NOVARTIS

Clinical Development

ICL670, Deferasirox

Clinical Protocol CICL670F2203 / NCT03203850

A phase II, multicenter, open-label, randomized two-year study to evaluate the efficacy and safety of deferasirox film-coated tablet versus phlebotomy in patients with Hereditary Hemochromatosis

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List of abbreviations

AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
CDS	Core data sheet
CI	Confidence interval
CRA	Clinical Research Associate
EBV	Epstein-Barr virus
EDC	Electronic data capture
ETDRS	Early treatment diabetic retinopathy study
EOS	End of study
EOT	End of treatment
CMV	Cytomegalovirus
CRO	Contract research organization
CSR	Clinical study report
CMO&PS	Chief Medical Office and Patient Safety
DILI	Drug-induced liver injury
DT	Dispersible tablet
ECG	Electrocardiogram
eCRF	Electronic case report/record form
ELISA	Enzyme-linked immunosorbent assay
FAS	Full analysis set
FCT	Film-coated tablet
GCP	Good clinical practice
GGT	Gamma-glutamyl transferase
HFE	High iron Fe gene
HH	Hereditary hemochromatosis
HSV	Herpes Simplex Virus
ICF	Informed consent form
ICH	International conference on harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International committee of medical journal editors
IEC	Independent ethics committee
IN	Investigator notification
IOP	Intraocular pressure
IRB	Institutional review board
IRT	Interactive response technology

[redacted]

LFT	Liver function test
LOCS	Lens Opacities Classification System
PI	Principal Investigator
PT	Preferred Term
SAP	Statistical analysis plan
SC	Steering committee
SF	Serum ferritin
SI	International system of units
SUSARs	Suspected unexpected serious adverse reactions
RR	Response rate
REB	Research ethics board
SAE	Serious adverse event
SJS	Stevens-Johnson syndrome
SmPC	Summary of product characterstic
SOC	System organ class
SOP	Standard operating procedure
ULN	Upper limit normal
UPCR	Urine protein/ creatinine ratio

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic samples	A biological specimen, including blood (plasma, serum), saliva, tissue, urine, stool, taken from a study subject or study patient
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained, i.e., prior to starting any procedures described in the protocol.
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug.”
Investigational treatment	Drug properties being tested in the study as well as their associated placebo and active treatment controls (when applicable) This also includes approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy, required or allowed by the protocol, when used within their approved indication/dosage.
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Subject number	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information, and biological samples
Randomization number	A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment
Statistical analysis plan	A regulatory document which provides evidence of preplanned analyses
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued, whichever is later
Study treatment	Any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason
Treatment group	A treatment group defines the dose and regimen
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points
Withdrawal of consent	Withdrawal of study consent: Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data

[redacted]

Protocol summary:

Title	A phase II, multicenter, open-label, randomized two-year study to evaluate the efficacy and safety of deferasirox film-coated tablet versus phlebotomy in patients with Hereditary Hemochromatosis (HH)
Brief title	Study to evaluate the efficacy and safety of deferasirox film-coated tablet versus phlebotomy in patients with HH
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	Iron overload due to HH typically manifests between the third and sixth decades of life and is more common in males. If untreated, iron accumulates in the organs and causes tissue injury and dysfunction. Although phlebotomy is generally tolerated well and is very effective, it may not always be feasible due to inconvenient clinic visits and discomfort associated with the procedure; This is particularly disadvantageous for patients with serum ferritin (SF) > 1000 µg/L who require more phlebotomy. In addition, a small percentage of patients may be ineligible for phlebotomy due to reduced venous access, congestive heart failure, or anemia. Oral iron chelation therapy will provide another option for patients either unwilling or unable to undergo a regular phlebotomy regimen. The purpose of this study is to evaluate the efficacy and safety of deferasirox FCT versus phlebotomy for the management of iron overload in adults with HH at risk of iron-related morbidity. This evaluation will provide information on the two treatment options in terms of the rate of response of proportion of patients reaching the study target SF ≤ 100 µg/L and their associated safety profiles. In addition to exploring the safety and efficacy of deferasirox FCT in hereditary hemochromatosis (HH), this study is being conducted to fulfill an FDA post-marketing requirement [PMC 750-10 (Exjade) /PMR 2888-8 (Jadenu)] to provide additional randomized data to confirm the ocular safety profile of deferasirox through detailed ocular assessments in patients treated with deferasirox FCT for 2 years.
Primary Objective(s) and Key Secondary Objective	Primary Objective: Assess the response rate in the deferasirox FCT and phlebotomy treatment arms where response is defined by achieving target SF ≤ 100 µg/L on or before 24 months. Key Secondary Objective: Characterize the ocular safety of deferasirox FCT and phlebotomy over 24 months.
Secondary Objectives	• Evaluate the safety and tolerability of deferasirox FCT and phlebotomy over 24 months. • Assess the change from baseline in visual acuity, intra-ocular pressure, retina or/and optic nerve abnormalities, and lens abnormalities at months 6, 12, 18, and 24 of deferasirox FCT and phlebotomy. • Assess the safety and tolerability of deferasirox FCT in patients who

	interrupt and re-initiate treatment due to SF ≤ 100 µg/L and ≥ 300 µg/L. • Assess the first time to response (defined as SF ≤ 100 µg/L) between the deferasirox and phlebotomy treatment groups.
Study design	This is a Phase II, multicenter, open-label, randomized two-year study in 150 adults confirmed by homozygous C282Y genotype with iron overload. Eligible patients will be identified during a 4-week screening period, then randomized in a 2:1 ratio (100 patients to deferasirox FCT and 50 patients to phlebotomy), and treated for 24 months (104 weeks). After end of treatment (EOT), there is a standard 30-day safety follow-up. If a patient discontinues from treatment in either arm and has completed at least 6 months of assessments, they will be encouraged to continue in a Post-treatment Ocular Follow-up phase and undergo ocular exams every 6 months as scheduled to receive a total of at least 5 ophthalmological examinations. End of study (EOS) occurs after the last patient has completed last visit which includes a 30-day safety follow-up. This last patient may have either completed 24 months (104 weeks) of treatment, or prematurely discontinued and completed ocular assessments. After completing the study or discontinuing from study treatment, patients will receive standard of care.
Population	Adult hereditary hemochromatosis patients with iron overload
Inclusion criteria	• Written informed consent must be obtained prior to any screening procedures. • Male or female ≥ 18-years-old • Documented genotype testing confirming homozygous for the C282Y mutation (C282Y/C282Y) • Transferrin saturation ≥ 45% (at either screening visit) • SF ≥ 500 µg/L (at either screening visit)
Exclusion criteria	1. Medical conditions that preclude inclusion: • Iron overload not due to HH • Condition which might significantly alter the absorption, distribution, metabolism or excretion of oral deferasirox • Systemic disease which prevents taking study treatment or any contraindication to phlebotomy • Inflammatory condition or immunological disease which may interfere with the SF interpretation, such as an active infection, collagen vascular disorders, irritable bowel syndrome, lupus, or immune thrombocytopenia • Significantly impaired gastrointestinal function or disease that may significantly alter the absorption of oral deferasirox, e.g. ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection. • Psychiatric or addictive disorder which prevent giving informed consent or undergoing any of the treatment options or unwilling or unable to comply with the protocol • Uncontrolled or significant cardiac disease or symptomatic cardiac

[redacted]

	arrhythmias, e.g., sustained ventricular tachycardia and clinically significant second or third degree AV block without a pacemaker. • Illicit drug use and/or alcohol use, defined as an average alcohol consumption greater than one standard drink a day for women or two standard drinks a day for men within the 12 months prior to enrolment. A standard drink is generally considered to be 12 ounces (or 355 ml) of beer, 5 ounces (or 148 ml) of wine, or 1.5 ounces (or 44 ml) of 80-proof distilled spirits • Cirrhosis, including Child-Pugh class A, B, and C, diagnosed by liver biopsy, elastography, radiologic exams, or clinical criteria. • Active hepatitis B or C (hepatitis B carrier will be allowed) • History of HIV seropositivity (ELISA or Western blot) • Malignancy of any organ system, treated or untreated, within the past 5 years whether or not there is evidence of local recurrence or metastases, except localized basal cell carcinoma of the skin. Hepatocellular carcinoma at any time is excluded. 2. Prior iron chelation therapy, prohibited concomitant medications with deferasirox. 3. Abnormal laboratory values: • Significant anemia that contraindicates phlebotomy (males with hemoglobin <130g/L, females with hemoglobin <120g/L in both screening visit samples • Platelets ≤ 50 x 10^9/L in both screening visit samples • Urine protein/urine creatinine ratio > 1.0 mg/mg in both non-first void urine screening visit samples • Creatinine clearance ≤ 40 ml/min in both screening visit samples • Serum creatinine > 1.5 x ULN in both screening visit samples • ALT ≥ 5 x ULN in both screening visit samples • Total bilirubin > 1.5 x ULN in both screening visit samples 4. Participation in an investigational study: • Observational registry study is allowable • Within 30 days prior to enrollment or within 5-half-lives of an investigational product, whichever is longer 5. Pregnancy and contraception: • Pregnant or nursing (lactating) women • Women of child-bearing potential unless using appropriate methods of contraception • Post-menopausal and not of childbearing potential if she has had 12 months of natural (spontaneous) amenorrhea with an expected clinical profile.
Investigational and reference therapy	Investigational drug: ICL670 (deferasirox): • Drug formulation: film-coated tablet (FCT) • Control arm: phlebotomy
Efficacy assessments	• Primary efficacy endpoint will be assessed by response rate where response is defined by achieving target SF ≤ 100 µg/L on or before 24

[redacted]

	months. SF is measured at screening, baseline, week 2, and thereafter every 4 weeks until week 104 (24 months). • Secondary efficacy endpoint will be assessed by the time to first response of achieving SF ≤ 100 µg/L.

Safety assessments	• Key secondary safety endpoint will be ocular safety as measured by incidence of the treatment emergent adverse events.
	• Ocular assessments, including visual acuity (ETDRS), slit lamp exam (with LOCS III), tonometry, and fundus examination and photography will be assessed every 6 months.
	• Laboratory parameters at screening, baseline, week 2, 4, then every 4 weeks until end of treatment (week 104):
	  • Hematology, chemistry (including renal and hepatic parameters) and urinalysis
	  • Coagulation, urine protein/creatinine ratio, transferrin saturation, and SF
	• Vital signs at screening, baseline, week 2, 4, then every 4 weeks until end of treatment (week 104)
	• ECG and audiometry test at screening, week 24, 52, 76 and 104

Other assessments	Not applicable

Data analysis	**Primary objective:**
	Assess the response rate (RR) of the deferasirox FCT and phlebotomy treatment arms where a response is defined by achieving target SF ≤ 100 µg/L on or before month 24. The estimate of the RR and the corresponding 95% CI will be provided for each arm. No formal hypothesis testing is planned in this study. Any patient who discontinues prematurely before meeting the criteria will be considered a non-responder.
	Key secondary objective:
	Evaluate ocular safety of deferasirox FCT and phlebotomy over 24 months by the incidence of treatment-emergent ocular AEs (new or worsening from baseline). It will be summarized categorically by system organ class and/or preferred term, overall and by severity, type of AE, and relation to study treatment.
	No hypothesis will be tested for this key secondary objective.
	Secondary efficacy objective:
	• Time to first response
	Response is defined when serum ferritin is ≤ 100 µg/L. For the analysis of time to first serum ferritin ≤ 100 µg/L, the following censoring rule will be applied:
	• For patients who did not achieve a response, they will be censored at the earliest of the following dates:
	  • Death or discontinuation date due to any reason, or
	  • Last SF assessment.
	Kaplan-Meier estimates will be presented. Median time to response (as well as 25th and 75th percentiles) will be presented along with 95% confidence intervals for the two arms.

[redacted]

	Secondary safety objectives: • Safety and tolerability of deferasirox FCT and phlebotomy over 24 months • Change from baseline in visual acuity (ETDRS), intra-ocular pressure, retina or/and optic nerve abnormalities, and lens abnormalities at months 6, 12, 18, and 24 • Safety and tolerability of deferasirox FCT in patients who interrupt due to SF ≤ 100 µg/L and re-initiate therapy when SF > 300 µg/L During the 24 months of the study, safety and tolerability between deferasirox FCT and phlebotomy will be assessed by the incidence of new or worsening AEs, abnormal and clinical significant laboratory values, and other abnormal safety findings. The change from baseline in visual acuity (ETDRS), intra-ocular pressure, retina or/and optic nerve abnormalities, and lens abnormalities will be summarized descriptively by treatment and by visit. Incidence of AEs in patients who interrupted deferasirox FCT due to SF ≤ 100 µg/L and re–initiated therapy in when SF > 300 µg/L will be reported.
Key words	Hereditary Hemochromatosis (HH), deferasirox, chelation, iron overload, phlebotomy, ocular safety

[redacted]

Global Amendment 01 (30-Aug-2018)

Amendment rationale

The purpose of this amendment is to modify the inclusion and exclusion criteria, to correct inconsistencies, typos, add some clarifications and to update withdrawal of consent language. Additionally, the local French amendment text is formally integrated in this global amendment. However, the French specific requirements remain valid for France only.

At the time of this amendment, 7 patients have been randomized and 2 patients failed screening, both of them had the baseline serum ferritin values between 500 - 700 µg/L. In addition, out of 14 patients in prescreen who failed due to inclusion criteria, 10 patients had baseline serum ferritin values between 500 ~700 µg/L.

The inclusion criteria for baseline serum ferritin will be changed from ≥ 700µg/L to ≥500µg/L, which could allow more patients with iron overload to become eligible for the study enrollment, while ensuring collection of long term patient safety data.

The rationale for baseline serum ferritin change is as following:

A Phase I/II dose escalation study in Hereditary Hemochromatosis (CICL670A2202), deferasirox dispersible tablet (DT) 10 to 15 mg/kg/day had an acceptable safety profile (Phatak 2010). In a one-year Phase 2 study in HH patients (CICL670EBR14T), deferasirox DT 10±5 mg/kg/day was well tolerated and effective in reducing iron burden (Cancado 2015). The inclusion criteria for these studies was serum ferritin between ≥ 300µg/L and ≤ 1500µg/L and serum ferritin ≥ 500ug/L respectively.

According to the guideline (EASL 2010, Bacon 2011), all patients with homozygous hereditary hemochromatosis and evidence of iron overload (i.e., transferrin saturation greater than or equal 45 percent and serum ferritin level greater than 300 ug /L in men and greater than 200 ug/L in women) should be treated, regardless of symptoms..

The total duration of treatment for each patient in this study is up to 24 months (104 weeks) in order to collect safety information with prolonged treatment. When SF reaches the study target ≤ 100 µg/L, deferasirox FCT must be interrupted. The patients with low baseline serum ferritin (300~500µg/L) are more likely to reach the 100 µg/L threshold sooner than 24 months and will not substantially contribute to long term safety. Therefore, only patients with baseline serum ferritin ≥ 500µg/L would be enrolled in the study.

Changes to the protocol

Cover page

- Amended to, authoring team member deleted according to new Novartis standard

List of abbreviation

- Amended to, updatet

[redacted]

Glossary of terms

- Amended to, added wording according to new Novartis standard about *personal data* and *withdrawal of consent*

Protocol summary

- Amended to, reflects the changes in different sections which are described in detail below

Section 5.2, Inclusion criteria

- (was) Serum Ferritin ≥ 700 µg/L

  Amended to:

  Serum Ferritin ≥ 500 µg/L (at either screening visit): See Rationale above

Section 5.3 Exclusion criteria

- (was) Malignancy of any organ system, treated or untreated, within the past 5 years whether or not there is evidence of local recurrence or metastases, except localized basal cell carcinoma of the skin or any history of hepatocellular carcinoma

  Amended to:

  Malignancy of any organ system, treated or untreated, within the past 5 years whether or not there is evidence of local recurrence or metastases, except localized basal cell carcinoma of the skin. Hepatocellular carcinoma at any time is excluded.

  Rationale: clarification about hepatocellular carcinoma and study participation
- (was) Significant anemia that contraindicates phlebotomy (males with hemoglobin < 13 mg/dL, females with hemoglobin < 12 mg/dL) in both screening visit samples

  Amended to:

  Significant anemia that contraindicates phlebotomy (males with hemoglobin < 130g/L, females with hemoglobin < 120g/L) in both screening visit samples ,

  Rationale: correction of values for hemoglobin and changing to SI units (International system of units)
- (was) Treatment with a systemic investigational drug within 4 weeks or topical investigational drug within 7 days of starting the study

  Amended to, deleted:

  Rationale: deleted bullet point was contradictive to preceding bullet point, additionally even topical drugs can have long elimination half lives
- (was) Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless using basic methods of contraception,

  Amended to, added:

  Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless using appropriate methods of contraception. Deferasirox may reduce the efficacy of hormonal contraception, thus it is recommended to use alternative methods of contraception.

[redacted]

See Section 8.4 for pregnancy reporting and follow-up requirements,.
Rationale: clarification

Table 6.2 Criteria for dose reduction / interruption and re-initiation of deferasirox FCT

- (was) Determine lactose intolerance
  Amended to, deleted,
  Rationale: the used deferasirox formulation no longer contains lactose
- Amended to, added:
  Drug reaction with eosinophilia and systemic symptoms (DRESS)
  Rationale: according to update in actual CDS (core data sheet) and SmPC (Summary of Product Characteristics).

Table 7.1 Visit evaluation schedule

- Amended to, added
  hematology and coagulation assessment at screening visit -2 weeks
  Rationale: alignment between text in protocol and table

Section 7.1.6, Withdrawal of Consent,

- Amended to, text revised:
  Rationale: reflecting the new Novartis global consent withdrawal language

Section 7.2.2.6.6 Coagulation

- (was) will be measured at the first screening visit
  Amended to, added coagulation measurement for both screening visits
  Rationale: alignment with assessments for hematology

Section 10.4.2 Statistical hypothesis, model, and method of analysis

- (was) $CI_i = \left[\left(1 + \frac{n-x+1}{x*F(1-\frac{\alpha}{2};2x,2(n-x+1))}\right)^{-1}, \left(1 + \frac{n-x}{(x+1)*F(1-\frac{\alpha}{2};2(x+1),2(n-x))}\right)^{-1}\right]$
  Where x is the number of responders, n is the number of patients, α = the level of significance. The primary analysis will be carried out in the FAS.
  Amended to, deleted,
  Rationale; used Clopper-Pearson method is a well established method and needs no further explanation

Section Table 10-1 Criteria for clinically notable and extended notable laboratory ranges

- Was: Hemoglobin < 10 gm/dL
  Amended to, Hemoglobin < 100 g/L
  Rationale: convert to L as reference volume

[redacted]

Previous amendments

French local amendment

Amendment rationale [redacted] to implement weekly monitoring of creatinine and creatinine clearance during "the first month after treatment initiation and when the dose is increased"

This affects sections 7.1, 7.1.4, and 7.2.2.6.3: added assessments of creatinine and creatinine clearance at Week 1 and Week 3 after start of treatment. Weekly checks of creatinine and creatinine clearance during the first month after a dose increase is required for patients enrolled in sites from France only and should be regarded as unscheduled visits.

IRB/IEC Approval

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Hereditary Hemochromatosis (HH) is an inherited disorder characterized by life-long increased absorption of iron from the gastrointestinal tract. Over time, the accumulated excess iron is deposited in multiple organs and potentially leads to end-organ damage, especially in the liver, heart, pancreas, and endocrine organs.

Type 1 HH is one of the most common genetic disorders among Caucasians and has a prevalence of 1:200-1:400. The most common (80-90%) mutation of this autosomal recessive disorder is a homozygous mutation of the High Iron Fe (HFE) gene which results in a change of cysteine at position 282 to tyrosine (C282Y mutation). The rest are either a change of histidine at position 63 to aspartate (H63D mutation) or compound heterozygotes with a single mutation in both the C282Y and H63D genes. Due to variable penetrance, many with 2 copies of the C282Y mutation show no clinical significance. Only 25% of homozygous individuals develop a clinical problem, indicating that there are other genetic or environmental influences (Hanson 2001).

Therapeutic phlebotomy is the standard of care treatment for iron overload in HH (Bacon 2011). Regular phlebotomy, such as weekly or biweekly, is done until iron stores normalize, followed by lifelong periodic phlebotomy therapy (often at quarterly intervals) based on iron re-accumulation.

1.2 Introduction to investigational treatment(s) and other study treatment(s)

1.2.1 Overview of deferasirox

Deferasirox (company research code: ICL670; trade name: Exjade®, Jadenu™) is an orally active iron chelator that binds iron with high affinity and promotes excretion of excess iron, primarily in the feces.

1.2.1.1 Non-clinical experience

In vitro and *in vivo* studies demonstrated the high potency of deferasirox in mobilizing tissue iron and promoting iron excretion, and deferasirox was eliminated from the body by hepatic glucuronidation and biliary excretion. Preclinical studies demonstrated that deferasirox did not affect fertility and is neither teratogenic nor carcinogenic. Based on non-clinical studies, use in humans includes restricted in pregnancy and breast feeding and requires renal function monitoring and periodic ocular testing. Detailed preclinical information on deferasirox is in the current Investigators' Brochure.

[redacted]

1.2.1.2 Clinical experience

Deferasirox was approved for the treatment of chronic iron overload due to frequent blood transfusions (aged 2 years and older in more than 100 countries) and non-transfusion-dependent thalassemia (aged 10 years and older in more than 70 countries). It is available as dispersible tablets (DT, trade name: Exjade®) and film-coated tablets [(FCT), tradename: Jadenu™ in the US (United States), Canada, and some other countries; and as Exjade in EU (European Union))].

Since approval on 2 November 2005, the dose-dependent efficacy of chelation therapy has been demonstrated for deferasirox DT in several large clinical trials with over 8121 patients exposed for up to 5 years and [redacted] The safety profile of deferasirox has been well characterized with the dispersible tablet formulation.

Because of the chronic nature of chelation therapy and the importance of patient compliance, an improved deferasirox formulation for oral administration was developed. FCT contains the same active substance, but was strength-adjusted to achieve comparable exposure to the dispersible tablet. It is available in three dose strengths (90 mg, 180 mg and 360 mg) and is dosed based on weight. It can be taken with or without a light meal (See Appendix 14.2 for examples). The currently available clinical trial data with the FCT formulation suggests a safety and efficacy profile that is consistent with the known profile of the DT deferasirox formulation.

2 Rationale

2.1 Study rationale and purpose

Iron overload due to HH typically manifests between the third and sixth decades of life and is more common in males. If untreated, iron accumulates in the organs and causes tissue injury and dysfunction. Therefore, these patients might benefit from an iron chelator. If untreated in the liver, iron deposition will cause fibrosis, which may ultimately progress to cirrhosis and increased susceptibility to hepatocellular carcinoma. (Bacon 2011, Beaton and Adams 2007). Effects on the liver are exacerbated in alcoholics and in patients with chronic hepatitis B or C. Other manifestations include arthropathy, endocrinopathies (hypogonadism, sexual dysfunction, pancreatitis, or diabetes), and rarely, cardiomyopathy/cardiac failure with mortality (Niederau 1996, Morrison 2003).

Although phlebotomy is generally tolerated well and is very effective, it may not always be feasible due to inconvenient clinic visits and discomfort associated with the procedure; therefore, compliance may wane with time. A small percentage of patients may be ineligible for phlebotomy due to reduced venous access, congestive heart failure, or anemia. Oral iron chelation therapy will provide another option for patients either unwilling or unable to undergo a regular phlebotomy regimen.

[redacted]

The aim of this study is to evaluate the efficacy and safety of deferasirox FCT versus phlebotomy for the management of iron overload in adults with HH at risk of iron-related morbidity. This evaluation will provide information on the two treatment options in terms of the response rate of proportion of patients reaching the study target SF ≤ 100 µg/L and their associated safety profiles.

Ocular disturbances have been reported with deferasirox. Although no additional ocular risk have emerged over 10 years of Exjade on the market and from clinical trials, the FDA requires further confirmation on ocular safety with a controlled study in chelation-naive patients. Therefore, in addition to exploring the safety and efficacy of deferasirox FCT in HH, this study is being conducted to fulfill an FDA post-marketing requirement [PMC 750-10 (Exjade) /PMR 2888-8 (Jadenu)] to provide additional randomized data to confirm the ocular safety profile of deferasirox through detailed ophthalmologic assessments in patients treated with deferasirox FCT for 2 years.

2.2 Rationale for the study design

This will be an open-label design since phlebotomy cannot be blinded. The safety and response rate of deferasirox versus the standard of care phlebotomy in reducing iron in adult patients with HH will be evaluated.

Patients will be randomized 2:1 to deferasirox FCT or phlebotomy.

2.3 Rationale for dose and regimen selection

A Phase I/II dose escalation study in HH (CICL670A2202), deferasirox DT 10 to 15 mg/kg/day had an acceptable safety profile (Phatak 2010). In a one-year Phase 2 study in HH patients (CICL670EBR14T), deferasirox DT 10±5 mg/kg/day was well tolerated and effective in reducing iron burden (Cancado 2015). Based on these 2 studies, the starting dose in this trial will be deferasirox FCT 7 mg/kg/day (equivalent to deferasirox DT 10 mg/kg/day). A dose adjustment between the two formulations is required because bioavailability was increased in FCT, and an equivalent deferasirox AUC was achieved at a lower dose, e.g., 1080 mg FCT vs. 1500 mg DT (CICL670F2102 study).

2.4 Rationale for choice of combination drugs

Not applicable

2.5 Rationale for choice of comparators drugs

The control arm is phlebotomy which is the standard of care for removing excess iron in non-anemic patients with HH. Most have unimpaired erythropoiesis so as blood is extracted, bone marrow is stimulated to make new red cells. Iron stores are reduced when iron is transported to make hemoglobin.

[redacted]

Depending on the hematocrit, each unit of blood (typically 500 mL) contains 200-250 mg iron and removal by phlebotomy decreases the ferritin level by approximately 30 µg/L (Bacon 1997). When SF is above normal, consensus opinion is that there is a benefit in early iron removal on a weekly or biweekly basis until iron stores are in the normal range (SF = 50-100 µg/L), then thereafter, every two to four months to prevent re-accumulation of iron absorbed from a regular diet (EASL 2010, Tavill 2001). Although there are no evidence-based studies, SF is the accepted standard for initiating and monitoring response to achieve a SF ≤ 100 µg/L, which is used as the primary endpoint of this study. Phlebotomy will be conducted at a frequency determined by the investigator's clinical practice.

2.6 Risks and benefits

Appropriate eligibility criteria and specific dose modification and stopping rules are included in this protocol. Risk is minimized by compliance with the eligibility criteria and study procedures, close clinical monitoring, and protocol-defined dose modification rules. The available clinical trial data with FCT suggests a safety and efficacy profile consistent with the known profile of the DT formulation. As with any treatment or procedure, deferasirox FCT or phlebotomy may cause unforeseen risks, which could be serious.

The efficacy and safety of deferasirox have been evaluated in a large prospective clinical trials program that has generated long-term data in iron overload patients with transfusional iron overload (thalassemia major, sickle cell disease, and myelodysplasia syndrome) (Cappellini 2006, Vichinsky 2007) and with non-transfusion dependent thalassemia. The accumulated data provides an acceptable safety and tolerability profile across all age groups. The majority of adverse events (AEs) are mild to moderate and manageable with dose adjustments or interruptions. The available clinical trial data with FCT suggests a safety and efficacy profile consistent with the known profile of the DT formulation.

No new safety concerns regarding ocular toxicity have emerged since the approval of deferasirox. The most common visual acuity events were blurred vision and visual impairment. The most common lens opacity was cataract, and retinal changes were due to degeneration, retinopathy, maculopathy or optic neuritis. As stated in the current Exjade and Jadenu USPIs, ocular disturbances (lens opacities, cataracts, elevations in intraocular pressure, and retinal disorders) were reported at a frequency of <1% with deferasirox therapy in the clinical studies. Optic neuritis occurs in 0.01% to 0.1% of patients. Ocular safety is a key secondary endpoint in this study, and ocular assessments are required to gather safety information.

In the dose escalation study in HH (ICL670A2202), elevations in liver transaminases and in serum creatinine were observed in a few patients, mainly those with a baseline SF < 1000 µg/L who received an initial deferasirox DT dose of 15 mg/kg/day. There are also post-marketing reports of elevated liver transaminases and serum creatinine in those who continued to receive deferasirox when SF was < 100 µg/L. In this study, phlebotomy and drug will be held for a SF ≤ 100 µg/L, the lowest level believed to be safe to chelate with deferasirox.

[redacted]

The AE profile in the above phase I/II HH study was consistent with the deferasirox registration studies in transfusional iron overload and post-marketing surveillance reports.

The control arm phlebotomy is the standard of care in HH and does not pose an unexpected risk in this population. An oral iron chelation therapy may provide an option for patients either unwilling or unable to undergo a regular phlebotomy regimen.

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below.

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4
Assess the response rate in the deferasirox FCT and phlebotomy treatment arms where response is defined by achieving target SF ≤ 100 µg/L on or before 24 months.	Proportion of patients achieving target SF ≤ 100 µg/L for the first time.	
Key Secondary		Refer to Section 10.5.1
Characterize the ocular safety of deferasirox FCT and phlebotomy over 24 months.	Incidence of ocular AEs overall and by severity, type of AE, and relation to study treatment.	
Secondary		Refer to Section 10.5.2 and Section 10.5.3
Evaluate the safety and tolerability of deferasirox FCT and phlebotomy over 24 months.	Incidence of AEs, AEs leading to discontinuation from study, laboratory abnormalities, and deaths.	
Assess the change from baseline in visual acuity, intra-ocular pressure, retina or/and optic nerve abnormalities, and lens abnormalities at months 6, 12, 18, and 24 of deferasirox FCT and phlebotomy.	Change from baseline at months 6, 12, 18 and 24 in visual acuity, tonometry, slit lamp, and fundus exams.	
Assess the safety and tolerability of deferasirox FCT in patients who interrupt and re-initiate treatment due to SF levels ≤ 100 µg/L and ≥ 300 µg/L.	Incidence of AEs in patients who interrupt due to reaching target SF ≤ 100 µg/L, then re-initiate therapy at ≥ 300 µg/L.	
Assess the first time to response (defined as SF ≤ 100 µg/L) between the deferasirox and phlebotomy treatment groups.	Time to reach target SF ≤ 100 µg/L in the deferasirox and phlebotomy arms for the first time.	

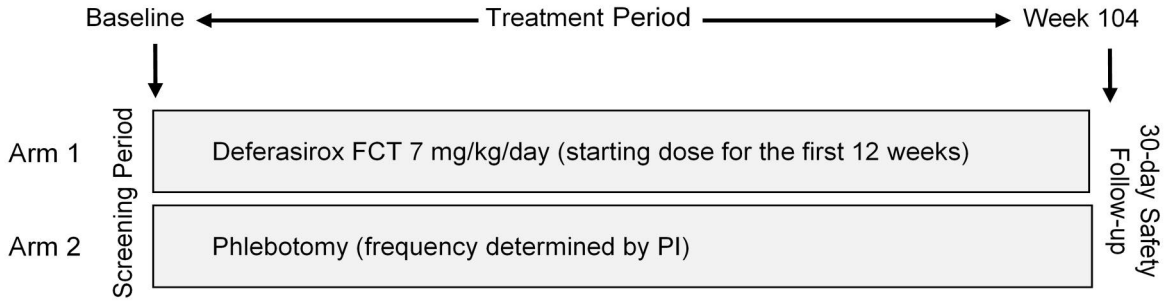
[redacted]

4 Study design

4.1 Description of study design

This is a Phase II, multicenter, open-label, randomized two-year study in 150 adults confirmed by HH genotype with iron overload. Eligible patients will be identified during a 4-week screening period, then randomized in a 2:1 ratio (100 patients to deferasirox FCT and 50 patients to phlebotomy), and treated for 24 months (104 weeks). After end of treatment (EOT), there is a standard 30-day safety follow-up. Please refer to Section 7 for screening and assessment details.

Figure 4-1 Study schema



An initial dose of deferasirox FCT 7 mg/kg/day will be used for 3 months (12 weeks), then adjusted according to the ferritin level. Dose adjustments based on safety are allowed at any time.

Phlebotomy will be conducted at a frequency determined by the physician.

Both phlebotomy and deferasirox FCT must be interrupted when the study-defined target SF ≤ 100 µg/L is achieved. Deferasirox FCT may be reinitiated when SF ≥ 300 µg/L, according to deferasirox label; phlebotomy may be reinitiated when SF > 100 µg/L, based on standard of care practice. Following end of treatment, patients will enter a 30-day safety follow-up period. Concomitant medications and AEs will be collected during this period.

4.1.1 Post-treatment Ocular Follow-up

If a patient discontinues from treatment in either arm and has completed at least 6 months of assessments, they will be encouraged to continue in a Post-treatment Ocular Follow-up phase to undergo scheduled ocular exams every 6 months to receive at least 5 ophthalmological examinations. If a patient discontinues between the scheduled 6-month exams, an ophthalmologic exam is part of the EOT and they will continue their regular schedule of ophthalmological exams every 6 months for a total of 6 ocular examinations. Please refer to

[redacted]

Section 7.2.2.5 for details. One month prior to each ophthalmological visit, a site coordinator will call to confirm the upcoming visit.

4.2 Timing of interim analyses and design adaptations

Not applicable

4.3 Definition of end of study

The end of study (EOS) will be when the latest of the following will have occurred:

A) All patients completed 24 months of treatment, and patients completed their EOT visits and 30-day safety follow-up; OR
B) Patients who discontinued from treatment prior to 6 months, or after 6 months but did not agree to participate in Post-treatment ocular follow-up: patients completed their EOT visits and 30-day safety follow-up; OR
C) Patients who discontinued from treatment after 6 months and agreed to Post-treatment ocular follow-up: patients completed their EOT visits, 30-day safety follow-up, and Post-treatment ocular follow-up up to Month 24.

After completing the study or discontinuing from study treatment, patients will receive standard of care. The primary analysis will be based on the final locked data and will be summarized in the clinical study report (CSR).

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. If this occurs, the patient should be seen as soon as possible and the same assessments should be performed as described in Section 7.1.5 for a discontinued or withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

5 Population

5.1 Patient population

One hundred and fifty adult HH patients with homozygous C282Y genotype and iron overload (based on elevated transferrin saturation and SF) may enroll if they meet all inclusion and none of the exclusion criteria.

5.2 Inclusion criteria

Written informed consent must be obtained prior to any screening procedures.

[redacted]

Patients eligible for inclusion must meet **all** following criteria prior to receiving study treatment:

1. Male or female ≥ 18-years-old
2. Documented genotype testing confirming homozygous for the C282Y mutation (C282Y/C282Y)
3. Transferrin saturation ≥ 45% (at either screening visit)
4. Serum ferritin (SF) ≥ 500 µg/L (at either screening visit)

5.3 Exclusion criteria

1. Medical conditions that preclude inclusion:
    - Iron overload not due to HH
    - Condition which might significantly alter the absorption, distribution, metabolism or excretion of oral deferasirox
    - Systemic disease which prevents taking study treatment or any contraindication to phlebotomy
    - Inflammatory condition or immunological disease which may interfere with the SF interpretation, such as an active infection, collagen vascular disorders, irritable bowel syndrome, lupus, or immune thrombocytopenia
    - Significantly impaired gastrointestinal function or disease that may significantly alter the absorption of oral deferasirox, e.g. ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection.
    - Psychiatric or addictive disorder which prevent giving informed consent or undergoing any of the treatment options or unwilling or unable to comply with the protocol
    - Uncontrolled or significant cardiac disease or symptomatic cardiac arrhythmias, e.g., sustained ventricular tachycardia and clinically significant second or third degree AV block without a pacemaker.
- Illicit drug use and/or alcohol use, defined as an average alcohol consumption greater than one standard drink a day for women or two standard drinks a day for men within the 12 months prior to enrolment. A standard drink is generally considered to be 12 ounces (or 355 ml) of beer, 5 ounces (or 148 ml) of wine, or 1.5 ounces (or 44 ml) of 80-proof distilled spirits
    - Cirrhosis, including Child-Pugh class A, B, and C, diagnosed by liver biopsy, elastography, radiologic exams, or clinical criteria
    - Active hepatitis B or C (hepatitis B carrier will be allowed)
    - History of HIV seropositivity (ELISA or Western blot)
    - Organ transplant recipient

[redacted]

- Malignancy of any organ system, treated or untreated, within the past 5 years whether or not there is evidence of local recurrence or metastases, except localized basal cell carcinoma of the skin, Hepatocellular carcinoma at any time is excluded.

2. Concomitant therapy that precludes enrollment:
   - Prior iron chelation therapy
   - Prohibited concomitant medications with deferasirox (see Section 6.4.3 for details)
3. Abnormal laboratory values:
   - Significant anemia that contraindicates phlebotomy (males with hemoglobin < 130g/L, females with hemoglobin < 120g/L) in both screening visit samples
   - Platelets ≤ 50 x 10^9/L in both screening visit samples
   - Urine protein/urine creatinine ratio > 1.0 mg/mg in both non-first void urine screening visit samples
   - Creatinine clearance ≤ 40 ml/min, or use the locally approved contraindication limit in prescribing information if it is stricter, in both screening visit samples
   - Serum creatinine > 1.5 x ULN in both screening visit samples
   - ALT ≥ 5 x ULN in both screening visit samples
   - Total bilirubin > 1.5 x ULN in both screening visit samples
4. Participation in an investigational study:
   - Observational registry study is allowable
   - Within 30 days prior to enrollment or within 5-half-lives of an investigational product, whichever is longer
5. Pregnancy and contraception:
   - Pregnant or nursing (lactating) women

   Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless using appropriate methods of contraception Deferasirox may reduce the efficacy of hormonal contraception, thus it is recommended to use alternative methods of contraception such as
   - Total abstinence

     Periodic abstinence (calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are unacceptable methods.
   - Female sterilization (bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. If oophorectomy alone, hormone levels must confirm menopause.
   - Male sterilization (at least 6 months prior to screening). The vasectomized male must be the sole partner.
   - Barrier methods of contraception: condom or occlusive cap

     For UK: spermicidal foam/gel/film/cream/vaginal suppository

[redacted]

- Placement of an intrauterine device or intrauterine system
- Women considered as post-menopausal and not of childbearing potential are allowed to be enrolled in the trial if they have had 12 months of natural (spontaneous) amenorrhea with an expected clinical profile, e.g., age appropriate and history of vasomotor symptoms.

See Section 8.4 for pregnancy reporting and follow-up requirements.

6 Treatment

6.1 Study treatment

The sponsor will provide the open-label study medication oral deferasirox FCT tablets: 90 mg, 180 mg and 360 mg. The control arm will undergo phlebotomy at intervals determined by the treating physician's clinical assessment for optimal iron control.

6.1.1 Dosing regimen

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
Deferasirox FCT	Tablet for oral use	7 mg/kg (Initial dose)	Daily
Phlebotomy	Venipuncture	NA	determined by PI

After a 4-week screening period, eligible patients will be randomized 2:1 to receive deferasirox FCT or phlebotomy.

Patients randomized to deferasirox FCT will receive 7 mg/kg once daily. The daily dose is calculated based on the patient's weight, then rounded up or down to the nearest whole tablet according to the available strengths of deferasirox FCT tablets (90 mg, 180 mg, and 360 mg; see Appendix 14.1). After 3 months (12 weeks), adjust dose as needed based on SF levels listed below with the maximum dose adjustment of 3.5 mg/kg/day per month.

- SF < 300 µg/L Decrease to 3.5 mg/kg/day
- SF 300-1000 µg/L Maintain 7 mg/kg/day
- SF > 1000-2000 µg/L Increase to 10.5 mg/kg/day
- SF > 2000 µg/L Increase to 14 mg/kg/day

When SF reaches the study target ≤ 100 µg/L, deferasirox FCT must be interrupted and the patient enters the maintenance phase.

During the maintenance phase, when SF ≥ 300 µg/L, deferasirox FCT 3.5 mg/kg/day may be re-initiated. If deferasirox FCT 3.5 mg/kg/day is not controlling SF and it continues to increase, increase to a maximum 7 mg/kg/day. Treat until the SF reaches ≤ 100 µg/L, then interrupt treatment again.

[redacted]

During regular study visits, the investigator or pharmacist will dispense the appropriate number of deferasirox FCT tablets to each patient. The number of tablets of each strength dispensed will be recorded in the study Drug Dosing Log. Each time deferasirox FCT is dispensed, the investigator must provide detailed instructions to patients, instruct them to take the assigned amount of study drug, and return all unused study medication every 4 weeks. Returned study medication must be counted and recorded. The field monitor must note the drug accountability during site visits and at the completion of the trial.

Medication labels must be in the local language and comply with the legal requirements of the countries where the study is implemented. Labels will have study identifier and storage conditions for the study drug, but no patient information.

Patients should swallow the required number of deferasirox FCT, with or without a light meal, and around the same time each day.

Patients should not make up missed doses. A missed dose is when the full dose is not taken within 8 hours of the usual time of the daily dose. Omit that day's dose, and resume with the next scheduled dose.

Dose adjustments for safety are allowed at any time and must be in increments or decrements of 3.5 or 7 mg/kg/day. For this study, the maximum dose of deferasirox FCT is 14 mg/kg/day.

Patients randomized to phlebotomy will receive treatment at a frequency determined by the treating physician's judgment for optimal iron control. Phlebotomy must be interrupted when a patient achieves the target SF $\leq$ 100 µg/L. Treatment may be re-initiated when SF > 100 µg/L.

Patients randomized to deferasirox FCT are not allowed to receive phlebotomy during the study treatment.

Patients randomized to the deferasirox FCT arm who discontinued from treatment may receive phlebotomy during Post-treatment Ocular Follow-up at a frequency determined by the physician.

6.1.2 Ancillary treatments

Not applicable

6.1.3 Rescue medication

Not applicable

6.1.4 Guidelines for continuation of treatment

Not applicable

[redacted]

6.1.5 Treatment duration

The total duration of treatment for each patient is up to 24 months (104 weeks). The total duration of the study for each patient is approximately 26 months (4-week Screening, 104-week Treatment, and 30-day Safety Follow-up).

6.2 Dose escalation guidelines

Not applicable

6.3 Dose modifications

6.3.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions are either recommended or mandated in order to allow patients to continue the study treatment of deferasirox FCT.

These dose modifications are summarized in Table 6-2. Deviations from the mandatory dose interruptions and/or reductions are not allowed. Permanent treatment discontinuation of deferasirox FCT is mandatory for specific events indicated in Table 6-2 or listed in Section 7.1.5.

These dose changes must be recorded on the Dosage Administration Record eCRF. It is important to keep an accurate dose adjustment records to enable an adequate evaluation of exposure.

Phlebotomy will be conducted at a frequency determined by the treating physician's clinical judgement for optimal iron control. The name of the facility, the date of phlebotomy, hematocrit level prior to phlebotomy and amount of blood withdrawn must be captured in Phlebotomy Record and local lab eCRFs. Phlebotomy must be interrupted when SF $\leq$ 100 µg/L and may be resumed when SF > 100 µg/L.

[redacted]

Table 6-2 Criteria for dose reduction / interruption and re-initiation of deferasirox FCT

Dose modifications for ICL670F2203	
Serum Ferritin (SF)	
After an initial starting dose (7 mg/kg/day) for 3 months (12 weeks), dose may be adjusted based on SF level. Dose increase cannot be more than 3.5 mg/kg/day at each adjustment.	
<300 µg/L	Decrease to 3.5 mg/kg/day
300-1000 µg/L	Maintain 7 mg/kg/day
>1000-2000 µg/L	Increase to 10.5 mg/kg/day
>2000 µg/L	Increase to 14 mg/kg/day (higher doses are not allowed.)
SF ≤ 100 µg/L at any time	Interrupt deferasirox FCT
SF ≥ 300 µg/L after dose interruption	Re-initiate deferasirox FCT 3.5 mg/kg/day. If SF continues to increase, increase to 7 mg/kg/day (maximum dose for maintenance phase).
Body Weight	
Increase/decrease if weight changes >10% compared to baseline weight or weight at last dose adjustment due to a change in weight	Dose of study medication will be adapted using Dosing Table (provided in Appendix 14.1) When weight changes >10% compared to baseline weight or weight at last dose adjustment due to a change in weight, re-calculate dose. Smaller variations in weight (<10%) do not require dose adjustments.
Investigations (Renal)	
Serum creatinine	
Single increase	Maintain dose and repeat assessment at next visit.
Increased creatinine ≥ 33% from baseline (average of 2 samples) resulting in creatinine > ULN x 2 consecutive samples (at least 2 weeks apart)	Decrease by 7 mg/kg/day or interrupt if already at 7 mg/kg/day or lower.
If dose is decreased, but increasing creatinine > ULN	Interrupt treatment.
After interruption, if creatinine returns to within normal limits on 2 consecutive visits.	Resume 50% of the most recent dose prior to interruption. If after another 4 weeks, creatinine remains stable, resume 100% dose (adjust for weight if needed).
Creatinine clearance > 40 and < 60 mL/min	Caution in patients if there are additional risk factors that may impair renal function, such as concomitant medications, dehydration, or severe infection.

[redacted]

Dose modifications for ICL670F2203	
Creatinine clearance < 40 mL/min or increased serum creatinine > 2x age-appropriate ULN	Deferasirox must be discontinued.
Urine protein/creatinine ratio	
Any proteinuria	If new or worsening pre-existing proteinuria (assessed by dipstick), collect a urine sample for assessment by the central/local laboratory. In case of a single increase of the urinary protein/creatinine ratio, repeat the assessment at the next visit.
> 0.5 urine protein/ creatinine ratio (mg/mg) in two consecutive non-first void urine samples (a minimum of 48h apart), if all other causes of proteinuria have been excluded.	Decrease deferasirox by 50%. If UPCR resolves (< 0.5mg/mg) at the next study visit, resume 100% dose.
> 1.0 (mg/mg) in two consecutive non-first void urine samples (a minimum of 48h apart)	Interrupt deferasirox FCT. If the increased UPCR resolves (< 0.5 mg/mg) at the next study visit, resume dose at 50% of the last dose. If UPCR remains within normal limits after 4 weeks at the 50% reduced dose, resume study medication at 100% of the last dose.
Persistent proteinuria	If proteinuria persists, discontinue study treatment if the investigator believes it is in the best interest of the patient. Novartis may be contacted by the investigator to discuss dosing options. Dose adjustment must be based on central/local laboratory results.
Investigations (Hepatic)	
Isolated direct (conjugated) Bilirubin elevation	
> ULN – 1.5 x ULN	Maintain dose
> 1.5 - 3.0 x ULN	Interrupt dosing. Monitor LFTs[a] weekly or more frequently if clinically indicated until resolved to ≤ 1.5 x ULN: If resolved ≤ 14 days, then maintain dose. If resolved > 14 days, then ↓ 1 dose level (3.5 mg/kg/day FCT)
> 3.0 - 10.0 x ULN*	Interrupt dosing. Monitor LFTs[a] weekly or more frequently if clinically indicated until resolved ≤ 1.5 x ULN: If resolved ≤ 14 days, then ↓ 1 dose level (3.5 mg/kg/day FCT) If resolved > 14 days, then discontinue patient from study drug. The patient must be monitored weekly (including LFTs[a]), or more frequently if clinically indicated until total bilirubin resolves to baseline or stabilizes over 4 weeks.

[redacted]

Dose modifications for ICL670F2203	
> 10.0 x ULN*	Discontinue patient from study drug The patient must be monitored weekly (including LFTs[a]) or more frequently if clinically indicated until total bilirubin resolves to baseline or stabilizes over 4 weeks.
Isolated AST or ALT elevation	
> ULN - 3.0 x ULN	Maintain dose
> 3.0 - 5.0 x ULN For patients with baseline ≤ 3.0 x ULN For patients with baseline > 3.0 - 5.0 x ULN	 Maintain dose. Repeat LFTs[a] as soon as possible, preferably within 48-72 hours from awareness of abnormal results. If abnormal lab values are confirmed upon a repeat test, then monitor LFTs[a] weekly or more frequently if clinically indicated until resolves ≤ 3.0 x ULN. Maintain dose
> 5.0 - 10.0 x ULN For patients with baseline ≤ 3.0 x ULN Baseline > 3.0 -5.0 x ULN	 Omit dose. Repeat LFTs[a] as soon as possible, preferably within 48-72 hours from awareness of abnormal results. Monitor LFTs[a] weekly or more frequently if clinically indicated until resolves ≤ 3.0 x ULN. If resolved ≤ 14 days, maintain dose. If resolved > 14 days, ↓ 1 dose level (3.5 mg/kg/day FCT). Maintain dose. Repeat LFTs[a] as soon as possible, preferably within 48-72 hours from awareness of abnormal results. If abnormal lab values are confirmed upon a repeat test, then monitor LFTs[a] weekly, or more frequently if clinically indicated until resolved to ≤ 5.0 x ULN.
> 10.0 - 20.0 x ULN	Omit dose. Repeat LFTs[a] as soon as possible, preferably within 48-72 hours from awareness of abnormal results. Monitor LFTs[a] weekly, or more frequently if clinically indicated until resolved to ≤ baseline, then↓ 1 dose level (3.5 mg/kg/day FCT).
> 20.0 x ULN	Discontinue patient from study drug. Repeat LFTs[a] as soon as possible, preferably within 48-72 hours from awareness of abnormal results. Monitor LFTs[a] weekly or more frequently if clinically indicated until resolved to baseline or stabilization over 4 weeks.
Combined[b] AST or ALT and total bilirubin elevations	
Normal baseline ALT and AST and total bilirubin: AST or ALT > 3.0 x ULN with total bilirubin > 2.0 x ULN without evidence of cholestasis[c] OR	Permanently discontinue deferasirox.

[redacted]

Dose modifications for ICL670F2203	
In patients with elevated baseline AST or ALT or total bilirubin: [AST or ALT > 2x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [total bilirubin > 2x baseline AND > 2.0 x ULN]	Repeat as soon as possible, preferably within 48 hours from awareness of abnormal results. Monitor LFTs[a] weekly or more frequently if clinically indicated until AST, ALT, or bilirubin resolve to baseline or stabilize over 4 weeks. Refer to Section 6.3.3.1 for additional follow-up evaluations as applicable.
Hepatic Impairment	
Moderate hepatic impairment (Child-Pugh Class B)	Interrupt deferasirox and monitor patient. If liver disease prognosis improves, re-start deferasirox 7 mg/kg/day FCT or 50% of previous dose, whichever is less. Increase dose 3.5 mg/kg/day FCT every 2 weeks to a maximum of 50% of previous dose if the investigator determines that the dose increase is in the best interest of the patient.
Severe hepatic impairment (Child-Pugh Class C)	Discontinue deferasirox.
Skin and subcutaneous tissue disorders	
Severe skin reaction	
Severe skin reactions, including Stevens-Johnson syndrome (SJS) and Toxic epidermal necrosis (TEN) Drug reaction with eosinophilia and systemic symptoms (DRESS)	Deferasirox must be immediately discontinued and not reintroduced
Skin rash (other than SJS)	
Mild/moderate severity (minimal symptoms which require no or minimal supportive treatment)	Continue study drug without dose adjustment. If the rash persists >1 week or becomes more severe, interrupt dosing. After the rash resolves, resume study drug at 50% of last dose. If the rash does not recur, increase dose to 100% of dose after 2 weeks.
Severe rash (distressing symptoms requiring interruption of study medication and/or systemic steroids)	Interrupt treatment until resolution of rash. After the rash resolves, resume at 50% dose. If necessary, a brief course of oral steroids may be given concurrently with resumption of study drug. If the rash does not recur, increase in steps of 3.5 mg/kg/day for deferasirox FCT every 2 weeks until last dose is achieved. If the rash recurs, discontinue study treatment.
Other adverse events	
Dose modification criteria for auditory and ocular disturbances	
Auditory (decreased hearing) and ocular (lens opacities) disturbances have been reported with deferasirox.	Auditory and ophthalmic testing (including funduscopy) is required before starting deferasirox. If disturbances are noted, consider reducing the dose or interruption. Repeat testing may be done per investigator's judgement.

[redacted]

Dose modifications for ICL670F2203	
Dose modification criteria for hypersensitivity reactions	
Cases of serious hypersensitivity reactions, such as anaphylaxis and angioedema, have been reported in patients receiving deferasirox. In the majority of cases, onset of the reaction occurred within the first month of treatment.	If reactions are severe, discontinue deferasirox and institute appropriate medical intervention. Due to the risk of anaphylactic shock, do not reintroduce deferasirox in patients who have experienced previous hypersensitivity reactions.
Dose modification criteria for cytopenias	
Unexpected Cytopenias	Post-marketing reports (both spontaneous and from clinical trials) of cytopenias occurred mostly in patients with pre-existing hematological disorders and were frequently associated with bone marrow failure. Their relationship with deferasirox was uncertain. The standard clinical management of such hematological disorders is regular monitoring of complete blood count. Consider interrupting deferasirox for unexplained cytopenia. Consider reintroducing deferasirox once the cause of cytopenia is identified.
Gastrointestinal disturbances	
Diarrhea, constipation, nausea, vomiting and abdominal pain.	At the first sign of diarrhea**, consider an anti-diarrheal medication, such as loperamide. Discontinue any laxative or stool softener and eat small, frequent meals. If appropriate, maintain adequate hydration with approximately 8 glasses of water per day. If the gastrointestinal issues (diarrhea, constipation, nausea, vomiting and abdominal pain) persist, discontinue study drug if the investigator believes that is in the best interest of the patient.

All dose modifications should be based on the worst preceding toxicity.

a. Core LFTs consist of ALT, AST, GGT, total bilirubin (fractionated [direct and indirect] if total bilirubin > 2.0 x ULN), and alkaline phosphatase (fractionated [quantification of isoforms], if alkaline phosphatase > 2.0 x ULN.)

b. "Combined" defined as total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold

If combined elevations of AST or ALT and total bilirubin do not meet the defined thresholds, please follow the instructions for isolated elevation of total bilirubin and isolated elevation of AST/ALT, and take conservative action based on the degree of the elevations (e.g. discontinue treatment at the situation when omit dose is needed for one parameter and discontinue treatment is required for another parameter). After all elevations resolve to the defined thresholds that allow treatment re-initiation, re-start treatment either at the same dose or at one dose lower if criterion is met for dose reduction.

c. "Cholestasis" defined as alkaline phosphatase elevation (> 2.0 x ULN and R < 2) in patients.

* Note: If total bilirubin > 3.0 x ULN is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose and continue treatment at the discretion of the investigator.

** Note: anti-diarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea.

6.3.2 Dose adjustments for QTcF prolongation

Not applicable

6.3.3 Follow-up for toxicities

If treatment is interrupted due to an AE or abnormal laboratory value, patients must be followed at least once a week for 4 weeks and subsequently at approximately 4 week intervals, until resolution or stabilization of the event, whichever comes first. If treatment is permanently discontinued due to an AE or abnormal laboratory value (that meets criteria for an AE or SAE), patients must be followed for at least 30 days following the last dose of treatment. All patients must be followed for an AE and SAE for 30 days following the last dose of treatment.

6.3.3.1 Follow up on potential drug-induced liver injury (DILI) cases

Increases in ALT and AST with an elevated total bilirubin can be seen in advanced stage HH, but is uncommon.

Increases in ALT and AST with an increased total bilirubin may be indicative of a potential DILI and should be considered as a clinically important event.

The threshold for potential DILI may depend on the patient's baseline AST/ALT and total bilirubin value; patients meeting any of the following criteria will require further follow-up as outlined below:

- Baseline normal ALT and AST and total bilirubin: AST or ALT > 3.0 x ULN combined with total bilirubin > 2.0 x ULN
- Elevated baseline AST or ALT or total bilirubin: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN] combined with [total bilirubin > 2 x baseline AND > 2.0 x ULN]
- Normal ALT and AST with increased total bilirubin: rule out Gilbert's syndrome, defined by increased indirect bilirubin.

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as alkaline phosphatase > 2.0 x ULN with R < 2 in patients.

Note: (R is calculated by ALT divided by alkaline phosphatase, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or alkaline phosphatase elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury.

In the absence of cholestasis, patients must immediately discontinue from study treatment and repeat LFTs as soon as possible, preferably within 48 hours from the awareness of abnormal results. Evaluation should include laboratory tests, detailed history, physical assessment and consideration of liver metastasis or new liver lesions, obstructions/compressions, etc.

[redacted]

1. Laboratory tests should include ALT, AST, albumin, creatinine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time/INR and alkaline phosphatase.
2. Collect detailed history, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, pre-existing liver conditions or risk factors.
3. Testing for acute hepatitis A, B, C or E infections and liver imaging (e.g. biliary tract) if warranted.
4. Additional testing for other hepatotropic viral infections (CMV, EBV or HSV), autoimmune hepatitis or consultation with a hepatologist for liver biopsy if clinically indicated.

All cases, confirmed on repeat testing, that meet the laboratory criteria defined above and have no other alternative cause for abnormal LFTs, must be considered "medically significant" and meeting the definition of SAE (Section 8.2.1) for reporting as an SAE using the term "potential drug-induced liver injury". All events should be followed with the outcome clearly documented.

6.4 Concomitant medications

6.4.1 Permitted concomitant therapy

The patient must be reminded to notify the investigational site about any new medications he/she takes after starting study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the Concomitant Medications or the Procedures and Significant Non-Drug Therapies eCRF.

6.4.2 Permitted concomitant therapy requiring caution and/or action

Concomitant administration of deferasirox and vitamin C has not been formally studied. Vitamin C up to 200 mg/day has not been associated with adverse consequences.

Caution must be exercised if taking deferasirox in combination with the following:

- Drugs with a known ulcerogenic potential, such as NSAIDs, corticosteroids, oral bisphosphonates, or anticoagulants which may increase the risk of gastrointestinal irritation and bleeding
- Deferasirox is a weak CYP3A4 inducer and may potentially decrease serum levels of substances metabolized through CYP3A4
- Deferasirox is a moderate inhibitor of CYP2C8 and may increase serum levels of substances metabolized through CYP2C8 (e.g. repaglinide, paclitaxel).
- Deferasirox can potentially increase the levels of substances metabolized through CYP1A2 (e.g. theophylline, clozapine, tizanidine). Monitor theophylline levels and consider theophylline dose reduction.

[redacted]

- Potent UGT inducers (e.g. rifampicin, phenytoin, phenobarbital, ritonavir) may decrease deferasirox concentration.

6.4.3 Prohibited concomitant therapy

- Aluminium-containing antacid therapies may bind to deferasirox.
- Bile acid sequestrants (e.g., cholestyramine, colesevelam, colestipol) decrease deferasirox systemic exposure.
- Other iron chelators (deferoxamine, deferiprone, deferasirox) during study treatment and Post-treatment Ocular Follow-up phases
- Any investigational drug other than study medication

6.4.4 Use of Bisphosphonates

Requires caution (See Section 6.4.2)

6.5 Patient numbering, treatment assignment or randomization

6.5.1 Patient numbering

Each patient is assigned a Subject Number (Subject No.) when enrolled for screening. It is retained as the primary identifier for the patient throughout his/her entire participation in the trial. [redacted] Upon signing the informed consent form (ICF), the patient is assigned to the [redacted] Subject No. available to the investigator through the Clinical Data Management System interface.

The investigator or designated staff will contact the Interactive Response Technology (IRT) provider and register the patient. Once assigned, the Subject No. must not be reused for any other subject and the Subject No. for that individual must not be changed, even if the patient is re-screened. If the patient fails to be randomized or start treatment, the reason must be entered on the Screening Disposition page.

IRT must be notified within 2 days that the patient was not randomized.

6.5.2 Treatment assignment or randomization

Patients will be assigned to one of the two treatment arms (Section 4.1 and Section 6.1), deferasirox FCT or phlebotomy in a 2:1 ratio.

Randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication randomization

[redacted]

list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to medication packs containing the study treatment.

Prior to dosing, all patients who fulfill all inclusion/exclusion criteria will be randomized via IRT to one of the treatment arms. The investigator or his/her delegate will call or log on to the IRT and confirm that the patient fulfills all inclusion/exclusion criteria. IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the patient. The randomization number will not be communicated to the caller.

6.5.3 Treatment blinding

This is an open-label study so investigators, patients, and sponsor will have full knowledge of treatment allocation. To minimize the potential impact of treatment knowledge, no aggregated statistical analyses (efficacy or safety) shall be performed by treatment (other than analyses specified in the protocol) until the primary analysis is conducted.

6.6 Study drug preparation and dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study drug will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

6.6.1 Study treatment packaging and labeling

Study treatment, deferasirox FCT, will be provided from the global clinical open supply and will be packaged and labeled under the responsibility of Novartis Drug Supply Management.

Study treatment labels will comply with the legal requirements of each country and will include storage conditions and a unique medication number (corresponding to study treatment and strength). They will supply no informaiton about the patient. Responsible site personnel will identify the study treatment package(s) to dispense by the medication number(s) assigned by IRT to the patient. Site personnel will add the patient number on the label. If the label has 2 parts (base plus tear-off label), immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the package and affix it to the patient's source document.

Table 6-3 Packaging and labeling

Study treatments	Packaging	Labeling (and dosing frequency)
deferasirox FCT	Tablets in bottles	Labeled as 'ICL670' Study treatment packaging has a 2-part label.

[redacted]

6.6.2 Drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the deferasirox FCT should be stored according to the instructions specified on the drug labels.

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit. Information provided by the patient and/or caregiver will be captured in the Drug Accountability Form.

6.6.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a Drug Accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

At study close-out and as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed Drug Accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.6.3.3 Handling of other study treatment (phlebotomy)

Patients randomized to the phlebotomy arm will go to a therapeutic phlebotomy center or hospital to receive treatment at a frequency that the investigator prescribes. The investigator or designee must collect an accurate record of the name of facility, the date of phlebotomy, hematocrit level prior to phlebotomy and amount of blood withdrawn at each treatment. This information must be captured in the source document at each visit and recorded on the eCRF.

6.6.4 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility as per local SOPs and regulations. Drug supply may be destroyed at the site if permitted by local regulations and authorized by Novartis in a prior agreement.

[redacted]

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all assessments and indicates with an "X" the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation.

Scheduled assessments should be done on the designated day, or as close to it as possible, i.e., not exceeding ± 3 days for assessments scheduled at Week 2 and Week 4, not exceeding ± 7 days for monthly visits until Week 104 (End of Treatment Visit), and not exceeding ± 30 days for assessments done approximately every 6 months, such as ocular and ECG assessments. In this clinical trial, a week is 7 calendar days, and 1 month is 30 days.

FRANCE SPECIFIC ONLY: The additional assessments of creatinine and creatinine clearance at Week 1 and Week 3 after start of treatment, and weekly checks of creatinine and creatinine clearance during the first month of dose increases, are specific to patients enrolled in sites from France. These assessments are NOT included in the Table 7-1, and should be recorded as unscheduled visits.

No eCRF will be used as a source document.

[redacted]

Table 7-1 Visit evaluation schedule

	Category	Protocol Section	Screening		Randomization	Treatment Period												End of study treatment (EoT)	30-day Follow up	Post-treatment Follow-up *
Weeks			**-4**	**-2**	**Day 1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28, 32, 36, 40, 44, 48**	**52**	**56, 60, 64, 68, 72**	**76**	**80, 84, 88, 92, 96, 100**	**104**	**108**	
Informed Consent	D	7.1.2	X																	
IRT Registration	S	7.1.2.1	X																	
Demography	D	7.1.2.3	X																	
Inclusion/ exclusion	D	7.1.2	X	X																
HH history	D	7.1.2	X																	
Medical History	D	7.1.2.3	X																	
Prior and concomitant medication / procedures	D	6.4	Continuously till 30 days after last dose of study treatment																	
Ocular History	D	7.1.2.3	X																	

[redacted]

	Category	Protocol Section	Screening		Randomization	Treatment Period												End of study treatment (EoT)	30-day Follow up	Post-treatment Follow-up *
Weeks			**-4**	**-2**	**Day 1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28, 32, 36, 40, 44, 48**	**52**	**56, 60, 64, 68, 72**	**76**	**80, 84, 88, 92, 96, 100**	**104**	**108**	
Cirrhosis History	D	7.1.2	X																	
Randomization	D	6.5			X															
Disposition	D	7.1.2		X														X		X
Molecular Testing of HH	D	7.2.2.6.1	X																	
Physical examination	S	7.2.2.1	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Vital signs	D	7.2.2.2	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Height	D	7.2.2.3	X																	
Weight	D	7.2.2.3	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Best Corrected Visual Acuity	D	7.2.2.5	X									X		X		X		X		X

[redacted]

	Category	Protocol Section	Screening		Randomization	Treatment Period												End of study treatment (EoT)	30-day Follow up	Post-treatment Follow-up *
Weeks			**-4**	**-2**	**Day 1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28, 32, 36, 40, 44, 48**	**52**	**56, 60, 64, 68, 72**	**76**	**80, 84, 88, 92, 96, 100**	**104**	**108**	
Slit Lamp Exam (w/ LOCS III)	D	7.2.2.5	X									X		X		X		X		X
Tonometry	D	7.2.2.5	X									X		X		X		X		X
Fundus Photography	D	7.2.2.5	X									X		X		X		X		X
ECG	D	7.2.2.7.1	X									X		X		X		X		
Audiometry	D	7.2.2.4	X									X		X		X		X		
Cirrhosis assessment	D	7.2.2.8	X																	
Hematology	D	7.2.2.6.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Chemistry	D	7.2.2.6.3	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Coagulation	D	7.2.2.6.6	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Urinalysis	D	7.2.2.6.4	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

[redacted]

	Category	Protocol Section	Screening		Randomization	Treatment Period												End of study treatment (EoT)	30-day Follow up	Post-treatment Follow-up *
Weeks			**-4**	**-2**	**Day 1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28, 32, 36, 40, 44, 48**	**52**	**56, 60, 64, 68, 72**	**76**	**80, 84, 88, 92, 96, 100**	**104**	**108**	
Urine protein/creatinine ratio	D	7.2.2.6.4	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Transferrin saturation	D	7.2.2.6.7	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Hepatitis tests	D	7.2.2.6.5	X																	
Serum Ferritin	D	7.2.1.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Serum Pregnancy	D	7.2.2.6.8	X																	
Urine Pregnancy	D	7.2.2.6.8			X													X		
Phlebotomy record	D	6.6.3.3	Continuously from 6 months before Randomization to End of study treatment.																	
Drug dispensing	S	6.6			X		X	X	X	X	X	X	X	X	X	X	X	X		
Study Drug administration	D	6.6			Daily intake of study drug															

[redacted]

	Category	Protocol Section	Screening		Randomization	Treatment Period											End of study treatment (EoT)	30-day Follow up	Post-treatment Follow-up *
Weeks			**-4**	**-2**	**Day 1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28, 32, 36, 40, 44, 48**	**52**	**56, 60, 64, 68, 72**	**76**	**80, 84, 88, 92, 96, 100**	**104**	**108**	
Adverse events	D	8.1	Continuously after ICF signature and till 30 days after last dose of study treatment																
Follow-up on potential drug induced liver injury (DILI) cases	D	6.3.3.1			If there is a potential DILI, a detailed history, additional lab tests (creatinine kinase, gamma-glutamyl transpeptidase, and alkaline phosphatase), testing for acute hepatitis infection or other hepatotropic viral infection or autoimmune hepatitis should be considered. This will be documented in an unscheduled visit.														
*Post treatment follow up: See Section 4.1.1																			

[redacted]

7.1.1 Molecular pre-screening

Not Applicable

7.1.2 Screening

Prior to screening, the patient must give full informed consent on the appropriate form. Once signed and dated by the patient, the investigator must review the study's inclusion and exclusion criteria with the patient to ensure that the patient is eligible to participate.

Two Screening Visits (at -4 weeks and at -2 weeks) are needed to perform key safety parameters prior to first dose administration per the deferasirox drug label and to confirm eligibility criteria.

Molecular testing of HH must be performed at the first screening visit if historical diagnosis is not available.

Specific safety assessments including ophthalmic and audiometry examinations, ECG, and cirrhosis assessment (unless diagnosis is available during the past 12 months, or SF is <1000 µg/L and AST/ALT are normal) must be performed prior to starting study drug. It is preferred that they are performed at the first screening visit (-4 weeks), but to make it possible for the site to plan the examinations properly, these assessments can be performed at the second screening visit (-2 weeks).

SF, serum creatinine and urine protein/creatinine ratio will be measured at both screening visits and used to assess eligibility. SF should be obtained in the absence of any infection or inflammation.

Serum Pregnancy test will be required for females of child-bearing potential only.

The full list of assessments to be performed during screening is detailed in Table 7-1.

Re-screening is permissible on a case-by-case basis. All assessments at screening visits must be repeated if a patient is re-screened, except for molecular testing of HH, Ocular, Audiometry, ECG, and cirrhosis assessments. Please contact Novartis for guidance and see Section 7.1.2.2 on how to process screen failures.

7.1.2.1 Eligibility screening

After registering in the IRT for screening, patient eligibility will be checked to ensure all screening procedures are completed. The eligibility check will be embedded in the IRT system. Please refer and comply with detailed guidelines in the IRT manual.

7.1.2.2 Information to be collected on screening failures

Patients who sign an informed consent, but fail to get randomized for any reason will be considered a screen failure. The reason for not starting must be entered on the Screening Phase Disposition page. Demographic information, informed consent, and

[redacted]

Inclusion/Exclusion pages must also be completed for Screen Failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced an SAE during the Screening Phase (see Section 8.2 for SAE reporting details). If the patient fails to be randomized, the IRT must be notified within 2 days of the screen fail that the patient was not randomized.

7.1.2.3 Patient demographics and other baseline characteristics

Data will be collected on patient characteristics, including demographic information (age, sex, ethnicity, etc.) medical history/ current medical conditions, prior or current medication, ocular and phlebotomy history. Retrospective data on phlebotomy history will be collected from the 6 months prior to randomization.

To determine eligibility, patients will undergo assessments per the inclusion and exclusion criteria, including molecular testing of HH if no historical diagnosis available, SF, transferrin saturation, hemoglobin, hematocrit, serum creatinine, total bilirubin, ALT/AST, hepatitis, further testing for HIV-positive (ELISA or Western blot), serum pregnancy, urinalysis, and weight.

Other assessments include ocular, audiometry, ECG, and cirrhosis assessment.

7.1.3 Run-in period

Not applicable

7.1.4 Treatment period

The study treatment duration is 24 months (104 weeks). Patient visits will occur bi-weekly for the first 4 weeks, then every 4 weeks from Week 4 until 104 (EOT).

All visits should be scheduled respective to the randomization date (Day 1), rather than in relation to previous visits.

After completing screening, eligible patients will be enrolled and randomized to receive phlebotomy or deferasirox FCT. For deferasirox FCT, the target daily dose is calculated by the physician based on the patient's actual body weight.

At the start of treatment, patients randomized to deferasirox FCT will receive 7 mg/kg once daily. Patient randomized to phlebotomy may receive treatment at a frequency determined by the treating physician.

For details on study design and dose adjustments, see Section 4 and Section 6.3.

For details on assessments during the treatment period, see Table 7-1.

FRANCE SPECIFIC ONLY: The additional assessments of creatinine and creatinine clearance at Week 1 and Week 3 after start of treatment, and weekly checks of creatinine and creatinine clearance during the first month of dose increases, both specific to patients enrolled

[redacted]

in sites from France only, are NOT included in the Table 7-1, and should be regarded as unscheduled visits.

7.1.5 Discontinuation of study treatment

Patients may voluntarily discontinue from the study treatment for any reason at any time. If a patient decides to discontinue from the study treatment, the investigator must make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision and record this information in the patient's chart and on the appropriate eCRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

The investigator may discontinue study treatment for a given patient if; he/she believes that continuation would be detrimental to the patient's well-being.

Study treatment must also be discontinued under the following circumstances:

Pregnancy
AEs listed in Table 6-2
Laboratory abnormalities listed in Table 6-2
Unwillingness to comply with the prescribed study treatment

Use of prohibited treatment refer to Section 6.4.3

Any other protocol deviation that results in a significant risk to the patient's safety

Patients who discontinue study treatment should NOT be considered withdrawn from the study. They should return for the assessments indicated in Section 7.2.2.5. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, email, letter) should be made to contact them as specified in Section 7.1.8.

The investigator must also contact the IRT to register the patient's discontinuation from study treatment.

7.1.5.1 Replacement policy

Not Applicable

7.1.6 Withdrawal of consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject does not want to participate in the study any longer, and does not allow further collection of personal data.

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

[redacted]

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

For US: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and Rest of World: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements. Follow up for safety evaluations

7.1.7 Follow up for safety evaluations

All patients must have safety evaluations for 30 days after the last dose of study treatment. If death occurs during this period, this will be collected in the End of Treatment Disposition eCRF and Death eCRF.

Data collected should be added to the AEs eCRF and the Concomitant Medications eCRF.

7.1.8 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source document the steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until due diligence has been completed. Patients lost to follow-up must be recorded on the appropriate Disposition eCRF.

7.2 Assessment types

7.2.1 Efficacy assessments

7.2.1.1 Serum Ferritin (SF)

In the absence of infection or inflammation, SF test will be performed at Screening visits (-4 weeks and -2 weeks) to assess eligibility. Thereafter SF testing will be done at Day 1, Weeks

[redacted]

2, 4 and then every 4 weeks till week 104 (EOT) to assess the response rate of deferasirox FCT and phlebotomy. For efficacy evaluation, the last available assessment before or on the date of randomization is taken as the "baseline" value.

7.2.2 Safety and tolerability assessments

Safety will be monitored by physical examination, vital signs, ocular, audiometry, ECG and laboratory evaluations (please refer to Table 7-3), as well as collecting AEs at every visit. For details on AE collection and reporting, refer to Section 8.

7.2.2.1 Physical examination

A physical examination will be performed at the first screening visit, randomization and all subsequent visits. The physical examination at randomization (Day 1) will serve as the Baseline physical examination for the entire study.

Physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological.

Information about the physical examination must be present in the source documentation at the study site.

Significant findings that were present prior to the signing of informed consent must be on the Medical History page of the patient's eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the AE summary page.

7.2.2.2 Vital signs

Vital signs will be measured at screening and at subsequent time points specified in Table 7-1. Assessment includes blood pressure (supine position preferred when ECG is collected), respiratory rate, pulse, and temperature.

7.2.2.3 Height and weight

Height will be measured at screening.

Body weight (in indoor clothing, but without shoes) will be measured at screening and at subsequent time points specified in Table 7-1.

7.2.2.4 Auditory examination

Patients will undergo auditory examinations locally approximately every 6 months (Screening, Weeks 24, 52, 76, and 104).

Interpretation of the audiometry examination must be made by a qualified physician and documented on the eCRF page.

[redacted]

Information about the audiometry examinations must be present in the source documentation at study site. Significant abnormal findings that meet the definition of an AE must be recorded in the AE summary page of the eCRF.

7.2.2.5 Ocular examination

Ophthalmologic examinations must be conducted approximately every 6 months for at least 5 ocular assessments at screening and Weeks 24, 52, 76, and 104 (EOT).

An exception is for patients eligible for the Post-treatment Ocular Follow-up phase and EOT occurs in the interval between the scheduled 6-month exams (the allowed assessment window is 30 days +/- of the scheduled date), an ophthalmologic exam is part of the EOT then they will continue their regular schedule of ophthalmological exams every 6 months (recorded in Post-treatment follow-up eCRFs at Weeks 52, 76 and 104 as appropriate) for a total of 6 ocular examinations. A reminder by the site at least one month prior to each upcoming ophthalmological visit should be made. To provide consistent assessments, it is recommended that ocular assessments be performed at the same site with the same equipment for each patient.

The ophthalmologic examination includes the following assessments:

- Best corrected visual acuity must be done using Early Treatment Diabetic Retinopathy Study (ETDRS)
- Slit lamp examination: any opacity graded using the Lens Opacities Classification System, version III (LOCS III)
- Intraocular pressure (IOP) measured by tonometry should be performed after the above two ocular tests
- Dilated fundus exam and color fundus photography

The dilated fundus exam must assess the vitreous, retina, macula, and optic nerve for both eyes. Wide-angle fundus photography of the retina and optic nerve is preferred; however, if unavailable, a regular camera capturing 7 standard stereoscopic fields is allowed.

Detailed instructions for the ophthalmic assessments are provided in the "Manual of Ophthalmic Procedures".

Table 7-2 Central imaging assessments collection plan

Procedure	Baseline	During Treatment
Color Fundus Photography	Required	Every 6 months (Screening and weeks 24, 52, 76, and 104)

The ocular examination will be performed by a local, qualified ophthalmologist and the results will be documented on the eCRF page. The color fundus photography will not be reported locally and instead be sent to an imaging Contract Research Organization (CRO) designated by Novartis for reading.

[redacted]

Details on transferring the color fundus photographs for reading by the imaging CRO are provided to investigators in the imaging CRO Site Operations Manual. The imaging CRO will maintain both the original source images as well as any alterations made to the images during interpretation. All details of the central review methodology will be described in the Central Imaging Review Charter.

Information and results of the local ocular examination must be present in the source documentation at the study site. Significant abnormal findings affecting the normal function of the eye or its structure, detected and diagnosed or verified by an ophthalmologist, which also meet the definition of an AE must be recorded in the AE summary page of the eCRF.

7.2.2.6 Laboratory evaluations

Table 7-3 Central Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, MCH, MCHC, MCV, Platelets, Red blood cells, White blood cells, RBC morphology, Differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils, bands)
Chemistry	Albumin, Alkaline phosphatase, ALT, AST, Bicarbonate, Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, Creatinine kinase, Direct (conjugated) Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, Lactate Dehydrogenase, Blood Urea Nitrogen, Uric Acid, Amylase, Lipase, Glucose (non-fasting)
Urinalysis	Microscopic Panel (red blood cells, white blood cells, casts, crystals, bacteria, epithelial cells) performed if a positive dipstick Macroscopic Panel (dipstick supplied by the central lab and performed by site): color, bilirubin, blood, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen
Coagulation	International normalized ratio
Hepatitis markers	HbsAg, HbsAb, HbcAb, HCV RNA, Anti-HCV
Additional tests	Serum ferritin, Creatinine clearance, Urine protein/creatinine ratio, Transferrin saturation (fasting), Molecular testing for HH.
Pregnancy Test	Serum pregnancy test, urine pregnancy test.

A central laboratory will be used for analysis of all specimens collected, except urinary dipstick analysis and urinary pregnancy test will be performed by the local lab.

Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the Central Laboratory Manual.

Local laboratory assessments may be performed if medically indicated or when the treating physician cannot wait for central laboratory results for decision-making. In this situation, a second blood sample obtained at the same time should be submitted to the central laboratory for analysis in parallel with local analysis.

Results of the local laboratory will be recorded in the eCRF if the following criteria are met:

[redacted]

- Treatment decision was made based on the local results, or
- No concomitant central lab results are available

Eligibility into the study will be based on central laboratory results.

7.2.2.6.1 **Molecular test for HH**

Blood samples for molecular testing of HH must be collected at the first screening visit if no historical diagnosis available.

7.2.2.6.2 **Hematology**

Hematology samples will be collected at Screening and at subsequent time points specified in Table 7-1**.**

Hematology parameters assessed are listed in Table 7-3.

7.2.2.6.3 **Clinical chemistry**

Clinical chemistry samples will be collected at Screening and at subsequent time points as specified in Table 7-1**.**

Clinical chemistry parameters assessed are listed in Table 7-3.

In accordance with the deferasirox label, serum creatinine, creatinine clearance, alkaline phosphatase, ALT/SGPT, AST/SGOT, direct (conjugated) bilirubin, indirect bilirubin, total bilirubin must be assessed in duplicate before the initiation of therapy to establish a reliable pre-treatment baseline.

FRANCE SPECIFIC ONLY: Serum creatinine and creatinine clearance should be assessed at weeks 2 and 4 after initiation of deferasirox FCT as central lab tests. For patients enrolled in sites in France, serum creatinine and creatinine clearance will also be assessed at weeks 1 and 3 after initiation of deferasirox FCT, and weekly during the first month after dose increases. The assessment is to be performed by the central lab however the local lab may be used. In the clinical database, “Unplanned Central Lab Cover Page” should be used to enter these unscheduled samples information at ‘Unplanned’ visit, or “Biochemistry Local Unplanned page” will be used in case of local lab assessment. The CRA will obtain the local laboratory reference ranges and a copy of the laboratory certification

Creatinine clearance will be calculated using the Cockcroft-Gault formula every time serum creatinine is collected.

7.2.2.6.4 **Urinalysis**

Urinalysis samples will be collected at Screening and at subsequent time points specified in Table 7-1**.**

Urinalysis parameters assessed are listed in Table 7-3.

[redacted]

Macroscopic urinalysis will be performed by the site (dipstick supplied by the central lab).

Microscopic urinalysis will be performed by the central lab if the urine dipstick is positive.

During screening, a non-first void morning urine sample (at least 15 ml) will be collected for a urinary protein/creatinine ratio (UPCR) to be assessed by the central lab for eligibility.

For patients who develop proteinuria or worsening pre-existing proteinuria (assessed by dipstick or central lab) at any visit, refer to Table 6-2.

7.2.2.6.5 **Hepatitis tests**

Hepatitis tests include hepatitis B surface antigen and antibody (HbsAg & HbsAb), hepatitis B core antibody (HbcAb), hepatitis C antibody (Anti-HCV), HCV PCR (Quantitative). Hepatitis testing will be conducted at the first Screening Visit to assess trial eligibility.

7.2.2.6.6 **Coagulation**

International normalized ratio (INR) will be measured at all screening visits and all visits during study treatment.

7.2.2.6.7 **Transferrin saturation**

Transferrin saturation (fasting) will be measured at all screening visits and all visits during study treatment.

7.2.2.6.8 **Pregnancy and assessments of fertility**

Serum and/or urine pregnancy tests will be performed for all females of child-bearing potential, according to the schedule in Table 7-1.

A urine pregnancy test will be at Day 1, EOT and at the investigator's discretion during the treatment period, as per Novartis guidelines for pregnancy testing in clinical trials when basic contraception is requested.

See Section 8.4 for pregnancy reporting and follow-up requirements.

7.2.2.7 Cardiac assessments

7.2.2.7.1 **Electrocardiogram (ECG)**

A standard 12 lead ECG will be performed locally approximately every 6 months (Screening, Weeks 24, 52, 76, and 104).

Additional unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study.

Interpretation of the tracing must be made by a qualified physician and documented on the ECG eCRF. Each ECG tracing should be labeled with the study number, patient initials

[redacted]

(where regulations permit), patient number, and date, and kept in the source documents at the study site. Clinically significant abnormalities present at screening should be reported on the Medical History eCRF. Clinically significant findings must be discussed with Novartis prior to enrolling the patient. New or worsened clinically significant findings occurring after informed consent must be recorded on the AE eCRFs.

7.2.2.8 Other assessment

Cirrhosis assessment will be performed locally unless diagnosis is available during the past 12 months, or SF is <1000 μg/L and AST/ALT are normal. The patient and physician have the option to choose an available test, e.g. liver biopsy, elastography ultrasound or radiologic exams, for cirrhosis assessment during screening, preferably at the first screening visit.

7.2.3 Pharmacokinetics

Not applicable

7.2.4 Biomarkers

Not applicable

7.2.5 Resource utilization

Not applicable

7.2.6 Patient reported outcomes

Not applicable

8 Safety monitoring and reporting

8.1 Adverse events (AEs)

8.1.1 Definitions and reporting

An AE is defined as the appearance (or worsening of any pre-existing) of undesirable sign(s), symptom(s), or medical condition(s) that occur after ICF has been signed.

Abnormal laboratory values or test results occurring after informed consent constitute an AE if they induce clinical signs or symptoms considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or stem cell support), or require changes in study medication.

Onset or worsening of AEs after informed consent should be recorded in the AE eCRFs. Conditions present at the time of informed consent should be recorded in the Medical History page of the eCRF. AE monitoring should be continued for at least 30 days (or 5 half-lives, whichever is longer) following the last dose of study treatment. AEs (including lab

abnormalities that constitute AEs) should be described with a diagnosis, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

Severity of AEs will be assessed as mild, moderate, or severe. Information about any deaths (related or not to an AE) will be collected through a Death form.

Detection of AEs should be sought by non-directed questioning of the patient during screening (after signing the ICF) and at each visit. AEs may also be volunteered by the patient during Screening, between visits, by physical examination, laboratory test, or other assessments. Each AE must be evaluated for:

1. Severity grade (mild, moderate, severe)
2. Duration (Start and end dates)
3. Relationship to study treatment (Reasonable possibility that AE is related: No or Yes)
4. Action taken with respect to study drug (None, Dose adjusted, Temporarily interrupted, Permanently discontinued, Unknown, or Not applicable)
5. Concomitant medication or therapy given (No concomitant medication/non-drug therapy; if Yes, provide the concomitant medication/non-drug therapy)
6. Seriousness criteria was met or not for an AE, as defined in Section 8.2.1
7. Outcome (Not recovered/not resolved, Recovered/resolved, Recovering/resolving, Recovered/resolved with sequelae, Fatal, Unknown)

For SAEs only, if there is improvement to a lower grade or worsening in toxicity, a new second entry with the start date should be reported in the eCRF.

All AEs should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the AE eCRF.

AEs must be followed until its resolution or until it is judged to be permanent. Assessment must be made at each visit (or more frequently, if necessary) of any change in severity, the suspected relationship to the study treatment, interventions required, and the outcome.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an AE (clinically significant, induce clinical signs or symptoms, require concomitant therapy or require a change in study treatment), should be recorded on the AE eCRFs. Whenever possible, a diagnosis, rather than a symptom, should be provided (e.g. anemia instead of low hemoglobin). They must be followed until resolved or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported AE, it is not necessary to separately record the lab/test result as an additional event.

[redacted]

Laboratory abnormalities, that do not meet the definition of an AE, should not be reported as AEs. A severe event does not automatically indicate an SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an AE and must be reported as such.

8.1.3 Adverse events of special interest

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor (through timely reporting in the clinical database) may be appropriate. Such events may require further investigation in order to characterize and understand them.

AESI are defined on the basis of an ongoing review of the safety data. AESI are discussed in detail in the Investigator Brochure.

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Note: hospitalizations for the following should not be reported as SAE:
  - Routine treatment or monitoring of the studied indication not associated with any deterioration in condition
  - Elective or pre-planned treatment for a pre-existing condition unrelated to the indication under study and has not worsened since signing the ICF
  - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note: treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a SAE.

[redacted]

8.2.2 Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided ICF and until at least 30 days after the patient has stopped study treatment, must be reported to Novartis within 24 hours of learning of its occurrence.

Any additional information for the SAE, including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one, should be reported separately as a new event.

Any SAEs experienced after the 30-day safety follow-up (or 5 half-lives, if half-life is established, whichever is longer) should be reported to Novartis only if the investigator suspects a causal relationship to the study treatment.

Information about all SAEs is collected and recorded on the SAE Report Form. All applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each site

Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Chief Medical Office and Patient Safety (CMO&PS) department associate may urgently require additional information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same drug that this SAE was reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Emergency unblinding of treatment assignment

Not applicable, this is an open-label treatment study.

[redacted]

8.4 Pregnancies

Serum and urine pregnancy tests will be performed for all females of child-bearing potential according to the schedule in Table 7-1. Urine pregnancy tests will also be performed at the investigator's discretion during the treatment phase per Novartis guidelines for pregnancy testing in clinical trials when basic contraception is requested

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

8.5 Warnings and precautions

No evidence at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those in the provided Investigator Brochure. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications and included in the ICF, which must be discussed with the patient.

8.6 Data Monitoring Committee

Not applicable

8.7 Steering Committee

The Steering Committee (SC) will be comprised of external experts in hematology, hepatology and ophthalmology who may be investigators participating in the trial and Novartis representatives from the Clinical Trial Team.

The SC will ensure transparent management of the study, according to the protocol, by recommending and approving modifications as circumstances require per SC charter. The SC will also review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results, including authorship rules. Details of the role of the Steering Committee will be defined in a Steering Committee charter.

[redacted]

9 Data collection and management

9.1 Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that revoked authorization to collect or use PHI, attempts will be made to obtain permission to collect follow-up safety information (e.g. has the subject experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

Prior to entering sensitive key personal identification information [redacted] the system will prompt site to verify that this data is allowed to be collected. If the site indicates that country rules or ethics committee standards do not permit collection of these items, the system will not solicit Subject Initials. Year of birth will be solicited (in the place of exact date of birth) to establish that the subject satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and eCRFs with the investigators and their staff. During the study, a field monitor will regularly visit the site to check the completeness of patient records, accuracy of entries on the eCRFs, adherence to the protocol according to Good Clinical Practice, progress of enrollment, and ensure that study drug is stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical

[redacted]

information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on eCRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed ICF (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

This study uses Electronic Data Capture (EDC). The eCRFs use validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. Designated site staff will be given access to the EDC system after they are trained and will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). Automatic validation programs check for data discrepancies in the eCRFs and allow modification or verification of the entered data by the investigator staff. The Investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate and that entry and updates are performed in a timely manner.

9.4 Database management and quality control

Data entered by investigational staff will be reviewed by Novartis personnel (or designated CRO) for completeness and accuracy. Electronic data queries stating the nature of the problem and requests for clarification for discrepancies and missing values will be sent to the investigational site via the EDC system. Designated investigator site staffs are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and AEs will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Samples for central lab and photographs for central reading will be processed centrally and the results will be sent electronically to Novartis.

Randomization codes and data for all study drug dispensed to the patient and all IRT-assigned dosage changes will be tracked. The IRT system will also manage the database. The data will be sent electronically to Novartis.

The occurrence of any protocol violations will be determined. After these actions have been completed and the data has been verified to be complete and accurate, the database will be declared locked. Authorization is required prior to making any database changes to locked

[redacted]

data, by joint written agreement between the Global Head of Biostatistics and Data Management and the Global Head of Clinical Development.

After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

10 Statistical methods and data analysis

Primary safety and efficacy analysis will be conducted on all patient data after final database lock.

10.1 Analysis sets

The following analysis sets will be used.

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned by randomization. According to the intent to treat principle, patients will be analyzed according to the treatment they have been assigned to during the randomization procedure.

10.1.2 Safety set

The Safety Set includes all patients who received at least one dose of study treatment or phlebotomy. Patients will be analyzed according to the study treatment received, where treatment received is defined as the randomized treatment if the patient took that treatment (at least one dose or phlebotomy) or the first treatment received if the randomized treatment was never received.

10.1.3 Per Protocol Analysis Set:

Not applicable

10.1.4 Pharmacokinetic analysis set

Not applicable

10.1.5 Other analysis sets

Not applicable

10.1.5.1 Efficacy/evaluable set

Not applicable

[redacted]

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data, including disease characteristics, will be listed and summarized descriptively by treatment group for the FAS and the Safety Set.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

For selected parameters, 25th and 75th percentiles will also be presented when applicable.

Relevant medical histories and current medical condition at baseline will be summarized separately by system organ class (SOC) and preferred term (PT) for each treatment group. Ophthalmic history and phlebotomy history will also be summarized and listed for each treatment group using FAS.

10.3 Treatments (study treatment, concomitant therapies, compliance)

The Safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented, as appropriate.

For deferasirox, the duration of exposure in months and in categories (<3 months, 3-<6 months, 6-<12 months, 12-<18 months and >18 months); as well as average planned dose, actual daily doses (mg/kg/day) and percentage of planned dose taken (ratio of cumulative actual on cumulative planned dose) will be summarized using descriptive statistics. The number of patients with dose adjustments (reductions, interruption, or permanent discontinuation) and the reasons will be summarized by treatment group; all dosing data will be listed.

For phlebotomy, summary statistics will be provided for the volume of blood removed and the frequency.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized by treatment group, according to the Anatomical Therapeutic Chemical classification system.

10.4 Primary objective

Assess the response rate (RR) of deferasirox FCT and phlebotomy treatment arms where response is defined by achieving target SF $\leq$ 100 μg/L on or before 24 months. Estimate of the RR and corresponding 95% CI will be provided for each arm. No formal hypothesis testing is planned in this study.

10.4.1 Variable

The primary endpoint is the response rate by month 24, i.e. the proportion of patients whose SF $\leq$ 100 μg/L at any time on or before month 24.

[redacted]

10.4.2 Statistical hypothesis, model, and method of analysis

The 2-sided 95% confidence interval will be constructed for the response rate by treatment arm based on the exact binomial distribution (Clopper-Pearson method).

10.4.3 Handling of missing values/censoring/discontinuations

For the primary analysis, patients are considered responders if they meet response criteria for the primary endpoint on or before month 24. Any patient who discontinues prematurely before meeting such criterion will be considered a non-responder.

10.4.4 Supportive and Sensitivity analyses

Not applicable

10.5 Secondary objectives

10.5.1 Key secondary objective

The key secondary objective for this study is to evaluate the ocular safety of deferasirox FCT and phlebotomy over 24 months.

To characterize long-term ocular safety, the incidence of treatment-emergent ocular AEs (new or worsening from baseline) will be summarized categorically by system organ class and/or preferred term, overall and by severity, type of AE, and relation to study treatment. Ocular AEs will be defined in the study Statistical Analysis Plan (SAP).

Treatment-emergent AEs are defined as AEs started during on-treatment period: from the day of the first dose of study medication or the first phlebotomy to 30 days after the last dose of study medication or last phlebotomy.

No hypothesis will be tested for this key secondary objective.

10.5.2 Secondary efficacy objective(s)

The secondary efficacy objective is time to first response of achieving SF $\leq$ 100 μg/L. For this analysis, the following censoring rule will be applied:

For patients who did not achieve a response, they will be censored at the earliest of the following dates:

- Death or discontinuation date due to any reason
- Last SF assessment.

Kaplan-Meier estimates will be presented. Median time to response (as well as 25^{th} and 75^{th} percentiles) will be presented along with 95% confidence intervals for the two arms.

[redacted]

10.5.3 Secondary safety objectives

Secondary safety objectives include:

- Safety and tolerability of deferasirox FCT and phlebotomy over 24 months
- Change from baseline in visual acuity (ETDRS), intra-ocular pressure, retina or/and optic nerve abnormalities, and lens abnormalities at months 6, 12, 18, and 24.
- Safety and tolerability of deferasirox FCT in patients who interrupt due to SF ≤ 100 µg/L and re-initiate therapy when > 300 µg/L.

See Section 3 for details on safety objectives. Descriptive statistics will be provided for all safety objectives using the Safety set.

Safety and tolerability between deferasirox FCT and phlebotomy during 24 months of study period will be assessed through the incidence of new or worsening AEs, abnormal and clinically significant laboratory findings, and other abnormal safety findings. See Section 10.5.3.2, Section 10.5.3.3, and Section 10.5.3.4 for details.

To assess the effect of deferasirox FCT and phlebotomy, the change from baseline in visual acuity (ETDRS), intra-ocular pressure, retina or/and optic nerve abnormalities, and lens abnormalities will be summarized descriptively by treatment and by visit. The detailed analysis will be detailed in the SAP.

Incidence of AEs in patients who interrupted deferasirox FCT at least once due to SF ≤ 100 µg/L and re-initiated ≥ 300 µg/L will be tabulated and listed. The detailed analysis will be detailed in the SAP.

10.5.3.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group.

The overall observation period will be divided into three mutually exclusive segments:

1. Pre-treatment period: from the day of a patient's informed consent to the day before the first dose of study medication or first phlebotomy
2. On-treatment period: from the day of the first dose of study medication to 30 days after the last dose of study medication or last phlebotomy
3. Post-treatment period: starting at day 30+1 after last dose of study medication or last phlebotomy.

10.5.3.2 Adverse events (AEs)

Summary tables for AEs will include only AEs that started or worsened during the on-treatment period, the treatment-emergent AEs.

[redacted]

The incidence of all treatment-emergent AEs (new or worsening from baseline) in both arms will be summarized by SOC and/or PT, severity, type of AE, relation to study treatment. CTCAE grade will not be used.

All deaths (on-treatment and post-treatment) will be summarized.

All AEs, deaths and SAEs (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

Project-specific AESI are defined in the case retrieval strategy (CRS) with regular updates whenever necessary.

Specific groupings of AESI will be considered, and the number of patients with at least one event in each grouping will be reported. Such groups consist of AEs for which there is a specific clinical interest in connection with deferasirox. Certain AEs may be reported within multiple groupings/AESI.

AESI are defined by MedDRA terms.

SAEs, non-SAEs and AESI during the on-treatment period will be tabulated.

10.5.3.3 Laboratory abnormalities

All laboratory values will be converted into SI units and reported by the severity grade, using low/normal/high classifications based on laboratory normal ranges, and by notable/extended ranges for selected parameters (see Table 10-1).

Table 10-1 Criteria for clinically notable and extended notable laboratory ranges

Parameter	Criteria
Absolute neutrophils	< 1.5×10^9/L (extended range < 0.5×10^9/L)
Platelets	< 100×10^9/L (extended range < 50×10^9/L)
Hemoglobin	< 100 g/L
ALT and AST	> 5× ULN and > 2× baseline (extended range > 10× ULN and > 2× baseline)
Total bilirubin	> 2 mg/dL
Serum creatinine	> 33% increase from baseline and > ULN at 2 consecutive measurements at least 7 days apart
Creatinine clearance	< 60 mL/min at 2 consecutive measurements at least 7 days apart (extended range < 40 mL/min)
Urinary protein/creatinine ratio	≥ 1.0 mg/mg at 2 consecutive measurements at least 7 days apart

The following summaries will be generated separately for hematology, biochemistry, and urinary laboratory tests:

- Shift tables using normal/notable/extended ranges to compare baseline to the worst on-treatment value

[redacted]

- Listing of all laboratory data with values flagged to show the corresponding normal/notable/extended ranges (see Table 10-1 above).

10.5.3.4 Other safety data

Data from ECG and auditory examinations will be listed and summarized separately with descriptive statistics as appropriate for the Safety set. All new or worsened abnormalities will be recorded as AEs.

Vital signs

The change from baseline in systolic and diastolic blood pressures, pulse rate, temperature and weight will be summarized by scheduled visit with n, mean, SD, minimum, median, and maximum values.

A listing will be provided for all vital signs and weight. Notable values will be flagged, according to criteria in Table 10-2.

Table 10-2 Definition of notable ranges for vital signs and weight

Parameter	Criteria for notable ranges
Systolic blood pressure	≥ 180 mmHg / ≤ 90 mmHg with increase / decrease from baseline ≥ 20 mmHg
Diastolic blood pressure	≥ 105 mmHg / ≤ 50 mmHg with increase / decrease from baseline ≥ 15 mmHg
Pulse rate	≥ 120 bpm / ≤ 50 bpm with increase / decrease from baseline ≥15 bpm
Weight	≥ 10% increase

10.5.3.5 Supportive analyses for secondary objectives

Not applicable

10.5.3.6 Tolerability

Not applicable

10.5.4 Pharmacokinetics

Not applicable

10.5.4.1 Data handling principles

Not applicable

10.5.5 Biomarkers

Not applicable

[redacted]

10.5.6 Resource utilization

Not applicable

10.5.7 Patient-reported outcomes

Not applicable

10.6 Exploratory objectives

Not applicable

10.7 Interim analysis

Not applicable

10.8 Sample size calculation

The primary objective of the study is to estimate response rates and therefore the sample size is not based on power calculations. Sample size calculations were performed for the deferasirox FCT and phlebotomy arms to estimate the response rate (RR) with reasonable accuracy (half-width of 95% confidence interval).

Based on the Exjade study ICL670A2202, the patient dropout rate at month 6 (core study) is 24% and 12% at month 12 (optional extension phase). Assuming decreasing dropout rate over time and expected better patient compliance with deferasirox FCT formulation, a sample size of 100 patients in the FCT arm is expected to have at least 60 patients followed for 24 months to fulfil the FDA post-marketing requirement with regard to the ocular toxicity assessment in patients receiving deferasirox.

With a sample size of 100 on deferasirox FCT and 50 patients on phlebotomy, the projected half-widths of the 2-sided 95% confidence interval assuming various response rates are displayed in Table 10-3. The 95% confidence interval half-width extends at most to 0.096 and 0.136 in the deferasirox FCT and phlebotomy arms, respectively.

Table 10-3 Half-width of 95% CI of response rates in deferasirox FCT and phlebotomy arms

Response rate (RR)	Half-width of the 95% CI for deferasirox FCT N=100	Half-width of the 95% CI for phlebotomy N=50
0.60	0.096	0.136
0.65	0.093	0.132
0.70	0.090	0.127
0.75	0.085	0.120
0.80	0.078	0.111
0.85	0.070	0.099
0.90	0.059	0.083

[redacted]

10.9 Power for analysis of key secondary variables

Not applicable

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed and will be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed ICF must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before starting the study. In addition, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to provide access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs, and regulatory authorities as required.

11.3 Informed consent procedures

After providing written (witnessed, where required by law or regulation) IRB/IEC/REB-approved informed consent, eligible patients may be included in the study. The patient should indicate assent by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any procedures described in the protocol. The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was obtained must be captured in the eCRF.

In a separate document, Novartis will provide investigators a proposed ICF that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes suggested by the investigator must be agreed to by Novartis before ICF is submitted to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Women of child-bearing potential must be informed that taking the study medication may involve unknown risks to the fetus if pregnancy occurs during the study. In order to participate, they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they must not enter in the study.

[redacted]

Additional consent form

Not applicable

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.4.

11.5 Publication of study protocol and results

Novartis is committed to following high ethical standards for reporting study results for its innovative medicine, including the timely communication and publication of clinical trial results, whatever their outcome. Novartis assures that the key design elements of this protocol will be posted on the publicly accessible database, e.g. ...clinicaltrials.gov, before starting the study. In addition, results of interventional clinical trials in adult patients are posted on ...novartisclinicaltrials.com, a publicly accessible database of clinical study results within 1-year of study completion (i.e., LPLV).

Novartis follows the ICMJE authorship guidelines (....icmje.org) and other specific guidelines of the journal or congress to which the publication will be submitted

Authors will not receive remuneration for their writing of a publication, either directly from Novartis or through the professional medical writing agency. Author(s) may be requested to present at poster or oral sessions at scientific congress; however, there will be no honorarium provided for such presentations.

As part of its commitment to full transparency in publications, Novartis supports the full disclosure of all funding sources for the study and publications, as well as any actual and potential conflicts of interest of financial and non-financial nature by all authors, including medical writing/editorial support, if applicable.

For the Novartis Guidelines for the Publication of Results from Novartis-sponsored Research, please refer to ....novartis.com.

11.6 Study documentation, record keeping and retention of documents

Every participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

[redacted]

Source data are original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the Principal Investigator. The eCRF is the primary data collection instrument. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the eCRFs and all other required reports. Data reported on the eCRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the eCRF must be recorded. Any missing data must be explained. For eCRFs an audit trail will be maintained by the system.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Novartis provides written permission to dispose of them or requires their retention for additional time because of applicable laws, regulations and/or guidelines.

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients. Patients must not be identified by name in any documents submitted to Novartis. Signed ICFs and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site prior to study start.

[redacted]

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment. Unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB, it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days), but not later than 10 working days.

13 References (available upon request)

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14 Appendices

14.1 Dosing tables (Deferasirox FCT)

For each patient the investigator and/or pharmacist will calculate a target daily dose taking into account patient's body weight. When the calculated dose cannot be reached with the deferasirox FCT strengths available, the closest daily dose available will be prescribed.

The following dosing table provides an efficient combination of tablet strengths reaching a certain daily dose for each body weight range.

These dosing tables have been constructed for each dosing group using lower and upper body weight limits of 35 and 140 kg, respectively. This is taking into account that the study will enroll male or female adults.

Table 14-1 Dosing table for 3.5 mg/kg/day of Deferasirox FCT

Pt Weight in Kg	Closest Dose	90 mg	180 mg	360 mg
35 - 38	90 mg	1	-	-
39 - 64	180 mg	-	1	-
65 - 90	270 mg	1	1	-
91 - 115	360 mg	-	-	1
116 - 140	450 mg	1	-	1

Table 14-2 Dosing table for 7 mg/kg/day of Deferasirox FCT

Pt Weight in Kg	Closest Dose	90 mg	180 mg	360 mg
35 - 45	270 mg	1	1	-
46 - 57	360 mg	-	-	1
58 - 70	450 mg	1	-	1
71 - 83	540 mg	-	1	1
84 - 96	630 mg	1	1	1
97 - 109	720 mg	-	-	2
110 - 122	810 mg	1	-	2
123 - 135	900 mg	-	1	2
136 - 140	990 mg	1	1	2

[redacted]

Table 14-3 Dosing table for 10.5 mg/kg/day of Deferasirox FCT

Pt Weight in Kg	Closest Dose	90 mg	180 mg	360 mg
35 - 38	360 mg	-	-	1
39 - 47	450 mg	1	-	1
48 - 55	540 mg	-	1	1
56 - 64	630 mg	1	1	1
65 - 72	720 mg	-	-	2
73 - 81	810 mg	1	-	2
82 - 90	900 mg	-	1	2
91 - 98	990 mg	1	1	2
99 - 107	1080 mg	-	-	3
108 - 115	1170 mg	1	-	3
116 - 124	1260 mg	-	1	3
125 - 132	1350 mg	1	1	3
133 - 140	1440 mg	-	-	4

Table 14-4 Dosing table for 14 mg/kg/day of Deferasirox FCT

Pt Weight in Kg	Closest Dose	90 mg	180 mg	360 mg
35	450 mg	1	-	1
36 - 41	540 mg	-	1	1
42 - 48	630 mg	1	1	1
49 - 54	720 mg	-	-	2
55 - 61	810 mg	1	-	2
62 - 67	900 mg	-	1	2
68 - 73	990 mg	1	1	2
74 - 80	1080 mg	-	-	3
81 - 86	1170 mg	1	-	3
87 - 93	1260 mg	-	1	3
94 - 99	1350 mg	1	1	3
100 - 106	1440 mg	-	-	4
107 - 112	1530 mg	1	-	4
113 - 118	1620 mg	-	1	4
119 - 125	1710 mg	1	1	4
126 - 131	1800 mg	-	-	5
132 - 138	1890 mg	1	-	5
139 - 140	1980 mg	-	1	5

[redacted]

14.2 Examples of light meal

Example 1:	amount	kcal	g total fats
Wheat Bread or Toast	2 slices	138	2
jams, preserves, all flavors	1 Tablespoon	109	0
banana	medium (7-7 7/8" long)	105	0
orange juice	1 cup	114	0
skim milk	1 cup	83	0
	Total:	**549**	**2**

Example 2:	amount	kcal	g total fats
Pita Bread	1 medium (5.25" across) pita	124	1
hummus or deli chicken/turkey	1 Tablespoon hummus or 2 oz. meat	27	1
apple	medium (2.75" across)	72	0
salsa, red, cooked	6 Tablespoons	26	0
carrots & celery sticks	4 carrot sticks (3" long) and small 5" stalk of celery	14	0
	Total:	**263-295**	**2**

Example 3:	amount	kcal	g total fats
yogurt, fruit, low-fat	6 oz.	173	2
banana	medium (7-7 7/8" long)	105	0
orange juice	1 cup	114	0
skim milk	1 cup	83	0
	Total:	**475**	**2**

Example 4:	amount	kcal	g total fats
vegetable chicken noodle soup, canned	1 cup	70	2
baked potato, peel not eaten	1 medium (2.25-3" across)	121	0
skim milk	1 cup	83	0
banana	medium (7-7 7/8" long)	105	0
	Total:	**379**	**2**

[redacted]

Example 5:	**amount**	**kcal**	**g total fats**
egg whites, cooked, no fat added	2 large egg whites	32	0
salsa, red, cooked	6 Tablespoons	26	0
Wheat Bread or Toast	2 slices	138	2
jams, preserves, all flavors	1 Tablespoon	109	0
orange juice	1 cup	114	0
skim milk	1 cup	83	0
	Total:	**502**	**2**

Example 6:	**amount**	**kcal**	**g total fats**
chicken, boneless, skinless baked	0.5 cup diced	111	2
salsa, red, cooked	6 Tablespoons	26	0
white rice, cooked, no fat added	0.5 cup	102	0
black beans, canned or cooked from dry, no fat added	0.5 cup	99	0
skim milk	1 cup	83	0
	Total:	**421**	**2**

[redacted]