NOVARTIS

Clinical Development

ICL670, deferasirox

Oncology Clinical Trial Protocol CICL670AIC04 / NCT02720536

Open-label, multicenter, single arm, phase III study to collect additional safety and efficacy data with deferasirox film-coated tablets in patients completing study CICL670F2201

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List of abbreviations

AE	Adverse Event
AML	Acute Myeloid Leukemia
ALT/SGPT	Alanine aminotransferase/serum glutamic pyruvic transaminase/SGPT
AST/SGOT	Aspartate aminotransferase/serum glutamic oxaloacetic transaminase/SGOT
AUC	Area under the concentration time curve
AUC_{last}	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass × time × volume-1) after single dose
AUC_{inf}	The AUC from time zero to infinity
C_{max}	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass × volume-1)
CMO&PS	Chief Medical Office and Patient Safety
CRO	Contract research organization
DFO	Deferoxamine mesylate
DT	Dispersible tablet
eCRF	Electronic case report/record form
ECG	Electrocardiogram
EOT	End of treatment
FCT	Film-coated tablet
FAS	Full analysis set
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICH	International conference on harmonization
ICMJE	International Committee of Medical Journal Editors
ICT	Iron chelation therapy
IEC	Independent Ethics Committee
IPSS-R	Revised International Prognostic Scoring System
IRB	Institutional Review Board
LIC	Liver iron concentration
LPLV	Last patient last visit
MDS	Myelodysplastic syndrome
MedDRA	Medical dictionary for regulatory activities terminology
NCCN	National Comprehensive Cancer Network
NSAIDs	Non-steroidal anti-inflammatory drugs
PHI	Protected health information
PRBC	Packed red blood cells
PRO	Patient reported outcome
QoL	Quality of life
RBC	Red blood cells
REB	Research Ethics Board
SAE	Serious adverse event
SUSARs	Suspected Unexpected Serious Adverse Reactions
UGT	Uridine 5'-diphospho-glucuronosyltransferase

[redacted]

ULN	Upper limit of normal range

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study.
Dose level	The dose of drug given to the patient (total daily or weekly etc.).
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the 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 whose properties are 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 that are 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 in within approved indication/dosage.
Other study treatment	Any drug administered to the patient as part of the required study procedures that were not included in the investigational treatment.
Patient number	A unique identifying number assigned to each patient who enrolls in the study.
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as Screening, Baseline, Titration, Washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
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	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason; may or may not also be the point/time of premature patient withdrawal.
Supportive treatment	Refers to any treatment required by the exposure to a study treatment, e.g. premedication of vitamin supplementation and corticosteroid for pemetrexed disodium.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points

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Protocol summary:

Title	Open-label, multicenter, single arm, phase III study to collect additional safety and efficacy data with deferasirox film-coated tablets in patients completing study CICL670F2201
Brief title	Extended evaluation of deferasirox film-coated tablet (FCT) formulation
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of the present study is to: • Assess the safety of the deferasirox FCT formulation in patients with transfusion-dependent thalassemia or myelodysplastic syndrome (MDS) (very low, low or intermediate risk). • Assess the efficacy of the deferasirox FCT in reduction or maintenance of iron burden as measured by serum ferritin level.
Primary Objective	The primary objective is to evaluate the overall safety of deferasirox FCT formulation in patients with transfusion-dependent thalassemia or MDS at very low, low or intermediate risk.
Secondary Objective	The secondary objective is: • To evaluate efficacy of deferasirox FCT on serum ferritin levels (decrease or maintenance, according to the individual therapeutic goal).
Study design	This is a an open-label, multicenter, single arm, phase III study aimed at collecting additional data on safety and tolerability as well as data on efficacy of the deferasirox FCT formulation in patients with thalassemia or MDS (very low, low or intermediate risk) when treated for more than 24 weeks on study CICL670F2201. The study treatment duration will be for a maximum of 24 months.
Population	The study population will consist of patients aged 10 years or older, male or female with transfusion-dependent thalassemia or MDS at very low, low or intermediate risk recruited at Region Europe participating sites that have completed the 24-week treatment under study CICL670F2201. Patients who have withdrawn prematurely from that study will not be enrolled.
Inclusion criteria	Patients eligible for inclusion in this study have to meet **all** of the following criteria: • Have completed 24-weeks of study treatment as described in protocol CICL670F2201. • Are deemed to be tolerating deferasirox treatment by the investigator. • Provided written informed consent/assent before any study-specific procedures are performed. For pediatric patients, consent will be obtained from parent(s) or legal patient's representative. Investigators will also obtain assent of patients according to local, regional or national guidelines.

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	• Are deemed to be tolerating deferasirox treatment by the investigator if continuing directly from study CICL670F2201. For reference, the inclusion criteria in the study CICL670F2201 were stated as follows: 1. Written informed consent/assent before any study-specific procedures. For pediatric patients, consent will be obtained from parent(s) or legal patient's representative. Investigators will also obtain assent of patients according to local, regional or national guidelines. 2. Male and female patients aged ≥ 10 years 3. Patients with transfusion-dependent thalassemia and iron overload, requiring deferasirox DT at doses of ≥ 30 mg/kg/day as per the investigator's decision, OR Patients with very low, low or intermediate (int) risk myelodysplastic syndrome (MDS) and iron overload, requiring deferasirox DT at doses of ≥ 20 mg/kg/day as per the investigator's decision. • The very low, low or intermediate (int) risk MDS should be determined by the Revised International Prognostic Scoring System (IPSS-R) and IPSS-R must be confirmed by a bone marrow examination within 6 months prior to study entry and must be hematologically stable with a patient's life expectancy of at least 1 year. 4. History of transfusion of at least 20 packed red blood cells (PRBC) units and anticipated to be transfused with at least 8 units of PRBCs annually during the studySerum ferritin > 1000 ng/mL, measured at Screening Visit 1 and Screening Visit 2 (the mean value will be used for eligibility criteria).
Exclusion criteria	The exclusion criteria will follow those described for CICL670F2201, which were as follows: 1. Creatinine clearance below the contraindication limit in the locally approved prescribing information. Creatinine clearance will be estimated from serum creatinine at Screening Visit 1 and Screening Visit 2 and the mean value will be used for eligibility criteria. 2. Serum creatinine > 1.5 × upper limit of normal range (ULN) at Screening measured at Screening Visit 1 and Screening Visit 2 (the mean value will be used for eligibility criteria). 3. Alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT) > 5 × ULN, unless liver iron concentration (LIC) confirmed as > 10 mg Fe/dw within 6 months prior to Screening Visit 1. 4. Significant proteinuria as indicated by a urinary protein/creatinine ratio > 0.5 mg/mg in a non-first void urine sample at Screening Visit 1 or Screening Visit 2. 5. Patients with significant impaired gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of oral deferasirox (e.g. ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection). 6. Clinical or laboratory evidence of active Hepatitis B or Hepatitis C (Hepatitis B surface Antigen (HBsAg) in the absence of Hepatitis B surface antibody (HBsAb) or HCV antibody positive with HCV RNA positive).

[redacted]

	7. Patients with psychiatric or addictive disorders which prevent them from giving their informed consent or undergoing any of the treatment options or patients unwilling or unable to comply with the protocol.
Investigational and reference therapy	Deferasirox FCT will be provided as 90 mg, 180 mg and 360 mg dose strengths for once daily oral use. No reference therapy is included in this study.
Efficacy assessments	Serum ferritin level
Safety assessments	Safety will be monitored by assessing the following parameters: • Hematology, blood chemistry (including renal and hepatic parameters) and urinalysis. • Adverse events (AEs) and in particular specific gastrointestinal events. • Vital signs. • Physical examinations. • Ocular examinations.Auditory examinations.
Other assessments	Not applicable
Data analysis	Data from all centers participating in this study will be pooled for analyses. Standard descriptive analyses will include: • Frequencies and percentages for categorical data; • n, mean, standard deviation, minimum, median, 25^{th} and 75^{th} percentiles and maximum for continuous data. Detailed statistical analysis methods will be defined in statistical analysis plan documentation.
Key words	New formulation, deferasirox, film-coated tablet, chelation, iron overload, safety, long-term

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Amendment 1 (25-Oct-2017)

Amendment rationale

This protocol amendment is substantial and it is issued for the following reasons:

- The description related to study treatment duration in Protocol Summary, Section 4.1 (Description of study design), Section 6.1.5 (Treatment duration), and Section 7.1.3 (Treatment period) has been amended to clarify that there is no obligation for a subject to be withdrawn from the study upon local commercial availability of the FCT.
- As this study has its own CTA and EUDRACT numbers and is not, as such, an extension study, the references to "Core and Extension" study were removed throughout the protocol. However, enrolment is only open to patients who had completed CICL670F2201 study.
- In alignment with the Exjade prescribing information, deferasirox is contraindicated in patients with estimated creatinine clearance less than 60 mL/min (Section 6.3.1.2), immediate discontinuation of patient if severe cutaneous adverse reaction occurs (Section 6.3.1.5) and guidance on treating patients who develop moderate hepatic impairment (Child-Pugh Class B) (Section 6.3.1.6) during the trial is provided.
- In addition guidance was added regarding the concomitant administration of deferasirox with CYP1A2 substrate theophylline (Section 6.4.2), cholestyramine (Section 6.4.3) and drugs that have ulcerogenic potential (Section 6.4.4) in alignment with the Exjade prescribing information.
- To correct discrepancies on the description of the visit intervals between Table 7-1 (Visit evaluation schedule) and protocol text in Section 4.1 (Description of study design), Section 6.3.1.3 (Changes in serum ferritin), Section 7.1.3 (Treatment period), and Section 7.2.1 (Efficacy assessments).
- To clarify the following aspects in Section 6.1.1 (Dosing regimen):
  - Regarding patient's recruitment.
  - Starting dose calculation for patients who completed CICL670F2201 study and switched to commercially available deferasirox dispersible tablet or other iron chelation therapy.
  - Timing of drug administration in accordance with the Investigator's brochure version 18.1.
- Clarification on drug supply disposal and destruction in Section 6.6.4.
- To correct the description for local clinical laboratory parameters collection plan (Hematology) described in Table 7-2 (Local clinical laboratory parameters collection plan).
- To remove reference related to collection of pregnancy outcomes for the pregnant partners of male patients in Section 8.4 (Pregnancies) in accordance with Novartis's pregnancy guidance working group.
- To clarify the demographic and other baseline data to be summarized descriptively in Section 10.2 in line with actual eCRF design. Specifically regarding:
  - Ethnicity

[redacted]

  - ECG
  - Audiometric test
  - Ocular exam
- To correct the description for duration of treatment exposure, actual and planned daily dose in Section 10.3 (Treatments).
- Clarification on the descriptive statistical analyses of the primary objective in Section 10.4.2 (Statistical hypothesis, model, and method of analysis). Objectives were unchanged.
- To update description for supportive sensitivity analyses in Section 10.4.4.
- To add description for secondary efficacy objective analyses in Section 10.5.1.
- To update description for adverse events analyses in Section 10.5.2.1.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- Protocol summary (Study design): Corrected to "The study treatment duration of treatment will be for a maximum of 24 months".
- Section 1.2.1.1 (Clinical experience with deferasirox) and Section 2.6 (Risks and benefits): Updated "to align with the Exjade prescribing information".
- Section 4.1: Corrected to
  - Following enrollment (Visit 3/Day 1) patients will return to the site at 2 week intervals until Visit 5 (Month 1). Thereafter, scheduled visits will be monthly.
  - The planned duration of treatment in this study is for a maximum of 24 months.
  - In Figure 4-1 references to "Core and Extension" study were removed and undated to reflect changes based on the amendment rationale.
- Section 6.1.1: Amended to
  - "Having completed the 24 weeks of CICL670F2201 study, patients recruited at Region Europe participating sites will be invited to participate in this study to continue FCT or switch from DT to the FCT formulation".
  - "Patients who completed CICL670F2201 study and had switched to commercially available DT or other ICT will have to undergo a 5-day washout period and will then be assigned FCT at a starting dose equivalent to their last deferasirox dose in CICL670F2201 study".
  - "Patients will swallow the required number of deferasirox FCT every day either on an empty stomach or with a light meal.
  - Removed reference related to "However, all patients should take their deferasirox FCT dose before 12:00 PM (noon)".
- Section 6.1.5: Corrected to"The duration of treatment in the current study is for a maximum of 24 months".
- Section 6.3.1.2: Added "Caution based on creatinine clearance".

[redacted]

- Section 6.3.1.3: Corrected to "Following enrollment (Visit 3/Day 1) serum ferritin will be monitored at 2 week intervals until Visit 5 (Month 1). Thereafter, scheduled assessments will be monthly".
- Section 6.3.1.5: added "Guidance regarding treatment discontinuation if severe cutaneous adverse reaction occurs".
- Section 6.3.1.6: added "Guidance related to dose modifications for patients with moderate hepatic impairment (Child-Pugh B)".
- Section 6.4.2: Added "Guidance related to concomitant use of deferasirox with CYP1A2 substrate theophylline".
- Section 6.4.3: Added "Guidance related to concomitant use of deferasirox with cholestyramine".
- Section 6.4.4: Added "Guidance related to concomitant use of deferasirox with drugs that have ulcerogenic potential".
- Section 6.6.4: Updated with "A signed Certificate of Destruction (or equivalent documentation as per local procedure) will be required for archiving in the Trial Master File".
- Section 7.1.3: Corrected to
  - "The planned duration of treatment in this study is for a maximum of 24 months".
  - "Treatment visits will commence at Visit 3 (Baseline). Patients will return to the site at 2 week intervals until Visit 5 (Month 1). Thereafter, scheduled visits will be monthly until EOT (Visit 28/Month 24)".
- Section 7.2.1: Corrected to "Serum ferritin testing will be performed at Screening Visit 1 and 2. Following enrolment (Visit 3/Day 1) serum ferritin will be tested at 2 week intervals until Visit 5 (Month 1). Thereafter, scheduled testing will be monthly".
- Table 7-2: Corrected to remove "differential" incorrectly associated with RBC morphology as following "Hematocrit, Hemoglobin, Platelets, RBCs, White blood cells count with differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils), RBC Morphology".
- Section 8.4: Removed the sentence regarding the collection of pregnancy outcomes for the female partners of male patients and consent to report information regarding these pregnancy outcomes.
- Section 10.2: Updated to
  - "Ethnicity (Hispanic/Latino, Chinese, Indian (Indian subcontinent), Japanese, Other)".
  - "Clinically significant abnormality in ECG (Yes, No)".
  - "Overall interpretation in audiometric test (Normal, Clinically insignificant abnormality, Clinically significant abnormality)".
  - "Overall interpretation in ocular exam (Normal, Clinically insignificant abnormality, Clinically significant abnormality)".
- Section 10.3: Removed reference related to "duration of exposure (<4 weeks, 4-<12 weeks, ≥ 12 weeks" and updated with "duration of exposure (at intervals as described in the Statistical Analysis Plan".

[redacted]

- Section 10.4.2: Updated to "Frequencies, percentages, and 95% confidence intervals (CIs) for overall incidences of any AEs during the on-treatment period".
- Section 10.4.4: Added "Prior chelation therapy (DFX, any other ICT)".
- Section 10.5.1: Added "The Baseline serum ferritin value will be defined as the average of the 2 measurements obtained during the Screening period".
- Section 10.5.2.1: Updated with:
  - An overall summary of type of AEs will be presented by severity.
  - Specific groupings of AEs of special interest will be considered and the number of patients with at least one event in each grouping will be reported.
  - Incidence of AEs of special interest will be summarized by grouping and preferred term.
- The following protocol sections were amended to reflect the changes given in the latest protocol template version dated 06-Apr-2017.
  - Section 6.3.1: For patients who do not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions are recommended in order to allow patients to continue the study treatment.
  - Removed "Section 6.3.3 (Anticipated risks and safety concerns of the study drug)".
  - Section 7.2.2.7.1: Clinically significant abnormalities present at Screening should be reported on the Medical History eCRF page.
  - Section 8.1.1: Information about any deaths (related to an AE or not) will also be collected using an end of treatment form.
  - Section 8.2.2:
    - 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.
    - Removed reference related to "the telephone and telefax numbers of the contact person in the local DS&E department".
    - Detailed instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each site.
    - Follow-up information is submitted in the same way as the original SAE Report.
    - Novartis DS&E is updated to "Chief Medical Office and Patient Safety".
  - Section 8.4: Novartis DS&E is updated to "Chief Medical Office and Patient Safety".
  - Section 11.5: Updated "To reflect recent changes in the Novartis Guidelines for the Publication of Results from Novartis-sponsored Research".

IRBs/IECs

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.

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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 protocol amendment.

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1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Chronic iron overload represents a serious complication of potentially lifesaving blood transfusions which are the mainstay of therapy in transfusion-dependent anemias. Since humans have no mechanism for the active elimination of iron from the body, excess iron received via transfusions deposit in various tissues of the body, particularly the liver, heart and endocrine organs, leading to end-organ dysfunction and eventually organ failure. Indeed, organ failure due to chronic iron overload represents the major cause of death in patients with β-thalassemia major who receive blood transfusions regularly without appropriate chelation therapy (Cappellini et al 2006).

Overview β-thalassemia

Beta-thalassemias are a group of hereditary blood disorders characterized by anomalies in the synthesis of the beta chains of hemoglobin resulting in variable phenotypes ranging from severe anemia to clinically asymptomatic individuals.

Beta-thalassemia is prevalent in the Mediterranean basin, the Middle East, Central Asia, India, Southern China, and the Far East, as well as countries along the north coast of Africa and in South America.

The total annual incidence of symptomatic individuals is estimated at 1 in 1 00 000 throughout the world and 1 in 10 000 people in the European Union. However, accurate data on carrier rates are lacking for many populations.

Three main phenotypic forms have been described: thalassemia major, thalassemia intermedia and thalassemia minor with β-thalassemia major being the most severe form of the disease. Individuals with β-thalassemia major usually present within the first 2 years of life with severe anemia requiring regular red blood cell (RBC) transfusions. Findings in untreated or poorly transfused patients with thalassemia major are growth retardation, pallor, jaundice, poor musculature, hepatosplenomegaly, development of masses from extramedullary hematopoiesis, and skeletal changes that result from expansion of the bone marrow. If left untreated, 80% of β-thalassemia major patients die within the first 5 years of life due to anemia-related conditions. As such, transfusion therapy remains the mainstay of treatment in β-thalassemia major patients. Regular transfusion therapy leads to iron overload with iron-related complications including endocrine complications, such as growth retardation, failure of sexual maturation, diabetes mellitus; cardiac complications, such as dilated myocardiopathy, and liver complications including fibrosis and cirrhosis.

The therapeutic concept of iron chelation has been established with more than 50 years of clinical experience with Desferal®, deferoxamine mesylate (DFO). However, poor oral bioavailability and short plasma half-life ($t_{1/2}$) has necessitated its application as slow subcutaneous or intravenous infusion. Iron-chelation therapy with DFO is extremely demanding with many patients experiencing considerable discomfort from administration of the drug, as well as a significant negative impact on their quality of life (QoL)

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(Arboretti et al 2001), thus resulting in poor compliance. The lack of compliance with DFO administration in patients who have serious blood disorders has necessitated recognition for the need of an effective iron chelator which can be given via the more convenient oral route.

Compliance with iron chelation therapy (ICT) mainly influences the frequency and severity of iron overload-related complications (Galanello and Origa 2010) with demonstrated improvement in organ dysfunction and survival in patients compliant with therapy (Gabutti and Piga 1996).

Transfusions and oral ICT have dramatically improved the QoL for patients with severe anemias. Previously a rapidly fatal disease in early childhood, β- thalassemia is now a chronic disease compatible with a prolonged life expectancy. Today, life expectancy varies between 25 and 55 years, depending on patient compliance with medical treatment, particularly iron chelation (Cappellini 2008).

Overview of myelodysplastic syndromes

The myelodysplastic syndromes (MDS) include a diverse group of acquired disorders of hematopoiesis, collectively characterized by bone marrow failure (i.e. inadequate production of healthy, mature blood cells) and a tendency for clonal evolution, including progression to acute myeloid leukemia (AML) defined by ≥ 20% blast cells in the marrow.

Although relatively rare, MDS are the most common malignant bone marrow disorders. In the general population, MDS occur in 5 per 1 00 000 people. However, among individuals > 70 years, the incidence increases between 22 and 45 per 1 00 000 and increases further with age (National Comprehensive Cancer Network ((NCCN) 2011). In most cases, the cause of MDS is unknown although some cases have been linked to exposure to chemotherapy, radiation, and pesticides.

Managing MDS is complicated by the generally advanced age of the patients, the attendant non-hematologic comorbidities, and the older patients' relative inability to tolerate certain intensive forms of therapy (NCCN 2011).

Signs and symptoms of MDS relate to hematopoietic failure, manifesting in anemia, thrombocytopenia or leukopenia. The anemia is often severe, leading to regular transfusions and reduced QoL.

Treatment goals for patients with lower risk MDS primarily involve managing cytopenias. While specific therapies and the use of growth factors may alleviate transfusion requirements in some patients, 60-80% of patients do not respond and require ongoing platelet and RBC transfusions due to impaired hematopoiesis.

In many patients, this leads to chronic RBC transfusion therapy, and the development of secondary iron overload. Furthermore, iron overload may already be present in many MDS patients even before the start of the transfusion regimen. The intestinal iron intake is stimulated due to anemia and/or ineffective erythropoiesis. Liver dysfunction, cirrhosis and endocrinopathies have been described in multi-transfused MDS patients (even with a short-term duration of transfusion), where even mild liver function abnormalities have been associated with marked hepatic iron overload and portal fibrosis on biopsy (Schafer et al 1981, Jaeger et al 1992).

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Iron overload may impact survival in MDS, which is especially relevant for low-risk patients. A retrospective analysis of 467 MDS patients demonstrated that cardiac failure and liver cirrhosis constituted 51% and 8% respectively of the non-leukemic causes of death (Malcovati et al 2005). Use of DFO in iron-overloaded MDS patients has been reported to improve organ dysfunction (Jensen et al 2003, Schafer et al 1985), and even improve cytopenias (Jensen et al 1996).

1.2 Introduction to investigational treatment

1.2.1 Overview of deferasirox film-coated tablet

The new deferasirox film-coated tablet (FCT) formulation for oral administration is being developed due to the chronic nature of chelation therapy and the importance of patient compliance. The FCT, which will be used in this study, contains the same active substance of the iron chelator deferasirox (Exjade® company research code ICL670) but has been strength-adjusted to achieve comparable exposure to the currently approved dispersible tablet (DT). The FCT is available in 3 dose strengths (90 mg, 180 mg and 360 mg) and is dosed based on body weight. The FCTs can be taken with or after a light meal.

1.2.1.1 Clinical experience with deferasirox

The efficacy and safety of deferasirox have been evaluated in a large prospective clinical trials program that has generated long-term data in patients with transfusional iron overload from a variety of transfusion-dependent anemias. Long-term studies (up to 5 years) in patients aged ≥ 2 have demonstrated that deferasirox, administered at doses of 10-40 mg/kg/day effectively reduce or maintain total body iron as assessed by serum ferritin or liver iron concentration (Cappellini et al 2011). Deferasirox was also shown to prevent or reduce cardiac iron overload in patients with thalassemia major as evidenced by changes in T2* cardiac MRI (Pennell et al 2010, Pennell et al 2011, Pennell et al 2012, Pennell et al 2014) and to be associated with improvement in liver pathology as evidenced by biopsy-assessed Ishak fibrosis staging and necro-inflammatory scores (Deugnier et al 2011), as well as improvement in hematopoietic parameters in myelodysplastic syndrome (MDS) patients using the International Working Group 2006 criteria (Gattermann et al 2012, List et al 2012). Improvements in hematopoietic parameters were also seen in patients with Aplastic Anemia (Lee et al 2013). Moreover, the data accumulated to date have well characterized the safety profile of deferasirox across all age groups and for a wide range of transfusion-dependent anemias including β-thalassemia, sickle cell disease, and MDS, indicating that the vast majority of adverse events are mild to moderate in severity and manageable with dose adjustments or interruptions. In patients with non-transfusion dependent thalassemia and iron overload, deferasirox at starting doses of 5 and 10 mg/kg/day with dose escalation up to 20 mg/kg/day was shown to reduce iron overload as evidenced by significant decreases in liver iron concentration and serum ferritin and with an overall safety profile comparable to placebo (Taher et al 2012). Continued treatment with up to 2 years resulted in continuous decrease in iron overload (Taher et al 2013). A new FCT formulation, containing the same deferasirox drug substance as the DT formulation has been developed. As of 31 May 2017, the FCT has been approved in several countries worldwide including the US, European Union, Canada and Switzerland under the name Jadenu or Exjade. The currently available limited

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clinical trial data with the new formulation, suggests a safety and efficacy profile that is consistent with the known profile of the DT deferasirox formulation. Hence, the continuously accumulating and available data to date confirm the favorable benefit-risk profile of deferasirox in patients with transfusional iron overload and those with non-transfusion dependent thalassemia.

2 Rationale

2.1 Study rationale and purpose

The availability of deferasirox DT (Exjade®) as a once-daily oral chelation treatment provided patients with a treatment that was a significant improvement over parenteral DFO therapy. This was confirmed in studies that measured satisfaction and QoL of oral vs. parenteral chelation (Cappellini et al 2007, Osborne et al 2007). Novartis is currently developing a deferasirox FCT with the same active substance as the deferasirox DT but with modified excipients.

After strength-adjustment, the new formulation was shown to achieve the same overall exposure (AUC_{last} and AUC_{inf}) as the currently approved DT formulation in a single-dose healthy volunteer study (ICL670F2102); the peak serum concentrations (C_{max}) were approximately 30% higher. In addition, a food effect study (ICL670F2103) indicated that the FCT can be taken with a light meal (the current deferasirox DT has to be taken on an empty stomach, at least 30 mins before a meal).

Thus, the FCT formulation has the advantage of more favorable pharmacokinetic properties (a reduced food effect and a more predictable dose-exposure relationship in clinical practice), better palatability, and a more convenient mode of administration compared to the currently available DT formulation. It is intended to be used for all currently approved deferasirox indications. Thus, the new FCT formulation could represent a significant improvement in patient care and support compliance with chelation therapy.

- Study CICL670F2201 was a randomized, open-label, multicenter, 2-arm, phase II study initiated to: Assess the safety of the DT and the FCT formulations in patients with transfusion-dependent thalassemia or MDS (very low, low or intermediate risk) treated over 24 weeks.

The present protocol describes study CICL670AIC04 “Open-label, multicenter, single arm, 24-month, phase III study to collect additional safety and efficacy data with deferasirox film-coated tablets in patients completing study CICL670F2201”, which aims to:

- Provide patients enrolled and completing 24 weeks of treatment in study CICL670F2201, the possibility to have additional treatment with the deferasirox FCT.
- Collect additional longer term data on the safety and the tolerability of the deferasirox FCT.
- Collect efficacy data on the deferasirox FCT in reduction or maintenance of iron burden as measured by serum ferritin level.

[redacted]

2.2 Rationale for the study design

This is an open-label, multicenter, single arm, phase III study that aims to provide additional drug exposure following study ICL670F2201, which is a randomized, open-label, multicenter, 2-arm, phase II study.

Two anemia types, transfusion-dependent thalassemia and MDS (very low, low or intermediate risk), were chosen for enrollment in study CICL670F2201. As transfusion-dependent thalassemia patients are more commonly children/adolescents while MDS patients are mostly adults and elderly, the population selected for CICL670F2201 allowed inclusion of patients from all deferasirox DT approved age groups. However, not more than 50% of MDS patients per arm were included in CICL670F2201. Patients assigned to either the deferasirox DT or deferasirox FCT arm and who completed the study period of 24 weeks are allowed to participate in this study. Patients who have withdrawn prematurely from CICL670F2201 will not be enrolled. Patients with a lag period between completion of CICL670F2201 and enrollment in this study can still be enrolled even if they had to switch to DT or other chelation therapy in this period.

The treatment duration of 24 weeks in CICL670F2201 is considered sufficient to assess the safety, pharmacokinetics (PK) and patient reported outcomes (PRO) of the 2 formulations. Previous studies of pediatric and adolescent patients have demonstrated differences in iron chelation medication compliance within this time period (Jordan et al 2012, Alvarez et al 2009). Long-term safety, tolerability, and efficacy will be assessed as objectives of this current study.

Overall safety is the primary objective of the current study and will be addressed by measuring the frequency and severity of adverse events (AEs) and changes in laboratory values. Time points for assessing laboratory values have been chosen based on the current labeling for deferasirox DT (Exjade®) in order to be as close as possible to the daily practice in administering the study treatment.

Recognizing that it is important to allow patients to continue their therapy under a controlled, even if less frequent monitoring plan, this multi-center, open-label study has been designed to provide additional supply of deferasirox FCT to patients recruited in Region Europe sites in study CICL670F2201 through a Novartis ORE-sponsored study, provided the patients have completed the CICL670F2201 study and are tolerating treatment.

2.3 Rationale for dose and regimen selection

Deferasirox FCT is available in 3 dose strengths (90, 180 and 360 mg). In CICL670F2201, all ICT naïve patients randomized to the study received a deferasirox DT starting dose of 20 mg/kg/day, or the equivalent FCT starting dose of 14 mg/kg/day. All iron chelation pre-treated patients received deferasirox DT or an equivalent FCT starting dose corresponding to their pre-washout dose. In CICL670F2201, patients on DT formulation were allowed dose adjustments with ± 5 to 10 mg/kg/day, but no more than 40 mg/kg/day while patients on FCT formulation were allowed dose adjustments with ± 3.5 to 7 mg/kg/day, but no more than 28 mg/kg/day.

At the start of this study, the following will occur:

[redacted]

- Patients continuing directly from the CICL670F2201 study who were originally randomized to the deferasirox FCT formulation will continue treatment at the same dose they were assigned at the end of the CICL670F2201 study.
- Patients continuing directly from the CICL670F2201 study who were originally assigned to the deferasirox DT formulation will be switched to the deferasirox FCT formulation and will be assigned a deferasirox FCT dose equivalent to the deferasirox DT dose they were assigned at the end of CICL670F2201 study (Appendix 14.2).
- Patients completing the CICL670F2201 study who had switched to commercially available DT or other ICT will have to undergo a 5-day washout period and then use an equivalent FCT starting dose corresponding to their pre washout iron chelator dose.

Dose adjustment for better treatment effects based on serum ferritin levels and investigator's judgment, will be allowed if necessary every 3 months, with ± 3.5 to 7 mg/kg/day, but no more than 28 mg/kg/day.

2.4 Rationale for choice of combination drugs

Not applicable.

2.5 Rationale for choice of comparators drugs

Not applicable.

2.6 Risks and benefits

The first worldwide marketing authorization for deferasirox was received on 02-Nov-2005 (International Birth Date) in United States (US). Deferasirox is approved in over 100 countries worldwide for the treatment of transfusional hemosiderosis in patients 2 years of age and older.

Deferasirox is available as a DT containing 125, 250, or 500 mg of drug substance under Exjade® brand name. In certain countries, deferasirox is available as DT containing 100 or 400 mg and as FCT containing 90, 180 or 360 mg of drug substance. In addition, granules corresponding to an amount equivalent to 90, 180, 360 mg and 400 mg of drug substance have also been developed. As of 31-May-2017, the FCT has been approved in several countries worldwide including the US, European Union, Canada and Switzerland under the name Jadenu or Exjade. Granules have been approved in the US and Japan, and received CHMP Opinion in European Union.

Approximately, 8 121 subjects have received deferasirox in clinical trials as of 31-Oct-2016. The cumulative patient exposure since the International Birth Date of the product is estimated to be approximately 335 128 patient-treatment years. Although reports of hypersensitivity, pancreatitis, toxic epidermal necrolysis and rare fatal outcomes of renal events are currently being incorporated into the core data sheet and prescribing information. The benefit-risk profile for deferasirox remains positive for the treatment of iron overload and justifies unaltered continuation of the development program.

The risk to subjects in this trial may be minimized by compliance with the eligibility criteria and study procedures, close clinical monitoring, specific dose modification (for patients who

do not tolerate the protocol-specified dosing schedule) and stopping rules (refer Section 6 for details).

3 Objectives and endpoints

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

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4
To evaluate the overall safety of deferasirox FCT formulation in patients with transfusion-dependent thalassemia or MDS at very low, low or intermediate risk	Overall safety, as measured by frequency and severity of AEs and changes in laboratory values of interest i.e. serum creatinine and creatinine clearance	
Secondary		Refer to Section 10.5.1
To evaluate efficacy of deferasirox FCT on serum ferritin levels (decrease or maintenance, according to the individual therapeutic goal).	Absolute and relative change of serum ferritin level over time	

Abbreviations: FCT=film-coated tablet; MDS=myelodysplastic syndrome

4 Study design

4.1 Description of study design

This is an open-label, multicenter, single arm, 24-month, phase III study aimed at collecting additional data on safety and tolerability as well as data on efficacy of the FCT formulation in patients with transfusion-dependent thalassemia or MDS (very low, low or intermediate risk) when treated for more than 24 weeks in CICL670F2201. It is a pre-requisite for the patient to provide written consent for participation in this study. This must be in place prior to performing any study-related procedures or assessments, including those described at the Screening Visits (Table 7-1).

Patients from Region Europe participating sites in study CICL670F2201 who have completed the 24-week treatment period with ongoing tolerance to deferasirox (in the Investigator's opinion) and fulfilling all other eligibility criteria (Section 5) will be given the opportunity to continue study treatment and follow-up assessments in this study. This will include patients from Region Europe who completed 24-weeks of treatment with either deferasirox FCT or deferasirox DT in CICL670F2201; and patients with a lag period between completion of CICL670F2201 and start of this study i.e. those patients who completed CICL670F2201 and have already switched to commercially available deferasirox DT or another ICT.

In CICL670F2201, iron-chelation naïve patients were assigned either deferasirox DT 20 mg/kg once daily or deferasirox FCT 14 mg/kg once daily. All iron chelation pre-treated

[redacted]

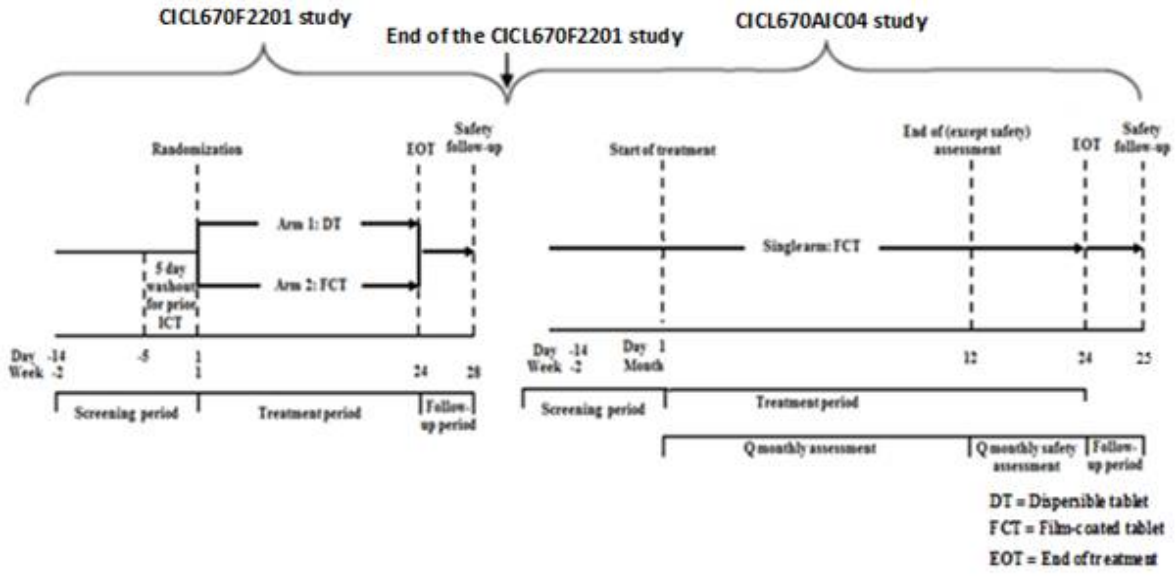
patients were assigned a deferasirox DT or an equivalent FCT starting dose corresponding to their pre-washout dose. At the start of this study, the following will occur:

- Patients continuing directly from CICL670F2201 who were originally randomized to the deferasirox FCT formulation will continue treatment at the same dose they were assigned at the end of CICL670F2201.
- Patients continuing directly from CICL670F2201 who were originally assigned to the deferasirox DT formulation will be switched to the deferasirox FCT formulation and will be assigned a deferasirox FCT dose equivalent to the deferasirox DT dose they were assigned at the end of CICL670F2201 (Appendix 14.2).
- Patients completing CICL670F2201 who had switched to commercially available DT or other ICT will have to undergo a 5-day washout period and then use an equivalent FCT starting dose corresponding to their pre washout iron chelator dose.

Study treatment should be administered by the patient once per day. Following enrollment (Visit 3/Day 1) patients will return to the site at 2 week intervals until Visit 5 (Month 1). Thereafter, scheduled visits will be monthly (please refer Table 7-1 for study visit evaluation schedule). Patients may return to the study center more frequently at the physician's discretion as clinically indicated or as per standard of care. Serious adverse events (SAEs) will be reported to the Novartis safety database within 24 hours of investigator or treating physician's knowledge of the event from the time the patient has signed informed consent until at least 30 days after the patient stopped study treatment. All other assessments are performed as per standard of care at the site and will not be captured in the eCRF.

Patients who discontinue study treatment before completing the study should be scheduled for a visit within 7 days after the last dose, at which time all of the assessments listed for the end of treatment (EOT) visit (i.e. Month 24). The planned duration of treatment in this study is for a maximum of 24 months.

Figure 4-1 Study design



[redacted]

4.2 Timing of interim analyses and design adaptations

Not applicable.

4.3 Definition of end of study

Completion of this study as a whole will occur upon the availability and accuracy verification of the last data point (Visit 28) required for statistical analysis.

Refer to Section 7.1 for details.

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in Section 7 for a prematurely 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 IECs of the early termination of the trial.

5 Population

5.1 Patient population

The study population will consist of patients aged 10 years or older, male or female with transfusion-dependent thalassemia or MDS at very low, low or intermediate risk recruited at all Region Europe participating sites that have completed the 24-week treatment under protocol CICL670F2201 and who have been randomized to the FCT formulation or to the DT formulation. Patients who will have withdrawn prematurely from CICL670F2201 will not be enrolled. Patients with a lag period between completion of CICL670F2201 and enrollment in this study can still be enrolled even if they had to switch to DT or other chelation therapy in this period, following washout.

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

5.2 Inclusion criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria:

- Have completed 24-weeks of study treatment as described in protocol CICL670F2201.
- Are deemed to be tolerating deferasirox treatment by the investigator.
- Provided written informed consent/assent before any study-specific procedures are performed. For pediatric patients, consent will be obtained from parent(s) or legal patient's representative. Investigators will also obtain assent of patients according to local, regional or national guidelines.
- Are deemed to be tolerating deferasirox treatment by the investigator if continuing directly from protocol CICL670F2201.

The inclusion criteria in study CICL670F2201 were stated as follows:

[redacted]

1. Written informed consent/assent before any study-specific procedures. For pediatric patients, consent will be obtained from parent(s) or legal patient's representative. Investigators will also obtain assent of patients according to local, regional or national guidelines.
2. Male and female patients aged ≥ 10 years
3. Patients with transfusion-dependent thalassemia and iron overload, requiring deferasirox DT at doses of ≥ 30 mg/kg/day as per the investigator's decision,

   OR

   Patients with very low, low or intermediate (int) risk myelodysplastic syndrome (MDS) and iron overload, requiring deferasirox DT at doses of ≥ 20 mg/kg/day as per the investigator's decision.
   - The very low, low or intermediate (int) risk MDS should be determined by the Revised International Prognostic Scoring System (IPSS-R) and IPSS-R must be confirmed by a bone marrow examination within 6 months prior to study entry and must be hematologically stable with a patient's life expectancy of at least 1 year.
4. History of transfusion of at least 20 packed red blood cells (PRBC) units and anticipated to be transfused with at least 8 units of PRBCs annually during the study
5. Serum ferritin > 1000 ng/mL, measured at Screening Visit 1 and Screening Visit 2 (the mean value will be used for eligibility criteria).

5.3 Exclusion criteria

Patients eligible for this study must not meet **any** of the exclusion criteria defined for study CICL670F2201, which were as follows:

1. Creatinine clearance below the contraindication limit in the locally approved prescribing information. Creatinine clearance will be estimated from serum creatinine at Screening Visit 1 and Screening Visit 2 and the mean value will be used for eligibility criteria.
2. Serum creatinine > 1.5 × upper limit of normal range (ULN) at Screening measured at Screening Visit 1 and Screening Visit 2 (the mean value will be used for eligibility criteria).
3. Alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT) > 5 × ULN, unless liver iron concentration (LIC) confirmed as > 10 mg Fe/dw within 6 months prior to Screening Visit 1.
4. Significant proteinuria as indicated by a urinary protein/creatinine ratio > 0.5 mg/mg in a non-first void urine sample at Screening Visit 1 or Screening Visit 2.
5. Patients with significant impaired gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of oral deferasirox (e.g. ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).
6. Clinical or laboratory evidence of active Hepatitis B or Hepatitis C (Hepatitis B surface Antigen (HBsAg) in the absence of Hepatitis B surface antibody (HBsAb) or HCV antibody positive with HCV RNA positive).

[redacted]

7. Patients with psychiatric or addictive disorders which prevent them from giving their informed consent or undergoing any of the treatment options or patients unwilling or unable to comply with the protocol.
8. Patients with a known history of HIV seropositivity (Elisa or Western blot).
9. History of malignancy of any organ system, treated or untreated, within the past 5 years whether or not there is evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin.
10. Patients participating in another clinical trial or receiving an investigational drug.
11. History of hypersensitivity to any of the study drug or excipients.
12. Significant medical condition interfering with the ability to partake in this study (e.g. systemic uncontrolled hypertension, unstable cardiac disease not controlled by standard medical therapy, systemic disease (cardiovascular, renal, hepatic, etc.).
13. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment. Effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least 6 weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.
    - Male partner sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient.
    - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository.
    - Placement of an intrauterine device or intrauterine system.

      Please note that deferasirox may reduce the efficacy of hormonal contraception thus it is recommended to use alternative methods of contraception as described above.

      Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of child bearing potential.
14. For prohibited medication please refer to Section 6.4.3.
15. Liver disease with severity of Child-Pugh Class B or C.

[redacted]

6 Treatment

6.1 Study treatment

The sponsor will provide the following open label study medication:

- Deferasirox FCT will be provided as 90 mg, 180 mg and 360 mg film-coated tablets for oral use.

6.1.1 Dosing regimen

Having completed the 24 weeks of CICL670F2201, patients recruited at Region Europe participating sites will be invited to participate in this study to continue FCT or switch from DT to the FCT formulation. Patients completing CICL670F2201 and switching to commercially available DT or other ICT will still be eligible to enroll in this study after a 5-day washout period during the Screening period.

All patients randomized in the DT arm in CICL670F2201 and well-managed on treatment with deferasirox DT will use an equivalent FCT dose. Patient switching from DT will use an equivalent FCT dose at the start of this study corresponding to their DT dose at the end of CICL670F2201 (see Appendix 14.2). A patient who is receiving an adjusted dose at the time of completing CICL670F2201 will commence this study receiving that adjusted dose until a time when the investigator deems it necessary to adjust the dose. Patients who completed CICL670F2201 and had switched to commercially available DT or other ICT will have to undergo a 5-day washout period and will then be assigned FCT at a starting dose equivalent to their last deferasirox dose on CICL670F2201.

Dose adjustment for better treatment effects will be allowed every 3 months based on serum ferritin levels and the investigator's judgment. The dose adjustments will be performed in steps of 3.5 to 7 mg/kg/day for deferasirox FCT.

For each patient the daily dose is calculated by the physician based on the patient's actual body weight, and 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). All doses planned and prescribed to the patient and all dose changes including reasons for change during the study must be recorded in the eCRF.

During the regular study visits, the investigator or pharmacist will dispense to the patient and/or legal patient representative, an appropriate number of deferasirox tablets depending on the patients calculated FCT dose. The number of tablets of each strength dispensed will be recorded in the Study Drug dosing Log. Each time the FCT deferasirox drug is dispensed to the patient and/or legal patient representative, the investigator will provide detailed instructions on how to prepare and administer the dose. Patients or legal patient representative will be instructed to take the assigned amount of study drug and will be obliged to return all unused study medication every month. Study medication returned by the patient will be counted and unused study medication will be recorded by the investigator/pharmacist involved in the study. Drug accountability will be noted by the field monitor during site visits and at the completion of the trial.

[redacted]

Medication labels will comply with the legal requirements of the countries where the study is implemented and be printed in the local language. They will supply no information about the patient. Only the patient identifier will be entered on the medication label by the investigator or pharmacist before the corresponding medication is handed out to the patient. The storage conditions for study drug will be described on the medication label.

Patients will swallow the required number of deferasirox FCT once per day either on an empty stomach or with a light meal (see Appendix 14.3 for examples on light meals).

It is recommended that the doses be timed such that they occur at almost the same time each day. For example, if the patient took the study medication at 10:00 AM on first day of treatment, the subsequent dose would also be taken at approximately 10:00 AM on the next day, and so on.

Deferasirox FCT dose adjustments based on safety are allowed at any time point in the study and will be in increments of 3.5-7 mg/kg/day. Throughout the study, the maximum dose of deferasirox FCT will be 28 mg/kg/day.

Table 6-1 Dose and treatment schedule for FCT formulation

Study treatments	Pharmaceutical form and route of administration	Starting Dose	Dose adjustment	Max dose	Frequency and/or Regimen
Deferasirox	Film-coated tablets, per oral	Described in Section 6.1.1 (see Appendix 14.2 for guidance)	± 3.5 - 7 mg/kg/day	28 mg/kg/day	Once daily

6.1.2 Ancillary treatments

Not applicable.

6.1.3 Rescue medication

Not applicable.

6.1.4 Guidelines for continuation of treatment

Guidelines for continuation of treatment are described in Section 6.3 Dose modifications.

6.1.5 Treatment duration

The duration of study treatment in the current study is for a maximum of 24 months.

6.2 Dose escalation guidelines

Not applicable.

[redacted]

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 recommended in order to allow patients to continue the study treatment.

These dose changes must be recorded on the Dosage Administration Record eCRF.

6.3.1.1 Change in patient weight

The dose of study medication will be adapted using dosing table (provided in Appendix 14.1) during the study, if the change (increase or decrease) in body weight exceeds 10% of the body weight compared to the Visit 3 or the last dose adjustment due to change in patient body weight.

6.3.1.2 Elevations in serum creatinine

Serum creatinine should be monitored during the study as stated in the visit evaluation schedule in Table 7-1.

In case of a single increase in serum creatinine, the assessment will be repeated at the next visit, or as clinically indicated.

A deferasirox dose reduction of 7 mg/kg/day for the FCT should be performed if there is a rise in serum creatinine of 33% above Baseline value (average of Visit 1 and 2) resulting in a serum creatinine above the ULN on 2 consecutive visits (a minimum of 7 days apart).

If after a dose reduction, a progressive increase in serum creatinine beyond the ULN is observed, a treatment interruption is recommended.

After a treatment interruption, if serum creatinine falls below the age appropriate ULN on 2 consecutive visits, it is recommended to resume therapy at 50% of the last dose, and after 1 month, if the serum creatinine increase does not recur, study medication can be returned to 100% of the last dose (including body weight adjustment if required).

Use of deferasirox is contraindicated in patients with estimated creatinine clearance less than 60 mL/min.

6.3.1.3 Changes in serum ferritin

Following enrollment (Visit 3/Day 1) serum ferritin will be monitored at 2 week intervals until Visit 5 (Month 1). Thereafter, scheduled assessments will be monthly. The dose of deferasirox FCT should be adjusted if necessary every 3 months based on the trends in serum ferritin and the investigator's judgment.

Dose adjustments should be made in steps of 3.5 or 7 mg/kg/day for deferasirox FCT and are to be tailored to the individual patient's response and therapeutic goals (reduction or maintenance of iron burden). In patients not adequately controlled with deferasirox FCT doses of 21 mg/kg/day, doses of up to 28 mg/kg/day may be considered. Doses above 28 mg/kg/day for deferasirox FCT are not allowed.

[redacted]

In patients whose serum ferritin level has reached the target (usually between 500 and 1000 ng/mL), dose reductions in steps of 3.5 or 7 mg/kg/day for deferasirox FCT should be considered to maintain serum ferritin levels within the target range. If serum ferritin falls below 500 ng/mL, an interruption of study treatment should be considered until serum ferritin rises above 500 ng/mL.

6.3.1.4 Changes in urine protein/creatinine ratio

Proteinuria should be monitored during the study as stated in the visit evaluation schedule in Table 7-1.

For patients who develop proteinuria or a worsening of pre-existing proteinuria (assessed by a dipstick) at any visit, urine samples should be collected and assessed by the local laboratory.

In case of a single increase of the urinary protein/creatinine ratio the assessment should be repeated at the next visit.

Deferasirox dose reduction by 50% should be performed if the urinary protein/creatinine ratio increases to > 0.5 (mg/mg) in 2 consecutive second-void urine samples (a minimum of 48 hours apart), if all other causes of proteinuria have been excluded.

Deferasirox must be temporarily interrupted if the urinary protein/creatinine ratio increases to > 1.0 (mg/mg) in 2 consecutive second-void urine samples (a minimum of 48 hours apart).

Should proteinuria persist, study treatment may be discontinued if the investigator believes it is in the best interest of the patient. Novartis may be contacted by the investigator to discuss dosing options if the investigator so desires.

Dose adjustment will be based on local laboratory results.

6.3.1.5 Skin rash

For skin rash of mild/moderate severity (defined as those causing minimal symptoms, which require no supportive treatment or minimal supportive treatment), study drug should be continued without dose adjustment. The skin rash may resolve spontaneously without further intervention.

If the rash persists for > 1 week or becomes more severe, treatment with study drug will be interrupted. After the rash resolves, the study drug should be resumed at 50% of the patient's last dose and if the rash does not recur, the dose should be increased back to 100% of the patient's dose after 2 weeks.

For a severe rash (distressing symptoms requiring discontinuation and/or systemic steroids), treatment should be discontinued until resolution of rash. Once the rash has resolved, treatment should be resumed at 50% of the patient's dose. If necessary, a brief course of oral steroids may be given concurrently with resumption of study drug. If the rash does not recur, treatment should be increased by steps of 3.5 mg/kg/day for deferasirox FCT every 2 weeks until the patient's last dose is achieved.

If the rash recurs, study treatment may be discontinued if the investigator believes that it is in the best interest of the patient. Novartis may be contacted by the investigator to discuss dosing options if the investigator so desires.

[redacted]

Other skin disorders

Severe cutaneous adverse reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis and drug reaction with eosinophilia and systemic symptoms have been reported during Exjade therapy. If any severe cutaneous adverse reactions is suspected, study treatment must be immediately discontinued and not be reintroduced.

6.3.1.6 Increased liver enzyme levels

If there is a persistent and progressive increase in serum transaminase levels (ALT/SGPT; aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT) that cannot be attributed to other causes, deferasirox should be interrupted. Once the cause of the liver function test abnormalities has been identified or after a return to normal levels, cautious re-initiation of deferasirox treatment at a lower dose followed by gradual dose escalation may be considered. In cases of a second rise in serum transaminase levels, the investigator should contact Novartis.

Although uncommon (0.3%), elevations of transaminases greater than 10 times the upper limit of the normal range, suggestive of hepatitis, have been observed in clinical trials.

Hepatic Impairment

EXJADE is not recommended in patients with severe hepatic impairment (Child-Pugh Class C). In patients with moderate hepatic impairment (Child-Pugh Class B), the dose should be considerably reduced followed by progressive increase up to a limit of 50%, and EXJADE must be used with caution in such patients.

6.3.1.7 Dose modification criteria for auditory and ocular disturbances

Auditory (decreased hearing) and ocular (lens opacities) disturbances have been reported with deferasirox treatment. Auditory and ophthalmic testing including fundoscopy is recommended before the start of deferasirox treatment and at regular intervals thereafter (every 12 months). If disturbances are noted, dose reduction or interruption may be considered and a repeated testing performed as per investigator's judgement.

6.3.1.8 Dose modification criteria for hypersensitivity reactions

Cases of serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been reported in patients receiving deferasirox, with the onset of the reaction occurring in the majority of cases within the first month of treatment. If reactions are severe, deferasirox should be discontinued and appropriate medical intervention instituted.

6.3.1.9 Dose modification criteria for cytopenias

There have been post-marketing reports (both spontaneous and from clinical trials) of cytopenias in patients treated with deferasirox. Most of these patients had pre-existing hematological disorders that are frequently associated with bone marrow failure. The relationship of these episodes to treatment with deferasirox is uncertain. In line with the standard clinical management of such hematological disorders, blood counts should be monitored regularly. Dose interruption of treatment with deferasirox should be considered in

patients who develop unexplained cytopenia. Reintroduction of therapy with deferasirox may be considered as per investigator decision, once the cause of the cytopenia has been identified.

6.3.1.10 Gastrointestinal disturbances

Some basic recommendations, based on practical experience, can be made to guide physicians in managing patients who experience diarrhea:

- At the first sign of diarrhea, consider anti-diarrheal medication such as loperamide.
- Remind patient to discontinue any laxative preparations or stool softeners they may be taking.
- Advise the patient to eat small but frequent meals.
- Determine if the patient is lactose intolerant.

Note: the deferasirox FCT does not contain lactose.

- Advise the patient to drink 8 to 10 glasses of clear liquid per day.

If the gastrointestinal issues (including diarrhea, constipation, nausea, vomiting and abdominal pain) still persist, then study drug may be discontinued if the investigator believes it is in the best interest of the patient.

Novartis may be contacted by the investigator to discuss dosing options if the investigator so desires.

6.3.2 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an AE or abnormal laboratory value must be followed at least once a week for 4 weeks, and subsequently at 4 week intervals, until resolution or stabilization of the event, whichever comes first.

6.4 Concomitant medications

6.4.1 Permitted concomitant therapy

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the 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 eCRF.

6.4.2 Permitted concomitant therapy requiring caution and/or action

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

Use of the following treatments as part of the routine clinical care for the patients is allowed:

- Patients are also to continue blood transfusions during the study protocol according to the regimen that they had been receiving prior to enrollment that could allow maintaining a hemoglobin level of ≥ 9 g/dL.

[redacted]

Caution must be exercised in patients who are taking study drug in combination with the following drugs:

- Deferasirox, as a weak CYP3A4 inducer, may potentially decrease serum levels of substances metabolised through CYP3A4 (e.g. cyclosporin, simvastatin, hormonal contraceptive agents).
- Deferasirox is a moderate inhibitor of CYP2C8 and therefore it may increase serum concentrations of substances metabolised through CYP2C8 (e.g. repaglinide, paclitaxel).
- Deferasirox increased the exposure of the concomitantly administered CYP1A2 substrate theophylline. Therefore, when deferasirox and theophylline are used concomitantly, monitoring of theophylline concentration and theophylline dose reduction should be considered. An interaction between deferasirox and other CYP1A2 substrates may be possible.

6.4.3 Prohibited concomitant therapy

Prohibited concomitant therapy includes:

- Aluminium containing antacid therapies.
- Concomitant use of deferasirox with potent UDP-glucuronosyltransferase (UGT) inducers (e.g. rifampicin, phenytoin, phenobarbital, ritonavir) or cholestyramine.
- Any ICT other than the study drug.
- Any investigational drug other than study medication.

6.4.4 Use of Bisphosphonates (or other concomitant agents)

Caution must be exercised while administering deferasirox concomitantly with drugs that have known ulcerogenic potential, such as oral bisphosphonates, NSAIDs, or corticosteroids, and in patients receiving anticoagulants (due to increase in the risk of gastrointestinal irritation and bleeding).

6.5 Patient numbering, treatment assignment or randomization

6.5.1 Patient numbering

Each patient in this study retains the same Patient Number that was attributed to him/her in CICL670F2201 study. This number consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each patient is numbered uniquely across the entire database.

If the patient fails to start treatment for any reason, the reason will be entered into the Screening Disposition page.

6.5.2 Treatment assignment or randomization

No randomization of patients will occur in this open-label study. All patients will be assigned to deferasirox FCT in this study; a washout period of 5-days will be performed for any patients who completed CICL670F2201 and switched to alternate commercial therapy.

[redacted]

All patients who fulfill all inclusion/exclusion criteria will be given the opportunity to enter the current study and receive the FCT formulation. Patients who were on the FCT formulation in CICL670F2201 will continue deferasirox FCT while patients on DT will be switched to FCT upon entry into the current study. Patients who completed CICL670F2201 but had switched to commercially available DT or other iron chelation will still be enrolled in the current study and receive FCT after a washout period.

6.5.3 Treatment blinding

Not applicable, this is an open-label study.

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(s) 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

Site personnel will add the patient number on the medication label. Immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique patient number.

The film-coated tablets are packaged in high-density polyethylene bottles with an induction seal and child-resistant closure.

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 study treatment 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

Not applicable.

6.6.3.2 Study drug accountability

Information on study drug will be collected on the Dose Administration Record eCRF and will include the planned dose (mg/kg/day), actual total daily dose (mg) taken, reason for the dose change, start date and end date.

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

Not applicable.

6.6.4 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate. A signed Certificate of Destruction (or equivalent documentation as per local procedure) will be required for archiving in the Trial Master File (TMF).

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments and indicates with an "X", the visits when they are performed.

Patients should be seen for all visits to perform the scheduled assessments on the designated day, or as close to is as possible, i.e., not exceeding ± 7 days. In this clinical trial, a week is 7 calendar days. Visits should be planned respective to Visit 3, rather than in relation to the previous visits.

All data obtained from these assessments must be supported in each patient's source documentation. No eCRF will be used as a source document. The table indicates which data are entered into the database (D) or remain in source documents only (S) (column category).

[redacted]

Table 7-1 Visit evaluation schedule

	Category	Protocol section	Screening (2 visits > 1week apart)[1]		Treatment Period														End of Treatment	Safety Follow-up
Visit no.			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17 to 27**	**28[2]**	
Study month			**-2W**		**D1**	**W2**	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**	**M13 to M23**	**M24 or Within 7 days of last dose**	**30 days after last dose**
Informed consent	(D)	7.1.1	X																		
Inclusion/ exclusion criteria	(D)	7.1.1.1	X	X																	
History of disease	(D)	7.1.1.3	X																		
Demography	(D)	7.1.1.3	X																		
Relevant medical history/current medical conditions	(D)	7.1.1.3	X																		
Prior chelation therapy	(D)	7.1.1.3	X																		
Transfusion/RBC History	(D)	7.1.1.3	X																		
Transfusions received	(D)	7.1.3	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical exam	(S)	7.2.2.1	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Weight[3]	(D)	7.2.2.3	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height	(D)	7.2.2.3	X																		
Vital signs	(D)	7.2.2.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Ocular exam[4]	(D)	7.2.2.4	X															X		X	
Audiometry[4]	(D)	7.2.2.4	X															X		X	
ECG	(D)	7.2.2.7.1	X															X		X	
Chest X-ray (if clinically indicated)[5]	(D)	7.2.2.6	X																		

[redacted]

	Category	Protocol section	Screening (2 visits > 1week apart)[1]		Treatment Period														End of Treatment	Safety Follow-up
Visit no.			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17 to 27**	**28[2]**	
Study month			**-2W**		**D1**	**W2**	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**	**M13 to M23**	**M24 or Within 7 days of last dose**	**30 days after last dose**
Prior and Concomitant medications	(D)	6.4	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events	(D)	7.2.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory assessments[6]- Blood																					
Hematology	(D)	7.2.2.5.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Biochemistry	(D)	7.2.2.5.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Serum ferritin	(D)	7.2.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum creatinine[7]	(D)	7.2.2.5.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Creatinine clearance	(D)	7.2.2.5.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hepatitis testing	(D)	7.2.2.5.5	X																		
Serum pregnancy test	(D)	7.2.2.5.4	X																		
Laboratory assessments- Urine																					
Urine dipstick	(D)	7.2.2.5.3	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Microscopic urine[8]	(D)	7.2.2.5.3	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Proteinuria[9] (urine protein/ creatinine ratio)	(D)	7.2.2.5.3	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine pregnancy test[10]	(D)	7.2.2.5.4			X															X	
Study drug administration[11]	(D)				Daily intake of study drug for up to 24 months																
Dispensed/returned FCT	(D)	6.1.1			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

[redacted]

	Category	Protocol section	Screening (2 visits > 1week apart)[1]		Treatment Period														End of Treatment	Safety Follow-up
Visit no.			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17 to 27**	**28[2]**	
Study month			**-2W**		**D1**	**W2**	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**	**M13 to M23**	**M24 or Within 7 days of last dose**	**30 days after last dose**
count																					

Abbreviations: ECG=electrocardiogram ; D=database; RBC=red blood cells ; S=source documents

Note: Treatment and follow-up visits are scheduled relative to Visit 3 (Baseline visit).

[1]Includes 5-day washout period for patients not continuing directly from CICL670F2201.

[2]End of Treatment visit will be undertaken for all patients completing the 24 months study, or discontinuing earlier for any reason.

[3]The dose of study medication will be adapted using Dosing Table (provided in Appendix 14.1) during the study if the change (increase or decrease) in body weight exceeds 10% of the body weight compared to the Visit 3 or the last dose adjustment due to change in patient's body weight.

[4]Not required if already performed within last 6 months and may be done additionally at discretion of investigator.

[5]An X-ray evaluation performed in the last 3 months before Screening Visit is acceptable.

[6]Refer to Table 7-2 for local laboratory parameters collection plan.

[7]Serum creatinine is assessed at Visit 1 and Visit 2 and their mean will be used to determine eligibility.

[8]Microscopic urine assessment is only required if positive urine dipstick (see Section 7.2.2.5.3).

[9]First morning void samples of urine must not be used (see Section 7.2.2.5.3).

[10] A pregnancy test can also be carried out for all women of childbearing potential if deemed necessary by the investigator (serum pregnancy test only at Screening Visit 1 and urine pregnancy test during Visit 3 and EOT (Visit 28), or at additional time points as per local country requirements.

[11]Study drug will be administered as described in Section 6.

[redacted]

7.1.1 Screening

Prior to commencement of the screening examination, the patient must have given full informed consent and have completed the study Informed Consent form. Once this has been signed and dated by the patient or the legal patient representative, then the investigator can take the patient through the study inclusion and exclusion criteria to make sure that the patient is fully eligible to participate.

Two Screening Visits are needed to perform key safety parameters prior to first dose administration as specified in the label.

Ocular and audiometry examinations must be performed at Screening, should a patient have evidence at the Screening Visit that the examination(s) were performed 6 months prior to Screening then the examination(s) do not need to be repeated. The examination(s) can be performed at any time at the investigators discretion if symptomatically/clinically indicated. Serum creatinine will be measured at Screening Visit 1 and Screening Visit 2 and the mean value will be used for eligibility criteria.

Proteinuria (Urine protein /creatinine ratio) will be measured at Screening Visit 1 and Screening Visit 2 for eligibility criteria.

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

The full list of assessments to be performed during the Screening period (including the 5-day washout period for patients who completed CICL670F2201 study and switched to commercially available DT or other chelation therapy) is detailed in Table 7-1.

Re-screening is permissible on a case by case basis. Please contact Novartis for guidance and see Section 7.1.1.2 to get information on how to process screen failures.

7.1.1.1 Eligibility screening

After registering for Screening, patient eligibility will be checked once all screening procedures are completed.

7.1.1.2 Information to be collected on screening failures

Patients who sign an informed consent but fail to start treatment for any reason will be considered a screen failure. The reason for not being started on treatment will be entered on the Screening Log. The demographic information and Screening log pages in the eCRF 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 a SAE during the Screening Phase (see Section 8 for SAE reporting details).

7.1.1.3 Patient demographics and other baseline characteristics

Data will be collected on patient characteristics including demographic information (age, sex, ethnicity, etc.) and other background or relevant medical history/current medical condition, transfusion history, disease history, prior chelation history, MDS classification using the revised International Prognostic Scoring System (IPSS-R), serum pregnancy test, vital signs at Visits 1 and/or 2.

To determine eligibility to be enrolled into the study, patients will also undergo assessments as per the inclusion and exclusion criteria which include hematology and biochemistry evaluations, hepatitis viral evaluation, serum creatinine and creatinine clearance, a known history of HIV positive test result (ELISA or Western blot) which is documented in the source documents, active Hepatitis B and/or C, serum pregnancy test and urinalysis.

Other assessments include chest X-ray (if clinically indicated), ocular examination, audiometry and electrocardiogram (ECG).

7.1.2 Run-in period

A washout period of 5 days is allowed for patients who completed CICL670F2201 and switched to commercially available DT or other iron chelation therapy. For details, refer Table 7-1.

7.1.3 Treatment period

The duration of study treatment in the current study is for a maximum of 24 months.

Treatment visits will commence at Visit 3 (Baseline). Patients will return to the site at 2 week intervals until Visit 5 (Month 1). Thereafter, scheduled visits will be monthly until EOT (Visit 28/Month 24).

Having completed the 24 weeks of CICL670F2201, patients recruited at Region Europe participating sites will be invited to continue FCT or switch from DT to the FCT formulation. Patients who completed CICL670F2201 but had switched to commercially available DT or other iron chelation will still be enrolled in the current study and receive FCT after a washout period.

All patients randomized in the DT arm in CICL670F2201 and well-managed on treatment with deferasirox DT will use an equivalent FCT dose. Patient switching from DT will use an equivalent FCT dose at the start of this study corresponding to their DT dose at the end of CICL670F2201 (see Appendix 14.2). A patient who is receiving an adjusted dose at the time of completing CICL670F2201 will commence this study receiving that adjusted dose until a time when it is deemed necessary to adjust the dose by the Investigator. Patients completing CICL670F2201 that had switched to commercially available DT or other ICT will have to undergo a 5-day washout period and then use an equivalent FCT starting dose corresponding to their pre-washout iron chelator dose.

Daily dose is calculated by the physician based on the patient's actual body weight.

For details on study design and dose adjustments, see Section 4 and Section 6.3. For details of assessments, see Table 7-1.

7.1.4 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 should 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 should 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 be discontinued under the following circumstances:

- Pregnancy
- Unwillingness to comply with procedures as outlined in the study protocol, including unwillingness to comply with the prescribed study treatment
- Discovery of patient ineligibility
- Intake of prohibited medications
- AE(s)
- Abnormal laboratory value(s)
- Unsatisfactory therapeutic effect
- Protocol violation
- Subject withdrew consent
- Lost to follow-up
- Administrative problems
- Death

Patients who prematurely discontinue study treatment should undergo an EOT visit (Month 24) within 7 days from last dose, at which time all of the assessments listed for EOT visit will be performed.

7.1.5 Withdrawal of consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact.

Novartis will continue to retain and use all research results that have already been collected for the study evaluation. All biological samples that have already been collected may be retained and analyzed at a later date (or as required by local regulations).

If a patient withdraws consent, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision and record this information.

Study treatment must be discontinued and no further assessments conducted.

Further attempts to contact the patient are not allowed unless safety findings require communication or follow up.

7.1.6 Follow-up for safety evaluations

All patients must have safety evaluations for 30 days after the last dose of study treatment.

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

[redacted]

7.1.7 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 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 should be recorded as such on the appropriate Disposition eCRF.

7.2 Assessment types

7.2.1 Efficacy assessments

Serum ferritin testing will be performed at Screening Visit 1 and 2. Following enrollment (Visit 3/Day 1) serum ferritin will be tested at 2 week intervals until Visit 5 (Month 1). Thereafter, scheduled testing will be monthly (refer Table 7-1). The Baseline serum ferritin value will be defined as the average of the 2 measurements obtained during the Screening period.

7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing physical examination, vital signs and laboratory evaluations 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 every visit. The physical examination at Visit 3 will serve as the Baseline physical examination for the entire study. The examination will entail an examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities and nervous system.

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 included in the Medical History page on the eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the AE page of the eCRF.

7.2.2.2 Vital signs

Vital signs include blood pressure and pulse measurements and will be measured at all study visits. After the patient has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured 3 times using an automated validated device, e.g. OMRON, with an appropriately sized cuff. The repeat sitting measurements will be made at 1 - 2 minute intervals and the mean of the 3 measurements will be used. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

[redacted]

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 as specified in Table 7-1.

7.2.2.4 Auditory and ocular examination

Patients will undergo auditory and ocular examinations at Screening Visit 1 and at unscheduled visits (if needed) as described in the Table 7-1.

The auditory examination includes the following assessments:

- Comprehensive audiometry threshold examination
- Speech recognition

The ophthalmologic examination includes the following assessments:

- Visual acuity test
- Tonometry
- Slit lamp exam of anterior segment
- Slit lamp exam of the lens
- Fundoscopic and retinal examination

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

7.2.2.5 Laboratory evaluations

A local laboratory will be used for analysis of all specimens collected (Table 7-2).

Table 7-2 Local clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, RBCs, White blood cells count with differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils), RBC Morphology
Biochemistry	Alkaline phosphatase, ALT/SGPT, AST/SGOT, Bicarbonate, Calcium, Chloride, Creatinine, inorganic phosphorus, potassium; sodium, total bilirubin, direct and indirect bilirubin*, BUN or CRP, serum ferritin
Urinalysis	Microscopic Panel** (RBCs, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells) Macroscopic Panel (Dipstick) (Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen)
Additional tests	Creatinine clearance, urine protein/creatinine ratio, serum pregnancy test, urine pregnancy test, hepatitis tests

RBCs = Red blood cells; WBCs = White blood cells; ALT/SGPT = alanine aminotransferase/serum glutamic pyruvic transaminase; AST/SGOT = Aspartate aminotransferase/serum glutamic oxaloacetic transaminase; BUN = Blood Urea Nitrogen; CRP = C-reactive protein.

*Direct and indirect bilirubin assessment is only required if total bilirubin is > 1.5 ULN

[redacted]

Test Category	Test Name

**Microscopic urine assessment is only required if positive urine dipstick

7.2.2.5.1 Hematology

Hematology samples will be collected at every visit as described in the visit evaluation schedule in Table 7-1.

Safety laboratory parameters monitored during the study will include hematocrit, hemoglobin, platelets, RBCs, white blood cells count with differential, RBC Morphology with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils).

7.2.2.5.2 Clinical chemistry

Clinical chemistry samples will be collected at every visit, as described in the visit evaluation schedule in Table 7-1.

Parameters to be measured will include: alkaline phosphatase, ALT/SGPT, AST/SGOT, bicarbonate, calcium, chloride, serum creatinine, inorganic phosphorus, potassium, sodium, total bilirubin (direct and indirect bilirubin only required if total bilirubin is >1.5 ULN), blood urea nitrogen (BUN) or urea, C-reactive protein (CRP). Also, serum ferritin level will be estimated from the blood serum (Section 7.2.1).

In accordance with the deferasirox label, serum creatinine, creatinine clearance, alkaline phosphatase, ALT/SGPT, AST/SGOT, direct bilirubin, indirect bilirubin, total bilirubin would have been assessed in duplicate before the initiation of therapy in the CICL670AIC04 study to establish a reliable pretreatment Baseline.

Creatinine clearance will be estimated using the Cockcroft-Gault equation or Schwartz formula for pediatric patients. This estimate will be provided each time serum creatinine is collected.

7.2.2.5.3 Urinalysis

Urinalysis samples will be collected at every visit (Table 7-1). A midstream, second voided morning urine sample will be obtained. Bilirubin, blood, glucose, ketones, leukocytes esterase, nitrite, pH, protein, specific gravity, urobilinogen will be assessed. Microscopic analysis will be performed only in case of positive dipstick.

In addition, urine samples for urinary protein/creatinine ratios will be collected at every visit (Table 7-1). First morning void samples must not be used for this analysis.

For patients who develop proteinuria or a worsening of pre-existing proteinuria (assessed by a dipstick) at any visit, please refer to Section 6.3.1.4.

7.2.2.5.4 Pregnancy and assessments of fertility

All female patients capable of becoming pregnant will have a pregnancy test (serum β- human chorionic gonadotropin) at Screening Visit 1. A urine pregnancy text will be performed at Visit 3 and at EOT (Visit 28/Month 24). The results of the test must be available prior to

initiating treatment with any study medication. Positive pregnancy tests will exclude a patient from participating in this trial.

Any pregnancy during the study must be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the local Novartis Clinical Safety & Epidemiology Department (see Section 8.4 for reporting a pregnancy/pregnancy related SAE) and deferasirox must be discontinued. Pregnancy follow-up must be recorded on the same form and must include an assessment of the possible relationship to the Novartis study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

7.2.2.5.5 Hepatitis test

Hepatitis test consists of the following items: Hepatitis B Surface Antibody (Anti-HBs), Hepatitis C Antibody (Anti-HCV), Hepatitis B surface Antigen (HBsAg), Qualitative w/confirmation, HCV PCR (Quantitative). Hepatitis test will be conducted at Screening Visit 1 to assess patient eligibility. A positive text will exclude patient from the study.

7.2.2.6 Radiological examinations

Chest X-ray will be performed at Screening Visit 1 (if clinically indicated). If any chest X-ray has been performed 3 months prior to study entry the last available result will be used.

7.2.2.7 Cardiac assessments

7.2.2.7.1 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed

- at Screening Visit 1
- at Visit 16 and
- at Visit 28 (EOT)

Interpretation of the tracing must be made by a qualified physician and documented on the ECG eCRF page. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), patient number, 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 page. Clinically significant findings must be discussed with Novartis prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after informed consent must be recorded on the AE eCRF page.

7.2.2.7.2 Cardiac imaging - MUGA (multiple gated acquisition) scan or echocardiogram

Not applicable.

7.2.2.7.3 Cardiac enzymes

Not applicable.

[redacted]

7.2.2.8 Tolerability

Not applicable.

7.2.3 Pharmacokinetics

Not applicable.

7.2.4 Biomarkers

Not applicable.

Other assessments

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

8.1.1 Definitions and reporting

An AE is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after signed informed consent has been obtained from the patient/legal patient representative.

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

Except for screening failures, AEs that begin or worsen after informed consent should be recorded in the AE eCRF. Conditions that were already present at the time of informed consent should be recorded in the Relevant Medical History/Current Medical Conditions eCRF page. Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible, 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 to an AE or not) will also be collected using an EOT form.

[redacted]

The occurrence of AEs should be sought by non-directive questioning of the patient during the screening process after signing informed consent and at each visit during the current study. Adverse events also may be detected when they are volunteered by the patient during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each AE should be evaluated to determine:

1. The severity grade (mild, moderate, or severe).
2. Its duration (Start and end dates or Ongoing at End of Study).
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes).
4. Action taken with respect to study treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable).
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy).
6. Whether it is serious, where a SAE is defined as in Section 8.2.1.

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

Once an AE is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an AE in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the AE eCRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal 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.

Laboratory abnormalities, that do not meet the definition of an AE, should not be reported as AEs. A severe event does not automatically indicate a 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 laboratory abnormality may be required by the protocol in which case the laboratory 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 are defined as events (serious or non-serious) which are ones 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 may be appropriate. Such events may require further investigation in order to characterize and understand them.

[redacted]

Adverse events of special interest are defined on the basis of an ongoing review of the safety data. Adverse events of special interest are discussed in detail in the IB.

8.2 Serious adverse events

8.2.1 Definitions

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

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is 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 that hospitalizations for the following reasons should not be reported as serious adverse events:
    - 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 that is unrelated to the indication under study and has not worsened since signing the informed consent
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that 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 serious adverse event

8.2.2 Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent 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 SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE 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.

Information about all SAEs is collected and recorded on the Serious Adverse Event 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.

[redacted]

Follow-up information is submitted in the same way as the original SAE Report. 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 and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the IB 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 further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification, to inform all investigators involved in any study with the same drug that this SAE has been 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 study.

8.4 Pregnancies

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 and deferasirox must be discontinued. 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 should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology 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 available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided IB. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.6 Data Monitoring Committee

Not applicable.

8.7 Steering Committee

Not applicable.

[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 have revoked authorization to collect or use PHI, attempts should 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.

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, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being 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 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 informed consent form (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.

[redacted]

9.3 Data collection

For studies using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol into the eCRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

9.4 Database management and quality control

For studies using eCRFs, Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff 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 adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

At the conclusion of the study, the occurrence of any protocol violations will be determined. After this action has 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 data, by joint written agreement between the Head of Biostatistics, PLSS and Data Management and the Global Head of Clinical Development.

For EDC studies, after database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

10 Statistical methods and data analysis

Data from all centers participating in this study will be pooled for analyses.

Standard descriptive analyses will include:

- Frequencies and percentages for categorical data;
- n, mean, standard deviation, minimum, median, 25th and 75th percentiles and maximum for continuous data.

Additional information for analysis methods will be available in statistical analysis plan documentation

[redacted]

10.1 Analysis sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises of all patients enrolled in this study.

10.1.2 Safety set

The Safety Set includes all enrolled patients who received at least one dose of study treatment (deferasirox FCT) and had at least one safety assessment on or after Visit 3 (Day 1).

An entry on the AE eCRF page of "no AE" constitutes as a safety assessment.

The safety analyses will be performed on the safety set and the efficacy (serum ferritin) on the on the FAS.

10.1.3 Other analysis sets

Not applicable.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data will be summarized descriptively by formulation and overall for the FAS.

Demographic data included age, age group (< 18 years, 18-< 50 years, 50-< 65 years, ≥ 65 years), gender, race, and ethnicity (Hispanic/Latino, Chinese, Indian (Indian subcontinent), Japanese, Other). Other background data included weight, weight group (< 20 kg, 20-< 35 kg, 35-< 55 kg, 55-< 75 kg, ≥ 75 kg), height, main underlying disease, history of splenectomy (Yes/No), history of chelation therapy (Yes/No), prior deferasirox (Yes/No), type of last chelation therapy prior to the study, Hepatitis B and C status, medical history by MedDRA primary SOC and preferred term, clinically significant abnormality in ECG (Yes, No), overall interpretation in audiometric test (Normal, Clinically insignificant abnormality, Clinically significant abnormality), overall interpretation in ocular exam (Normal, Clinically insignificant abnormality, Clinically significant abnormality), baseline creatinine, baseline creatinine group (≤ ULN, > ULN), baseline creatinine clearance, baseline creatinine clearance group (< 60, 60-< 90, 90-< 160, ≥ 160 mL/min), baseline ALT/SGPT, baseline ALT/SGPT group (≤ ULN, > ULN-5 × ULN, > 5×ULN), baseline AST/SGOT, baseline AST/SGOT group (≤ ULN, > ULN-5 × ULN, > 5 × ULN), urine protein/creatinine ratio (≤ 0.2 mg/mg, > 0.2-≤ 1 mg/mg, > 1 mg/mg).

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

10.3 Treatments (study treatment, concomitant therapies, compliance)

The following variables will be summarized with descriptive measures for the Safety Set: duration of exposure (at intervals as described in the Statistical Analysis Plan); average planned (mg/kg/day) and average actual daily dose (mg/day); cumulative planned (mg/kg) and total actual dose (mg); percentage of planned dose taken; frequency of interruptions,

[redacted]

decreases and increases in planned dose overall and by reason for change as recorded in the eCRF.

The total patient-years while on treatment, calculated as the sum of (overall drug exposure)/365.25 will be provided.

The duration of exposure is defined as the number of weeks between the start and end of study medication. The end of study medication day is the last day with a non-zero actual dose of study medication as recorded on the drug administration pages.

The average daily dose (planned or actual) is calculated as the mean dose over all days between first and last dose, including interim days with zero dose (interruptions). The cumulative dose is calculated as the sum over the daily doses of all days between first and last dose. The current weight is used when calculating the actual daily dose.

The percentage of planned dose taken is derived as $100 \times$ cumulative actual dose (mg)/cumulative planned dose (mg/kg).

Prior and concomitant medications and significant non-drug therapies will be summarized using frequency tables according to WHO Anatomical Therapeutic and Chemical class and WHO generic term. Prior medications are defined as drugs taken prior to the first dose of study medication. Concomitant medications are medications taken between the first and last day with study medication, excluding medications started on the last day of study medication. Medications which start prior to the first dose of study medication and continue thereafter are counted in both summaries.

10.4 Primary objective

The primary objective of this study is to evaluate the overall safety of the deferasirox FCT formulation, as measured by frequency and severity of AEs and changes in laboratory parameters, in patients with transfusion-dependent thalassemia or MDS at very low, low or intermediate risk.

10.4.1 Variable

The primary objective of this study is safety. The safety set will be used for the analysis of safety parameters.

The overall observation period in this study will be divided into 3 mutually exclusive segments:

1. Pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
2. On-treatment period i.e. from day of first dose of study medication to 30 days after last dose of study medication
3. Follow-up period i.e. starting at day 31 after last dose of study medication

Any AEs during on-treatment period and changes from Baseline over time during on-treatment period for serum creatinine, creatinine clearance, ALT/SGPT, AST/SGOT, RBC, platelets and white blood cell will be analyzed.

[redacted]

10.4.2 Statistical hypothesis, model, and method of analysis

Descriptive statistical analyses will be performed to summarize the primary endpoints and include:

- Frequencies, percentages, and 95% confidence intervals (CIs) for overall incidences of any AEs during the on-treatment period.
- Number (n), mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum time to AE.
- Number (n), mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum for laboratory values for selected laboratory parameters at Baseline, and after Months 6 and 12.
- Mean ± SE plots for laboratory values for selected laboratory parameters at Baseline, and after Months 6 and 12.

For all analysis purposes Baseline refers to the Day 1 (Visit 3) of the current study.

10.4.3 Handling of missing values/censoring/discontinuations

No missing data will be imputed.

10.4.4 Supportive and Sensitivity analyses

Overall AEs and selected laboratory parameters (serum creatinine and creatinine clearance) of the primary objective will be analyzed for the following subgroups: Main underlying diseases (MDS and Beta-thalassemia), age groups (10-< 18, 18-< 65 and ≥ 65 years), actual average daily dose categories (< 7 mg/kg/day, 7-21 mg/kg/day, and ≥ 21 mg/kg/day) and prior chelation therapy (DFX, any other ICT).

10.5 Secondary objectives

10.5.1 Secondary efficacy objective

To evaluate efficacy of deferasirox FCT on serum ferritin levels (decrease or maintenance, according to the individual therapeutic goal)

Serum ferritin level will be summarized at Baseline and at Months 6 and 12 and change from Baseline for the FAS.

The Baseline serum ferritin value will be defined as the average of the 2 measurements obtained during the Screening period.

The absolute and relative change with 95% CI from Baseline at Months 6 and 12 will be calculated.

10.5.2 Other Safety objectives

All safety analyses described below will be based on the safety set.

[redacted]

10.5.2.1 Adverse events (AEs)

Summary tables for AEs have to include only AEs that started or worsened during the on-treatment period, the ***treatment-emergent*** AEs. However, all safety data (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged.

The incidence of treatment-emergent AEs (new or worsening from Baseline) will be summarized by system organ class and or preferred term, severity, type of AE, relation to study treatment and AEs requiring dose adjustment or interruption. Exposure-adjusted AE incidence defined as the number of patients with new or worsened AEs during period/[total number of days patient was on treatment summed for all patients/365.25 days] will be presented.

An overall summary of type of AEs (e.g. serious, leading to study drug discontinuation, requiring dose adjustment or/and interruption) will be presented by severity.

Specific groupings of AEs of special interest 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 treatment or adverse events which are similar in nature (although not identical). Note that certain AEs may be reported within multiple groupings/AEs of special interest.

AEs of special interest are defined by MedDRA terms. Definition for retrieval and maintenance is done in separate document in the Novartis Documentum management system at the path "CREDI Projects/I/ICL670A/Integrated Medical Safety". The latest document has to be used.

Incidence of AEs of special interest will be summarized by grouping and preferred term.

10.5.2.2 Laboratory abnormalities

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

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
- listing of all laboratory data with values flagged to show the corresponding normal/notable/extended ranges

Laboratory values (and changes from Baseline) will be summarized by descriptive statistics (n, mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum) by scheduled visits.

Table 10-1 Definition of notable/extended ranges for laboratory tests

Laboratory test	Criteria for notable ranges

[redacted]

Laboratory test	Criteria for notable ranges
Platelet count	< 100 × 10^9/L (extended range < 50 × 10^9/L)
Absolute neutrophils	< 1.5 × 10^9/L (extended range < 0.5 × 10^9/L)
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 at 2 consecutive measurements at least 7 days apart)
Urinary protein/urinary creatinine ratio	> 1.0 (mg/mg) at 2 consecutive measurements at least 7 days apart
ALT/SGPT and AST/ SGOT	> 5 × ULN and 2 × Baseline (extended range > 10 × ULN and > 2 × Baseline value)

ULN = Upper limit of normal range; ALT/SGPT = alanine aminotransferase/ serum glutamic pyruvic transaminase; AST/SGOT = Aspartate aminotransferase/serum glutamic oxaloacetic transaminase

Creatinine clearance will be estimated using the Cockcroft-Gault equation and the Schwartz formula (for pediatric population) and will be displayed using relative change from baseline by categories.

10.5.2.3 Other safety data

Electrocardiogram

ECG will be performed at Baseline and after 12 months. Abnormalities will be reported together with an overall interpretation of the findings. Any abnormalities at Baseline will be summarized. The investigator will flag all abnormalities which are new or worsened since Baseline. All new or worsened abnormalities will be recorded on the AE eCRF page. All findings of patients with new or worsened clinically significant abnormalities will be listed.

Vital signs

Vital signs and body weight measured more than 30 days after discontinuation of study medication will be excluded from the analysis.

The absolute change from Baseline weight will be summarized by scheduled visit with n, mean, SD, minimum, median, and maximum values.

The criteria for notably abnormal vital signs and weight are displayed 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 of ≥ 20 mmHg
Diastolic blood pressure	≥ 105 mmHg/≤ 50 mmHg with increase/decrease from Baseline of ≥ 15 mmHg
Pulse rate	≥ 120 bpm/≤ 50 bpm with increase/decrease from Baseline of ≥ 15 bpm
Weight	≥ 7% increase or decrease from Baseline weight

[redacted]

10.5.2.4 Supportive analyses for secondary objectives

Not applicable.

10.5.2.5 Tolerability

Not applicable.

10.5.3 Resource utilization

Not applicable.

10.5.4 Patient-reported outcomes

Not applicable.

10.6 Exploratory objectives

Not applicable.

10.7 Interim analysis

Not applicable.

10.8 Sample size calculation

No formal sample size has been calculated. All patients enrolled into the CICL670F2201 study who have completed 24 months treatment will be offered participation in this current protocol and those consenting to participate will contribute to the pool of data.

According to enrolment of CICL670F2201 in Region Europe, a maximum of 90 patients should be eligible for enrollment in this study.

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, shall 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 informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study

[redacted]

in accordance with these documents and all of the instructions and procedures found in this protocol and to give 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

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the 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 actually obtained will be captured in their CRFs.

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission 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 should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study 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 should not be entered in the study.

Additional consent form

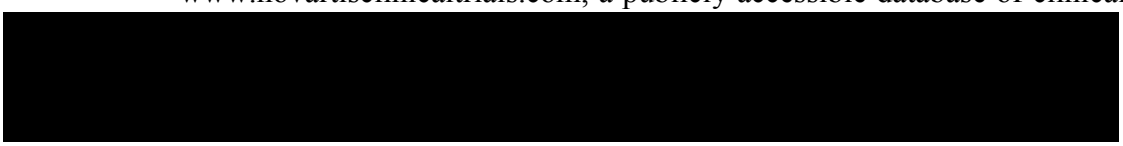
Not applicable.

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. www.clinicaltrials.gov before study start. In addition, results of interventional clinical trials in adult patients are posted on www.novartisclinicaltrials.com, a publicly accessible database of clinical study results within



1 year of study completion (i.e., LPLV), those for interventional clinical trials involving pediatric patients within 6 months of study completion.

Novartis follows the ICMJE authorship guidelines (www.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 poster or oral presentation 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 www.novartis.com.

11.6 Study documentation, record keeping and retention of documents

Each 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.

Source data are all information, 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 site Principal Investigator. The study case report form (eCRF) is the primary data collection instrument for the study. 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 electronic CRFs 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 Sponsor provides written permission to dispose of them or, requires their retention for an additional period of 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 names in any documents submitted to Novartis. Signed informed consent forms 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.

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, if any, 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, and 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.

[redacted]

13 References (available upon request)

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14 Appendices

14.1 Dosing tables (Deferasirox FCT)

To guide the investigator and/or pharmacist on the number of deferasirox FCT tablets of a given strength to prescribe to a given patient, taking into account the patient's body weight and protocol specified dosing scheme described above, a table is provided below. Where the calculated dose cannot be constituted by the available tablet strengths, the closest dose is applied. An example illustrating this approach is provided here below:

For a patient whose body weight is 46 kg, and whose planned deferasirox FCT dose is 14 mg/kg/day, the calculated deferasirox FCT daily dose would be 644 mg. So taking into account the available strengths of 90, 180 and 360 mg deferasirox FCT tablets, the patient should receive the closest daily dose of 630 mg which can be easily constituted by taking 1 × 90 mg + 1 × 180 mg + 1 × 360 mg deferasirox FCT tablets = 3 tablets.

The dosing tables below have been constructed with cut-offs for lower and upper body weights being 20 and 147 kg respectively depending on the dose administered. This is taking into account that CICL670F2201 study enrolled male or female patients ≥ 10 years.

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

Pt Weight in kg	Closest Dose (mg)	90 mg	180 mg	360 mg
20 - 38	90	1		
39 - 64	180		1	
65 - 89	270	1	1	
90 - 115	360			1
116 - 141	450	1		1

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

Pt Weight in kg	Closest Dose (mg)	90 mg	180 mg	360 mg
20 - 32	180		1	
33 - 44	270	1	1	
45 - 57	360			1
58 - 70	450	1		1
71 - 83	540		1	1
84 - 96	630	1	1	1
97 - 109	720			2
110 - 122	810	1		2
123 - 134	900		1	2
135 - 147	990	1	1	2

[redacted]

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

Pt Weight in kg	Closest Dose (mg)	90 mg	180 mg	360 mg
20 - 21	180		1	
22 - 29	270	1	1	
30 - 38	360			1
39 - 46	450	1		1
47 - 55	540		1	1
56 - 64	630	1	1	1
65 - 72	720			2
73 - 81	810	1		2
82 - 89	900		1	2
90 - 98	990	1	1	2
99 - 106	1080			3
107 - 115	1170	1		3
116 - 124	1260		1	3
125 - 132	1350	1	1	3
133 - 141	1440			4

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

Pt Weight in kg	Closest Dose (mg)	90 mg	180 mg	360 mg
20 - 22	270	1	1	
23 - 28	360			1
29 - 35	450	1		1
36 - 41	540		1	1
42 - 47	630	1	1	1
48 - 54	720			2
55 - 60	810	1		2
61 - 67	900		1	2
68 - 73	990	1	1	2
74 - 80	1080			3
81 - 86	1170	1		3
87 - 92	1260		1	3
93 - 99	1350	1	1	3
100 - 105	1440			4
106 - 112	1530	1		4
113 - 118	1620		1	4
119 - 125	1710	1	1	4
126 - 131	1800			5
132 - 137	1890	1		5
138 - 144	1980		1	5

[redacted]

Table 14-5 Deferasirox FCT dosing table for 17.5 mg/kg/day

Pt Weight in kg	Closest Dose (mg)	90 mg	180 mg	360 mg
20 - 23	360			1
24 - 28	450	1		1
29 - 33	540		1	1
34 - 38	630	1	1	1
39 - 43	720			2
44 - 48	810	1		2
49 - 53	900		1	2
54 - 59	990	1	1	2
60 - 64	1080			3
65 - 69	1170	1		3
70 - 74	1260		1	3
75 - 79	1350	1	1	3
80 - 84	1440			4
85 - 89	1530	1		4
90 - 95	1620		1	4
96 - 100	1710	1	1	4
101 - 105	1800			5
106 - 110	1890	1		5
111 - 115	1980		1	5
116 - 120	2070	1	1	5
121 - 125	2160			6
126 - 131	2250	1		6
132 - 136	2340		1	6
137 - 141	2430	1	1	6

Table 14-6 Deferasirox FCT dosing table for 21 mg/kg/day

Pt Weight in kg	Closest Dose (mg)	90 mg	180 mg	360 mg
20 - 23	450	1		1
24 - 27	540		1	1
28 - 31	630	1	1	1
32 - 36	720			2
37 - 40	810	1		2
41 - 44	900		1	2
45 - 48	990	1	1	2
49 - 53	1080			3
54 - 57	1170	1		3
58 - 61	1260		1	3
62 - 66	1350	1	1	3

[redacted]

Pt Weight in kg	Closest Dose (mg)	90 mg	180 mg	360 mg
67 - 70	1440			4
71 - 74	1530	1		4
75 - 78	1620		1	4
79 - 83	1710	1	1	4
84 - 87	1800			5
88 - 91	1890	1		5
92 - 96	1980		1	5
97 - 100	2070	1	1	5
101 - 104	2160			6
105 - 108	2250	1		6
109 - 113	2340		1	6
114 - 117	2430	1	1	6
118 - 121	2520			7
122 - 126	2610	1		7
127 - 130	2700		1	7
131 - 134	2790	1	1	7
135 - 138	2880			8
139 - 143	2970	1		8

Table 14-7 Deferasirox FCT dosing table for 24.5 mg/kg/day

Pt Weight in kg	Closest Dose (mg)	90 mg	180 mg	360 mg
20 - 23	540		1	1
24 - 27	630	1	1	1
28 - 30	720			2
31 - 34	810	1		2
35 - 38	900		1	2
39 - 41	990	1	1	2
42 - 45	1080			3
46 - 49	1170	1		3
50 - 52	1260		1	3
53 - 56	1350	1	1	3
57 - 60	1440			4
61 - 63	1530	1		4
65 - 67	1620		1	4
68 - 71	1710	1	1	4
72 - 74	1800			5
75 - 78	1890	1		5
79 - 82	1980		1	5
83 - 85	2070	1	1	5

[redacted]

Pt Weight in kg	Closest Dose (mg)	90 mg	180 mg	360 mg
86 - 89	2160			6
90 - 93	2250	1		6
94 - 97	2340		1	6
98 - 100	2430	1	1	6
101 - 104	2520			7
105 - 108	2610	1		7
109 - 111	2700		1	7
112 - 115	2790	1	1	7
116 - 119	2880			8
120 - 122	2970	1		8
123 - 126	3060		1	8
127 - 130	3150	1	1	8
131 - 133	3240			9
134 - 137	3330	1		9
138 - 141	3420		1	9

Table 14-8 Deferasirox FCT dosing table for 28 mg/kg/day

Pt Weight in kg	Closest Dose (mg)	90 mg	180 mg	360 mg
21 - 24	630	1	1	1
25 - 27	720			2
28 - 30	810	1		2
31 - 33	900		1	2
34 - 36	990	1	1	2
37 - 40	1080			3
41 - 43	1170	1		3
44 - 46	1260		1	3
47 - 49	1350	1	1	3
50 - 52	1440			4
53 - 56	1530	1		4
57 - 59	1620		1	4
60 - 62	1710	1	1	4
63 - 65	1800			5
66 - 69	1890	1		5
70 - 72	1980		1	5
73 - 75	2070	1	1	5
76 - 78	2160			6
79 - 81	2250	1		6
82 - 85	2340		1	6

[redacted]

Pt Weight in kg	Closest Dose (mg)	90 mg	180 mg	360 mg
86 - 88	2430	1	1	6
89 - 91	2520			7
92 - 94	2610	1		7
95 - 97	2700		1	7
98 - 101	2790	1	1	7
102 - 104	2880			8
105 - 107	2970	1		8
108 - 110	3060		1	8
111 - 114	3150	1	1	8
115 - 117	3240			9
118 - 120	3330	1		9
121 - 123	3420		1	9
124 - 126	3510	1	1	9
127 - 130	3600			10
131 - 133	3690	1		10
134 - 136	3780		1	10
137 - 139	3870	1	1	10
140 - 142	3960			11

14.2 Equivalent dose guidance

All patients randomized in the DT arm in CICL670F2201 study and well-managed on treatment with deferasirox DT will use an equivalent FCT dose (refer Table 14-9 for guidance).

All patients randomized in the FCT arm in CICL670F2201 study and well-managed on treatment with deferasirox FCT will use the same starting FCT dose.

Table 14-9 Patients switching from DT to FCT formulation

Previous dose	Equivalent dose to be used
Deferasirox DT (mg/kg/day)	Deferasiorx FCT (mg/kg/day)
5	3.5
10	7
15	10.5
20	14
25	17.5
30	21
35	24.5
40	28

[redacted]

14.3 Examples of light meal

Table 14-10 Examples of light meal

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

[redacted]

	amount	K cal	g total fats
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			
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]