PRODUCT:	Deferiprone
STUDY CODE:	LA38-0411
DATE:	01 MAY 2017

Clinical Study Protocol

(Ferriprox in patients with iron overload in sickle cell disease trial - FIRST)

LA38-0411

The efficacy and safety of Ferriprox® for the treatment of transfusional iron overload in patients with sickle cell disease or other anemias

Version: Final version 10.1 (U.S. only)

Date: 01 MAY 2017

PROTOCOL SYNOPSIS

Title of the Study:	The efficacy and safety of Ferriprox® for the treatment of transfusional iron overload in patients with sickle cell disease or other anemias.
Protocol Code:	LA38-0411
Development Phase:	Phase IV
Sponsor:	ApoPharma Inc.
Principal Investigator:	Janet Kwiatkowski, MD The Children's Hospital of Philadelphia Philadelphia, PA, USA
Study Center:	Multicenter
Planned Study Period:	Individual patient treatment duration of 52 weeks. At the end of the 52 weeks of treatment, patients will be invited to participate in a 2-year extension phase.
Study Objectives:	Primary: To determine the efficacy of deferiprone vs. deferoxamine in the treatment of iron overload in patients with sickle cell disease or other anemias. Secondary: o To evaluate the effect of deferiprone vs. deferoxamine on the patients' quality of life; o To evaluate the safety and tolerability of deferiprone vs. deferoxamine.
Study Design:	This study is a 52-week, prospective, multi-center, two-arm, randomized, open-label, parallel design study of deferiprone vs. deferoxamine. **Baseline Phase** During the Baseline Phase, patients who sign an informed consent will undergo initial screening. On the final day of the Baseline Phase, patients' eligibility will be determined, based on the inclusion/exclusion criteria, and qualified patients will enter the Treatment Phase. **Treatment Phase** At the beginning of the Treatment Phase, patients will be randomized in a 2:1 ratio to receive (1) deferiprone or (2) deferoxamine. The Treatment Phase will be 52 weeks in duration.

Investigational Product:	Ferriprox® (deferiprone) 500 mg tablets and/or deferiprone 80 mg/mL oral solution
Comparator Product:	Deferoxamine 2 g vial for injection
Treatment (duration, treatment arm, dose, route):	**Deferiprone**: During the study, patients will be prescribed Ferriprox 500 mg tablets or deferiprone 80 mg/mL oral solution, according to patient preference or product's availability, for administration three times a day (tid). The dose of deferiprone will be based on the transfusional iron input and the severity of iron load at baseline, and may be adjusted on the basis of the magnitude of change in iron overload during the study. <u>Deferiprone 25 mg/kg tid:</u> Patients with transfusional iron input ≤ 0.3 mg/kg/day in the 3 months prior to baseline **AND** Patients with a baseline measure of iron load of: - Serum ferritin <2500 µg/L **AND** - LIC <15 mg/g dry weight **AND** - Cardiac T2* > 20 ms <u>Deferiprone 33 mg/kg tid:</u> Patients with a transfusional iron input > 0.3 mg/kg/day in the 3 months prior to baseline **OR** Patients with at least one baseline measure of iron load as follows: - Serum ferritin ≥2500 µg/L **OR** - LIC ≥15 mg/g dry weight **OR** - Cardiac T2* ≤ 20 ms Dosing of all patients will be initially started at 15 mg/kg tid for 1 week, which will be increased to 20 mg/kg tid in Week 2 and to 25 mg/kg tid in Week 3, which will be the treatment dose for the remainder of the trial,

unless a patient meets the 33 mg/kg tid dosing criteria. In that case, the dose of deferiprone will be increased further to 33 mg/kg tid in Week 4 and this dose will be the treatment dose for the remainder of the trial.

The dose of deferiprone will also be increased to 33 mg/kg tid at any time during the trial if the mean daily transfusional iron input increases to more than 0.3 mg/kg body weight for at least 3 consecutive months OR at Week 26 if there is less than 10% improvement from baseline to Week 26 in at least one of the measures indicative of iron overload (serum ferritin, cardiac MRI T2* or LIC).

Dose reduction recommendations will be based on regular assessment of safety markers for adverse reactions that are possibly dose dependent, such as gastrointestinal upset, increases in serum liver enzyme levels and arthropathies.

Deferoxamine:

During the study, patients will be prescribed deferoxamine as per the approved US prescribing information at doses of 20 – 40 mg/kg/day in children (<16 years of age) and 40–50 mg/kg/day in adults (≥16 years of age) as 8 – 12 h subcutaneous infusion for 5 – 7 days per week. The dose of deferoxamine will be based on the transfusional iron input, on the severity of iron load at baseline, and on the magnitude of its change during the study.

<u>Deferoxamine 20 mg/kg/day (children) or 40 mg/kg/day (adults):</u>

Patients with transfusional iron input ≤ 0.3 mg/kg/day in the 3 months prior to baseline

AND

Patients with a baseline measure of iron load of:

- Serum ferritin <2500 µg/L *

  AND

- LIC <15 mg/g dry weight

  AND

- Cardiac T2* > 20 ms

* If there is a delay in obtaining the results of the baseline serum ferritin assessment from the central laboratory, the most recent result (obtained within the last 3 months) should be used to calculate the starting DFO dosage. This dosage must remain in effect until the baseline serum ferritin results become available, at which time it is to be adjusted if necessary. If no serum ferritin measure has been obtained within the last 3 months, the start of dosing must be deferred until the baseline results are available.

Deferoxamine up to 40 mg/kg (children) or 50 mg/kg (adults):

Patients with a transfusional iron input > 0.3 mg/kg/day in the 3 months prior to baseline

OR

Patients with at least one baseline measure of iron load as follows:

- Serum ferritin ≥2500 µg/L

  OR
- LIC ≥15 mg/g dry weight

  OR
- Cardiac T2* ≤ 20 ms

Children (<16 years of age)

The dose of deferoxamine will also be increased up to 40 mg/kg for 5 – 7 days per week at any time during the trial if the mean daily transfusional iron input increases to more than 0.3 mg/kg body weight for at least 3 consecutive months OR at Week 26 if there is less than 10% improvement from baseline to Week 26 in at least one of the measures of iron overload (serum ferritin, cardiac MRI T2* or LIC).

Adults (≥16 years of age)

The dose of deferoxamine will be increased up to 50 mg/kg for 5 – 7 days per week at any time during the trial if the mean daily transfusional iron input increases to more than 0.3 mg/kg body weight for at least 3 consecutive months OR at Week 26 if there is less than 10% improvement from baseline to Week 26 in at least one of the measures of iron overload (serum ferritin, cardiac MRI T2* or LIC).

Dose reduction recommendations will be based on regular assessment of safety markers.

Target Population: Three hundred (300) male and female patients with sickle cell disease or other anemias will be enrolled and randomized to receive deferiprone or deferoxamine in a 2:1 ratio. At least 80% of the patients will have sickle cell disease. Stratified randomization based on disease category (sickle cell disease vs. other anemias) and on the transfusional iron input in the 3 months prior to baseline (> 0.3 mg/kg/day vs. ≤ 0.3 mg/kg/day) will be employed to ensure that the 2:1 ratio is maintained within each of the 4 strata: 1) sickle cell disease with transfusional iron input > 0.3 mg/kg/day, 2) sickle cell disease with transfusional iron input ≤ 0.3 mg/kg/day, 3) other anemias with transfusional iron input > 0.3 mg/kg/day, and 4) other anemias with transfusional iron input ≤ 0.3 mg/kg/day.

Efficacy Endpoints:

Primary:

The change from baseline to Week 52 in liver iron concentration(measured by MRI).

Secondary:

1. Change from baseline to Week 52 in patient-reported quality of life (SF-36 or Child Health Questionnaire);
2. Change from baseline to Week 52 in cardiac MRI T2*;
3. Change from baseline to Week 52 in serum ferritin.

Safety Endpoints:

1. Frequency, severity and time to onset/duration of adverse events (AEs);
2. Frequency of serious adverse events (SAEs);
3. Discontinuation due to AEs;
4. Hematology assessments;
5. Blood clinical biochemistry assessments;
6. 12-lead ECG.

Sample Size:

Three hundred (300) male and female patients will be enrolled into the study. In a randomized study of two iron chelators for the treatment of iron overload in patients with sickle cell disease (Vichinsky E *et al.* 2007), mean ±SD reductions of 4.0 ± 1.5 mg/g dw and 4.5 ± 2.0 mg/g dw in LIC, as measured by SQUID, were observed (Figure 1 of the article, numerical values obtained from the authors) in patients from the baseline LIC categories of >7-14 mg/g dw or >14 mg/g dw after they were treated with 35-50 mg/kg or ≥50 mg/kg of deferoxamine respectively, for 52 weeks. Assuming the same mean reduction in LIC for deferiprone but a higher SD of ±4.0 mg/g dw for both treatments due to possibly higher variability associated with MRI measurement, the sample size of 300, with >80% being patients with sickle cell disease, will provide over 95% power for demonstrating non-inferiority of deferiprone to deferoxamine in patients with sickle cell disease.

The sample size estimate is based on a non-inferiority margin of 2 mg/g dw for the reduction of LIC and an alpha of 0.05, two-sided (or an alpha of 0.025, one-sided). It has been reported that in a typical patient with thalassemia major, the LIC could increase by 5 mg/g dw after 1 year without chelation therapy. As the cause of iron overload is the same in thalassemia and sickle cell disease, the same increase in LIC may be expected if patients with sickle cell disease are transfused at the same rate and not treated with a chelator. Hence, the difference in reduction of LIC between deferoxamine therapy and a placebo (effect size) can be estimated to be 9 (i.e., 4 – (-5)) mg/g dw. This means that the non-inferiority margin of 2 mg/g dw would be about 20% of the effect size.

With the enrolment of 300 patients, there is a greater than 99% chance (power) of occurrence of at least 1 adverse event with an anticipated incidence rate of 2%, or greater than 95% chance for an anticipated incidence rate as low as 1%.

Main Inclusion Criteria:

1. Male or female ≥ 2 years of age;
2. Have sickle cell disease (confirmed by Hb electrophoresis or more specific tests) or other conditions with iron overload from repeated blood transfusions (see exclusion criteria for exceptions);
3. Baseline LIC >7 mg/g dw (measured by MRI);
4. Patients who have received no less than 20 transfusions of RBCs;
5. Patients who have received at least 1 transfusion per year in the last 2 years and who are expected to have a continuing requirement (based on Investigator's judgement) during the duration of the trial

Main Exclusion Criteria:

1. Thalassemia syndromes;
2. Myelodysplastic syndrome (MDS) or myelofibrosis;
3. Diamond Blackfan anemia;
4. Primary bone marrow failure;
5. Patients with a baseline LIC >30 mg/g dw (measured by MRI);
6. Unable or unwilling to undergo a 7-day washout period if currently being treated with deferiprone or deferoxamine or deferasirox;
7. Previous discontinuation of treatment with deferiprone or deferoxamine due to adverse events;
8. History or presence of hypersensitivity or idiosyncratic reaction to deferiprone or deferoxamine;
9. Treated with hydroxyurea within 30 days;
10. History of malignancy;
11. Evidence of abnormal liver function (serum ALT level(s) > 5 times upper limit of normal at screening or creatinine levels >2 times upper limit of normal at screening);
12. 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;
13. Clinically significant abnormal 12-lead ECG findings;
14. Cardiac MRI T2* <10 ms
15. Myocardial infarction, cardiac arrest or cardiac failure within 1 year before screening/baseline visit;

16. Unable to undergo MRI
17. Presence of metallic objects such as artificial joints, inner ear (cochlear) implants, brain aneurysm clips, pacemakers, and metallic foreign bodies in the eye or other body areas that would prevent use of MRI imaging

Schedule of Study Procedures:

Following screening assessments, eligible patients will undergo baseline assessments within two months of the screening assessments.

1. MRI scans will be performed at Screening/Baseline, and Weeks 26 and 52 (End of Study) or Early Termination visits, whichever comes first for:
   - Liver MRI for LIC calculation;
   - Cardiac MRI T2* ;
2. Serum ferritin will be measured at Baseline and Weeks 12, 26, 40 and 52 (End of Study) or Early Termination visits, whichever comes first;
3. Hematology assessments will be performed at Screening/Baseline, weekly until Week 26, and then biweekly until Week 52 (End of Study) or Early Termination visits, whichever comes first;
4. Chemistry assessments will be performed at Screening/Baseline, and monthly up to Week 52 (End of Study) or Early Termination visits, whichever comes first.
5. Quality of life patient-reported questionnaire will be completed at Baseline and Weeks 26 and 52 (End of Study) or Early Termination visits, whichever comes first.

Data Analysis:

<u>Primary Efficacy Endpoint</u>

The change from baseline to Week 52 in LIC will be compared between the two treatment groups using an analysis of covariance (ANCOVA) model including treatment variable as the main factor, and total transfusional iron input during the study and baseline LIC as covariates. The 95% confidence interval (CI) of the difference (deferiprone minus deferoxamine) in change of LIC from baseline to Week 52 between the two treatment groups will be computed. For the demonstration of non-inferiority, the upper limit of the 95% CI should be no more than 2 mg/g dw.

<u>Secondary Efficacy Endpoints</u>

The change from baseline to Week 52 in patients' reported quality of life (SF-36 or Child Health Questionnaire) will be compared between the two treatment groups. Detailed information on the statistical method to be used will be provided in the statistical analysis plan. The change from baseline to Week 52 in cardiac MRI T2* and serum ferritin will be

compared between the two treatment groups, using an ANCOVA model including treatment variable as the main factor and total transfusional iron input during the study and baseline cardiac MRI T2* or serum ferritin as covariates. As with LIC, the 95% CI of the difference between the two treatment groups will be computed for both MRI T2* and serum ferritin. The MRI T2* data will be log-transformed before any statistical testing.

The longitudinal data of patient-reported quality of life (SF-36 or Child Health Questionnaire), LIC, cardiac MRI T2*, and serum ferritin will also be analyzed for time trend by using the appropriate mixed model or its equivalent for the quality of life data. Transfusional iron input during the study will be assessed and compared among treatment groups and hematologic diagnoses.

Subgroup Analysis

The comparison of the two treatment groups for the primary and secondary efficacy endpoints will be performed in:

- Patients with sickle cell disease (SCD) only;
- non-SCD patients.

Safety Analysis

The safety data for continuous variables will be summarized using descriptive statistics, and the safety data for discrete variables will be presented as frequency tables. The proportions of drop-outs will be compared between the deferiprone group and the deferoxamine group using Fisher's exact test.

CLINICAL STUDY ADMINISTRATIVE STRUCTURE

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Table of Contents Page No.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	Adverse Drug Reaction
AE	Adverse Event
AF	Assent Form
ANC	Absolute Neutrophil Count
ANCOVA	Analysis of Covariance
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area Under the Curve
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CI	Confidence Interval
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DFO	Deferoxamine
DFX	Deferasirox
DSMB	Data Safety Monitoring Board
dw	dry weight
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
Hb	Hemoglobin
HbS	Hemoglobin S
HbSC	Sickle-hemoglobin C disease
HIV	Human Immunodeficiency Virus
HR	Heart rate
ICF	Informed Consent Form
ICH	International Conference on Harmonisation

ID	Identification
IRB/IEC	Institutional Review Board/Independent Ethics Committee
ITT	Intent to Treat
IUD	Intrauterine Device
IVRS	Interactive Voice Response System
LIC	Liver Iron Concentration
LOCF	Last Observation Carried Forward
MDS	Myelodysplastic Syndrome
ME	Medical Event
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mg/g	milligram per gram
mg/kg/day	milligram/kilogram/day
mL	millilitre
MMRM	Mixed-Effects Model for Repeated Measures
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
OC	Observed Case
OCRDC	Oracle Clinical Remote Data Capture
PDR	Patient Data Report
PP	Per-Protocol
RBCs	Red Blood Cells
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCD	Sickle Cell Disease
SOC	System Organ Class
SOP	Standard Operating Procedure
tid	three times a day
UDP	uridine 5’-diphosphate
WHO	World Health Organization

1 BACKGROUND AND RATIONALE

Pursuant to the Accelerated Approval of Ferriprox by the FDA in October 2011, ApoPharma committed to conduct a confirmatory trial of deferiprone in transfused patients, focussing primarily on transfused patients with sickle cell disease (SCD). This will be a 52-week, prospective, multi-center, two-arm, randomized, open-label, parallel design of deferiprone therapy vs. deferoxamine. At least 80% of the patients enrolled in the study will be patients with SCD, but patients with other anemias requiring blood transfusion and with iron overload will also be included. Excluded from the study will be patients with thalassemia syndromes, myelodysplastic syndrome (MDS), myelofibrosis, Diamond Blackfan Anemia, and primary bone marrow failure.

1.1 Sickle Cell Disease

SCD is an inherited hemoglobinopathy, displaying a varied phenotypic expression as a result of diverse genetic and environmental factors. It is determined by combinations of 2 abnormal alleles of the beta globin gene, among which at least one carries the beta6 glu-val mutation (Lal A & Vichinsky. 2005). The disease is clinically silent until expression of the gamma genes is substituted by expression of the beta genes (at between 3 and 9 months of age).

Haemoglobin is the iron-containing oxygen-transport metalloprotein in the red blood cells (RBCs) responsible for tissue oxygenation. Normal RBCs contain mainly haemoglobin A; people with sickle cell conditions have the genetic variation HbS. RBCs containing mostly HbS do not survive as long as normal RBCs (typically, about 16 days, compared to about 120 days for normal cells) (Lal A & Vichinsky. 2005). The RBCs containing HbS can become crescent (sickle)-shaped, leading to loss of their mobility and flexibility (Kikuchi BA. 2003). As a result, these RBCs have difficulty passing through small blood vessels. This in turn leads to blood-cell agglomeration, impeding the circulation of blood and delivery of oxygen to vital tissues and organs (Kikuchi BA. 2003). Tissue that does not receive a normal blood flow eventually becomes ischemic (Hess DC *et al.* 1991). The anaemia and blockage of blood flow results in a variety of problems, such as painful crises, susceptibility to infection, priapism, skin ulcers, acute chest syndrome, acute splenic sequestration, pulmonary disease, renal and hepatic dysfunction, and cerebrovascular disease, ultimately causing premature death (Hess DC *et al.* 1991; Nathan DG & Orkin. 1998). Abnormal cardiac findings, with the notable development of a progressive proliferative systemic vasculopathy, pulmonary hypertension, and left ventricular diastolic dysfunction, are also present in most patients with sickle cell disease (SCD) and are primarily the result of chronic anaemia, cardiac chamber dilation, and compensatory increase in left and right ventricular mass (Gladwin MT & Sachdev. 2012; Knight-Perry JE *et al.* 2011).

Some patients undergo transfusions to improve blood rheology by replacing sickled RBCs with normal RBCs. Blood transfusions have been indicated for the prevention of and treatment of vaso-occlusive complications such as painful crisis, stroke, acute chest syndrome, acute multi-organ failure, acute splenic sequestration, or medical intervention (preoperative preparation) (Vichinsky E. 2001). Although chronic blood transfusions can

reduce the incidence of sickle cell–induced morbidity and mortality, repeated transfusions result in progressive accumulation of iron in the blood (Inati A *et al.* 2010). Excess iron accumulates in organs, particularly the liver and endocrine glands, generating iron-induced morbidity and eventually causing premature death if left untreated (Ballas SK. 2001). A study in transfusion-dependent patients with SCD demonstrated increased iron deposition, with mean liver iron of 13.68 mg/g dry weight (range of 2.9 to 26.19 mg/g dry weight) and peak mean serum ferritin of 4614 ± 1989 µg/L over a transfusion period of 57 ± 35 months (range 12 to 146 months) (Harmatz P *et al.* 2000).

In the sickle cell centres of the Cardeza Foundation and Thomas Jefferson University Hospital, approximately 50% of the patients with SCD admitted to the hospital received an average of 10 units of RBCs per year; 17% to 37% of these patients developed iron overload. Compared to the non-iron-overloaded group, the iron-overloaded patients with serum ferritin level > 1,500 µg/L and transferrin saturation > 50% had a higher incidence of painful episodes per year (64% vs. 38%), organ failure (71% vs. 19%), and mortality (64% vs. 5%). Patients who died had significantly higher mean levels of serum ferritin than the surviving patients (2,379 versus 597 µg/L, $p<0.05$). The results of this study indicate that iron overload is a determinant of morbidity and mortality in adult patients with SCD (Ballas SK. 2001). Results from a natural history study demonstrated that the unadjusted death rate of transfused patients with SCD (7.0/100 person years) was even higher than in patients with thalassemia (2.2/100 person years) (Fung EB *et al.* 2007). Iron metabolism and trafficking in patients with SCD have some distinctive characteristics. The high levels of inflammatory cytokines in SCD may enhance macrophage/ reticuloendothelial cell iron and/or renal cell iron retention. This makes tissues that retain iron different in SCD, and thus the organs that fail due to excess iron load in patients with SCD are somewhat different from those of patients with thalassemia (Walter PB *et al.* 2009). Indeed, unlike thalassemia patients, cardiac iron overload is not frequently observed in patients with SCD (Kaushik N *et al.* 2012). Nonetheless, cardiac siderosis does occur in some transfused SCD patients who have been transfused for more than 10 years (Wood JC. 2008).

Care for SCD now commonly uses transfusion, which potentially results in iron overload and necessitates chelation (Walter PB *et al.* 2009).

1.2 Ferriprox®

Ferriprox (deferiprone) is an iron chelator that was first approved for “Treatment of iron overload in patients with thalassemia major for whom deferoxamine therapy is contraindicated or who present serious toxicity with deferoxamine therapy” in 1999 by the European Medicines Agency (EMA), and it is currently approved in more than 60 countries. It was approved by the Food and Drug Administration (FDA) of the USA in October 2011 for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate. The recommended initial dose of Ferriprox is 25 mg/kg, orally, three times per day for a total of 75 mg/kg/day. The maximum dose is 33 mg/kg, three times per day for a total of 99 mg/kg/day.

Deferiprone (3-hydroxy-1,2-dimethylpyridin-4-one) is a bidentate iron chelator that preferentially binds trivalent iron (Fe^{3+}) in a 3:1 (deferiprone : iron) complex. The effectiveness of deferiprone has been assessed by urinary iron excretion, sequential measurements of serum ferritin levels, iron concentration in the liver and in the heart, and by clinical outcomes such as its ability to prevent iron-induced cardiac disease and prolong survival in transfused patients with thalassemia. The results of ApoPharma-sponsored clinical studies and of independent trials have demonstrated that therapy with deferiprone is associated with good compliance and stabilization or decline of the body iron load. See clinical study reports LA01, LA02, LA03, LA04, LA06, LA10, LA11, LA12, LA15, LA16, and LA30 (ApoPharma Inc. 2006a; ApoPharma Inc. 2006b; ApoPharma Inc. 2006c; ApoPharma Inc. 2009; Apotex Research Inc. 1998; Apotex Research Inc. 2000a; Apotex Research Inc. 2000b; Apotex Research Inc. 2001; Apotex Research Inc. 2003; Apotex Research Inc. 2005; Apotex Research Inc. 2006).

In humans, deferiprone is rapidly absorbed from the upper part of the gastrointestinal tract after oral administration and appears in blood within 5 to 10 minutes (min). The mean time for deferiprone concentrations to peak in serum is 45 to 60 min in fasting patients and approximately 2.2 h in non-fasting patients. Less than 20% of deferiprone is bound to serum proteins. The majority of the administered dose of deferiprone is metabolized, mainly via Phase II metabolism through *O*-glucuronidation. *In vitro* studies suggest that UDP glucuronosyltransferase 1A6 is primarily responsible for the glucuronidation of deferiprone. The predominant deferiprone metabolite is a 3-*O*-glucuronide conjugate. Glucuronidation of deferiprone results in a loss of the iron binding capacity due to the inactivation of the 3-hydroxy functional group and facilitates elimination through increased hydrophilicity. In most patients, more than 90% of deferiprone is eliminated from serum within 5 to 6 hours. The elimination half-life of deferiprone is 2 to 3 hours, with about 75% to 90% of the total deferiprone excreted in urine in the first 24 hours in the form of free deferiprone, the 3-*O*-glucuronide metabolite and iron-deferiprone complex. Food decreased the rate of absorption of the parent drug and the subsequent rate of formation of deferiprone glucuronide in healthy patients, while the overall bioavailability (AUC) remained unchanged.

The safety profile of deferiprone has been extensively characterized. The most significant serious adverse event (SAE) associated with deferiprone use is agranulocytosis, sometimes referred to as severe neutropenia, defined as a confirmed absolute neutrophil count less than 0.5×10^9/L.

In pooled clinical trials, the incidence of agranulocytosis/severe neutropenia was 1.7% of patients. The mechanism of deferiprone-associated agranulocytosis is unknown. Agranulocytosis and neutropenia usually resolve upon discontinuation of deferiprone, but there have been post-marketing reports of agranulocytosis leading to death. A recent review of 20 years of data confirmed that deferiprone-induced agranulocytosis is not dose-related within the therapeutic range, and its occurrence peaks at 5 months after initiation of therapy, declining in frequency after that period (Tricta et al. 2016).

The most common observed event reported during clinical trials was chromaturia, due to iron excretion. Nausea, vomiting, abdominal pain, alanine aminotransferase increased, arthralgia, and neutropenia were the most common adverse events. Please refer to the US

full prescribing information (USPI) and the Investigator's Brochure for complete safety information.

The table below lists the adverse events associated with deferiprone therapy that occurred in at least 1% of patients in the ApoPharma clinical trials.

Body System Preferred Term	% Patients
BLOOD AND LYMPHATIC SYSTEM DISORDERS	
Neutropenia	6.2
Agranulocytosis	1.7
GASTROINTESTINAL DISORDERS	
Nausea	12.6
Abdominal pain/discomfort	10.4
Vomiting	9.8
Diarrhea	3.0
Dyspepsia	2.0
INVESTIGATIONS	
Alanine Aminotransferase increased	7.5
Neutrophil count decreased	7.3
Weight increased	1.9
Aspartate Aminotransferase increased	1.2
METABOLISM AND NUTRITION DISORDERS	
Increased appetite	4.0
Decreased appetite	1.1
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	
Arthralgia	9.8
Back pain	2.0
Pain in extremity	1.9
Arthropathy	1.4
NERVOUS SYSTEM DISORDERS	
Headache	2.5

Data cut-off date: 31 August 2010

1.3 Deferoxamine

Deferoxamine (DFO) was the first commercially available iron chelator, which was approved in 1968 for the treatment of acute iron intoxication and of chronic iron overload due to transfusion-dependent anemias. To be effective, DFO must be delivered as a constant infusion, usually subcutaneously, for 8 to 12 hours a night, at least five days per week at recommended doses of 20-60 mg/kg/day. Deferoxamine chelates iron by forming a stable complex that prevents the iron from entering into further chemical reactions. It readily chelates iron from ferritin and hemosiderin but not readily from transferrin; it does not combine with the iron from cytochromes and hemoglobin. Long-term use of DFO is associated with stabilization or decline in all three measures of iron load and with

decreased iron-induced morbidity and with improved survival of transfusion-dependent thalassemia patients (Borgna-Pignatti C *et al.* 2004; Kwiatkowski JL. 2008).

However, there are some important adverse reactions to deferoxamine. These include local skin reactions which are almost universal, and auditory and visual disturbances. There is a susceptibility to certain gram-negative infections, in particular *Yersinia enterocolitica*, in patients who receive deferoxamine.

1.4 Study Rationale

Deferiprone is an iron chelator that has been demonstrated to be effective in reducing iron load in transfusional siderosis. Its safety profile has been extensively characterized by more than 25 years of clinical experience, including 14 years of post-marketing experience outside of the US. The post-marketing experience with deferiprone exceeds 44,000 patient years of drug exposure. The clinical trial and post-marketing populations comprise predominantly patients with thalassemia, although a small number of patients with sickle cell disease were included in clinical studies.

Previous studies have shown that the iron excretion obtained with deferiprone at doses of 75 and 100 mg/kg/day is sufficient to neutralize the iron accumulation that would inevitably occur in patients with SCD who are regularly transfused (Collins AF *et al.* 1994). In this study, deferiprone decreased the total body iron load significantly in 3 of the 4 patients with SCD. In a randomized clinical trial that included a total of 101 patients (60 patients with thalassemia intermedia and 41 patients with SCD), deferiprone was shown to reduce serum ferritin levels (information supplied by independent investigators; Maggio AF et al.).

The current study is designed to collect additional information on the safety and efficacy of deferiprone in patients with sickle cell disease or other anemias (excluding thalassemia syndromes, MDS, myelofibrosis, Diamond Blackfan anemia and primary bone marrow failure) and transfusional hemosiderosis. As per the natural history study conducted by Fung et al. (Fung EB *et al.* 2007), the unadjusted death rate in transfused patients with SCD is 7.0/100 person years. Therefore, assuming that 100% of the patients enroll in this study are patients with SCD, 21 deaths are expected to occur during this 52-week study.

2 OBJECTIVES

2.1 Primary Objective

To determine the efficacy of deferiprone vs. deferoxamine in the treatment of iron overload in patients with sickle cell disease or other anemias.

2.2 Secondary Objectives

The secondary objectives are:

- To evaluate the effect of deferiprone vs. deferoxamine on the patients' quality of life;
- To evaluate the safety and tolerability of deferiprone vs. deferoxamine.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design

This study is a 52-week, prospective, multi-center, two-arm, randomized, open-label, parallel design of deferiprone therapy vs. deferoxamine. The study will consist of a Baseline Phase and a Treatment Phase. Three hundred (300) male and female patients with sickle cell disease (SCD) or other anemias requiring blood transfusion will be enrolled.

3.2 Discussion of Study Design

This study has been designed to evaluate the efficacy, safety, and tolerability of deferiprone vs. deferoxamine in patients with SCD or other anemias requiring iron chelation. Patients will participate in a Baseline Phase followed by a Treatment Phase.

Excluded from the study will be patients with thalassemia syndromes, myelodysplastic syndrome (MDS), myelofibrosis, Diamond Blackfan anemia and primary bone marrow failure.

Baseline Phase:

During the Baseline Phase, patients who sign an informed consent/assent form will undergo initial screening. On the final day of the Baseline Phase, patients' eligibility will be determined, based on inclusion/exclusion criteria, and qualified patients will enter the Treatment Phase.

Treatment Phase:

At the beginning of the Treatment Phase, patients will be randomized in a 2:1 ratio to receive (1) deferiprone or (2) deferoxamine. The Treatment Phase will be 52 weeks in duration. At the end of the 52 weeks of treatment, patients will be invited to enter a 2-year extension phase.

Deferiprone treatment arm:

During the study, patients will be prescribed Ferriprox 500 mg tablets or deferiprone 80 mg/mL oral solution, according to patient preference or product's availability, for administration three times a day (tid). The dose of deferiprone will be based on the transfusional iron input and the severity of iron load at baseline, and may be adjusted on the basis of the magnitude of change in iron overload during the study.

Deferiprone 25 mg/kg tid:

Patients with transfusional iron input ≤ 0.3 mg/kg/day in in the 3 months prior to baseline

AND

Patients with a baseline measure of iron load of:

- Serum ferritin <2500 μg/L

AND

- LIC <15 mg/g dry weight

AND

- Cardiac T2* > 20 ms

Deferiprone 33 mg/kg tid:

Patients with a transfusional iron input > 0.3 mg/kg/day in the 3 months prior to baseline

OR

Patients with at least one baseline measure of iron load as follows:

- Serum ferritin ≥2500 μg/L

OR

- LIC ≥15 mg/g dry weight

OR

- Cardiac T2* ≤ 20 ms

Dosing of all patients will be initially at 15 mg/kg tid for 1 week, which will be increased to 20 mg/kg tid in Week 2 and to 25 mg/kg tid in Week 3, which will be the treatment dose for the remainder of the trial, unless a patient meets the 33 mg/kg tid dosing criteria. In that case, the dose of deferiprone will be increased further to 33 mg/kg tid in Week 4, and this dose will be the treatment dose for the remainder of the trial.

The dose of deferiprone will also be increased to 33 mg/kg tid at any time during the trial if the mean daily transfusional iron input increases to more than 0.3 mg/kg body weight for at least 3 consecutive months OR at Week 26 if there is less than 10% improvement from baseline to Week 26 in at least one of the measures indicative of iron overload (serum ferritin, cardiac MRI T2* or LIC).

Dose reduction recommendations will be based on regular assessment of safety markers for adverse reactions that are possibly dose dependent, such as gastrointestinal upset, increases in serum liver enzyme levels, and arthropathies.

Deferoxamine treatment arm:

During the study, patients will be prescribed deferoxamine as per the approved US prescribing information at doses of 20 – 40 mg/kg/day for children (<16 years of age) and 40–50 mg/kg/day in adults (≥16 years of age) as 8 – 12 h subcutaneous infusion for 5 – 7 days per week. The dose of deferoxamine will be based on the transfusional iron input, on the severity of iron load at baseline, and on the magnitude of its change during the study.

Deferoxamine 20 mg/kg/day (children) or 40 mg/kg/day (adults):

Patients with transfusional iron input ≤ 0.3 mg/kg/day in the 3 months prior to baseline

AND

Patients with a baseline measure of iron load of:

- Serum ferritin <2500 μg/L *

AND

- LIC <15 mg/g dry weight

AND

- Cardiac T2* > 20 ms

* If there is a delay in obtaining the results of the baseline serum ferritin assessment from the central laboratory, the most recent result (obtained within the last 3 months) should be used to calculate the starting DFO dosage. This dosage must remain in effect until the baseline serum ferritin results become available, at which time it is to be adjusted if necessary. If no serum ferritin measure has been obtained within the last 3 months, the start of dosing must be deferred until the baseline results are available.

Deferoxamine up to 40 mg/kg/day (children) or 50 mg/kg/day (adults):

Patients with a transfusional iron input > 0.3 mg/kg/day in the 3 months prior to baseline

OR

Patients with at least one baseline measure of iron load as follows:

- Serum ferritin ≥2500 μg/L

OR

- LIC ≥15 mg/g dry weight

OR

- Cardiac T2* ≤ 20 ms

Children (<16 years of age)

The dose of deferoxamine will also be increased up to 40 mg/kg for 5 – 7 days per week at any time during the trial if the mean daily transfusional iron input increases to more than 0.3 mg/kg body weight for at least 3 consecutive months OR at Week 26 if there is less than 10% improvement from baseline to Week 26 in at least one of the measures of iron overload (serum ferritin, cardiac MRI T2* or LIC).

Adults (≥16 years of age)

The dose of deferoxamine will be increased up to 50 mg/kg for 5 – 7 days per week at any time during the trial if the mean daily transfusional iron input increases to more than 0.3 mg/kg body weight for at least 3 consecutive months OR at Week 26 if there is less

than 10% improvement from baseline to Week 26 in at least one of the measures of iron overload (serum ferritin, cardiac MRI T2* or LIC).

Dose reduction recommendations will be based on regular assessment of safety markers.

Efficacy, safety and tolerability evaluations will occur according to the schedule of evaluation (Appendix 18.1). Rescue medication (intravenous administration of deferoxamine or combination of 2 iron chelators: deferiprone, deferoxamine or deferasirox) for the treatment of iron overload will not be allowed during the Treatment Phase. Should iron overload symptoms become intolerable for the patient despite dose adjustment, the Investigator should withdraw the patient from the study.

If a patient withdraws early, he or she will return to the clinic for an Early Termination Visit as soon as possible, and no later than 1 month following treatment discontinuation. All of the efficacy and safety evaluations will be performed at the last study visit or the Early Termination visit, whichever comes first.

3.3 Study Sites and Study Duration

Study sites will be located in but not limited to countries in North America, Europe, and the Middle East. While the goal will be to keep the number of sites to a minimum, it is expected that the study will engage sites worldwide due to the anticipated difficulty in enrolling patients with a 33% probability of being allocated to the deferoxamine treatment arm.

Each patient is expected to participate in the study for approximately 60 weeks (from the Screening Visit to the End of Study Visit).

4 STUDY POPULATION

4.1 Number of Patients

Three hundred (300) male and female patients with SCD disease or other anemias requiring blood transfusion will be enrolled in the study. Excluded from the study will be patients with thalassemia syndromes, MDS, myelofibrosis, Diamond Blackfan anemia, and primary bone marrow failure. At least 80% of the enrolled patients will have sickle cell disease.

Patients who withdraw from the study after starting study medication will not be replaced.

4.2 Inclusion Criteria

Patients will be included in the study only if they meet **all** of the following criteria:

1. Male or female ≥ 2 years of age;
2. Have sickle cell disease (confirmed by Hb electrophoresis or more specific tests) or other conditions with iron overload from repeated blood transfusions (see exclusion criteria for exceptions);

3. Baseline LIC >7 mg/g dw (measured by MRI);
4. Patients who have received no less than 20 transfusions of RBCs;
5. Patients who have received at least 1 transfusion per year in the last 2 years and who are expected to have a continuing requirement (based on Investigator's judgement) during the duration of the trial;
6. Patients, and when applicable their legal representatives, will provide a signed and dated written assent/informed consent prior to the first study intervention; patients will be able to adhere to study restrictions, appointments and evaluation schedule.
7. Female patients of childbearing potential must have a negative pregnancy test result at Screening and Baseline Visits. In addition, a female patient of childbearing age who is sexually active must confirm that during the study and for 30 days following the completion of the study or early termination she:

    - will use an effective method of contraception, OR
    - has had a tubal ligation (supporting evidence required), OR
    - has had a hysterectomy (supporting evidence required), OR
    - participates in a non-heterosexual lifestyle, OR
    - indicates her only male sexual partner has been sterilized (supporting evidence required).

    Effective methods of contraception include oral contraceptives, intrauterine devices (IUDs) or condom, providing it is used with contraceptive foam or cream, or abstinence from sexual intercourse. Supporting evidence for sterilization consists of a surgical report or letter from the family physician;
8. If the patient is a heterosexual sexually-active fertile male, patient must confirm, in writing, that he and/or his female partner will use an effective method of contraception for the length of the trial and for 30 days following completion of the study or early termination. Effective methods of contraception for males include condoms or sterilization or abstinence from sexual intercourse.

4.3 Exclusion Criteria

Patients will be excluded from the study for **any** of the following reasons:

1. Thalassemia syndromes;
2. Myelodysplastic syndrome (MDS) or myelofibrosis;
3. Diamond Blackfan anemia;
4. Primary bone marrow failure;

5. Patients with a baseline LIC >30 mg/g dw (measured by MRI);
6. Unable or unwilling to undergo a 7-day washout period if currently being treated with deferiprone or deferoxamine or deferasirox;
7. Previous discontinuation of treatment with deferiprone or deferoxamine due to adverse events;
8. History or presence of hypersensitivity or idiosyncratic reaction to deferiprone or deferoxamine;
9. Treated with hydroxyurea within 30 days;
10. History of malignancy;
11. Evidence of abnormal liver function (serum ALT level(s) > 5 times upper limit of normal at screening or creatinine levels >2 times upper limit of normal at screening);
12. 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.
13. Clinically significant abnormal 12-lead ECG findings;
14. Cardiac MRI T2* <10 ms
15. Myocardial infarction, cardiac arrest or cardiac failure within 1 year before screening/baseline visit;
16. Bowel disease causing malabsorption;
17. HIV positive patient;
18. Unable to undergo MRI;
19. Presence of metallic objects such as artificial joints, inner ear (cochlear) implants, brain aneurysm clips, pacemakers, and metallic foreign bodies in the eye or other body areas that would prevent use of MRI imaging;
20. History of alcohol or drug abuse;
21. Treatment with an investigational drug within 30 days or 5 half-lives (whichever is longer) preceding the first dose of study medication;
22. Participation in another clinical trial during the conduct of this study;
23. Pregnant, nursing females and females of childbearing potential who are sexually active and unwilling, or unable, to use an acceptable method of contraception;
24. Mental incapacity, unwillingness or language barriers precluding adequate understanding or co-operation;
25. Any condition that, in the opinion of the Investigators, would adversely affect ability to complete the study or its assessments.

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, such patients should be withdrawn from the study.

4.5 Withdrawal Criteria

A patient has the right to withdraw from the study at any time and for any reason without consequence to future care by the Investigator or study center. The reason for withdrawal will be sought.

When a patient decides to withdraw from the study, he/she should always be contacted, not only to determine the reason(s) for withdrawing, but also to determine if there were any adverse events (AEs). Whenever possible, the patient should return for a clinic visit at the time of or soon after discontinuation of study medication but no later than 1 month after treatment discontinuation. All investigational products and materials should be returned. If any AEs occurred, the Investigator must attempt to follow up with the outcome for 30 days post-study withdrawal.

Data collected for patients who are withdrawn after receiving the study drug should be evaluated for efficacy and safety.

If, for any reason, the Investigator decides to withdraw a patient before completing the study, the reason for withdrawal must be entered into the source document and the electronic case report form (eCRF).

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

- Patient request;
- Medical reasons considered significant by the patient and/or Investigator;
- Requirement for concomitant medication that may interfere with the evaluation of study medication, or may be contraindicated;
- Occurrence of other illnesses that affect the patient's further participation in the study or evaluation of study medication;
- Significant changes in QTcF interval (defined as QTcF change of greater than 60 ms) are detected;
- Any other situation where, in the opinion of the Investigator, continuation of the study would not be in the best interest of the patient.

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

- Pregnant or planning to become pregnant (see Section 9.2 Procedures in Case of Pregnancy);
- Occurrence of any adverse reaction characterized as life-threatening or disabling;

- Non-compliance with blood counts. During the first 6 months, if a patient misses a weekly ANC monitoring visit, then missing a further 3 of the next 5 visits (i.e., a total of 4 out of 6) will result in automatic withdrawal. During the last 6 months, ANC monitoring will be done biweekly, and missing 3 consecutive biweekly blood counts will result in automatic withdrawal.
- Termination of the study by the Sponsor;
- Patient experiences severe neutropenia/ agranulocytosis (refer to Section 8.2.4.9 for definition and management).

4.6 Treatment Interruptions

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

- If the patient develops an infection during the study, deferiprone must be interrupted immediately and neutrophil count should be obtained and monitored more frequently (every 2 days if ANC <1.5 x 10^9/L). Patients should be advised to report immediately to their physician any symptoms indicative of infection such as fever, sore throat, and flu-like symptoms. They will be provided with a thermometer, and instructed to seek immediate medical attention at a hospital or clinic if they experience fever (temperature >38.0° C/100.4°F). Body temperature may be measured at the mouth, axilla, or ear. Patients/legal guardians will be provided with an emergency services card with contact information, and will be advised to carry this card at all times. In presence of confirmed fever and/or infection, 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 deferiprone can be re-initiated once all symptoms have been resolved and it is deemed safe by the Investigator.
- If temperature is >38.0°C/100.4°F and ANC is ≤0.5 x 10^9/L, the following must be done:
  - Commence therapy with antibiotics immediately (treatment should depend on the site of the suspected infection and on local antibiotic policy)
  - Perform a chest x-ray, and collect blood and other relevant cultures (if possible, collect culture samples before initiating antibiotics)
- If the patient develops moderate neutropenia while on deferiprone (refer to Section 8.2.4.9 for definition), therapy must be interrupted immediately and neutrophil count must be obtained and monitored every 2 days. Therapy with deferiprone can be re-initiated once two successive ANCs are >1.5 x 10^9/L and it is deemed safe by the Investigator. The patient will be withdrawn from the study if the ANC remains <1.5 x 10^9/L by the end of a two-week period (14 days) (Section 8.2.4.9).

4.7 Pregnancy

All female participants of childbearing potential will be administered a serum and urine pregnancy test prior to starting study medication. A negative test result will be required prior to study entry. Patients of childbearing potential should not become pregnant during the study and therefore must agree to use an approved method of contraception (as

defined in Appendix 18.2) for 30 days prior to Day 1 (at least 3 months for hormonal contraceptives), throughout the course of the trial, and for 30 days following early termination or the last visit.

In the situation where a female patient is withdrawn prematurely from the study because of a pregnancy, study medication must be stopped immediately, the Sponsor must be informed immediately via the Pregnancy Report Form, and the patient must be closely followed up during her pregnancy, as much as possible. Update reports must be provided to the ApoPharma Medical Safety department at mid-pregnancy and at delivery or at termination of the pregnancy.

Male patients must inform the Investigator if their female partner becomes pregnant during the trial or within one month after trial completion.

4.8 Allocation of Patient Numbers

After signing of the Informed Consent/Assent Form (ICF/AF) by patients and/or patients' legal representatives, if applicable, patients will be assigned a unique patient ID number.

A patient ID number will consist of six digits. The first three digits represent the site code (00X for the X site). These three digits will be used in combination with a three-digit rolling number that will be sequentially assigned by the site to patients who sign the ICF/AF. This number would start at 001 for each site. For example, if site 001 has eight patients, the patient ID number would be 001001 to 001008. The patient ID number would start again for site 002 at 002001. If a patient is withdrawn after receiving his or her patient ID number, the number will not be reused. For the purpose of the study, patients will be referred to by their patient ID number.

4.9 Method of Assignment to Treatment

At the baseline visit, patients will be randomly assigned to receive deferiprone or deferoxamine in a 2:1 ratio. Stratified randomization based on disease category (sickle cell disease vs. other anemias) and on the transfusional iron input in the 3 months prior to baseline (> 0.3 mg/kg/day vs. ≤ 0.3 mg/kg/day) will be employed to ensure that the 2:1 ratio is maintained within each of the 4 strata: 1) sickle cell disease with transfusional iron input > 0.3 mg/kg/day, 2) sickle cell disease with transfusional iron input ≤ 0.3 mg/kg/day, 3) other anemias with transfusional iron input > 0.3 mg/kg/day, and 4) other anemias with transfusional iron input ≤ 0.3 mg/kg/day. A randomization list will be generated for each stratum, assigning study medication to individual randomization numbers in blocks of 6. Treatment assignment and drug allocation will be performed by an Interactive Voice Response System (IVRS).

5 STUDY PROCEDURES

5.1 Entry Procedures

An Informed Consent Form (ICF)/assent form (AF) approved by a recognized IRB/IEC, and local regulatory bodies, if applicable, will be signed and dated by the patient and when applicable, the patient's authorized legal representative prior to the patient's participation in this study. The patient and/or legal representative, if applicable, will then

be provided with a copy of the signed ICF/AF. The original ICF/AF will be kept by the Investigator. Patients who sign an ICF/AF will undergo Baseline Phase procedures.

All transfusions must be performed during a study visit (i.e., during weekly, biweekly, monthly, quarterly, or semi-annual visits) for the entire study duration, except for those patients who may require emergency transfusion. Data of all transfusions performed during the trial, including type of transfusion (simple, exchange, partial exchange), volume of blood that the patient received during the transfusion, 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.

5.2 Screening/Baseline Visit (Day -60 to Day -1: Visit -1)

Assessment of eligibility:

The following procedures will take place at the Screening/Baseline visit:

- Explain the study to the patient and/or parent/legal representative, obtain written informed consent/assent, and give a copy to the patient and/or parent/legal representative;
- Assign the patient ID number (see Section 4.8);
- Review previous/current chelation therapy;
- Record demographic information;
- Obtain medical history;
- Obtain transfusion history;
- Record prior and current medication(s);
- Collect blood sample for hematology, biochemistry (fasting glucose; patient must come to the site following a 10-hour fast), and serology (to be conducted within 14 days of starting study medication; will be considered as the baseline procedures for biochemistry);
- Collect blood sample for pregnancy testing for all females of childbearing potential. A negative result will be required for start of dosing;
- Collect urine for urinalysis;
- Perform physical examination (to be completed by Investigator or a qualified delegate);
- Take vital signs, weight, and height;
- Perform 12-lead ECG;
- If patient is identified as potentially eligible based on the available data (medical history, transfusional history, current medication(s), physical examination, vital signs), perform MRI scan for:

  - Liver, and transmit to a central laboratory for interpretation and LIC calculation (to be conducted within two months prior to starting study drug; will be considered as the baseline procedure);
  - Cardiac MRI T2*, and transmit to a central laboratory for interpretation (to be conducted within two months prior to starting study drug; will be considered as the baseline procedure);
- Conduct contraceptive counselling for all sexually active patients;
- Review inclusion/exclusion criteria;
- Remind the patient, and/or if applicable patient's authorized legal representative, that she/he must carefully keep track of medical events and medication used to treat them;
- Instruct eligible patients to start washout of current chelation therapy (if required) 7 days prior to the baseline visit, and washout of hydroxyurea (if required) 30 days prior to the baseline visit;
- Schedule next study visit.

5.3 Baseline Visit (Day 0, Visit 0)

Enrolment and Baseline Assessments:

Once the results of the screening/baseline visit procedures have been obtained, they should be reviewed against the inclusion/exclusion criteria to confirm the patient's eligibility to enter the trial. If the patient is determined to be eligible, perform the following Baseline assessments:

- Collect blood sample for hematology (the results of this procedure will be considered the baseline values). An ANC value of $>1.5 \times 10^9$/L will be required for start of dosing;
- Collect blood sample for serum ferritin;
- Collect blood and urine samples for pregnancy testing for all females of childbearing potential. A negative result of the urine test will be required for start of dosing. This result will have to be reconfirmed by the results of the serum pregnancy test;
- Determine if patient has had any medical events or used any new medications/ changed medications or changed dose or frequency of medication since the screening visit. If so, document them as specified in Sections 8.2.1 and 8.2.4.3;
- Confirm eligibility;
- Randomize patient;
- Take vital signs (including weight);

- Collect blood sample for assessing genetic polymorphism related to deferiprone - induced agranulocytosis (optional);
- Complete patient-reported quality of life questionnaire (SF-36 or Child Health Questionnaire);
- Review and update transfusion history;
- Conduct contraceptive counselling for all sexually active patients;
- Perform dose calculation;
- Dispense study medication as per Section 7.4;
- Instruct the patient, and/or if applicable patient's authorized legal representative, how to take the medication;
- Remind the patient, and/or if applicable patient's authorized legal representative, that all used (empty bottles) and unused medication must be returned at each monthly study visit;
- Provide a patient diary card, explain how to complete it, and remind patient to return completed card at next visit;
- Remind patient to visit the site or a local laboratory for the weekly blood draws;
- Remind the patient, and/or if applicable patient's authorized legal representative, that she/he must carefully keep track of adverse events and medication used to treat them;
- Remind the patient, and/or if applicable patient's authorized legal representative, that if study medication is stopped early, she/he must return to the clinic for an Early Termination Visit as soon as possible, but no later than 1 month following study medication discontinuation;
- Remind patient, and/or if applicable patient's authorized legal representative, that if an infection develops, therapy must be interrupted immediately. Patients should be advised to report immediately to their physician any symptoms indicative of infection such as fever, sore throat, and flu-like symptoms. In presence of confirmed fever and/or infection, they will be required to have their neutrophil counts tested as soon as possible and no later than 24 hours after the symptoms of infection are detected;
- Provide patient and/or if applicable patient's authorized legal representative with an emergency card and advise her/him to carry this card at all times;
- Schedule next study visit.

5.4 Weekly or Biweekly Assessments

The hematology assessments that are required weekly (± 3 days) up to Week 26 and biweekly (± 3 days) thereafter can be conducted at local laboratories or study sites, and will consist of the following procedures:

- Collect blood sample for hematology. Hematology results should be reviewed by the Investigator as soon as they are received from the laboratory;
- If a patient is receiving a blood transfusion during this visit or has received blood transfusions since the last visit (except for those patients who received an emergency transfusion), record the type of transfusion (simple, exchange, partial exchange), volume of blood that the patient received during the transfusions, and the mean hematocrit of the packed red blood cell units transfused (data obtained from the site's blood bank).

5.5 Telephone Calls (Weeks 1, 2 and 3)

The patient and/or legal representative must be contacted by telephone weekly (every 7 ± 3 days) on Weeks 1, 2 and 3 to ensure that the titration of dose or treatment is proceeding satisfactorily.

If the patient appears to be having difficulty with the treatment, patient and/or legal representative should be contacted again, as frequently as necessary.

Remind the patient/legal representative that if treatment is stopped early, patient must return to the clinic for an Early Termination Visit as soon as possible, but no later than 1 month following treatment discontinuation.

Remind patients to interrupt therapy immediately if they develop an infection. Patients must be advised to report promptly to the Investigator any symptoms indicative of infection such as fever, sore throat, or flu-like symptoms. In presence of confirmed fever and/or infection, they will be required to have their neutrophil counts tested as soon as possible and no later than 24 hours after the symptoms of infection are detected.

All telephone contacts must be fully documented as follows:

- Record date and time of contact;
- Record name of person contacted (patients, parent, legal representative);
- Remind the patient and/or legal representative of the study medication dose and instructions on how to take medication;
- Record any adverse events
- Note if the patient has used any concomitant medications. If so, document them as specified in Sections 8.2.4.3, 8.2.4.8, and 8.2.1;
- Remind patient to visit the site or a local laboratory for the weekly blood draws;
- Reconfirm the next study visit;
- Include the name and signature of the person contacting the patient.

5.6 Monthly Visits (Weeks 4, 8, 16, 20, 32, 36, 44 and 48 Visits)

Weeks 4, 8, 16, 20, 32, 36, 44 and 48 visits assessments will consist of the following procedures. Each visit could occur between -7 or +7 days from the indicated visit day.

- Take vital signs and weight;
- Collect blood sample for hematology and biochemistry;
- Collect blood sample for pregnancy testing for all females of childbearing potential. A negative result will be required for study continuation;
- Review patient diary card with the patient, and/or if applicable patient's authorized legal representative, then collect and file the diary card with the source documents; provide new diary card, and remind patient how to complete the diary card.
- Determine if patient has had any AEs or SAEs or used any concomitant medications. If so, document them as specified in Sections 6.3 and 8.2.4;
- Conduct contraceptive counselling for all sexually active patients;
- Collect and account for the medication dispensed at the previous applicable visit;
- Verify/adjust dose level, according to recommendations;
- Dispense the study medication as per Section 7.4;
- Instruct the patient, and/or if applicable patient's authorized legal representative, how to take the medication;
- Remind the patient, and/or if applicable patient's authorized legal representative, that all used and unused medication bottles must be returned at the next monthly, quarterly or semi-annual study visit;
- Provide a new patient diary card and explain how to complete it;
- Remind the patient, and/or if applicable patient's authorized legal representative, that she/he must carefully keep track of adverse events and medication used to treat them as well as any other medication taken;
- Remind the patient, and/or if applicable patient's authorized legal representative, that if study medication is stopped early, she/he must return to the clinic for an Early Termination Visit as soon as possible, but no later than 4 weeks following study medication discontinuation;
- Remind patient, and/or if applicable patient's authorized legal representative, if an infection develops, therapy must be interrupted immediately. Patients should be advised to report immediately to their physician any symptoms indicative of infection such as fever, sore throat, and flu-like symptoms In presence of confirmed fever and/or infection, they will be required to have their neutrophil counts tested as soon as possible and no later than 24 hours after the symptoms of infection are detected;
- If the patient is receiving a blood transfusion during this visit or has received blood transfusions since the last visit (except for those patients who received an emergency transfusion), record the type of transfusion (simple, exchange, partial exchange), volume of blood that the patient received during the transfusions, and

the mean hematocrit of the packed red blood cell units transfused (data obtained from the site's blood bank);

- Remind patient to visit the site or a local laboratory for the weekly (applicable at Weeks 4, 8, 16, and 20) or biweekly (applicable at Weeks 32, 36, 44, and 48) blood draws;
- Schedule next study visit.

5.7 Quarterly Visits (Weeks 12 and 40 Visits)

Weeks 12 and 40 visits assessments will consist of the following procedures. Each visit could occur between -7 and +7 days from the indicated visit day.

- Take vital signs and weight;
- Collect blood sample for serum ferritin, hematology and biochemistry;
- Collect blood sample for pregnancy testing for all females of childbearing potential. A negative result will be required for study continuation;
- Review patient diary card with the patient, and/or if applicable patient's authorized legal representative, then collect and file the diary cards with the source documents; provide new diary card, and remind patient how to complete the diary card.
- Determine if patient has had any AEs or SAEs or used any concomitant medications. If so, document them as specified in Sections 6.3 and 8.2.4;
- Conduct contraceptive counselling for all sexually active patients;
- Collect and account for the medication dispensed at the previous applicable visit;
- Verify/adjust dose level, according to recommendations;
- Dispense the study medication as per Section 7.4;
- Instruct the patient, and/or if applicable patient's authorized legal representative, how to take the medication;
- Remind the patient, and/or if applicable patient's authorized legal representative, that all used and unused medication bottles must be returned at the next monthly or semi-annual study visit;
- Provide a new patient diary card and explain how to complete it;
- Remind the patient, and/or if applicable patient's authorized legal representative, that she/he must carefully keep track of adverse events and medication used to treat them as well as any other medication taken;
- Remind the patient, and/or if applicable patient's authorized legal representative, that if study medication is stopped early, she/he must return to the clinic for an Early Termination Visit as soon as possible, but no later than 4 weeks following study medication discontinuation;

- Remind patient, and/or if applicable patient's authorized legal representative, that if an infection develops, therapy must be interrupted immediately. Patients should be advised to report immediately to their physician any symptoms indicative of infection such as fever, sore throat, and flu-like symptoms In presence of confirmed fever and/or infection, they will be required to have their neutrophil counts tested as soon as possible and no later than 24 hours after the symptoms of infection are detected;
- If the patient is receiving a blood transfusion during this visit or has received blood transfusions since the last visit (except for those patients who received an emergency transfusion), record the type of transfusion (simple, exchange, partial exchange), volume of blood that the patient received during the transfusions, and the mean hematocrit of the packed red blood cell units transfused (data obtained from the site's blood bank);
- Remind patient to visit the site or a local laboratory for the weekly (applicable at Week 12) or biweekly (applicable at Week 40) blood draws;
- Schedule next study visit.

5.8 Semi-Annual Visit (Week 26 Visit)

Week 26 visits assessments will consist of the following procedures. This visit should occur between -7 and +7 days from the indicated visit day.

- Perform physical examination;
- Take vital signs (including weight and height);
- Collect blood sample for serum ferritin, hematology, biochemistry and serology;
- Collect blood sample for pregnancy testing for all females of childbearing potential. A negative result will be required for study continuation;
- Collect urine for urinalysis;
- Perform 12-lead ECG;
- Perform MRI scan for:
  - Liver, and transmit to a central laboratory for interpretation and LIC calculation;
  - Cardiac MRI T2*, and transmit to a central laboratory for interpretation;
- Complete patient-reported quality of life questionnaire (SF-36 or Child Health Questionnaire);
- Review patient diary card with the patient, and/or if applicable patient's authorized legal representative; then collect and file the diary card with the source documents, provide new diary card, and remind patient how to complete the diary card.

- Determine if patient has had any AEs or SAEs or used any concomitant medications. If so, document them as specified in Sections 6.3 and 8.2.4;
- Receive and account for the medication dispensed at the previous applicable visit;
- Conduct contraceptive counselling for all sexually active patients;
- Verify/adjust dose level, according to recommendations;
- Dispense the study medication as per Section 7.4;
- Instruct the patient, and/or if applicable patient's authorized legal representative, how to take the medication;
- Remind the patient, and/or if applicable patient's authorized legal representative, that all used and unused medication bottles must be returned at the next monthly or quarterly study visit;
- Provide a new patient diary card and explain how to complete it;
- Remind the patient, and/or if applicable patient's authorized legal representative, that she/he must carefully keep track of adverse events and medication used to treat them as well as any other medication taken;
- Remind the patient, and/or if applicable patient's authorized legal representative, that if study medication is stopped early, she/he must return to the clinic for an Early Termination Visit as soon as possible, but no later than 4 weeks following study medication discontinuation;
- Remind patient, and/or if applicable patient's authorized legal representative, that if an infection develops, therapy must be interrupted immediately. Patients should be advised to report immediately to their physician any symptoms indicative of infection such as fever, sore throat, and flu-like symptoms In presence of confirmed fever and/or infection, they will be required to have their neutrophil counts tested as soon as possible and no later than 24 hours after the symptoms of infection are detected;
- If the patient is receiving a blood transfusion during this visit or has received blood transfusions since the last visit (except for those patients who received an emergency transfusion), record the type of transfusion (simple, exchange, partial exchange), volume of blood that the patient received during the transfusions, and the mean hematocrit of the packed red blood cell units transfused (data obtained from the site's blood bank);
- Remind patient to visit the site or a local laboratory for the biweekly blood draws;
- Schedule next study visit.

5.9 End of Study Visit (Week 52 or Early Termination Visit)

The End of Study assessment (at 52 weeks ± 7 days from the start of study medication) or Early Termination will consist of the following procedures:

- Perform physical examination;
- Review medical history and concurrent medications;
- Take vital signs, weight, and height;
- Collect blood sample for serum ferritin, hematology, biochemistry (fasting glucose; patient must come to the site following a 10-hour fast), and serology;
- Collect blood sample for pregnancy testing for all females of childbearing potential;
- Collect urine for urinalysis;
- Perform 12-lead ECG;
- Perform MRI scan for:
    - Liver, and transmit to a central laboratory for interpretation and LIC calculation;
    - Cardiac MRI T2* and transmit to a central laboratory for interpretation;
- Complete patient-reported quality of life questionnaire (SF-36 or Child Health Questionnaire);
- Review patient diary card with the patient, and/or if applicable patient's authorized legal representative, then collect and file the diary card with the source documents;
- Determine if patient has had any AEs or SAEs or used any concomitant medications. If so, document them as specified in Sections 6.3 and 8.2.4;
- If the patient has received blood transfusions since the last visit (except for those patients who received an emergency transfusion), record the type of transfusion (simple, exchange, partial exchange), volume of blood that the patient received during the transfusions, and the mean hematocrit of the packed red blood cell units transfused (data obtained from the site's blood bank);
- Collect and account for the medication dispensed at the previous applicable visit;
- Explain to the patient, and/or if applicable the patient's authorized legal representative, that she or he should inform the site if she/he experiences any serious medical problems (SAEs) in the 30 days following the last dose;
- Follow up on any continuing adverse events or serious adverse events until resolution, until the condition stabilizes, until the event is otherwise explained, or until the patient is lost to follow-up.

5.10 Early Termination

Patients can be withdrawn from the study at any time. Reasons for withdrawal will be documented in the source document and eCRF, and early termination visit procedures should be performed within 1 month.

These data should be recorded and entered in the eCRF, as they constitute essential data from an evaluation that should be conducted prior to discharging any patient from the study.

6 TREATMENT

6.1 Study Medication

The treatment phase of the study will last 52 weeks, beginning on the day of the first dose of the study medication. Dispense the study medication as per Section 7.4. As per Section 4.6.5 and 4.6.6 of the ICH Consolidated Guideline on GCP, the Investigator is responsible for ensuring that the investigational products are used only in accordance with the approved protocol, that the correct use of the medication has been clearly explained by the Investigator or delegate to each patient, and that the patient continues to take the medication according to those instructions throughout the trial.

Deferiprone treatment arm:

During the study, patients will be prescribed Ferriprox 500 mg tablets or deferiprone 80 mg/mL oral solution, according to patient preference or product's availability, for administration three times a day (tid). The dose of deferiprone will be based on the transfusional iron input and the severity of iron load at baseline, and may be adjusted on the basis of the magnitude of change in iron overload during the study.

Deferiprone 25 mg/kg tid:

Patients with transfusional iron input ≤ 0.3 mg/kg/day in the 3 months prior to baseline

AND

Patients with a baseline measure of iron load of:

- Serum ferritin <2500 µg/L

AND

- LIC <15 mg/g dry weight

AND

- Cardiac T2* > 20 ms

Deferiprone 33 mg/kg tid:

Patients with a transfusional iron input > 0.3 mg/kg/day in the 3 months prior to baseline

OR

Patients with at least one baseline measure of iron load as follows:

- Serum ferritin ≥2500 μg/L

OR

- LIC ≥15 mg/g dry weight

OR

- Cardiac T2* ≤ 20 ms

Dosing of all patients will be initially at 15 mg/kg tid for 1 week, which will be increased to 20 mg/kg tid in Week 2 and to 25 mg/kg tid in Week 3, which will be the treatment dose for the remainder of the trial, unless a patient meets the 33 mg/kg tid dosing criteria. In that case, the dose of deferiprone will be increased further to 33 mg/kg tid in Week 4 and this dose will be the treatment dose for the remainder of the trial.

The dose of deferiprone will also be increased to 33 mg/kg tid at any time during the trial if the mean daily transfusional iron input increases to more than 0.3 mg/kg body weight for at least 3 consecutive months OR at Week 26 if there is less than 10% improvement from baseline to Week 26 in at least one of the measures indicative of iron overload (serum ferritin, cardiac MRI T2* or LIC).

Dose reduction recommendations will be based on regular assessment of safety markers for adverse reactions that are possibly dose dependent, such as gastrointestinal upset, increases in serum liver enzyme levels, and arthropathies.

Deferoxamine treatment arm:

During the study, patients will be prescribed deferoxamine as per the approved US prescribing information at doses of 20 – 40 mg/kg/day for children (<16 years of age) and 40–50 mg/kg/day in adults (≥16 years of age) as 8 – 12 h subcutaneous infusion for 5 – 7 days per week. The dose of deferoxamine will be based on the transfusional iron input, on the severity of iron load at baseline, and on the magnitude of its change during the study.

Deferoxamine 20 mg/kg/day (children) or 40 mg/kg/day (adults):

Patients with transfusional iron input ≤ 0.3 mg/kg/day in the 3 months prior to baseline

AND

Patients with a baseline measure of iron load of:

- Serum ferritin <2500 μg/L *

AND

- LIC <15 mg/g dry weight

AND

- Cardiac T2* > 20 ms

* If there is a delay in obtaining the results of the baseline serum ferritin assessment from the central laboratory, the most recent result (obtained within the last 3 months) should be used to calculate the starting DFO dosage. This dosage must remain in effect until the baseline serum ferritin results become available, at which time it is to be adjusted if necessary. If no serum ferritin measure has been obtained within the last 3 months, the start of dosing must be deferred until the baseline results are available.

Deferoxamine up to 40 mg/kg/day (children) or 50 mg/kg/day (adults):

Patients with a transfusional iron input > 0.3 mg/kg/day in the 3 months prior to baseline

OR

Patients with at least one baseline measure of iron load as follows:

- Serum ferritin ≥2500 μg/L

OR

- LIC ≥15 mg/g dry weight

OR

- Cardiac T2* ≤ 20 ms

Children (<16 years of age)

The dose of deferoxamine will also be increased up to 40 mg/kg for 5 – 7 days per week at any time during the trial if the mean daily transfusional iron input increases to more than 0.3 mg/kg body weight for at least 3 consecutive months OR at Week 26 if there is less than 10% improvement from baseline to Week 26 in at least one of the measures of iron overload (serum ferritin, cardiac MRI T2* or LIC).

Adults (≥16 years of age)

The dose of deferoxamine will be increased up to 50 mg/kg for 5 – 7 days per week at any time during the trial if the mean daily transfusional iron input increases to more than 0.3 mg/kg body weight for at least 3 consecutive months OR at Week 26 if there is less than 10% improvement from baseline to Week 26 in at least one of the measures of iron overload (serum ferritin, cardiac MRI T2* or LIC).

Dose reduction recommendations will be based on regular assessment of safety markers.

6.2 Rationale for Selection of Doses

Deferiprone:

In thalassemia syndromes, the dose of 25 to 33 mg/kg body weight three times a day for a total daily dose of 75 to 99 mg/kg, seven days a week, has been approved on the basis

that it is able to reduce or control transfusional iron burden. The transfusion regimen in SCD patients in this study is similar to that employed in patients with thalassemia major, and as such, is expected to be capable of offsetting iron accumulation in the majority of transfusion-dependent patients (Bansal RK. 2002; Longo F *et al.* 1999; Pennell DJ *et al.* 2006; Piga A *et al.* 2003; Rombos Y *et al.* 2000; Taher A *et al.* 2005; Wonke B *et al.* 1998). The recommended initial dose of deferiprone is 25 mg/kg, orally, three times per day for a total of 75 mg/kg/day. The maximum dose is 33 mg/kg, three times per day for a total of 99 mg/kg/day.

Deferoxamine:

Initial and maximal doses recommendations for deferoxamine are based on its prescribing information.

6.3 Prior and Concomitant Medications

All medications taken during the 3 months prior to dosing up to the end of the study (Week 52 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 nutrition supplements must be recorded in the source document and the appropriate sections of the eCRF. During treatment with deferiprone, patients **must not** receive any other investigational product or any drugs that are known to cause neutropenia or agranulocytosis. See Appendix 18.3 for a list of prohibited drugs.

6.4 Rescue Medication

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

6.5 Treatment Compliance

Patients will be instructed on how to take the study medication. A medication usage diary card will be provided to the patients by the study staff. Patients will record the number of tablets or volume of oral solution taken, or the volume of injection solution administered and the time of injection. For deferiprone, compliance will be evaluated monthly by the Investigator or delegate by monthly pill counts or volume of drug returned by the patient. For deferoxamine, compliance will be evaluated by the number of infusions performed, which will be recorded monthly through the use of infusion pumps that keep records of those numbers, and by physical assessment of the infusion sites. Reasons for non-compliance with the treatment will be recorded in the source document and in the eCRFs. The Investigator should discuss treatment compliance with the patient and, if applicable, his/her parent or legal representative, at each visit.

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

Compliance ≤80% and an over-compliance of ≥120% will be reported as a protocol deviation.

7 MATERIALS AND SUPPLIES

7.1 Study Medication

Deferiprone:

Deferiprone will be supplied to the clinical sites by ApoPharma Inc. as 500 mg film-coated scored tablets and/or 80 mg/mL oral solution. It will be manufactured by Apotex Inc., Toronto, Ontario, Canada, and will have been tested and released according to appropriate standards and regulations.

Deferoxamine:

Deferoxamine will be obtained from Hospira Inc. It will be provided by ApoPharma Inc. to the clinical sites as 2 g vials of sterile deferoxamine mesylate. The vials are to be stored as per label requirement, and their contents are to be dissolved according to the instructions provided by the investigator or qualified designate.

7.2 Packaging and Labelling

Study medication will be supplied by the Sponsor to the Investigator for each patient enrolled and randomized in the clinical trial. Study medication provided must only be used to treat patients enrolled in this clinical trial.

Ferriprox tablets will be supplied in bottles of 100 tablets each, high-density polyethylene (HDPE) bottles with child-resistant closure and appropriately labelled. Deferiprone 80 mg/mL oral solution will be supplied in 250 mL bottles with child-resistant closure and appropriately labelled.

Deferoxamine will be supplied in vials of 2 g and appropriately labelled.

The contents of the label will be in accordance with all applicable regulatory requirements. The label will include protocol number, expiry date, lot/batch number, investigational statement, storage temperature, dosage, direction for use, visit number, and name and address of the Sponsor.

7.3 Storage and Disposition of Study Medications

The study medication will be stored in a locked room/cabinet at each site. The supply of study medication will be stored as per label requirements in a secure location under the control of the Investigator. The Sponsor will provide a digital temperature monitoring device (if required) and a temperature log to facilitate daily recording of the temperature

of the study medication storage facility. The site must report temperature deviations immediately to the Sponsor and quarantine the product until the Sponsor deems it acceptably for human use.

7.4 Drug Dispensing Procedures

Dispensing of study medication is to be done by appropriately qualified staff (e.g., physician, pharmacist, or nurse).

At the baseline visit, any patient for whom all necessary dosage information is available will be dispensed enough study medication for the next 4 weeks. However, if (1) a patient's baseline serum ferritin result is not yet available, AND (2) a higher dosage is not indicated on the basis of the other iron overload markers (transfusional iron input, LIC, and cardiac MRI T2*), dispensing will be done as follows:

For patients randomized to DFP: All participants will be dispensed a 3-week supply of medication based on the scheduled titration (15 mg/kg tid for the first week, 20 mg/kg tid for the second week, and 25 mg/kg tid for the third week). At the Week 3 visit, at which time the baseline serum ferritin results will be available, they will be dispensed a 1-week supply at either 25 or 33 mg/kg tid as appropriate.

For patients randomized to DFO:

- If a serum ferritin value from within the last 3 months is available, the patient will be dispensed enough medication for 1 week based on that earlier value, and must continue to be dispensed the same dose on a weekly basis (i.e., returning to the site each time for the next week's supply) until the baseline serum ferritin result is available. Once it is available, the dosage will either be left as is or adjusted accordingly.

- If no serum ferritin value has been obtained within the last 3 months, the start of DFO dosing **must be deferred** until the baseline result is available.

At the Week 4 visit and thereafter, medication will be dispensed monthly for all patients.

Patients reporting that their medication has been lost or misplaced will be asked to attend the study site to receive replacement medication. Requests for replacement must be made in writing to the Sponsor's Project Leader (PL), Clinical Research by the appropriate clinical site (pharmacist/physician/Investigator), who will approve the request. The replacement will then be made through the IVRS system by the study coordinator. All information related to the lost/misplaced medication and the replacement medication must be recorded in the drug accountability forms.

7.5 Study Medications Accountability and Inventory Control

A "Site Investigational Drug Inventory Record" and "Patient Investigational Drug Dispensing Record" form will be provided by the Sponsor to the Investigator.

Investigational product accountability lies with the Investigator at all times. The Investigator must maintain an updated Site Investigational Drug Inventory Record at the study site. This log will include at minimum:

- Name of Sponsor
- Name of Investigator
- Study identifier
- Date and quantity of investigational product received from Sponsor
- Lot/Batch number

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

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

At the conclusion of the study, a final inventory must be performed by the Investigator (or delegate). If any tablets 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.

All investigational products that have been returned by the patient or that are unused for any other reasons will be returned to the Sponsor or discarded by the site according to internal procedures, which must include the issuance of appropriate signed destruction certificates including mode of destruction and complete drug accountability of destroyed materials.

7.6 Other Study Supplies

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

8 MEASUREMENTS AND EVALUATIONS

Efficacy and safety measurements/evaluations will be performed at visits outlined in Appendix 18.1 – Schedule of Study Procedures.

8.1 Efficacy

8.1.1 Primary Efficacy Measure

8.1.1.1 Liver Iron Concentration

The liver contains 70% or more of total body iron (Angelucci E *et al.* 2000), justifying the use of liver iron concentration (LIC) as a measure of body iron load (Brittenham GM *et al.* 2001; Olivieri NF & Brittenham. 1997; Overmoyer BA *et al.* 1987; St Pierre TG *et al.* 2005). In the absence of effective iron chelation therapy, transfusion-dependent patients experience a progressive increase in LIC (Cazzola M *et al.* 1983). Although liver iron concentrations may differ from the concentrations of iron in other organs, it has been reported that patients with LIC greater than 7 mg iron/g liver (dry weight; dw) are at increased risk of iron-induced toxicity such as cardiac disease, hepatic fibrosis, diabetes mellitus and death (Hoffbrand AV *et al.* 2003; Olivieri NF & Brittenham. 1997; Telfer PT *et al.* 2000). The current goal for chelation therapy in transfusion-dependent patients is to maintain an "optimal" body iron burden corresponding to hepatic storage concentrations of less than 7 mg/g dw (Olivieri NF & Brittenham. 1997). MRI scans will be performed at the screening/baseline, Week 26, and Week 52 (or early termination) visits, and will be transmitted to a central laboratory for interpretation and LIC calculation.

8.1.2 Secondary Efficacy Measures

8.1.2.1 Patient Reported Quality of Life

SF36:

The SF-36 is a multi-purpose, short-form health survey with only 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. A sample of the questionnaire is included in Appendix 18.5. The SF-36 Questionnaire will be completed by patients aged 18 years old and above at the baseline, Week 26, and Week 52 (or early termination) visits.

Child Health Questionnaire:

The Child Health Questionnaire™ (CHQ) is a family of generic quality of life instruments that have been designed and normed for children. The CHQ measures 14 unique physical and psychosocial concepts. The versions to be used in this study are the Child Health Questionnaire-Parent Form 50 (CHQ-PF50), composed of 50 questions, and the Child Health Questionnaire Child Form 87 (CHQ-CF87), composed of 87 questions. Samples of the questionnaires are included in Appendix 18.5. When possible, both versions will be completed for patients aged 17 years and under at the baseline, Week 26, and Week 52 (or early termination) visits.

8.1.2.2 Cardiac MRI T2*

Myocardial MRI T2* can be used to monitor the myocardial iron load resulting from chronic transfusions, with low T2* levels reflecting a high cardiac iron concentration and high T2* values reflecting low cardiac iron. This technique has been calibrated with cardiac iron concentration in post mortem hearts (Carpenter JP *et al.* 2011). Studies in non-iron-overloaded patients reveal that none have a cardiac T2* <20 ms, a value that is

now widely used clinically as the threshold for cardiac iron overload (Wood JC. 2007). The ability of cardiac MRI T2* to identify patients at risk of iron-induced cardiac disease and premature death has been reported (Kirk P *et al.* 2009), and its predictive value has been prospectively evaluated in 652 transfusion-dependent thalassemia patients from 21 UK centers who had cardiac MRI T2* assessment and who had their cardiac status followed over time (Kirk P *et al.* 2009). The results of that study demonstrated that the lower the cardiac MRI T2* value (i.e., the higher the cardiac iron load), the higher the risk of developing iron-induced cardiac failure within the subsequent 12 months. MRI scans for the assessment of cardiac MRI T2* will be performed at the screening/baseline, Week 26, and Week 52 (or early termination) visits, and will be transmitted to a central laboratory for interpretation.

8.1.2.3 Serum Ferritin

The most commonly used method for the assessment of body iron burden is the measurement of serum ferritin concentration (Borgna-Pignatti C & Castriota-Scanderbeg. 1991; Brittenham GM *et al.* 1981; Brittenham GM *et al.* 1993; Finch C. 1994; Finch CA *et al.* 1986; Lipschitz DA *et al.* 1974; Worwood M *et al.* 1980). Ferritin is the major storage protein for iron. It is present in low concentrations in the plasma and is a reflection of total body iron. Due to the continual transfusional iron input and the lack of a natural excretory pathway for the excess iron, a progressive increase in serum ferritin concentration occurs in transfusion-dependent patients in the absence of effective iron chelation therapy. Sequential measures of serum ferritin concentration remain the most common method for assessment of body iron burden, and in clinical practice it is the standard for identifying trends in iron status within individuals and across populations. For an individual, serum ferritin is therefore a useful index of changes in iron load status, and for decades, a serum ferritin level above 2,500 µg/L has been considered an important indicator of the relative risk of death (Hoffbrand AV *et al.* 2003; Olivieri NF *et al.* 1994; Telfer PT *et al.* 2000). Serum ferritin will be assessed at baseline and at the Weeks 12, 26, 40 and 52 (or early termination) visits.

8.2 Safety

The Investigator is responsible for monitoring the safety of patients who have entered the study. Safety and tolerability of deferiprone will be assessed during the study by physical examinations, vital signs, clinical laboratory tests, spontaneous reporting of symptoms by patients, and by nurses' and physicians' observations.

8.2.1 Medical History, Physical Examination, Vital Signs and Prior and Concomitant Medication Use

A medical history will be collected at screening/baseline, and reviewed at the end of study visit (Week 52 or early termination). A complete physical examination will be performed at screening/baseline, and Weeks 26 and 52 visits according to the schedule of events (Appendix 18.1).

- Vital signs (temperature, heart rate, respirations, blood pressure) and weight will be measured at screening/baseline, baseline and each monthly visit (Weeks 4, 8, 12, 16, 20, 26, 32, 36, 40, 44, 48 and 52 (or early termination)). Height will be measured only at screening/baseline, semi-annual and week 52 (or early termination) visits.

- Information about concomitant medications will be collected at screening/ baseline, baseline and each monthly visit (Weeks 4, 8, 12, 16, 20, 26, 32, 36, 40, 44, 48 and 52 (or early termination)). The following must be recorded in the Source Documents and eCRFs:
    - All medications used during the 3 months prior to the screening/baseline visit;
    - Any previous use of deferiprone, deferoxamine and deferasirox;
    - Any medications that the patient continues to take during the trial;
    - Any medications which the patient starts to take during the trial.
    - The name, dose, route, frequency, indication, and start and stop dates of all medications used during the trial must be noted in the Source Documents and eCRFs as well as whether or not the medication was used to treat an medical events/adverse event.

8.2.2 Clinical Laboratory Tests

Lab reports must be promptly interpreted by the Investigator. Any abnormal results should be assessed for clinical significance. Any clinically relevant abnormalities/changes which occur during the trial that are not part of a larger medical condition that is already recorded must be recorded on the source documents and the Adverse Events section of the eCRF.

The following clinical laboratory tests will be performed. 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.

Hematology:
Hematology assessments consisting of hemoglobin, total WBC, ANC and platelets will be performed at screening/baseline, baseline, weekly after start of dosing until Week 26, and then biweekly until Week 52 (or early termination).

Biochemistry:
Biochemistry assessments will be performed at the screening/baseline visit and then monthly: Weeks 4, 8, 12, 16, 20, 26, 32, 36, 40, 44, 48 and 52 (or early termination). Biochemistry evaluation will consist of total protein; GGT; lactate dehydrogenase (LDH); sodium, potassium, chloride, glucose (fasting at screening and Week 52 or early termination visits only); total, direct and indirect bilirubin; AST; ALT; albumin; blood urea nitrogen; calcium; creatinine; uric acid; alkaline phosphatase; and amylase.

Serology:
Serology assessments will be performed at the screening/baseline, Week 26, and end of study (Week 52 or early termination) visits. Serology evaluation will consist of Hepatitis B and C and HIV testing.

Urinalysis:
Urinalysis assessments will be performed at the screening, Week 26, and end of study (Week 52 or early termination) visits. Urinalysis by urine dipstick will consist of pH, specific gravity, glucose, protein, ketones, and blood. If indicated by the dipstick results, sediment microscopy will be performed. If there is blood in the urine or three or more "plus signs" for protein, samples must be sent for microscopy.

Pregnancy Test:
Serum pregnancy tests will be performed at the screening/baseline and baseline visits and monthly (Weeks 4, 8, 12, 16, 20, 26, 32, 36, 40, 44, 48 and 52 (or early termination)). Urine pregnancy test will be performed at the baseline visit.

8.2.3 ECG

A standard 12-lead ECG will be performed at the screening, Week 26, and end of study (Week 52 or early termination) visits. As a minimum, the following parameters will be assessed: HR, PR, QRS, QT, QTcF, and QTcB. Results will be interpreted by the Investigator. The overall interpretation will also be documented.

8.2.4 Adverse/Medical Events and Serious Adverse Events

All adverse/medical events encountered during the study will be reported on the source documents and the eCRF, and will be carefully monitored and assessed with respect to seriousness, severity, and relationship to the study or study drug. Adverse/medical events will be followed until the event is resolved, condition stabilizes (for conditions with long recovery period or those that progressed to chronic form) or the event is otherwise explained or the patient is lost to follow-up. It is the responsibility of the Investigator to ensure that adequate medical care is provided to patients during the study. All SAEs occurring within 30 days following the completion/discontinuation of the study must be reported to the Sponsor regardless of the suspected drug/event causal relationship. SAEs for which the Investigator suspects a causal relationship to the study drug must be reported to the Sponsor irrespective of the time elapsed since the last dose of the study drug.

8.2.4.1 Definition of Medical/Adverse Events

Medical Event: Any new untoward medical occurrence or worsening of a pre-existing condition in a patient that occurs after signing the ICF but before receiving an investigational product.

Adverse Event: An AE is any untoward medical occurrence in a clinical investigation in a patient administered a pharmaceutical or other therapeutic product, not necessarily

having a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign, symptom or disease temporally associated with the use of a product, whether or not considered related to that product.

An AE does include:

- exacerbation of a pre-existing illness. This includes 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

An AE does not include:

- a pre-existing disease or condition present or detected at the start of the study that does not worsen
- 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 the disease or disorder, unless it has worsened
- an overdose of either the study treatment or concurrent medication without any signs of symptoms

8.2.4.2 Adverse/Medical Event Considerations

Note that the definition of AEs/MEs could include accidents (e.g., motor vehicle accidents) and the reasons for changes in concomitant medication (drug and/or dose), medical, nursing and/or pharmacy consultation, admission to hospital and surgical operations, and the worsening of a pre-existing medical condition.

Planned hospital admissions and/or surgical operations/procedures for an illness or disease that existed before the investigational product was given or the patient was enrolled in a clinical trial are not to be considered AEs/MEs.

If a patient's dosage is reduced or treatment is discontinued as a result of an AE, study site personnel must clearly document the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

Prior to enrolment, study site personnel will note the occurrence and nature of each patient's medical condition(s) in the source documents and the appropriate section of the eCRF. During the study, site personnel will again note any change in the condition(s) and the occurrence and nature of any AEs/MEs.

Abnormal laboratory findings (e.g., clinical chemistry, hematology, urinalysis), 12-lead ECG abnormalities or other abnormal assessments (e.g. vital signs) which are not part of a larger medical condition which is already recorded as an adverse event and which are judged by the Investigator to be clinically significant must be recorded as AEs or SAEs if they meet the definition of an AE as defined in Section 8.2.4.1 or SAE as defined in Section 8.2.4.6. The Investigator should exercise his or her medical and scientific

judgement in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

8.2.4.3 Procedures for Adverse/Medical Event Monitoring and Recording

MEs will be collected from the time the ICF is signed, and AEs will be collected from the time the treatment starts. The AEs and SAEs related to the underlying condition will be recorded separately.

Patients will be instructed to report AEs/MEs to the Investigator. Reports of adverse events will be elicited using a verbal probe and recorded in the source documentation and on the Adverse Event page of the eCRF. The Investigator or delegate should always ask the same open-ended and non-leading verbal questions of the patient to inquire about AE/ME occurrence. Appropriate questions include:

"How are you feeling?" or "How do you feel?" or for pediatric patients, "How does your child seem to feel?"

"Have you had any (other) medical problems since your last visit/assessment?" or "Have you felt any different in any way since starting the new medication/treatment or since your last visit/assessment?" or for pediatric patients, "Has your child had any (other) medical problem or seemed to act differently in any way since his/her last visit/assessment?"

"Have you taken any new medicines, other than those provided in this study, since your last visit/assessment?" or for pediatric patients, "Has your child needed to take any medicines, other than those provided in this study, since his/her last visit/assessment?"

Based on the patient's response to these questions, the Investigator 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?

All AEs/MEs will be recorded and evaluated by the Investigator for their seriousness, severity, and relationship to the investigational product or study.

The Investigator should 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.

The Investigator must also question the patient about any previously reported AEs that have not resolved.

The Investigator will then rate the intensity, seriousness, and causality of the AEs and will also document any measures taken to address the AE. Causality should be rated in terms of relationship to the study medication as follows: not related, possibly related, probably related, definitely related. See Section 8.2.4.4 for further definitions of

relationship to study medication. All of this information should be clearly recorded in the source documents.

The Investigator should employ this probe at each assessment. AEs will be collected throughout the study.

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

8.2.4.4 Causality

The relationship of an adverse event to study drug should be determined by the Investigator after thorough consideration of all facts that are available. Assessment of causality is based on considering 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 - information on drug withdrawal could also be lacking.

Probably related: Reasonable time sequence to administration of study drug, but unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required.

Definitely related: Plausible time relationship to study drug administration; event 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 rechallenge procedure if necessary.

8.2.4.5 Severity

Severity refers to the accumulated intensity of discomfort/impairment of health since the last recording of AEs. The Investigator will rate the intensity, seriousness, and causality

of the AEs. To achieve maximum consistency in the assessment of severity of adverse/ medical events, it is recommended that National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) scale be used whenever possible, to assist the Investigator in determining the severity of adverse/medical event. Severity of adverse/medical events will be reported on the eCRF as mild, moderate, or severe according to the definitions provided below. Grading based on the CTCAE scale will not be entered into the eCRFs.

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

8.2.4.6 Serious Adverse Event

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

1) Death
2) A life-threatening adverse event
3) Inpatient hospitalization or prolongation of existing hospitalization
4) A persistent or significant disability or incapacity
5) A congenital anomaly in the offspring of a patient who received the study treatment
6) Important medical events that may not result in death, be life-threatening, or require hospitalization but which in the Investigator's judgement may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events 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 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 a serious adverse event.
- With regard to the criteria in (6) above, medical and scientific judgement should be used in deciding whether prompt reporting is appropriate in this situation.

8.2.4.7 Procedures for Serious Adverse Event Reporting

Patients will be instructed to report SAEs to the Investigator immediately (**within 24 hours)** by telephone. The Investigator must report all SAEs to the Sponsor **within 24 hours** of occurrence or notification by the patient. These events must be faxed to the Sponsor using the Sponsor's standard SAE form. The Sponsor will provide a list of project contacts for SAE receipt, fax numbers and telephone numbers.

The Investigator will always provide an assessment of causality at the time of the initial report.

A follow-up SAE form must be completed by the responsible Investigator/delegate and faxed to the Sponsor **within 5 calendar days**. Furthermore, as additional relevant follow-up information becomes available, the Investigator must complete a follow-up SAE form and fax it to the Sponsor.

The Sponsor will submit serious adverse drug events to the appropriate regulatory agencies, in line with local regulatory requirements and timelines.

Investigators must also report all SAEs to their respective IRB/IEC responsible for the study. The Sponsor will promptly inform all other sites of SAEs occurring at a single site that are at least possibly related to the study medication and are unexpected. All site Investigators will report these events to their IRB/IEC following the same timelines as above or following local IRB/IEC policy, whichever takes precedence.

8.2.4.8 Follow-up and Documenting of SAEs

SAEs that occur during the study and for 30 days after the patient takes the last dose of study medication must be documented in the patient's medical record and on the SAE Report form. A separate SAE Report form should be used for each SAE. 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 and not the individual signs/ symptoms should be documented as the SAE.

All SAEs must be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the patient is lost to follow-up. The Investigator is responsible to ensure that follow-up includes any supplemental investigations as may be

indicated to elucidate as completely as practical the nature and/or causality of the SAE. 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 recognized follow-up period, the Sponsor should be provided with a copy of any post-mortem findings, including histopathology. New or updated information should be recorded on the originally completed SAE page, with all changes signed and dated by the Investigator.

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

8.2.4.9 Adverse Event of Special Interest – Neutropenia (Definitions and Management)

Definitions

Mild Neutropenia: A confirmed ANC $\geq 1.0 \times 10^9$/L and $< 1.5 \times 10^9$/L.

Moderate Neutropenia: A confirmed ANC $\geq 0.5 \times 10^9$/L and $< 1.0 \times 10^9$/L.

Severe Neutropenia/Agranulocytosis: A confirmed ANC $< 0.5 \times 10^9$/L.

An absolute neutrophil count (ANC) is confirmed as being less than a specified value if two consecutive counts (maximum 3 days apart) are both less than the specified value. If both consecutive counts are below 1.5×10^9/L but not in the same severity category of neutropenia, a third count will be required to determine the severity.

Management

Mild Neutropenia (two consecutive Absolute Neutrophil Counts $\geq 1.0 \times 10^9$/L and $< 1.5 \times 10^9$/L):

Patients receiving deferiprone treatment who experience mild neutropenia (ANC $\geq 1.0 \times 10^9$/L and $< 1.5 \times 10^9$/L) should continue treatment. The patient's ANC will be monitored every 2 days until resolution of the event, defined as two consecutive ANC $\geq 1.5 \times 10^9$/L. If the ANC remains $\geq 1.0 \times 10^9$/L and $< 1.5 \times 10^9$/L by the end of a two-week period (14 days):

- The patient will be withdrawn from the study and monitored until resolution of the event.
- The patient will be advised regarding protective isolation.
- The Investigator will notify ApoPharma Inc. by fax.
- The Investigator will examine patient the same day (if possible) including drug history and physical examination.

However, if the patient has a mild neutropenia and develops an infection, therapy must be interrupted immediately and neutrophil count must be obtained and monitored more frequently (every 2 days if ANC <1.5 x 10^9/L) until resolution of the event, defined as two consecutive ANC ≥ 1.5 x 10^9/L. Patients should be advised to report immediately to their physician any symptoms indicative of infection such as fever, sore throat, and flu-like symptoms. In presence of confirmed fever and/or infection, they will be required to have their neutrophil counts tested as soon as possible and no later than 24 hours after the symptoms of infection are detected. Patients will be provided with an emergency services card with contact information, and the patient/legal guardian will be advised to carry this card at all times. Therapy with deferiprone can be initiated once all symptoms have been resolved and it is deemed safe by the Investigator.

Moderate Neutropenia (two consecutive Absolute Neutrophil Counts ≥ 0.5 x 10^9/L and < 1.0 x 10^9/L):

Patients receiving deferiprone treatment who experience moderate neutropenia (ANC ≥ 0.5 x 10^9/L and < 1.0 x 10^9/L) will immediately interrupt treatment, and the patient's ANC will be monitored every 2 days until resolution of the event, defined as two consecutive ANC ≥ 1.5 x 10^9/L. If the ANC remains < 1.5 x 10^9/L by the end of a two-week period (14 days):

- The patient will be withdrawn from the study and monitored until resolution of the event.
- Provide protective isolation; if clinically indicated, admit patient to hospital and obtain q4h vital signs.
- The Investigator will notify ApoPharma Inc. by fax.
- The Investigator will examine the patient the same day, if possible, including drug history and physical examination.
- If possible, obtain viral studies (CMV, parvovirus, hepatitis A/B/C), serum ALT, BUN, creatinine, and 10 mL serum split into two 5-mL aliquots for frozen storage, for future analysis.

Severe Neutropenia/Agranulocytosis (two consecutive Absolute Neutrophil Counts < 0.5 x 10^9/L):

Patients receiving deferiprone and who experience severe neutropenia/agranulocytosis (ANC < 0.5 x 10^9/L) will immediately discontinue treatment. The patients will be withdrawn from the study and will be followed daily until two successive ANCs are ≥1.5 x 10^9/L:

- The patient will be withdrawn from the study and monitored until resolution of the event.
- Provide protective isolation; if clinically indicated, admit patient to hospital and obtain q4h vital signs.
- The Investigator will notify ApoPharma Inc. by fax.
- The Investigator will examine the patient the same day, if possible, including drug history and physical examination.
- If possible, obtain viral studies (CMV, parvovirus, hepatitis A/B/C), serum ALT, BUN, creatinine, and 10 mL serum split into two 5-mL aliquots for frozen storage.
- Collect a blood sample to attempt to identify genetic or other biomarkers related to agranulocytosis (optional).
- If possible, obtain bone marrow aspirate for:
    - Histology
    - Progenitor culture
    - Frozen storage (1 mL sample)
- If possible, obtain bone marrow biopsy (minimum length 3 mm).
- Perform septic work-up including chest X-ray, blood, urine and throat cultures.
- Obtain q4h temperatures from patient (monitored by family at home if patient is not in the hospital).
- If warranted, administer granulocyte stimulating factors, such as G-CSF 10 µg/kg, as an inpatient if possible, beginning the same day that the ANC is confirmed as $< 0.5 \times 10^9$/L; administer daily until ANC is $> 1.5 \times 10^9$/L on two 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.

9 PROCEDURES IN CASE OF MEDICAL EMERGENCY

The Investigator is responsible for ensuring that procedures and expertise are available to cope with medical emergencies during the study period. An emergency may constitute an SAE.

9.1 Precautions/Overdose

An overdose is defined as taking more than the prescribed individual dose or more than maximum daily dose.

Deferiprone:

Deferiprone use can be associated with neutropenia, including agranulocytosis, the cause of which is currently unknown. Because of the awareness of this risk, weekly monitoring for neutrophil count was proposed in the first marketing authorization application for deferiprone and has been in effect since. However, a recent review of both clinical and post-marketing data accumulated over the last two decades confirmed that deferiprone-induced agranulocytosis is not dose-related within the therapeutic range, and its occurrence peaks at 5 months after initiation of therapy, declining in frequency after this period. It was concluded that weekly monitoring is a prudent approach but that it does not preclude agranulocytosis from occurring and it could even provide false security, as agranulocytosis could occur shortly after the finding of a normal neutrophil count. The relevance of weekly monitoring of the neutrophil count appears to decrease even further after the first six months of therapy, when agranulocytosis occurs less often. Based upon analysis of data collected over the past 20 years, it appears that patient education may be the key to minimizing risks associated with agranulocytosis during deferiprone therapy. A better approach to minimizing the risks in patients receiving long-term deferiprone therapy is for ANC monitoring to be done weekly only at the beginning of the treatment and to emphasize the importance of educating patients on the need to immediately stop deferiprone and to maintain ANC monitoring upon signs of infection.

Neurological disorders such as cerebellar symptoms, diplopia, lateral nystagmus, psychomotor slowdown, hand movements, and axial hypotonia have been observed in children who were treated with deferiprone at doses more than twice the maximum recommended dose of 100 mg/kg/day for transfusion-related iron overload for up to 16 months. The neurological disorders progressively regressed after deferiprone discontinuation.

Deferoxamine:

Inadvertent administration of an overdose or inadvertent intravenous bolus administration/ rapid intravenous infusion may be associated with hypotension, tachycardia, and gastrointestinal disturbances; acute but transient loss of vision, aphasia, agitation, headache, nausea, pallor, CNS depression including coma, bradycardia and acute renal failure have been reported. Acute respiratory distress syndrome has been reported following treatment with excessively high intravenous doses of deferoxamine in patients with acute iron intoxication and in patients with thalassemia.
Overdose per se will not be reported as an AE. The signs and symptoms or clinical sequelae resulting from overdose will be reported if they fulfill the AE or SAE definition.

9.2 Procedures in Case of Pregnancy

If a female study patient becomes pregnant, or plans to become pregnant, during the course of the study, the patient must inform the Investigator, and deferiprone must be stopped and the patient will be immediately withdrawn from the clinical trial. The Investigator must report all pregnancies that occur during the study and within 30 days

after the last dose of study medication, using the Pregnancy Reporting Form and information collected in eCRF. The patient will be followed up and the pregnancy outcome will be reported. Pregnancy outcomes include live birth, spontaneous abortions (loss of pregnancy before 20 weeks of gestation), elective termination, and fetal death/still births (loss of pregnancy after 20 weeks of gestation). Within any of these categories, the fetus or infant must be evaluated for the presence of any congenital anomalies. Any maternal/fetal complications should be also reported. If possible, the health of the child will be followed for 1 year.

The same pregnancy and post-gestation monitoring procedures will also apply in the case where a male patient reports that his female partner has become pregnant. In this case, however, there will be no requirement for the patient to withdraw from the trial.

10 STUDY COMMITTEE

10.1 Data Safety Monitoring Board

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

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. The DSMB will be notified of any changes to the protocol or the study conduct. All DSMB meeting minutes and board composition will be submitted to the regulatory authorities with the final clinical study report.

11 DATA HANDLING AND STATISTICAL ANALYSIS

11.1 Data Collection and Handling Procedures

11.1.1 Documentation of Data

All data obtained during this study are raw data and will be entered promptly by the Investigator or delegate in the source document. eCRF entries are derived from source documents. An explanation must be documented for any missing data. The Investigator will be required to place all source documents in the patients' medical record files. Details of the eCRF completion will be explained to the Investigator.

11.1.2 Corrections to Study Documentation

Any errors in the study documentation must be crossed out with a single line, leaving the original entry legible. The correction must then be dated and initialled. Incorrect entries must not be covered with correcting fluid, obliterated, or made illegible in any way.

11.1.3 Data Processing

During the study, the study statistician will have read-only access to the data for program development. Integrity of the database will be assured by limiting access through passwords and account control and through regular, secure backups of both the clinical data management files and SAS-related files.

11.1.4 Coding

The following coding dictionaries will be used:

Diseases:	Medical Dictionary for Regulatory Activities (MedDRA)
Adverse events:	MedDRA
Drugs:	World Health Organization (WHO) Drug Dictionary

11.1.5 Data Handling

Discrepancies will be reviewed and resolved online by the clinical study site users or reviewed off-line by Clinical Data Management, the CRO and/or Clinical Research and sent to the study site. A Patient Data Report (PDR) is a generated compilation of data from the database that is presented in a PDF document. The PDR originates from the same HTML files as the eCRFs and can either be generated with no data, with patient and eCRF information (such as patient ID number #, site name, etc.), and/or with all collected response data. A copy of the final PDRs will be sent to the clinical study site after database freeze.

11.1.6 Missing, Unused and Spurious Data

All missing data will be subject to data queries as specified above. All eCRF data will be entered into the electronic database and will be considered for analysis as specified in the statistical analysis plan.

11.2 Statistical Analysis

11.2.1 Primary Efficacy Endpoint

The change from baseline to Week 52 in liver iron concentration (measured by MRI).

11.2.2 Secondary Efficacy Endpoints

- Change from baseline to Week 52 in patient-reported quality of life (SF-36 or Child Health Questionnaire);
- Change from baseline to Week 52 in cardiac MRI T2*;
- Change from baseline to Week 52 in serum ferritin.

11.2.3 Safety Endpoints

- Frequency, severity and time to onset/duration of adverse events (AEs);
- Frequency of serious adverse events (SAEs);
- Discontinuation due to AEs;
- Hematology assessments including hemoglobin, total WBC, ANC and platelets;
- Blood serum clinical biochemistry assessments;
- 12-lead ECG.

11.2.4 Determination of Sample Size

Three hundred (300) male and female patients will be enrolled into the study. In a randomized study of two iron chelators for the treatment of iron overload in patients with sickle cell disease (Vichinsky et al., 2006), mean ±SD reductions of 4.0 ± 1.5 mg/g dw and 4.5 ± 2.0 mg/g dw were observed (Figure 1 of the article, numerical values obtained from the authors) in patients from the baseline LIC categories of >7-14 mg/g dw or >14 mg/g dw after they were treated with 35-50 mg/kg or ≥50 mg/kg of deferoxamine respectively, for 52 weeks. Assuming the same mean reduction in LIC for deferiprone but a higher SD of ±4.0 mg/g dw for both treatments due to possibly higher variability associated with MRI measurement, the sample size of 300, with >80% being patients with sickle cell disease, will provide over 95% power for demonstrating non-inferiority of deferiprone to deferoxamine in patients with sickle cell disease.

The sample size estimate is based on a non-inferiority margin of 2 mg/g dw for the reduction of LIC and an alpha of 0.05, two-sided (or an alpha of 0.025, one-sided, Appendix 18.5). It has been reported that in a typical patient with thalassemia major, the LIC could increase by 5 mg/g dw after 1 year without chelation therapy. As the cause of iron overload is the same in thalassemia and sickle cell disease, the same increase in LIC may be expected in patients with sickle cell disease who are transfused at the same rate and not treated with a chelator. Hence, the difference in reduction of LIC between deferoxamine therapy and a placebo (effect size) can be estimated to be 9 (i.e., 4 – (-5)) mg/g dw. This means that the non-inferiority margin of 2 mg/g dw would be about 20% of the effect size.

With the enrolment of 300 patients, there is also greater than 99% chance (power) of occurrence of at least 1 adverse event with an anticipated incidence rate of 2%, or greater than 95% chance for an anticipated incidence rate as low as 1%.

11.2.5 Study Populations

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

11.2.5.1 Intent-to-Treat

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

11.2.5.2 Per-Protocol

The Per-Protocol (PP) population will include all enrolled patients who complete the study, have no major protocol violations, and have an efficacy rating at the end of the study. Prior to database lock, major protocol violations will be reviewed and excluded from the PP population. Major protocol violations will include (but not be limited to) the following:

- Patients who did not fulfill the LIC > 7 mg/g inclusion criterion.
- Patients who were not compliant with the treatment (<80% compliance).
- Patients who took iron chelator medications other than the assigned study medication during the course of the study.

Only the primary efficacy analysis will be performed with the PP population.

11.2.5.3 Safety

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

11.3 Statistical Plan

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

11.4 Definition of Analysis

For patients who were terminated from the study prior to Month 12, if their last efficacy measures were obtained within 30 days of Month 12, the data obtained will be treated as the Month 12 data. For early termination that occurred outside this window, the last observation carried forward (LOCF) method will be used to fill the missing data when the early termination was not caused by worsening of disease conditions or inadequate efficacy of the drug. For early termination due to worsening of disease conditions or inadequate efficacy of the drug, as indicated in the eCRF, the “worst value” method will be used. That is, the worst value of all patients for the corresponding treatment group will be used to impute the missing data at that time point. For missing data due to missed visit, the LOCF method will be used to fill the void.

As a sensitivity analysis, the analysis will be repeated with the LOCF method being used for all drop-out patients in the deferoxamine group. Other sensitivity analyses, where appropriate, will be detailed in the SAP.

For safety data analysis, no imputation will be performed on the missing data, and analysis will be based on observed cases (OC).

11.4.1 Planned Analyses

11.4.1.1 Patient Disposition and Drug Exposure

Patient disposition will be summarized and presented, including the number and percentages of patients who were screened, enrolled, received at least one dose of study medication, completed the study, and withdrew (including reasons for withdrawals). The proportions of drop-outs will be compared between the deferiprone group and the deferoxamine group using Fisher's exact test.

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

11.4.1.2 Patient Characteristics

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

11.4.1.3 Efficacy Analyses

Primary Efficacy Endpoint

The change from baseline to Week 52 in LIC will be compared between the two treatment groups using an analysis of covariance (ANCOVA) model, including treatment variable as the main factor and total transfusional iron input during the study and baseline LIC as covariates. The 95% confidence interval (CI) of the difference (deferiprone minus deferoxamine) in change of LIC from baseline to Week 52 between the two treatment groups will be computed. For the demonstration of non-inferiority, the upper limit of the 95% CI should be no more than 2 mg/g dw.

Secondary Efficacy Endpoints

The change from baseline to Week 52 in patient-reported quality of life (SF-36 or Child Health Questionnaire) will be compared between the two treatment groups. Detailed information on the statistical method to be used will be provided in the statistical analysis plan. The change from baseline to Week 52 in cardiac MRI T2* and serum ferritin will be compared between the two treatment groups using an ANCOVA model, with treatment variable as the main factor and total transfusional iron input during the study and baseline cardiac MRI T2* or serum ferritin as covariates. As with LIC, the 95% CI of the difference between the two treatment groups will be computed for both MRI T2* and serum ferritin. The MRI T2* data will be log-transformed before any statistical testing.

The longitudinal data of patient-reported quality of life, LIC, cardiac MRI T2*, and serum ferritin will also be analyzed for time trend by using the appropriate mixed model,

or its equivalent for the quality of life data. Transfusional iron input will be assessed and compared among treatment groups and hematologic diagnoses. .

Subgroup analysis:

The comparison of the two treatment groups for the primary and secondary efficacy endpoints will be performed in:

- SCD patients only;
- non-SCD patients.

More subgroup analysis, where appropriate, may be defined in the SAP.

11.4.1.4 Safety Analyses

All safety data collected will be presented in listings and summary tables to give an overview of the safety findings.

Adverse Events

A summary table of adverse events will include the following information:

- number of patients exposed to study treatment,
- number of patients experiencing at least one AE,
- number of patients experiencing at least one severe AE,
- number of patients experiencing at least one serious AE,
- number of patients experiencing at least one drug-related AE,
- number of deaths,
- total number of patients withdrawn (and reason for withdrawal) and
- number of withdrawals due to an AE.

All adverse experiences will be coded using MedDRA. Adverse events will be defined as: 1) AEs that occurred or worsened (increased in severity and/or frequency) on or after the first dose of study medication. 2) AEs with a missing start date and a stop date on or after the first dose of study medication. 3) AEs with both a missing start and stop date. AEs will be summarized by treatment and by MedDRA system organ class (SOC) and Preferred Term. SAEs that occurred within 14 days after treatment discontinuation will be considered treatment-emergent AEs. Serious adverse events that occurred within 30 days after treatment discontinuation will be included in the database.

Adverse events will be summarized by treatment group using the total number of AEs, the total number and percent of patients who experience an AE, and the number and percent of patients who experienced an AE within each SOC (and preferred term within an SOC). AEs will also be presented by severity (mild, moderate, severe), by seriousness (serious, non-serious) and by relationship to study medication (at least possibly related, not related). The number of patients withdrawn will also be presented.

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

A listing of serious adverse events and a listing of withdrawals due to AEs will be presented. Patient deaths will be listed separately and discussed with patient narratives.

Vital Signs

Descriptive statistics (mean, median, standard deviation, minimum and maximum) will be presented for temperature, heart rate, respiratory rate, systolic blood pressure, diastolic blood pressure, and weight, at baseline and at each relevant visit. Changes from baseline to each post-baseline time-point will also be presented with descriptive statistics.

ECGs

Clinically significant 12-lead ECG abnormalities will be reported. The number and percentage of patients with normal and abnormal 12-lead ECG results will be provided for each scheduled visit.

Biochemistry, Hematology and Urinalysis

Descriptive statistics for each clinical laboratory test will be presented for each scheduled visit. Change from baseline to each visit will also be presented. According to the laboratory normal ranges, laboratory test results will be categorized as low (< lower normal limit), normal (within normal range), and high (> upper normal limit). Shift tables comparing the distributions of these three categories at baseline versus end of treatment will be presented.

Clinically significant laboratory values will be reported in the AE analysis.

Concomitant Medications

Medications will be coded using the WHO Drug Dictionary. Medications taken during the course of the trial (on or after the first study drug dose and before or on the study termination date) will be considered as concomitant medications. Medications started after the study termination date will not be reported in tables, but will be presented in patient data listings. Concomitant medications used to treat AEs will be differentiated from others.

Concomitant medications will be summarized by preferred term only. To count the number of patients who took a medication, a patient who took the same medication multiple times will only be counted once for that medication. Medications will be tabulated in decreasing order of the total number of patients who took each medication.

In addition, the total number of patients to ever take any concomitant medications will be presented.

Concomitant medications will be presented based on the Safety population.

The safety analyses will be performed in:

- SCD patients only;
- non-SCD patients.

12 DATA MANAGEMENT CONSIDERATIONS

12.1 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 eCRFs provided by the Sponsor. Clinical data will be entered and stored into a validated database. Data will be coded using MedDRA and the WHO Drug Dictionary . The eCRFs will be provided in the Oracle Clinical Remote Data Capture (OCRDC) system hosted by the Sponsor. Trained users will access the system via a secured gateway. Users will be authorized to access data for their study site only. Data will be entered directly into the system from the source documents. Online 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. An electronic signature will be required by the Investigator on the eCRFs, and the monitor will verify the eCRFs on-line.

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

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

The database will be backed up daily.

12.2 Source Documents

The Investigator 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 trial necessary for the reconstruction and

evaluation of the trial. Examples include medical history, physical examination, laboratory results, MRI scans, and 12-lead ECG results.

The Investigator will also retain all patients' specific printouts, reports of tests and procedures performed as requirements of the study. The source documents must be available at the time of any site visit from the Sponsor/CRO and/or regulatory authorities.

During monitoring visits, the monitor will need to validate data in the eCRFs against these sources of data.

For every patient, the hospital/patient records should clearly indicate at least:

- That he/she participated in the study, e.g., by including patient identification (patient ID number) and study identification (study code or other).
- Diagnosis/indication under investigation.
- Medical history.
- A list of treatments withdrawn in order to meet inclusion criteria for participation in the study.
- A list of treatments, including investigational product(s), received or changed during the study.
- A record of all visits to the study site during the study period, including those for study purposes only.
- A list of all AEs, including SAEs, adverse drug reactions (ADRs), and serious adverse drug reactions (SADRs).

12.3 Electronic Data Capture (EDC)

ApoPharma will provide the Investigators with training on the EDC system. Data are entered by clinical study site personnel from the source data directly into the eCRF. Support is provided to data entry users at the site via a Help Desk.

Discrepancies are reviewed and resolved on-line by the clinical study site users, or reviewed off-line by Clinical Data Management, a CRO, and/or Clinical Research, and sent to the study site.

13 MONITORING, AUDITS AND INSPECTIONS

13.1 Monitoring

The Sponsor has the obligation to follow this study closely throughout its course. Monitoring of the investigational sites will be conducted by the Sponsor and/or contracted to a qualified (through audit) CRO who will provide an appropriately trained Clinical Research Associate (CRA). The CRA will have regular contacts with the investigational site. These contacts will include visits to confirm that facilities remain acceptable, that the investigational site is adhering to the protocol and that data are being

accurately recorded in the eCRFs, and to provide information and support to the Investigator. The CRA will ensure that the investigational product is accounted for and that written informed consent/assent (where applicable) was obtained from each patient. Source data will be verified, and the data in the eCRF will be compared with the source data. The source documents must be available at the time of the site visits.

13.2 Audits and Inspections

In accordance with the principles of ICH E6 Guideline for Good Clinical Practice, the study may be inspected by regulatory authorities and audited by the Sponsor or their designees. The Investigator and relevant clinical support staff will be required to attend audits and inspections and make all necessary documentation and data available upon request.

During the course of the study or after study completion and site closure, one or more Investigator site audits may be undertaken by auditors from the Sponsor or their delegates. The purpose of these audits is to determine whether or not the study is being/has been conducted and monitored in compliance with the ICH E6 Guideline for Good Clinical Practice, approved protocol and amendment requirements, applicable local Standard Operating Procedures (SOPs) and local laws and regulations. It is the Investigator's and his/her staff's responsibility to promptly address deficiencies stemming out of regulatory inspections and the Sponsor's or delegated audits, as well as to ensure that agreed-upon corrective and preventative actions are implemented promptly.

An inspection by any regulatory authority or a Sponsor audit 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 inform the Sponsor immediately.

14 REGULATORY REQUIREMENTS AND OBLIGATIONS

14.1 Informed Consent/Assent

The Investigator will ensure that the patient and/or his/her legal representative is given full and adequate oral and written information about the nature, purpose, possible risks and possible benefits of the study.

The Investigator must make a conscientious effort to be fully satisfied that the patient and/or his/her legal representative has truly understood that for which the consent has been given. The patient and/or his/her legal representative must also be notified that he/she is free to withdraw his/her participation in the study at any time, and that such withdrawal will not affect his/her present or future care.

The patient and/or his/her legal representative should be given ample opportunity to ask questions and discuss the study with the family. The consent document signed by the patient must not be phrased in a manner that might be understood to abrogate the rights of the patient and/or his/her legal representative or the responsibility of the Investigator or Sponsor. The consent/assent form used to obtain the patient's consent **must** be the most up-to-date consent/assent form approved by the IRB/IEC.

Written informed consent/assent will be obtained from the study patient and/or legal representative as described in the Declaration of Helsinki, June 1964, as clarified by the World Medical Association (WMA) General Assembly, Washington 2002, CFR Part 50 prior to entering the patient into the study. The consent/assent form will be signed and dated by the patient or legal representative prior to the first study intervention. A completed copy of each patient's signed and dated consent/assent form will be retained in the patient's chart.

The patient will be provided with a copy of the signed and dated ICF/assent form. Site variations may occur owing to the individual preferences of each ethics committee. Copies of the consent/assent form intended for use at each clinic will be forwarded to the Sponsor for approval prior to the submission of these documents to each ethics committee.

Should a protocol amendment be made, the ICF/assent may need to be revised to reflect the changes to the protocol. The revised consent/assent form will be forwarded to the Sponsor for approval prior to the submission to the IRB/IEC. The Investigator must then ensure firstly that the revised consent/assent form is reviewed and receives favourable written approval from the IRB or IEC, and secondly that it is signed by all patients subsequently entered in the trial and those currently in the trial. The Investigator must provide written approval from the IRB/IEC to the Sponsor.

14.2 Institutional Review Board/Independent Ethics Committee

The Investigators agree to provide the IRB/IEC with all appropriate documents, including a copy of the protocol/amendments, ICFs, advertising text (if any), Investigator's Brochure (if any), and any written information to be given to the patient. The Investigators must obtain IRB/IEC favourable written approvals for the protocol/ amendments, the ICFs and any applicable translations, and any written information to be given to the patient prior to their enrolment, and any advertising to be used for patient recruitment. The Investigator must provide a copy of the written approval of the IRB/IEC to the Sponsor before commencement of the study. The names of the members of IRB/IEC and their titles/institutional affiliations will be provided to the Sponsor and the Investigators prior to the start of the study. The Sponsor further requires copies of all correspondence with the IRB/IEC.

In the event that the protocol is amended, the protocol amendment must be approved by the IRB/IEC prior to its implementation, unless the changes are administrative in nature. If an ICF needs to be revised to reflect the changes to the protocol, the revised consent form will be forwarded to the Sponsor for approval prior to the submission to the IRB/IEC. The Investigator must then ensure firstly that the revised consent form is reviewed and receives favourable written approval from the IRB/IEC, and secondly that it is signed by all patients subsequently entered in the trial and those currently in the trial. The Investigator must provide the written approval to the Sponsor.

The Investigator is also obliged to report all SAEs to the IRB/IEC as per local requirements. The Investigator must submit reports of the study at least annually to the IRB/IEC for review.

The Investigator must notify the IRB/IEC that the study has been completed within 3 months of its completion. A final clinical study report will be made available to the IRB/IEC. The Investigator must maintain an accurate and complete record of all submissions made to the IRB/IEC, including a list of reports and documents.

14.3 Patient Data Protection

To ensure the patient's identity remains unknown to the Sponsor, the Sponsor will identify all data by patient ID number.

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

The Investigator is responsible for keeping a patient identification list or form of all patients entered, including enrolment code, patient ID number, full name, and last known address and phone number.

14.4 Assumption of Liability and Indemnification

The Sponsor shall indemnify, defend, and hold harmless the Investigator(s) (which term includes the Investigator(s)'s institutions, employees, agents, representatives and associates) from and against any demands, claims, costs, judgments, liabilities, damages, losses and expenses, including reasonable legal fees (collectively, a "Loss"), that may be suffered or incurred by the Investigator(s) as a result of personal injuries or damage to property due to or arising out of the conduct of this clinical trial.

Notwithstanding the foregoing, the Sponsor shall have no obligation or liability pursuant to the foregoing indemnity should the Loss result directly or indirectly from the Investigator(s)'s:

a. negligence or wilful misconduct;

b. failure to comply with the terms of the protocol or written instructions regarding the use of any product(s) used in this clinical trial;

c. failure to adhere to any government regulations or requirements; or

d. failure to conduct the study in accordance with standard medical practice.

The Investigators shall promptly notify the Sponsor in writing of any demand, claim, proceeding or other matter (a "Claim") for which indemnity may be claimed. The notification shall specify the all known particulars of the Claim, including, if available, the amount of the Claim. If the Investigator(s) fails to give timely notice of any Claim and as a result the Sponsor is prevented from effectively contesting liability for the Claim, the Sponsor shall be relieved of its obligations hereunder. The Investigator(s) shall take all commercially reasonable action to preserve the right to object to and defend against any Claim.

The Investigator(s) shall fully co-operate with the Sponsor with respect to all Claims and shall keep the Sponsor fully advised with respect thereto, including promptly supplying copies of all relevant documentation as it becomes available.

The Sponsor shall have the right but not the obligation, at its expense, and at any and all times participate in or assume control of the negotiation, settlement or defence of any Claim. Should the Sponsor elect not to assume control of the negotiation, settlement or defence of a Claim, the Investigator shall not settle the Claim without the written consent of the Sponsor, which consent shall not be unreasonably withheld.

If the Sponsor assumes control of the defence of a Claim, which it thereafter fails to defend, the Investigator shall be entitled to assume control thereof and the Sponsor shall be bound by the results obtained by the Investigator with respect to the Claim.

14.5 Compliance

This study will be conducted in compliance with the study protocol, ICH GCP E6, the Organization for Economic Co-operation and Development (OECD) Good Laboratory Practices and all applicable regulations, including the Federal Food, Drug and Cosmetic Act, U.S. applicable Code of Federal Regulations Title 21, Parts 11, 50, 54 (financial disclosure), 56, 312 and 314, Directive 2001/20/EC of the European Parliament and of the Council of 04 April 2001, on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practices in the conduct of clinical trials on medicinal products for human use; any IRB requirements relative to clinical studies and the Declaration of Helsinki, June 1964, as clarified by the WMA General Assembly, Washington 2002 and Directive 2005/28/EC of the European Parliament and of the Council of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorization of the manufacturing or importation of such products.

14.6 Amendments to the Protocol

No amendments may be made to this protocol without the agreement of both the Sponsor and the Investigators. All changes to this protocol must be documented by signed protocol amendment.

The amendment will be implemented by the study site from the day the document is signed by the Principal Investigator and the Sponsor, whichever comes later. If the change affects the safety of patients or involves intervening in the patient's treatment of care, the scope of the investigation or the scientific quality of the study, the amendment must also have IRB/IEC approval, and it also has to be notified to or approved by regulatory authorities before it is implemented. Examples of these types of changes include:

- Any change in drug dosage or duration of exposure of individual patients to the study agent beyond that in the current protocol, or any significant change in the number of patients under study.
- Any significant change in the design of a protocol (such as the addition or dropping of a control group).
- The addition or dropping of a test or procedure.

A change intended to eliminate an apparent immediate hazard to patients may be implemented immediately and without written amendment to this protocol, provided that the regulatory authorities and the IRB/IEC are notified as soon as possible afterwards.

When a proposed change to the protocol that meets the statutory criteria for amendment as defined by the FDA and EMA substantially alters the study design or potential risk to the patient, the patient's re-consent to continue participation will be obtained. This action will require a revised ICF. The revised ICF will require approval from the Sponsor and the IRB/IEC.

14.7 ApoPharma Inc. Obligations

The obligations described below contain excerpts from the ICH guidelines (Good Clinical Practice: Consolidated Guidance: E6, 1996) and the Sponsor's policy governing Sponsor and Investigator obligations.

The Sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded) and reported in compliance with the protocol, GCP guidelines and the appropriate regulatory requirements.

The Sponsor will have the ultimate and final authority in the trial on matters of policy and finance. At the time the study is initiated, the protocol and eCRFs will be reviewed thoroughly with the clinical Investigators and their staff. During the course of the study, the CRA and a Sponsor representative will be available to discuss by telephone, questions regarding AEs, removal of patients from the trial, conduct of the study and other clinical study matters.

The Sponsor will be responsible for:

1. Providing sufficient investigational product for all patients for the duration of the study.
2. Providing all study-related supplies.
3. Reporting the occurrence of SAEs to the Investigators and to regulatory agencies of findings that could affect adversely the safety of patients, impact the conduct of the trial, or alter the IRB/IEC approval/favourable opinion to continue the trial.
4. Designing the study database, monitoring data entry, and ongoing validation of the database.
5. Submitting data clarification forms that are generated as a result of data collected from the investigator sites.
6. Providing adequate support to the Investigators so that the trial is conducted safely and effectively according to the standards of GCP.
7. Reporting the findings of this study annually, or as required, to regulatory agencies and providing a written report of the study upon its completion.
8. Retaining all documentation and records as required by the relevant regulatory agencies.

9. Monitoring and auditing of data at the clinical sites as well as staff interviews for the duration of the trial [or after study completion (e.g., for regulatory authority inspection readiness)] to ensure the study is being conducted according to ICH GCP E6 as well as any applicable local regulations and laws (e.g., adherence to the protocol, patient enrolment, investigational product accountability, and accuracy of data forms).

14.8 Investigators' Obligations

1. Investigators must be registered clinical practitioners, qualified to carry out the study, taking into account the nature of the study and the particular phase and nature of the investigation undertaken.
2. Investigators must provide the Sponsor with appropriate regulatory documentation and up-to-date curricula vitae for themselves and co-Investigators participating in the clinical trial. They must also furnish the Sponsor with the names of all ancillary staff (pharmacists, nurses, etc.) who are directly involved in the study.
3. Investigators are responsible for providing suitable facilities to allow the study to be conducted efficiently and effectively.
4. Investigators are responsible for obtaining written IRB/IEC approval before initiation of the study from their respective institutions. This also includes an IRB/IEC approval of the ICF and any applicable amendments.
5. Investigators are responsible for obtaining written informed consent from the patients and/or legal representatives, prior to the initiation of any study procedures. The patient should receive a copy of the written ICF.
6. Investigators are responsible for conducting the study according to the protocol for the accurate and complete reporting of results in accordance with GCP, and for maintaining accurate investigational product accountability records.
7. Investigators must record in detail all AEs occurring during the course of the study. They must report all SAEs immediately to the Sponsor and the IRB/IEC, and notify the Sponsor immediately when a patient has been removed from the study because of a SAE. The responsible Investigators should institute appropriate diagnostic and therapeutic measures and should keep the patient under observation for as long as it is medically indicated.
8. Investigators must provide completed eCRFs and resolve discrepancies in a timely manner.
9. Investigators must ensure that the study documents are retained in a safe and secure location for 15 years following the completion of the study. No documents may be destroyed without written permission of the Sponsor.

14.9 Data Quality Compliance

To ensure accurate, complete, and reliable data, the Sponsor or its representatives will do the following:

The Clinical Research Division will:

- Provide instructional material to the study sites.
- Sponsor a Start-up Training Session to instruct the Investigators and study coordinators. This session will give instruction on the protocol, the completion of the eCRFs, study procedures, GCP and ICH guidelines and the Operations Manual.
- Make periodic visits to the study sites.
- Be available for consultation and stay in contact with the study site personnel by mail, telephone and fax.

The Clinical Data Management Division will:

- Review and evaluate eCRF data and use standard computer edits to detect errors in data collection.
- Conduct a quality review of the database.

The Quality Assurance Division will:

- Audit all or parts of the study and all or parts of its documentation including those generated at investigators' sites, local and central laboratories, and support sites.
- Audit the final report to ensure that, as far as can be reasonably established, the methods described and the results reported accurately reflect the raw data generated during the study.
- Conduct, if necessary, process audits including samples of data and documentation to assure compliance with ICH GCP E6, applicable local regulations, guidelines and laws as well as the study protocol and relevant Sponsor Policies, Standard Operating Procedures and Work Instructions.

14.10 Study Reports

One report on safety and efficacy will be prepared by the Sponsor at the completion of the study. The lead Investigator may have an opportunity to review the study report. Appropriate Sponsor members will sign the study report to indicate approval.

The Sponsor will be responsible for all submissions to the regulatory agencies.

14.11 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 the whole as more fully described in the clinical trial agreement agreed upon with the Investigator and/or the site.

14.12 Publications/Poster/Presentation

Data derived from the trial are the exclusive property of the Sponsor, and the Sponsor will be responsible for the primary publication of the trial data. The Investigators may, within 6 months of completion of the final report, indicate their interest in publishing the results of this study. No publication should be made by any Investigator prior to the publication of the study results, unless within 6 months of the final report the Sponsor declares no interest in the publication of the study results.

The Sponsor reserves the right to receive any posters or abstracts a minimum of 30 days ***prior*** to submission for presentation and a minimum of 60 days for manuscripts prepared by the Investigator(s) based on data from this clinical trial, ***prior*** to submission for publication. The Sponsor also reserves the right to review and comment on any posters, abstracts, or publication intended for presentation or publication that are based on data from this clinical trial.

14.13 Early Study Termination

The Sponsor reserves the right to discontinue this trial at any time. The study may be terminated by the Investigator at his/her respective site following consultation with the Sponsor. The Investigator will immediately, on discontinuance of the clinical trial, in its entirety or at a clinical trial site, inform both the clinical trial patients and the IRB/IEC responsible for the study of the discontinuance, provide them with the reasons for the discontinuance and advise them in writing of any potential risks to the health of clinical trial patients or other persons. It is the Sponsor's responsibility to report discontinuance of the study to regulatory agencies, and provide them with the reasons for the discontinuance and advise them in writing of any potential risks to the health of clinical trial patients or other persons. The Sponsor must then inform the Investigators.

In the event of a discontinuation, the Investigators will ensure return of all investigational products to the Sponsor with all outstanding investigational materials (e.g., eCRFs, SAE forms) within 1 month. If possible, Investigators should complete all assessments as per the study termination assessments (see Section 5.8).

15 CONFIDENTIALITY

Each Investigator must sign a confidentiality agreement, in form and content satisfactory to the Sponsor, concerning the protection of the Sponsor's confidential and proprietary information disclosed to or obtained by the Investigator during the course of the study. Other than for study recruitment purposes and progress reports required by the regulatory agencies, the information contained in this document and all future information relating to this study is privileged, confidential, and proprietary and may not be used or disclosed without the express written consent of the Sponsor or unless otherwise required by law (in which case the requirement to make such disclosure shall be communicated to the Sponsor in advance and in writing). All information provided to the Investigator by the Sponsor is to be considered strictly confidential unless otherwise specified.

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17 SIGNED AGREEMENT TO THE PROTOCOL

17.1 Principal Investigator Signature Page

I confirm that I have read this protocol and I understand it. I agree to conduct this study in accordance with ICH Good Clinical Practice guidelines, all of the specifications in this study protocol, and local regulatory requirements. I will be responsible for obtaining approval from the IRB/IEC responsible for my institution before the start of the study. I will adhere to the protocol and comply with the guidelines. I agree to fully co-operate with compliance checks by allowing access to all documentation by authorized individuals.

Study Title: The efficacy and safety of Ferriprox® for the treatment of transfusional iron overload in patients with sickle cell disease or other anemias.

Study Code: LA38-0411

Study Site:

Investigator Signature

_____

Investigator Name

_____ _____

Investigator Signature Date: (DD MMM YYYY)

_____

Name of Facility

_____

Location of Facility

17.2 Protocol Approval Signature Page

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

Study Title: The efficacy and safety of Ferriprox® for the treatment of transfusional iron overload in patients with sickle cell disease or other anemias.

Study Code: LA38-0411

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Date: (DD MMM YYYY)

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Apotex Inc., Canada

04 MAY 2017
Date: (DD MMM YYYY)

18 APPENDICES

18.1 Schedule of Events

	Baseline Phase			Treatment Phase				
STUDY PROCEDURE	**Screening/ Baseline**	**Baseline**	**Hematology Assessments [1]**	**Telephone Calls (Week 1, 2, 3)**	**Monthly Visits (Week 4, 8,16, 20, 32, 36, 44, 48)**	**Quarterly Visits (Week 12, 40)**	**Semi-Annual Visit (Week 26)**	**End of Study / Early Termination Visit[2] (Week 52)**
Informed Consent/Assent	X							
Eligibility Criteria	X							
Previous/current chelation therapy	X							
Confirmation of eligibility		X						
Demographic	X							
Randomization		X						
Medical history	X	V						R
Transfusion history	X	X						
Prior and Current medications	X	V						X
Hematology	X[3]	X[4]	X		X	X	X	X
Biochemistry	X[3,4]	V			X	X	X	X
Serum Pregnancy testing (females of childbearing potential only)	X[3]	X			X	X	X	X
Urine Pregnancy testing (females of childbearing potential only)		X						
Serology	X[3,4]	V					X	X
Urinalysis	X[3,4]	V					X	X
Physical examination	X[3,4]	V					X	X
Vital signs (including weight and height)[5]	X	X[4]			X	X	X	X
12-lead ECG	X[3,4]	V					X	X
Blood sample for genetic polymorphism of agranulocytosis (optional)		X						
Contraceptive counselling	X	X			X	X	X	

	Baseline Phase			Treatment Phase				
STUDY PROCEDURE	**Screening/ Baseline**	**Baseline**	**Hematology Assessments [1]**	**Telephone Calls (Week 1, 2, 3)**	**Monthly Visits (Week 4, 8,16, 20, 32, 36, 44, 48)**	**Quarterly Visits (Week 12, 40)**	**Semi-Annual Visit (Week 26)**	**End of Study / Early Termination Visit[2] (Week 52)**
Quality of Life Questionnaire (SF-36/ Child Health Questionnaire)		X					X	X
Serum Ferritin		X				X	X	X
Liver MRI/LIC	X[4,6]						X	X
Cardiac MRI T2*	X[4,6]						X	X
Dose Calculation/Verify and adjust dose level		X			X	X	X	
Contact IVRS/IWRS		X			X	X	X	X
Dispense study medication		X			X	X	X	
Dispense Patient Diary Card		X			X	X	X	
Review and Collect Diary Card					X	X	X	X
Medical events/Adverse events	X	X		X	X	X	X	X
Concomitant medications				X	X	X	X	X
Transfusion information (if applicable)[7]			X		X	X	X	X
Return used and unused study medication					X	X	X	X

X- To do, V- To verify, R- To review

1. Hematology testing is to be done weekly up to Week 26 and biweekly thereafter.
2. Early Termination: if patient withdraws from the study prior to Week 52, the patient must be seen for an early termination visit.
3. These evaluations must be done within 14 days prior to baseline visit. Females of childbearing potential must be making use of an approved birth control method at least one month prior to starting study medication.
4. Results from these tests will be considered the baseline values.
5. Height will only be measured at screening/baseline, semi-annual and Week 52 visits.
6. These evaluations must be conducted within two months prior to starting study medication
7. Collect volume of blood that the patient received during the transfusion and the mean hematocrit of the packed red blood cell units transfused.

18.2 Acceptable Methods of Contraception and Definitions Related to Childbearing Potential

1. Approved methods of contraception will consist of the following for the purposes of this study or must follow local requirements:

- Oral contraceptive medications with condom or spermicide
- Hormonal implants with condom or spermicide
- Injectable contraceptive medications with condom or spermicide
- Condom used with spermicide.

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

2. Women who are not able to bear children and therefore do not need to practice a medically accepted method of contraception will include those who:

- Have had a tubal ligation
- Are post-menopausal (i.e. last menstrual period was more than 2 years ago)
- Have had an hysterectomy or oophorectomy
- Participate in a non-heterosexual lifestyle,
- Have a male sexual partner has been sterilized (supporting evidence required).

3. Patients who are peri-menopausal (i.e., less than 2 years since their last menstrual period), must have a pregnancy test and must use one of the medically accepted methods listed above (under point 1) if they wish to participate in the study.

18.3 List of Prohibited Drugs

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

1. Any investigational drug
2. Chloramphenicol (CHLOROMYCETIN)
3. Clozapine (CLOZARIL), Doxepin HCl (SINEQUAN), Amitriptyline HCl/Perphenazine (ETRAFON) and other tricyclic antidepressants
4. Clomipramine hydrochloride (ANAFRANIL)
5. Propranolol hydrochloride (INDERAL)
6. Bepredil (VASCOR)
7. Aminoglutethimide (CYTADREN)
8. Interferon (INTRON A)
9. Para-aminophenol or pyrazolone derivatives
10. Phenytoin (DILANTIN), Carbamazepine
11. Chlordiazepoxide (LIBRIUM) and other benzodiazepines
12. Phenylbutazone
13. Mefenamic Acid (PONSTAN)
14. Metoclopramide HCl (REGLAN)
15. Chlorpromazine, prochlorperazine and other phenothiazines
16. Procainamide
17. Levamisole (ERGAMISOLE)
18. Diclofenac Sodium (VOLTAREN)
19. Hydroxyurea (Hydrea)
20. Trimethoprim/sulfamethoxazole (Bactrim/Septra)
21. Aminopyrine

18.4 Sample Size Calculation Output

Power Analysis of a Non-Inferiority Test of The Difference of Two Means
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Numeric Results for Non-Inferiority Test (H0: D <= -|E|; H1: D > -|E|)
Test Statistic: T-Test

		Equivalence Margin	Actual Difference	Significance Level		Standard Deviation1	Standard Deviation2
Power	**N1/N2**	**(E)**	**(D)**	**(Alpha)**	**Beta**	**(SD1)**	**(SD2)**
0.95017	79/158	-2.000	0.000	0.02500	0.04983	4.000	4.000

References

Chow, S.C.; Shao, J.; Wang, H. 2003. Sample Size Calculations in Clinical Research. Marcel Dekker. New York.

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Report Definitions

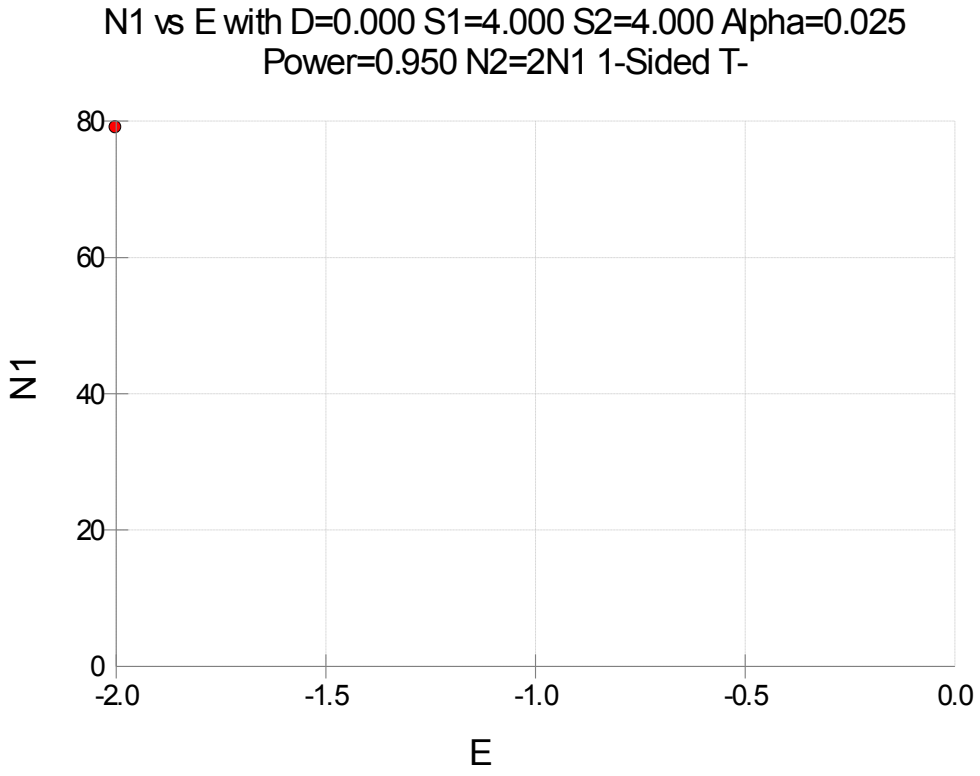
Group 1 is the treatment group. Group 2 is the reference or standard group.
Power is the probability of rejecting a false null hypothesis. Power should be close to one.
N1 is the number of subjects in the first (treatment) group.
N2 is the number of subjects in the second (reference) group.
|E| is the magnitude of the margin of equivalence. It is the largest difference that is not of practical significance.
D is the mean difference at which the power is computed. D = Mean1 - Mean2.
Alpha is the probability of a false-positive result.
Beta is the probability of a false-negative result.
SD1 and SD2 are the standard deviations of groups 1 and 2, respectively.

Summary Statements

Group sample sizes of 79 and 158 achieve 95% power to detect non-inferiority using a one-sided, two-sample t-test. The margin of equivalence is -2.000. The true difference between the means is assumed to be 0.000. The significance level (alpha) of the test is 0.02500. The data are drawn from populations with standard deviations of 4.000 and 4.000.

Power Analysis of a Non-Inferiority Test of The Difference of Two Means

Chart Section



18.5 Questionnaires

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.
Thank you for completing this survey!

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a	<u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b	<u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c	Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d	Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3
e	Climbing <u>one</u> flight of stairs	☐ 1	☐ 2	☐ 3
f	Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g	Walking <u>more than a mile</u>	☐ 1	☐ 2	☐ 3
h	Walking <u>several hundred yards</u>	☐ 1	☐ 2	☐ 3
i	Walking <u>one hundred yards</u>	☐ 1	☐ 2	☐ 3
j	Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

800 Boylston Street
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(857) 453-6665
www.healthactchq.com

CHQ: Child Health Questionnaire (For content review only)

The Child Health Questionnaire™ (CHQ) is a family of generic quality of life instruments that have been designed and normed for children 5-to-18 years of age. The CHQ measures 14 unique physical and psychosocial concepts. The parent form is available in 2 lengths - 50 or 28 items. Scores can be analyzed separately, the CHQ Profile Scores, or combined to derive an overall physical and psychosocial score, the CHQ Summary Scores. In April 2008 HealthActCHQ released the first-ever electronic CHQ Scoring and Interpretation Manual. The 212-page Manual provides information about the conceptual framework and development of the CHQ, the proprietary scoring algorithms, norms and rules for interpretation. The interactive CD-rom features hyperlinks in both the Table of Contents and the Appendix of Tables for smooth navigation. Users can also click on URLs within the Manual to access the latest updates on translations and the online Bibliography at the HealthActCHQ website. The CHQ surveys and translations are made available upon approval of registration and payment.

In the US, normative values and benchmarks for the parent-reported versions of the CHQ are available for some conditions. The CHQ has been extensively translated using rigorous international guidelines. The youth self-report version is 87 items, and was developed for ages 10 and older. Authorized translations are available from HealthActCHQ. Norms, benchmarks, and summary scoring for the youth version will be forthcoming upon the development and testing of a short-form by the Principal Developer.

Child Health Questionnaire Parent Form 28 Questions

- In general, how would you rate your child's health?
- Has your child been limited in any of the following activities due to health problems - doing things that take a lot of energy, such as playing soccer or running; doing things that take some energy such as riding a bike or skating; bending, lifting, or stooping
- Has your child's been limited in the amount of time he/she could spend on schoolwork or activities with friends due to emotional difficulties or problems with his/her behavior?
- Has your child been limited in the kind of schoolwork or activities he/she could do with friends due to problems with his/her physical health?
- How often has your child had bodily pain or discomfort?
- How often did each of the following statements describe your child - argued a lot; had difficulty concentrating or paying attention; lied/cheated?
- Compared to other children your child's age, in general how would you rate his/her behavior?
- How much of the time do you think your child: felt lonely; acted nervous; bothered or upset?
- How satisfied do you think your child has felt about: his/her school ability; friendships; life overall?
- My child seems to be less healthy than other children I know; My child has never been seriously ill; I worry more about my child's health than other people.
- Compared to one year ago, how would you rate your child's health now?
- How much emotional worry or concern did each of the following cause you - your child's physical health; emotional well-being or behavior?
- Were you limited in the amount of time you had for your own needs because of your child's - physical health; emotional well-being or behavior?
- How often has your child's health or behavior - limited the types of activities you could do as a family; interrupted various everyday family activities (eating meals, watching tv)?
- In general, how would you rate your family's ability to get along with one another?

Child Health Questionnaire Parent Form 50 Questions

- In general, how would you rate your child's health?
- Has your child been limited in any of the following activities due to health problems - doing things that take
  a lot of energy, such as playing soccer or running; doing things that take some energy such as riding a bike or skating; ability (physically) to get around the neighborhood, playground, or school; walking one block or climbing
  one flight of stairs; bending, lifting,/stooping; taking care of him/herself?
- Has your child's school work or activities with friends been limited in any of the following ways due to emotional difficulties or problems with his/her behavior - limited in the kind of schoolwork or activities with friends he/she could do; limited in the amount of time he/she could spend on schoolwork or activities with friends; limited in performing schoolwork or activities with friends?
- Has your child's school work or activities with friends been limited in any of the following ways due to problems with his/her physical health - limited in the kind of schoolwork or activities with friends he/she could do; limited in the amount of time he/she could spend on schoolwork or activities with friends?
- How much bodily pain or discomfort has your child had?
- How often has your child had bodily pain or discomfort?
- How often did each of the following statements describe your child - argued a lot; had difficulty concentrating or paying attention; lied/cheated; stole things; had tantrums?
- Compared to other children your child's age, in general how would you rate his/her behavior?
- How much of the time do you think your child: felt like crying; felt lonely; acted nervous; bothered or upset; cheerful?
- How satisfied do you think your child has felt about: his/her school ability; athletic ability; friendships; looks/appearance; family relationships; life overall?
- My child seems to be less healthy than other children I know; My child has never been seriously ill; When there is something going around my child usually catches it; I expect my child will have a very healthy life; I worry more about my child's health than other people.
- Compared to one year ago, how would you rate your child's health now?
- How much emotional worry or concern did each of the following cause you - your child's physical health; emotional well-being or behavior; attention or learning abilities?
- Were you limited in the amount of time you had for your own needs because of your child's - physical health; emotional well-being or behavior; attention or learning abilities?
- How often has your child's health or behavior - limited the types of activities you could do as a family; interrupted various everyday family activities; limited your ability as a family to "pick up and go"; caused tension or conflict; been a source of disagreements or arguments in your family; caused you to cancel or change plans (personal or work) at the last minute?
- In general, how would you rate your family's ability to get along with one another?

Child Health Questionnaire Child Form 87 Questions

- In general, how would you say your health is?
- Has it been difficult for you to do the following activities due to health problems - doing things that take a lot of energy, such as playing soccer or running; doing things that take some energy such as riding a bike or
  skating; walk several blocks or climb several flights of stairs; ability (physically) to get around the neighborhood, playground, or school; walk one block or climbing one flight of stairs; do your tasks around the house; bend, lift or stoop; eat, dress, bathe or go to the toilet by yourself; get in/out of bed?

- Has it been difficult to do certain kinds of schoolwork or activities with friends because of problems like feeling sad or worried; spend the usual amount of time on schoolwork or activities with friends; get schoolwork done at all or do any activities with friends?
- Has it been difficult to do certain kinds of schoolwork or activities with friends because of problems with your behavior; spend the usual amount of time on schoolwork or activities with friends; get schoolwork done at all or do any activities with friends?
- Has it been difficult to do certain kinds of schoolwork or activities with friends because of problems with your physical health; spend the usual amount of time on schoolwork or activities with friends; get schoolwork done at all or do any activities with friends?
- How much bodily pain or discomfort have you had?
- How often have you had bodily pain or discomfort?
- How often did each of the following statements describe you; acted too young for your age; argued; had a hard time paying attention; did not do what your teacher or parent asked you to do; wanted to be alone;

  lied/cheated; had a hard time getting others to like you; felt clumsy; ran away from home; had speech problems; stole things at home or outside the home; acted mean or moody if you did not get what you wanted; got really mad when you did not get what you wanted; found it hard to be with others; had a hard time getting along
  with others.
- Compared to other children your age, in general how would you rate your behavior?
- How much of the time do you: feel sad; feel like crying; feel afraid or scared; worry about things; feel lonely; feel unhappy; feel nervous; feel bothered or upset; feel happy; feel cheerful; enjoy the things you do; have fun; feel jittery or restless; have trouble sleeping; have headaches; like yourself?
- How good or bad have you felt about: yourself; your school work; your ability to play sports; your friendships; the things you can do; the way you get along with others; your body and your looks; the way you seem to feel most of the time; the way you get along with your family; the way life seems to be for you; your ability to be a friend to others; the way others seem to feel about you; your ability to talk with others; your health in general?
- My health is excellent; I was so sick once I thought I might die; I do not seem to get very sick; I seem to be less healthy than other kids I know; I have never been very, very sick; I always seem to get sick; I think I will be less healthy when I get older; I think I will be very healthy when I get older; I never worry about my health; I think I am healthy now; I think I worry more about my health than other kids my age.
- Compared to one year ago, how would you rate your health now?
- How often has your health or behavior - limited the types of activities you could do as a family; interrupted various everyday family activities; limited your ability as a family to "pick up and go"; caused tension or
  conflict; been a source of disagreements or arguments in your family; caused your family to cancel or change
  plans at the last minute?
- In general, how would you rate your family's ability to get along with one another?

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