, TSAT, and SF measures will be performed to compare the rate of change in these measures between the two treatment groups.

9.4.1.4 Analysis of Safety

Descriptive statistics (mean, standard deviation, minimum, and maximum) will be produced for continuous variables, and frequency tables will be produced for discrete variables by treatment group. Summaries of adverse events and serious adverse events will be produced by treatment group. Shift tables will be generated for comparing the screening/baseline values and end of study values of the relevant measures.

For weight and height, the change from baseline to last assessment will be compared between the two treatment groups using an ANCOVA model with baseline value as a covariate and treatment as the main factor. A similar ANCOVA model will be used for the analysis of the z-scores for height. The rate of change in height will be assessed using regression analysis.

The following safety data will be summarized by treatment group:

- Adverse events (AEs), adverse drug reactions (ADRs), serious adverse events (SAEs), and serious adverse drug reactions (SADRs)
- Number of discontinuations due to AEs
- Hematology assessments
- Biochemistry assessments
- Vital signs
- Urinalysis
- Prior and concomitant medications

Prolactin will be measured at baseline and Month 12. The change in prolactin level from baseline to Month 12 will be compared between the two treatment groups using an ANCOVA model with baseline value as a covariate and treatment as the main factor.

9.4.2 Interim Analyses

There is no interim analysis planned for this study.

9.5 Criteria for Evaluability of Patient Data

Patients with protocol deviations will be assessed, and the deviations will be determined as minor or major before the randomization codes are broken. Patients with major protocol deviations will be excluded from the PP population.

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 or the sponsor's vendor. Trained users will access the system via a secured gateway. Users will only be authorized to access data for their study site. Data will be entered directly into the system from the source documents in lieu of 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 (e.g., Quality Assurance); "read only" access will be provided to avoid unintentional corruption of the database.

The database will be backed up regularly.

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 ECG 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, study sites may be inspected by regulatory authorities and/or audited by ApoPharma Quality Assurance (QA) or their third-party 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 third-party 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/Assent

Prior to entering a patient into the study, the investigator or a designate must obtain written informed consent from the parent/guardian and/or where applicable a 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. In the case of patients who are capable of assenting, informed assent is to be obtained as well. The investigator will ensure that the parent/guardian/patient/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 other family members. The investigator must make a conscientious effort to be fully satisfied that this individual has truly understood that for which the consent has been given. The parent/guardian/ legal representative must be notified that he/she is free to discontinue the patient's participation in the study at any time, and that such withdrawal will not affect present or future care. In the case of a child 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 model versions of the informed consent/assent forms to the sites as separate documents. Each site may then revise these versions according to the requirements of its individual IRB/IEC.

The parent/guardian 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 the parent/ guardian of 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 the parent/guardian (and patient, if applicable) of the possibility that representatives from regulatory authorities and/or the sponsor may require access to hospital or clinic records for verification of data pertinent to the study, including their child's 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

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