NOVARTIS

Clinical Development

Deferasirox FCT (ICL670)

Oncology Clinical Protocol CICL670F2429 / NCT03372083

A single-arm interventional Phase IV, post-authorisation study evaluating the safety of pediatric patients with transfusional hemosiderosis treated with deferasirox crushed film coated tablets

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List of tables

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List of abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATC	Anatomical Therapeutic Classification
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
cm	Centimeters
CMO&PS	Chief Medical Office and Patient Safety
CMV	Cytomegalovirus
CrCl	Creatinine clearance
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DFP	Deferiprone
DFO	Deferoxamine
DFX	Deferasirox
DILI	Drug-induced liver injury
DRESS	Drug reaction with eosinophilia and systemic symptoms
DT	Dispersible tablet
EBV	Epstein-Barr virus
EC	European Commission
ECG	Electrocardiogram
EDC	Electronic data capture
ELISA	Enzyme linked immunosorbent assay
EM	Erythema multiforme
EMA	European Medicines Agency
EoT	End of study treatment
EU	European Union
FAS	Full Analysis Set
FCT	Film-coated tablet
FDA	Food & Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
HBsAb	Hepatitis B surface antibodies
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HSV	Herpes simplex virus
IB	Investigators brochure
IBD	Development International Birth Date
ICF	Informed consent form
ICH	International Conference on Harmonization

[redacted]

ICMJE	International Committee of Medical Journal Editors
ICT	Iron chelation therapy
IEC	Independent Ethics Committee
IN	Investigator notification
INR	International normalized ratio
IRB	Institutional Review Board
IPSS-R	Revised International Prognostic Scoring System
IRT	Interactive Response Technology
L	Liter
LFT	Liver function tests
LIC	Liver iron concentration
LLN	Lower limit of normal
LPLV	Last patient last visit
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDS	Myelodysplastic Syndrome
MedRA	Medical dictionary for regulatory activities
mg	Milligrams
mL	Milliliters
MRI	Magnetic resonance imaging
MRI T*2	Magnetic resonance T*2 imaging
mSICT	Modified Satisfaction with Iron Chelation Therapy
MUGA	Multiple gated acquisition
ng	Nanogram
ObsRO	Observer reported outcomes
o.d.	omnia die/once a day
PASS	Post-Authorization Safety Study
PCR	Polymerase chain reaction
PHI	Protected Health Information
PK	Pharmacokinetic
p.o.	Per os/by mouth/orally
PRAC	Pharmacovigilance Risk Assessment Committee
PRO	Patient reported outcomes
PT	Prothrombin time
PTY	Patient-years
q.d.	Once daily
RBC	Red blood cells
REB	Research Ethics Board
RNA	Ribonucleic acid
R Value	ALT/ALP in x ULN
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SCr	Serum creatinine
SF	Serum ferritin
SI	International system of units
SJS	Stevens-Johnson Syndrome

[redacted]

SOC	System organ class
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reaction
TBIL	Total bilirubin
TDT	Transfusion dependent thalassemia
TEAE	Treatment-emergent adverse events
TEN	Toxic epidermal necrolysis
UGT	UDP glucuronosyltransferase
UK	United Kingdom
ULN	Upper limit of normal
UPCR	Urine protein/creatinine ratio
WBC	White blood cell
WHO	World Health Organization

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Baseline	The first visit on study following the screening period
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or study patient
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
End of study treatment (EoT)	The visit at which patients will have permanently discontinued study treatment
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
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Screening	An assessment that determines study eligibility against defined inclusion and exclusion criteria
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
Subject Number (Subject No.)	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Treatment emergent adverse events	Adverse events that a subject experiences within 30d after last dose of study treatment
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints
Withdrawal of consent	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

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Amendment 1 (25-Apr-2018)

Amendment rationale

As of 25-Apr-2018, seven patients have been enrolled into the study.

Deferasirox FCT 90 mg, 180 mg, and 360 mg (Deferasirox FCT), is commercially available in some participating countries but not in all countries.

The purpose of this amendment is to enable Novartis Drug Supply Management to supply labeled study drug to countries where Deferasirox FCT is not commercially available and also to enable countries where Deferasirox FCT is commercially available to follow their local processes for using commercial products in clinical trials.

Two guidance were provided related to collection of Observer Reported Outcomes (ObsROs)

- The GI symptom questionnaire was removed from the Week 1 day 1 visit because for all 3 questionnaires, the Screening visit 1 ObsRO will be considered baseline. Additionally, patients who are on prior chelation therapy other than deferasirox are not able to complete the GI questionnaires at Week 1 day 1 because of the 5 day washout period required. The questionnaires investigate the impact of chelation treatment received 7 days prior to the visit.
- Chelation naïve patients and patients treated with chelation therapy who stopped treatment more than 7 days prior to Screening visit 1 (SV1) will not complete ObsROs questionnaires at SV1. The questionnaires investigate impact of chelation treatment received within 7 days prior to SV1 and as such are not applicable to naive patients and patients treated with chelation therapy who stopped treatment more than 7 days prior to SV1.

In addition, some updates have been made to provide further clarification on some aspects of the study as listed below.

Changes to the protocol

- Section 1.2.1.2: The cumulative world-wide exposure with commercial deferasirox was updated.
- Section 6.6: Additional clarification provided for drug dispensation to be registered in IRT.
- Section 6.3.1.6.1: Guidance provided on skin reactions was moved from section 6.3.1.6.2 to this section.
- Section 6.3.1.6.2: Guidance on skin reaction deleted and moved to section 6.3.2.6.1.
- Section 6.4.1: Clarification provided that history of transfusion must be collected for the last 3 months prior to Screening visit 1 and during the study.
- Section 6.6: Guidance provided that “All drug dispensation will be registered in IRT. Countries with commercially available deferasirox will register only the quantity dispensed as there are no unique kit numbers on commercial drugs.”
- Section 6.6.1.1: Drug supply process clarified, indicating that Novartis will supply labeled drug to countries where deferasirox FCT is not commercially available.

[redacted]

- Section 6.6.1.2: Drug supply process clarified, indicating that countries where deferasirox is commercially available will use commercially available deferasirox FCT as study drug and follow their local processes for using commercial products for clinical trials.
- Section 6.6.2: Drug supply and storage process was clarified, indicating that countries where deferasirox FCT is not commercially available will be supplied centrally with study drug (ICL670) and upon receipt, the investigator or designee will confirm study drug receipt in IRT and store as appropriate. Countries with commercially available deferasirox FCT will use commercial deferasirox FCT.
- Table 6-6: For countries where Deferasirox FCT is not commercially available, “study treatment” and “labeled drug” was changed from “Deferasirox FCT” to “ ICL670”
- Table 6-7: For countries where Deferasirox FCT is not commercially available, “study treatment” was changed from “Deferasirox FCT” to “ ICL670” and “bulk medication” was changed to “labeled medication”
- Section 6.6.3.2: Drug accountability clarified that all drug dispensation will be registered in IRT.
- Table 7.1: Visit window of ± 3 days provided for visits Week 2, Week 3 and Week 4 and visit window of ± 7 days is provided for visits Week 8, Week 12, Week 16, Week 20, Week 24 (End of Treatment).
- Table 7.1: Clarification is provided to indicate in which visits IRT will be used.
- Table 7.1: “Study drug administration” was changed to “study drug dispensation” for better clarity. Drug dispensation is removed from Week 2 visit and Week 3 visit because each study drug bottle contains 35 tablets and is sufficient for treatment for 1 months. If study drug is dispensed at Week 1 visit, it should be sufficient for treatment for one months and additional drug dispensation at Week 2 and Week 3 visits are not required.
- Table 7.1: The GI symptom questionnaire was removed from the Week 1 day 1 visit because for all 3 questionnaires, the Screening visit 1 ObsROs assessment will be considered the baseline.
- Table 7.1: Three footnotes were added to provide further clarification:
  - SV2 is applicable only to patients who are chelation naïve or are currently treated with chelation therapy other than deferasirox.
  - Chelation naïve patients and patients treated with chelation therapy who stopped treatment more than 7 days prior to Screening visit 1 (SV1) will not complete ObsROs questionnaires at SV1.
  - The choice of method for ocular and auditory assessments will be at the discretion of the investigators.
- Section 7.1.2: Guidance added that the investigator or responsible site personnel will register Screening visit 1 in IRT.
- Section 7.1.2.1: Statement that “the investigator or responsible site personnel will register the patient in IRT once eligibility is confirmed” was deleted and moved to section 7.1.4
- Section 7.1.4: Clarification provided to indicate that once patients have completed the screening period, patients will be enrolled and eligibility registered in IRT.

[redacted]

- Section 7.1.6: The text "All biological samples that have already been collected may be retained and analyzed at a later date (or as required by local regulations)" was removed from the protocol because the study will use local labs only and therefore there will be no collection or retention of biological samples by Novartis.
- Section 7.1.9: A new section has been added to indicate that, unscheduled safety assessments may be performed as clinically indicated at the discretion of the investigator at any time during the study.
- Section 7.2.2.5: References made to blood sample collection, sample shipment, reporting of results and local laboratory manuals were deleted. Blood samples will be analyzed in the local laboratories and not shipped to Novartis so the statement regarding shipment to Novartis is not applicable. Additionally statement that investigator will be provided with local laboratory manual is not applicable.
- Table 7-2: The following parameters that were omitted in the original protocol have been added to the chemistry panel in line with other Exjade protocols: Uric acid, Total protein, Bicarbonate, Albumin, Chloride, Glucose, Inorganic phosphate, Potassium, Sodium, Calcium and Magnesium.
- Section 7.2.2.5.2 Clinical Chemistry: The additional parameters specified below were added at Screening visit 1, Week1, 3, 4, 8, 12, 16, 20 and End of Treatment visits: Uric acid, Total protein, Bicarbonate, Albumin, Chloride, Glucose, Inorganic phosphate, Potassium, Sodium, Calcium and Magnesium..
- Section 7.2.2.6: Clarification provided that ocular assessments will be according to institution's practice.
- Section 7.2.2.7: Clarification provided that auditory assessments will be according to institution's practice.
- Section 7.2.8: ObsRO assessments schedules updated to indicate that GI symptom questionnaire will not be completed at Week 1 day 1. Further to that, guidance is provided that, chelation naïve patients and patients treated with chelation therapy who stopped treatment more than 7 days prior to Screening visit 1 (SV1) will not complete questionnaires at SV1. Additionally, guidance is provided that ObsRO questionnaires will be completed at study site (during study visits).
- Section 10.5.7: Section update to indicate that GI symptom questionnaire will not be completed at Week 1 day 1 visit. For all questionnaires, Screening visit 1 PRO will be considered baseline so there is no added value to complete another questionnaire at Week 1 day 1 prior to study treatment.
  Additionally, analyses were updated as follows:
  - Clarified that for mSICT and palatability questionnaires, only descriptive statistics will be provided for the chelation naïve patients.
  - GI symptoms analysis updated as below:
- In addition, clarifications were added to correct typographical errors and inconsistencies in different sections.
- 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.

[redacted]

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board

(IRBs)/Independent Ethics Committee (IECs) and Health Authorities where applicable / required.

The changes described in this amended protocol are non-substantial and do not require IRB/IEC approval prior to implementation.

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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Protocol summary:

Title	A single-arm interventional Phase IV, post-authorisation study evaluating the safety of pediatric patients with transfusional hemosiderosis treated with deferasirox crushed film coated tablets
Brief title	Phase IV safety study of crushed deferasirox film coated tablets in pediatric patients with transfusional hemosiderosis
Sponsor and Clinical Phase	Novartis Phase IV
Investigation type	Drug
Study type	Interventional
Purpose and rationale	During the evaluation of the film-coated tablet (FCT) application for deferasirox, the European Health Authorities (CHMP/PRAC) have expressed that the safety in the youngest children (particularly those <6 years) need further evaluation, especially when the tablets are crushed. The authorities have requested Novartis to conduct an additional post-authorization safety study (PASS) to characterize the pediatric safety profile of deferasirox and to provide safety data on selected gastrointestinal adverse events (esophagitis, stomatitis, mouth ulceration, gastric ulcers, hemorrhage, abdominal pain, diarrhea, nausea, and vomiting).
Primary Objective	● To assess the safety of crushed deferasirox FCT with respect to selected gastrointestinal (GI) disorders in pediatric patients aged ≥2 to < 6 years with transfusional iron overload up to 24 weeks including 30 days safety follow up ● The primary endpoint is the number and percentage of patients with selected gastrointestinal disorders (esophagitis, stomatitis, mouth ulceration, gastric ulcers, haemorrhage, abdominal pain, diarrhea, nausea and vomiting) up to 24 weeks including 30 days safety follow-up.
Secondary Objectives	To evaluate adverse events (AEs) suspected to be related to the crushed deferasirox FCT during the study ● To assess the overall safety of crushed FCT of deferasirox ● To assess the efficacy of deferasirox FCT treatment ● To evaluate patient treatment satisfaction, palatability and gastrointestinal (GI) symptoms with Observer Reported Outcomes (ObsROs)
Study design	● The study employs an interventional, prospective, single arm, open label, global, multi-center, non-randomized trial design to monitor and assess the safety profile of the crushed deferasirox FCT in pediatric patients between age ≥2 to <6 with transfusional hemosiderosis over 24 weeks. This study will aim to enroll at least 40 patients. ● The study will include a screening period (from Day 0-14) with two visits at least 7 days apart to assess eligibility of patients that are chelation naïve or on a prior iron chelator treatment other than DFX. For Patients on DFX treatment prior to study entry only one screening visit (screening visit 1) will occur to determine eligibility. Any current chelation therapy except deferasirox will be discontinued to undergo a 5-day washout period prior to commencing a 24 week treatment period with crushed deferasirox FCT. ● All patients will have weekly visits for the first month to monitor renal function. Hepatic function will be assessed biweekly during the first month. Thereafter, monthly safety assessments will be performed, including the monitoring of serum ferritin values and trends in order to adapt patient treatment. Eligibility, application of dosing standards and adjustments, as well as safety and serum ferritin assessments as specified in the protocol, will occur in accordance with the EU label throughout the study. ● Patients will continue therapy up to 24 weeks.
Population	Pediatric patients between the age ≥2 to <6 years with transfusional hemosiderosis that are candidates for treatment with deferasirox.
Inclusion criteria	Patients that are candidates for treatment with deferasirox ● Patients ≥2 to <6 years old diagnosed with transfusional hemosiderosis ● Documented history of red blood cell transfusions ● Written informed consent/assent before any study-specific procedures. The

[redacted]

<table>
<tr><td></td><td>consent will be obtained from caregiver(s) or patient's legal representative. Investigators will also obtain assent of patients according to local, regional, or national regulations.
● For patient on prior DFX: Serum ferritin (SF) >500 ng/mL, measured at screening visit 1 and requiring a DFX daily dose equivalent to FCT ≥ 7mg/kg/day
● For patients on a prior iron chelator other than DFX or iron chelation naïve: Serum ferritin (SF) >1000 ng/mL measured at screening visits 1 and 2</td></tr>
<tr><td>Exclusion criteria</td><td>● Patients that receive more than one iron chelator at the same time as current iron chelation treatment. (Patients who have received combination therapy in their medical history but are currently being treated with a single ICT agent are eligible).
● Patients continuing on deferoxamine or deferiprone in addition to study treatment. (Patients switching to or continuing on deferasirox are eligible).
● Unresolved adverse event if the patient was previously treated with deferiprone or deferoxamine or deferasirox
● Significant proteinuria as indicated by a urinary protein/creatinine ratio > 0.5 mg/mg in a non-first void morning urine measured at screening visit 1
● Serum creatinine >age adjusted ULN measured at any screening visit
● Creatinine clearance below 90 mL/minute measured at any screening visit. Creatinine clearance will be estimated from serum creatinine measured at each respective visit
● Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >2.5 x ULN measured at screening visit 1
● Total Bilirubin (TBIL) >1.5 x ULN measured at screening visit 1.
● Patients with chronic or acute significant impaired gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral deferasirox FCT (e.g. ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection)
● History of and/or prior laboratory evidence of active Hepatitis B or Hepatitis C (Hepatitis B surface antigen [HBsAg] in the absence of hepatitis B surface antibodies [HBsAb] OR Hepatitis C virus [HCV] antibody positive with HCV RNA positive)
● Liver disease with severity of Child-Pugh Class B or C
● History of hypersensitivity to any of the study drugs or excipients
● Patients participating in another clinical trial or receiving an investigational drug
● Patients with a known history of human immunodeficiency virus (HIV) seropositivity
● Patients unwilling or unable to comply with the protocol
● 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 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
● 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.)
● Female patients who reach menarche and they or their caregivers refuse pregnancy testing and/or if there is a positive pregnancy test result</td></tr>
<tr><td>Investigational and reference therapy</td><td>After the screening period, chelation-naïve patients will be dispensed deferasirox FCT at a starting dose of 14 mg/kg/day, refer to Table 6-2. Dose should be adjusted for efficacy and safety parameters with a maximum dose of 28mg/kg/day.

For patients already well-managed on any prior iron chelation treatment (ICT) including deferoxamine or deferasirox dispersible tablet (DT), a starting dose of crushed deferasirox FCT is outlined in the table:
<table>
<tr><th colspan="2">ICT dose prior to enrollment</th><th>Equivalent dose of deferasirox FCT on study</th></tr>
<tr><th>Deferoxamine (mg/kg/day)</th><th>Deferasirox DT (mg/kg/day)</th><th>Deferasirox FCT (mg/kg/day)</th></tr>
<tr><td>10</td><td>5</td><td>3.5</td></tr>
<tr><td>20</td><td>10</td><td>7</td></tr>
<tr><td>30</td><td>15</td><td>10.5</td></tr>
</table></td></tr>
</table>

	40	20	14
	50	25	17.5
	60	30	21
	70	35	24.5
	80	40	28
	Dose equivalence between deferiprone (DFP) and deferasirox (DFX) has not been established in clinical studies. For patients pre-treated with deferiprone, the starting dose of deferasirox should be 14 mg/kg/day. For the first month after treatment initiation, weekly safety assessments of renal function and biweekly assessments of hepatic function will be performed. Thereafter, monthly safety assessments will be performed during the duration of the study. Monthly serum ferritin values and trends will be used to adapt the treatment of the patients together with safety data.		
Efficacy assessments	Serum ferritin		
Safety assessments	Adverse events and in particular selected gastrointestinal AEs (esophagitis, stomatitis, mouth ulceration, gastric ulcers, hemorrhage, abdominal pain , diarrhea, nausea, and vomiting) Hematology, blood chemistry (including renal and hepatic parameters) and urinalysis ● Electrocardiogram (ECG) ● Vital signs ● Auditory and ocular examination		
Other assessments	Deferasirox FCT treatment using ObsROs: ● Modified Satisfaction with Iron Chelation Therapy (mSICT) ● Palatability ● GI symptoms		
Data analysis	● Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be used to summarize continuous variables (e.g., laboratory assessments) and frequency counts and percentages will be provided for categorical variables. ● For the primary endpoint, 95% confidence interval (CI) for percentage will also be computed based on Clopper-Pearson (Exact) method.		
Key words	Children, iron chelation therapy, transfusional hemosiderosis, deferasirox, film-coated tablet, gastrointestinal		

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1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Transfusion-dependent hemoglobinopathies represent a major global health burden with >300,000 born annually with thalassemia or sickle cell disease. Iron overload is an inevitable clinical consequence for these patients. Iron chelation therapy is, therefore, an important and integral part of their supportive care.

Humans are unable to actively eliminate body iron. This becomes clinically relevant when there is accumulation of toxic quantities of iron due to repeated blood transfusions as in transfusion dependent anemias, or when there is excessive uptake of dietary iron as in hereditary hemochromatosis. Excess iron is deposited as insoluble hemosiderin mainly in the liver, endocrine organs and myocardium. The exact mechanism of iron damage is unknown, but organ failure correlates closely with tissue iron burden. Excess iron deposition, especially in the liver, heart and endocrine organs, results in progressive tissue damage and organ failure, and is linked to iron-related promotion of free hydroxyl radical formation. In addition, the risk of some complications increases with age (Taher 2010). Serum ferritin (SF) has been traditionally used to assess transfusional iron overload with a well -established correlation to liver iron concentration, a more direct measurement of liver tissue iron.

Complications of chronic iron overload (cardiac, hepatic and endocrine failure) represent the major causes of morbidity and mortality in patients with transfusional hemosiderosis who receive regular blood transfusions without appropriate chelation therapy. Iron chelators gradually mobilize iron most probably by continuously binding tiny amounts of soluble iron present in a 'transit pool' which is in equilibrium with hemosiderin. Solubilized, chelated iron can then be excreted in the urine and/or feces. Adherence to iron chelation therapy is crucial to reduce or prevent iron overload and has been correlated with improved patient survival (Kushner 2001, Borgna-Pignatti 2004, Gabutti and Piga 1996). The goal of chelation is to maintain SF <1000 ng/mL; however many patients live with significantly higher levels due to compliance issues with chelation therapy (Standard of Care Guidelines for Thalassemia 2012). Pediatric patients who are not adequately chelated risk delayed sexual maturation, retarded growth, progressive liver and heart disease, and a reduced life expectancy. (Vichinsky 2008)

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

Clinical studies have shown deferasirox to effectively chelate iron in patients with transfusional iron overload as demonstrated by decreases in liver iron concentration (LIC), serum ferritin (SF) and cardiac iron (MRI T2*) at adequate doses. The most common adverse reactions that are associated with drug administration in patients of all ages were gastrointestinal events, rash, and mild non-progressive increases in serum creatinine.

To further characterize the safety of deferasirox dispersible tablet (DT) in children two large observational studies were conducted:

Study CICL670A2411: A 5 year observational study on the safety of deferasirox (DT) in a pediatric patient population aged 2 years to 6 years at enrollment with transfusional iron

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overload. The study enrolled 267 patients that received at least one dos e of deferasirox. The median and mean duration of exposure to deferasirox was 59.9 months and 44.1 months respectively in this pediatric population. Almost half of the patients completed 5 years of observation on treatment with deferasirox.

Study CICL670A2301: A non-interventional international sentinel site surveillance of patients with transfusional hemosiderosis treated with Exjade® (deferasirox) DT in actual practice setting. Study CICL670A2301 enrolled adult and pediatric patients ≥2 years old with chronic transfusional iron overload treated with deferasirox. Patients were followed for 3 years. There were 69 pediatric and 51 adult patients enrolled. The median duration of exposure to deferasirox DT was 29.9 months; 10 months in the adult study population and 30.6 months in the <18 years group. In the pediatric subpopulation 65.2% completed 3 years of observation on deferasirox treatment.

In the pediatric population of these observational studies the most commonly affected primary system organ classes (SOCs) were gastrointestinal disorders and infections and infestations. GI related disorders occurred in about 40% of patients and less than half of them were suspected to be related to study drug by the investigator. AE related to the upper GI tract were rarely reported in the group of AE which occurred in more than 5%.

Both recently completed long term safety studies indicated no new or unexpected safety findings in a pediatric population with transfusional iron overload. In accordance with the previous clinical studies, the data confirmed that deferasirox was generally well-tolerated with a clinically manageable safety profile.

This trial will use crushed deferasirox film coated tablets (FCT). Deferasirox FCT was approved by the FDA in March 2015 and by EMA in March, 2016.

1.2.1 Overview of deferasirox film-coated tablet (FCT)

Deferasirox is an orally active tridentate iron chelator and is indicated for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in adult and pediatric patients (aged 2 years and older) as well as in patients with non -transfusional dependent thalassemia syndromes aged 10 years and older.

Deferasirox FCT received first approvals in March 2015 by the US FDA and by EMA in March 2016. Deferasirox FCT, is an immediate release solid oral dosage form, is based on wet granulation technology with a higher drug load of 54.0%. The FCT does not contain lactose, and sodium lauryl sulfate surfactant was replaced by Polaxamer 188.

In the EU label of Exjade FCT, crushing of the film coated tablet is allowed.

In this study deferasirox FCT must be crushed and administered by sprinkling the full dose on soft food (e.g. yogurt or apple sauce) and consumed immediately and completely. Three dosage strengths of deferasirox FCT are available: 90 mg, 180 mg, and 360 mg. The use of crushed deferasirox FCT is supported by the in-vitro dissolution, stability and delivered dose data which indicated that no significant difference between intact and crushed deferasirox FCT.

The film -coated tablets (FCT) are of the same qualitative and quantitative composition as deferasirox granules that are currently being investigated worldwide; both FCT and granules are using the same active ingredients at the same doses, and the same excipients (with exception

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of the film-coating ingredients only used in the FCT). The recommendations how patients should be taking the crushed deferasirox film-coated tablet and the recommendations for application of the Deferasirox Granules in ongoing clinical trials are similar.

1.2.1.1 Non-clinical experience

Preclinical studies revealed that deferasirox did not affect fertility and it is neither teratogenic nor carcinogenic. Detailed information regarding the preclinical evaluation of deferasirox is provided in the deferasirox Investigator's Brochure.

1.2.1.2 Clinical experience

The cumulative world-wide exposure with commercial deferasirox is estimated to be 383,491 Patient Years (PTY) as of October 31, 2017, and approximately 8,110 patients have been treated with deferasirox in Novartis-sponsored investigational clinical trials cumulatively since the Development International Birth Date (IBD).

Clinical studies have shown deferasirox to effectively chelate iron in patients with transfusional iron overload as demonstrated by decreases in liver iron concentration (LIC), serum ferritin, and cardiac iron (as assessed by magnetic resonance imaging [MRI] T2*) in patients with various underlying anemias (Nick 2003, Cappellini 2006, Vichinsky 2007, Porter 2008, Pennell 2010). Furthermore, deferasirox has been shown in various studies (ICL670A108, 2409, US02, US03, etc.…) to be efficacious in reducing the iron overload in lower-risk MDS patients as measured by SF and/or LIC.

Deferasirox has demonstrated acceptable safety and tolerability in adult and pediatric patients with transfusional iron overload (Piga 2006, Cappellini 2006, Cappellini 2011). The most frequent reactions reported during chronic treatment with deferasirox in adult and pediatric patients included gastrointestinal disturbances in about 26% of patients (mainly nausea, vomiting, diarrhea, or abdominal pain) and skin rash in approximately 7% of patients. These reactions were dose-dependent, mostly mild to moderate, generally transient, and mostly resolve even if treatment is continued. Deferasirox can cause gastrointestinal hemorrhages, which can be fatal, especially in elderly patients who have advanced hematologic malignancies and/or low platelet counts.

Mild, nonprogressive increases in serum creatinine, mostly within the normal range, occurred in approximately 36% of patients. These were dose-dependent, often resolved spontaneously and some were alleviated by reducing the dose. Acute renal failure and increases in serum creatinine (≥2x upper limit of normal ULN), have been reported following prescription use of deferasirox; these were usually reversible after treatment interruption. Renal tubulopathy has been reported with deferasirox. The majority of patients were children and adolescents with beta-thalassemia and serum ferritin levels <1,500 microgram/L.

Elevations of liver function transaminases were reported as an adverse reaction in approximately 2% of patients. These were not dose dependent and most of these patients had elevated levels prior to receiving deferasirox due to a high background incidence of chronic viral hepatitis and of liver damage secondary to chronic iron overload. Elevations of transaminases >10 x ULN, suggestive of hepatitis, were uncommon (0.3%). There have been

[redacted]

post-marketing reports of hepatic failure; most involved patients with significant comorbidities including liver cirrhosis and multi-organ failure.

In a 1-year, randomized, double-blind, placebo-controlled study in patients with non-transfusion-dependent thalassemia syndromes and iron overload (CICL670A106), diarrhea (9.1%), rash (9.1%) and nausea (7.3%) were the most frequent study drug-related adverse events reported by patients receiving 10 mg/kg/day deferasirox. Abnormal serum creatinine and creatinine clearance values were reported in 5.5% and 1.8%, respectively of patients receiving 10 mg/kg/day deferasirox. Elevations of liver transaminases >2x baseline and 5x ULN were reported in 1.8% of patients treated with 10 mg/kg/day deferasirox.

There have been post-marketing reports of Stevens-Johnson syndrome, hypersensitivity vasculitis, urticaria, alopecia, toxic epidermal necrolysis, and hypersensitivity reactions (including anaphylaxis and angioedema). Rare cases of erythema multiforme have been reported during deferasirox treatment. There have also been post-marketing reports (both spontaneous and from clinical trials) of cytopenias including neutropenia, thrombocytopenia, and aggravated anemia in patients treated with deferasirox. Most of these patients had pre - existing hematologic disorders that are frequently associated with bone marrow failure. The relationship of these episodes to deferasirox is uncertain. Cases of serious acute pancreatitis were observed with and without documented underlying biliary conditions.

In a 5-year observational study (CICL670A2411) in which 267 children aged 2 to <6 years (at enrollment) with transfusional hemosiderosis received deferasirox DT, there were no unexpected safety findings regarding AEs or laboratory abnormalities. Increases in serum creatinine of >33% and above the upper limit of normal (ULN) on ≥2 consecutive occasions were observed in 3.1% of children and elevation of alanine aminotransferase (ALT) greater than 5 times the ULN was reported in 4.3% of children. The most frequently observed AEs with reported suspected relationship to study drug were increase in ALT (21.1%), increase in aspartate aminotransferase (AST, 11.9%), vomiting (5.4%), rash (5.0%), increase in blood creatinine (3.8%), abdominal pain (3.1%) and diarrhea (1.9%). Overall growth and development were not affected in this pediatric population.

Because of the importance of tolerability and patient compliance, a new deferasirox formulation, film-coated tablet (FCT), for once daily (q.d.) oral administration has been developed with improved palatability.

A randomized study CICL670F2201 was designed to investigate the safety and outcomes of patients treated with deferasirox dispersible tablets (DT) or deferasirox FCT. In total, 173 patients were randomized 1:1 to DT (n = 86) or FCT (*n* = 87; Table I). Most patients had TDT (*n* = 70 in each arm); 16 patients in each arm had MDS and most had IPSS-R low-risk MDS (DT, *n* = 8 [9.3%]; FCT, *n* = 10 [11.5%]). The primary endpoints were Treatment Emergent Adverse Events (TEAEs) and changes from baseline during on -treatment period for the following laboratory assessments: serum creatinine, recalculated creatinine clearance, alanine aminotransferase (ALT), aspartate aminotransferase (AST), red blood cells (RBC), platelets, and white blood cells (WBC). Key secondary endpoints included the percentages of selected gastrointestinal events, pharmacokinetic (PK) analysis and Patient Reported Outcomes (PRO).

Investigator-reported AEs regardless of relationship to deferasirox were reported in 77 (89.5%) patients on DT and 78 (89.7%) patients on FCT). The most frequently reported AEs were

[redacted]

diarrhea, nausea, and abdominal pain, with similar proportions of patients experiencing these events in each treatment arm. AEs with a suspected relationship to deferasirox were reported in 54 (62.8%) patients on DT and 41 (47.1%) patients on FCT, and were predominantly (≥10%) diarrhea (DT 19.8%; FCT 13.8%), increased UPCR (DT 10.5%; FCT 17.2%), abdominal pain (DT 16.3%; FCT 8.0%), vomiting (DT 15.1%; FCT 4.6%) and nausea (DT 12.8%; FCT 9.2%). The exposure-adjusted incidence for GI related events was lower in the FCT group (137 per 100 patient years) as compared to the DT group (153 per 100 patient years).

In summary, deferasirox is a once-daily oral iron chelator that has been approved for treating chronic iron overload, with demonstrated efficacy in the reduction or maintenance of body iron stores, and an acceptable safety profile with dispersible and non-dispersible formulations.

2 Rationale

2.1 Study rationale and purpose

During the evaluation of the FCT application, the European Health Authorities (CHMP/PRAC) have expressed that the safety in the youngest children (particularly < 6 years) is not known, especially when the tablets are crushed, and have requested Novartis to conduct an additional post-authorization safety study (PASS) to characterize the pediatric safety profile and to provide safety data on selected AEs (esophagitis, stomatitis, mouth ulceration, gastric ulcers, haemorrhage, abdominal pain, diarrhea, nausea, and vomiting).

A PASS is defined in Directive 2001/83/EC (DIR) Art 1(15) as any study relating to an authorized medicinal product conducted with the aim of identifying, characterizing or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.

Study CICL670F2429 will serve to fulfill the post-authorization measure imposed by the European Health Authority.

2.2 Rationale for the study design

This study employs a prospective, single-arm, global multi-center, interventional open-label, non- randomized design to identify and assess AEs suspected to be related to study drug when administered up to 24 weeks in pediatric patients age ≥2 to <6 years with transfusional hemosiderosis.

This design requires crushing the study medication, deferasirox FCT, and a detailed safety assessment mandated by the study protocol. Crushing the deferasirox FCT is mandatory. The selected age category addressed the need to investigate the safety in younger children.

The single-arm, open-label study design is well established for this type of request and the schedule of assessment is appropriate for this study and according to the current standards of care and as suggested by the Health Authority.

[redacted]

2.3 Rationale for dose and regimen selection

Deferasirox FCT dosing will be calculated for pediatric patients and the investigator's overall clinical assessment of the subject at each study visit in accordance with the protocol. The initial dose of deferasirox will be determined by the subjects prior history of chelation (iron chelation naïve or prior DFX or any other prior iron chelator other than DFX) from a standardized conversion of prior iron chelation therapy to deferasirox FCT. DFX FCT dosing is based on body weight (mg DFX/ kg body weight); please refer to Table 6-1.

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 goal of iron chelation therapy is to remove the amount of iron administered in transfusion and as required, to reduce the existing iron burden. The decision to initiate iron chelation therapy should be individualized and based on anticipated clinical benefits and risks.

The risks associated with the use of deferasirox in this population of subjects with transfusional hemosiderosis are well described in clinical trials. As with other iron chelator treatment, the risk of toxicity of deferasirox may be increased when inappropriately high doses are given in patients with a low iron burden or with serum ferritin levels that are only slightly elevated. In patients with no LIC assessment, caution should be taken during chelation therapy to minimize the risk of over-chelation.

Chelation should be regularly adjusted to meet a patient's specific needs, based on transfusion requirements (i.e., decreased or increased for patients with low or high iron intake, respectively), severity of iron overload, and treatment goal (i.e., to maintain or reduce iron body levels).

Patients with pre-existing renal conditions or patients who are receiving medicinal products that may depress renal function may be more at risk of complications and weekly monitoring of serum creatinine and/or creatinine clearance is recommended in the first month after initiation or modification of therapy and monthly thereafter. Concomitant administration of deferasirox with drugs that have known ulcerogenic potential, such as non-steroidal anti- inflammatory drugs, corticosteroids, or oral bisphosphonates, and use of deferasirox in patients receiving anticoagulants may increase the risk of gastrointestinal irritation.

The risk to subjects in this trial may be minimized by compliance with the eligibility criteria and study procedures including, close clinical monitoring, safety assessment and dose adjustment.

As with other iron chelator treatment, the risk of toxicity of deferasirox FCT may be increased when inappropriately high doses are given in patients with a low iron burden or with serum ferritin levels that are only slightly elevated.

[redacted]

Benefits to eligible subjects include the removal of excess iron and decrease in the risks associated with transfusional hemosiderosis.

3 Objectives and endpoints

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

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4
To assess the safety of crushed deferasirox FCT with respect to selected gastrointestinal (GI) disorders in pediatric patients aged ≥2 to < 6 years with transfusional iron overload up to 24 weeks including 30 days safety follow up	Number and percentage of patients with selected gastrointestinal disorders (esophagitis, stomatitis, mouth ulceration, gastric ulcers, haemorrhage, abdominal pain, diarrhea, nausea, and vomiting) up to 24 weeks including 30 days safety follow-up	
Secondary		Refer to Section 10.5
Evaluate AEs suspected to be related to the crushed deferasirox FCT	Number and percentage of patients who experienced AEs suspected to be related to study drug up to 24 weeks including a 30 day follow up overall and by SOC.	
To assess the overall safety of crushed FCT of deferasirox	Overall safety up to 24 weeks including 30 days safety follow-up as measured by frequency and severity of adverse events, serious adverse events (SAEs) and AEs leading to discontinuation and absolute change from baseline over time (shift tables will also be provided) for serum creatinine, creatinine clearance, UPCR, total bilirubin, ALP, ALT, AST). Other safety data (e.g., ECGs, vital signs, ocular, auditory examinations) will also be summarized.	
To assess the efficacy of deferasirox FCT treatment	Change from baseline over time in SF up to 24 weeks of treatment	
To evaluate patient treatment satisfaction, palatability, and GI symptoms with Observer-reported Outcomes (ObsROs)	Domain scores with ObsROs (Modified Satisfaction with Iron Chelation Therapy [mSICT], palatability, and GI symptom) questionnaires	
Other secondary		Refer to Section 10.5.2
None		
Exploratory		Refer to Section 10.6
None		

[redacted]

4 Study design

4.1 Description of study design

The study employs an interventional, prospective, single arm, open label, global multi-center, non-randomized trial design to monitor and assess the safety profile of the crushed deferasirox FCT in pediatric patients between age ≥ 2 to < 6 years with transfusional hemosiderosis over 24 weeks.

This study will enroll at least 40 patients worldwide.

The study will include a screening period (from Day 0-14) with two visits at least 7 days apart to assess eligibility of patients that are chelation naïve or on a prior iron chelator treatment other than DFX. For Patients on DFX treatment prior to study entry only one screening visit (screening visit 1) will occur to determine eligibility and monitoring will be monthly after baseline assessments (day1). (For additional details refer to Section 8.1). Any current chelation therapy except deferasirox will be discontinued to undergo a 5-day washout period prior to commencing a 24 weeks treatment period with crushed deferasirox FCT, refer to Section 8.2 for additional details.

All patients will have weekly visits for the first month.

Safety assessments will be performed weekly after treatment initiation and thereafter monthly during the study. Monthly serum ferritin values and trends will be used to adapt the treatment of the patients together with safety data.

Patients will continue therapy for up to 24 weeks.

30-day follow-up

All patients must be followed for AEs and SAEs for 30 days after the last dose of study treatment to determine any potential treatment emergent adverse event regardless of whether the patient continues prescribed iron chelation treatment after last dose of study medication. Patients who discontinue study drug before week 24 should be scheduled for a visit within 7 days of ending treatment at which time all of the assessments listed for the final visit will be performed (end of treatment visit). At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 30 days following the last dose of study drug.

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 of the last data point.

[redacted]

4.4 Early study termination

The study can be terminated at any time for any reason due to an unavoidable event 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 discontinued or withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

5 Population

5.1 Patient population

Pediatric patients ≥2 years old to <6 years old with transfusional hemosiderosis that are candidates for treatment with deferasirox. Patients enrolled in this study are not permitted to participate in additional parallel investigational drug or device studies. Patients who failed screening may be re-screened with Novartis confirmation. Patients who complete the study may not be re-enrolled for a second course of treatment.

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

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

1. Patients ≥2 to <6 years old diagnosed with transfusional hemosiderosis
2. Documented history of red blood cell transfusions
3. Written informed consent/assent before any study-specific procedures. The consent will be obtained from caregiver(s) or patient's legal representative. Investigators will also obtain assent of patients according to local, regional, or national regulations.
4. For patients on prior DFX: Serum ferritin (SF) >500 ng/mL, measured at screening visit 1 and requiring a DFX daily dose equivalent to FCT ≥ 7mg/kg/day.
5. For patients on a prior chelator other than DFX (e.g. deferiprone or deferoxamine) or chelation naive: Serum ferritin (SF) >1000 ng/mL measured at screening visits 1 and 2.

5.3 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria:

1. Patients that receive more than one iron chelator at the same time as current iron chelation treatment. (Patients who have received combination therapy in their medical history but are currently being treated with a single ICT agent are eligible.)
2. Patients continuing on deferoxamine or deferiprone in addition to study treatment. (Patients switching to or continuing on deferasirox are eligible).
3. Unresolved adverse events if the patient was previously treated with deferiprone or deferoxamine or deferasirox.

[redacted]

4. Significant proteinuria as indicated by a urinary protein/creatinine ratio > 0.5 mg/mg in a non-first void sample urine measured at screening visit 1.
5. Serum creatinine > age adjusted ULN measured at any screening visit
6. Creatinine clearance below 90 mL/minute measured at any screening visit. Creatinine clearance using the Schwartz formula will be estimated from serum creatinine measured at each respective visit.
7. ALT and/or AST > 2.5 x ULN measured at screening visit 1.
8. Total bilirubin (TBIL) >1.5 x ULN measured at screening visit 1.
9. Patients with significant impaired GI function or GI disease that may significantly alter the absorption of oral deferasirox FCT (e.g. ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).
10. History of and/or laboratory evidence of active Hepatitis B or Hepatitis C (HBsAg in the absence of HBsAb OR HCV Ab positive with HCV RNA positive.
11. Liver disease with severity of Child-Pugh Class B or C.
12. History of hypersensitivity to any of the study drug or excipients.
13. Patients participating in another clinical trial or receiving an investigational drug.
14. Patients with a known history of HIV seropositivity.
15. Patients unwilling or unable to comply with the protocol.
16. 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.
17. Significant medical condition interfering with the ability to partake in this study (e.g. uncontrolled hypertension, unstable cardiac disease not controlled by standard medical therapy, systemic disease: cardiovascular, renal, hepatic, etc.).
18. Female patients who reach menarche and they or their caregivers refuse pregnancy testing and/or if there is a positive pregnancy test result.

6 Treatment

6.1 Study treatment

The investigational study drug for this trial is crushed deferasirox (ICL670) FCT for oral use. Deferasirox FCT dosing is based on subject's weight, outlined below in Table 6-1.

To guide the investigator and/or pharmacist/designee on the number of deferasirox FCT tablets of a given strength to prescribe/dispense to a given subject, taking into account the subject's body weight and protocol specified dosing scheme, a dosing table (Table 6-1) has been provided.

For each patient the investigator, pharmacist and/ or designee will calculate a target daily dose taking into account patient's body weight. When the exact calculated dose cannot be reached with the deferasirox FCT strengths available, the closest daily dose available will be prescribed and dispensed. The following dosing Table 6-1 provides an efficient combination of FCT strengths reaching a certain daily dose for each body weight range.

[redacted]

Example illustrating this approach is provided below:

For a patient with a body weight of 20 kg and a deferasirox FCT dose of 14 mg/kg/day, the calculated daily dose is 280 mg. Taking into account the available deferasirox FCT strengths of 90, 180 and 360 mg, the closest daily dose the patient can receive is 270 mg, by taking 2 crushed FCT tablets: 1 x 90 mg + 1 x 180 mg. This combination can be found in the # of Tablets to dispense column to the far right in Table 6-1, for patients receiving 14 mg/kg/day of deferasirox FCT with a body weight between 17-22 kg.

Table 6-1 Deferasirox FCT Weight Dosing Table

Body weight ranges per dosing group (kg)								# of Tablets to dispense		
3.5 mg/kg/ day [kg]	**7 mg/kg/ day [kg]**	**10.5 mg/kg/ day [kg]**	**14 mg/kg/ day [kg]**	**17.5 mg/kg/ day [kg]**	**21 mg/kg/ day [kg]**	**24.5 mg/kg/ day [kg]**	**28 mg/kg/ day [kg]**	**90 mg**	**180 mg**	**360 mg**
19-38	10-19	7-12	5-9	5-7	5-6	5		1		
39-64	20-32	13-21	10-16	8-12	7-10	6-9	5-8		1	
	33-45	22-30	17-22	13-18	11-15	10-12	9-11	1	1	
	46-57	31-38	23-28	19-23	16-19	13-16	12-14			1
		39-47	29-35	24-28	20-23	17-20	15-17	1		1
		48-55	36-41	29-33	24-27	21-23	18-20		1	1
			42-48	34-38	28-32	24-27	21-24	1	1	1
			49-54	39-43	33-36	28-31	25-27			2
				44-48	37-40	32-34	28-30	1		2
				49-54	41-45	35-38	31-33		1	2
					46-49	39-42	34-36	1	1	2
					50-53	43-45	37-40			3
						46-49	41-43	1		3
						50-53	44-46		1	3
							47-49	1	1	3
							50-52			4

These dosing tables have been constructed for each dosing group considering lower (5th) and upper (98th) percentiles form weight charts for children aged ≥2 to <6 years. This is taking into account that the study will enroll male or female children, ≥ 2 and < 6 years For patients with a low body weight and lower daily DFX dosing requirements (e.g. below 19 kg body weight in the 3.5 mg/kg/day dosing group) the needs will not allow for the use of the smallest tablet strength available. In such cases a written request will be sent to Novartis, to advise on the individual patient enrolment / dose adjustments options.

The patient will be dispensed deferasirox FCT in accordance with the protocol. For patients already well-managed on prior treatment with deferoxamine or deferasirox DT, a starting dose of crushed deferasirox FCT is outlined below in Table 6-2.

[redacted]

Table 6-2 Equivalent dose of deferasirox FCT

ICT Dose Prior to Enrollment		Starting Dose
Deferoxamine (mg/kg/day)	**Deferasirox DT (mg/kg/day)**	**Deferasirox FCT (mg/kg/day)**
10	5	3.5
20	10	7
30	15	10.5
40	20	14
50	25	17.5

Dose equivalence between deferiprone and deferasirox has not been established in clinical studies. For patients pre-treated with deferiprone, the starting dose of deferasirox FCT should be 14mg/kg/day.

Safety assessment will be performed weekly after treatment initiation and thereafter monthly during the study. Monthly serum ferritin values and trends will be used to adapt the treatment of the patients together with safety data.

Patients will continue therapy for 24 weeks.

6.1.1 Dosing regimen

The recommendations for deferasirox FCT daily dose for pediatric patients' age ≥ 2 to <6 years with transfusional iron overload are the same as for adult patients, i.e. based on the weight of the patient. Changes in weight of pediatric patients over time must be taken into account when calculating the dose.

In children with transfusional iron overload aged between 2 and 5 years, exposure is lower than in adults. This age group may, therefore, require higher doses than are necessary in adults. However, the initial dose should be the same as in adults, with close monitoring by the investigator, followed by individual titration.

Table 6-3 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
Crushed Deferasirox FCT	Film-coated tablets p.o	Minimum dose 3.5 mg/kg/day Targeted starting dose 14 mg/kg/day Maximum dose 28 mg/kg/day Dosage is ascertained by patient weight. Please refer to dose weight Table 6-1 for the recommended dose in mg/ kg/day	Once daily; all doses must be crushed prior to administration

Deferasirox FCT is for oral use. The full daily dose of one or more film-coated tablets must be crushed in the home environment and administered by sprinkling the full dose on to soft food (e.g., yogurt or apple sauce [pureed apple]). The dose must be immediately and completely consumed, and not stored for future use. The study medication should be taken once daily, preferably at the same time each day.

Subjects who have been established on other chelation therapy will perform a 5 day wash-out from the former medication details are provided in Section 7.1.2.

[redacted]

The patient's daily dose will be rounded to the nearest whole tablet according to the available strengths of deferasirox FCT tablets (90 mg, 180 mg, and 360 mg). The appropriate daily dose will be calculated by the investigator based on the patient's actual body weight see Table 6-1.

The investigator and/or designee will instruct the caregiver and patient to crush the study drug and then take the full daily dose of one or more film-coated as prescribed. Examples among others of an adequate method of crushing of the FCT may be between two pieces of wax paper with a rolling pin or with a commercially available pill crusher. All doses planned and prescribed to the patient, and all dose changes including reasons for change during the study must be recorded in the case report form (CRF).

During regular study visits, the investigator or pharmacist will give to the patient the appropriate number of deferasirox tablets based on the patient's calculated dose. The number of tablets of each strength of deferasirox dispensed will be recorded in the study site's Study Drug Log.

Patients will be obliged to return all unused study medication at their next visit. Study medication returned by the patients will be counted and unused study medication will be recorded by the investigator/pharmacist/designee involved in the study.

Drug accountability will be noted by the field monitor during site visits and at the completion of the trial.

6.1.2 Ancillary treatments

Not Applicable

6.1.3 Rescue medication

Not Applicable

6.1.4 Guidelines for continuation of treatment

For patients who are unable to tolerate the protocol-specified dosing schedule, dose reductions are permitted at the discretion of the investigator in order to keep the patient on study drug. These changes must be recorded on the dosage administration record electronic (e)CRF.

The majority of dose reductions, modifications, interruptions are covered in Section 6.3 and with further details in Table 6-4. For all cases where a dose adjustment is considered necessary, but is not covered in the following sections, the investigator will send a written request to Novartis. The request must justify the dose change and provide all supportive clinical and laboratory information for complete evaluation by Novartis. Any dose adjustment for reasons not included in this section needs to be authorized by Novartis. A written reply will be promptly sent back to the investigator by Novartis.

6.1.5 Treatment duration

The planned duration of treatment is 24 weeks. Patients may be discontinued from treatment with the study drug earlier due to unacceptable toxicity or at the discretion of the investigator or the patient. Premature patient withdrawal refers to the point/time when the patient exits from the study prior to planned completion of all study treatment administration and/or

assessments. At this time, all study treatment is discontinued and after the 30-day safety follow-up (as possible), no further assessments are planned.

Patients may continue or resume prescribed iron chelation therapy as per investigator discretion.

6.2 Dose escalation guidelines

ICL670F2429 not being an early development study, dose escalation guidelines do not apply; for information on dosing regimen, please refer to section 6.1 of the protocol.

6.2.1 Starting dose rationale

Not applicable

6.2.2 Provisional dose levels

Not Applicable

6.2.2.1 Implementation of dose escalation decisions

Not Applicable

6.2.2.2 Intra-Patient dose escalation

Not Applicable

6.2.3 Definitions of dose limiting toxicities (DLTs)

Not Applicable

6.3 Dose modifications

6.3.1 Dose modification and dose delay

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

These dose modifications are summarized in Table 6-4. Deviations to mandatory dose interruptions and/or reductions are not allowed. Permanent treatment discontinuation is mandatory for specific events indicated as such in Table 6-4 or listed in Section 7.1.5.

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

6.3.1.1 Change in patient's weight

The dose of study medication is to be adapted as per locally approved prescribing information during the study if the change (increase or decrease) in body weight exceeds 10% of the body weight compared to baseline or the last dose adjustment due to change in patient's body weight.

[redacted]

6.3.1.2 Elevations in serum creatinine

Serum creatinine must be monitored during the study as stated in visit schedule, refer to Table 7-1.

For pediatric patients the following dose adjustment guidance applies:

- At single increase in serum creatinine (SCr) >ULN and increased by ≥ 33% from baseline, maintain DFX dose level and repeat the assessment at next visit as clinically indicated.
- If serum creatinine (SCr) >ULN and increased by ≥ 33% from baseline on 2 consecutives visits, deferasirox dose reduction by 7 mg/kg/day for the FCT is required.
- If after dose reduction, resolution of serum creatinine occurs (<33%) and within normal limits, dose can be re-escalated to 100% of the last dose.

If increase in serum creatinine recurs again within 2 months according to guidelines above, therapy needs to be reduced to 50% of the last dose.

After 2 months, if the serum creatinine increase does not recur, study medication may be re-escalated to 100% of the last dose depending on the clinical judgement of the investigator.

If after an initial dose reduction, a progressive increase in serum creatinine beyond the ULN is observed, or SCr increase recurs, repeat at adequate dose, a treatment interruption is recommended.

After a treatment interruption, if serum creatinine falls below the age-appropriate ULN on two 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) depending on the clinical judgement of the investigator.

6.3.1.3 Changes in creatinine clearance

Pediatric patient who met the eligibility criteria and who experience a renal function decrease < LLN (CrCl < 9 0 ml/min) at 2 consecutive visits and the decrease cannot be attributed to other causes, DFX must be dose reduced by 7 mg/kg/day.

If after dose reduction the renal function increases > LLN (CrCl > 90 ml/min), dose may be re-escalated to the last daily dose prior dose reduction depending on the clinical judgement of the investigator.

If after dose reduction the renal function remains < LLN (CrCl < 90 ml/min), treatment must be interrupted. Treatment may be reinitiated depending on the clinical judgement of the investigator.

If creatinine clearance falls below 60ml/min study treatment must be discontinued.

6.3.1.4 Changes in serum ferritin

Serum ferritin must be monitored as stated in visit evaluation schedule, see Table 7-1.

For iron chelation naïve subjects study entry dose adjustments are allowed after 4 weeks on study based on serum ferritin and investigator's judgement. For iron-chelation pre-treated

[redacted]

subjects, the dose of deferasirox should be adjusted if necessary every 3 months based on the trends in serum ferritin and investigator's judgement.

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

In patients whose SF level has reached the target (usually between 500 and 1000 ng/mL), dose reductions in steps of 3.5 or 7 mg/kg/day are recommended to maintain SF levels within the target range. If SF falls below 500 ng/mL, an interruption of study treatment is recommended until SF rises above 500 ng/mL.

6.3.1.5 Changes in urine protein/creatinine ratio

Proteinuria must be monitored as stated in visit evaluation schedule see Table 7-1.

For patients who develop proteinuria or a worsening of pre-existing proteinuria (assessed by a dipstick) at any visit, microscopic urine assessment should be performed.

In case of a single increase of the UPCR by quantitative urinalysis measurement, the assessment should be repeated at the next visit. Deferasirox dose reduction by 50% is recommended if the UPCR increases to >0.5 (mg/mg) in two consecutive non first 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 UPCR ratio increases to >1.0 (mg/mg) in two consecutive non first void urine samples (a minimum of 48 hours apart).

After resolution (<0.5mg/mg), dose can be resumed again at 100%.

If increase in UPCR > 0.5mg/mg recurs again within 2 months, study drug needs to be reduced to 50% of the last dose. After 2 months, if increase in UPCR does not recur, study medication can be returned to 100% of the last dose.

If increase recurs in UPCR (> 1.0 (mg/mg) recurs in one single non-first void urine samples: Interrupt study treatment.

After resolution (≤ 0.5mg/mg), dose can be resumed again at 50% of the last dose after 1 month, if increase in UPCR does not recur for another month, study medication can be returned to 100% of the last dose.

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 laboratory results.

6.3.1.6 Skin disorders

6.3.1.6.1 Stevens - Johnson syndrome and other severe skin reactions

Severe skin reactions, including Stevens-Johnson syndrome have been reported during deferasirox therapy. If Stevens-Johnson syndrome is suspected, study treatment must be

[redacted]

immediately discontinued and not reintroduced. The risk of other severe skin reactions (toxic epidermal necrolysis [TEN], drug-reaction with eosinophilia and systemic symptoms [DRESS]) cannot be excluded. If Stevens Johnson syndrome or any other severe skin reaction is suspected, deferasirox must be discontinued immediately and not reintroduced. Further management is at the discretion of the investigator.

6.3.1.6.2 Skin Rash (other than e.g. SJS, TEN, DRESS)

For skin rash of mild/moderate severity (defined as those causing minimal symptoms which require no or minimal supportive treatment), deferasirox 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 deferasirox will be interrupted. After the rash resolves, resume deferasirox at 50% of the subject's last dose, If the rash does not recur, increase dose back to 100% of the subject's dose after 2 weeks.

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

Rare cases of erythema multiforme (EM) have been reported during deferasirox treatment. Cases if suspected EM must be reported and DFX dose adjusted in accordance with the above recommendations for severe rash.

If rash recurs, study drug may be discontinued if the investigator believes that is in the best interest of the patient.

6.3.1.7 Increased liver enzyme levels

If there is a persistent and progressive increase in serum transaminase levels (ALT/AST) that cannot be attributed to other causes, deferasirox must 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. Refer to table 6.4 for further modification, interruption guidance.

6.3.1.8 Hepatic Impairment

In subjects with moderate hepatic impairment (Child-Pugh Class B), put the study medication on hold and monitor the patient for total bilirubin, serum albumin, prothrombin time, International Normalized Ratio (INR), ascites and hepatic encephalopathy. If liver disease prognosis improves, study medication may be reintroduced at 7 mg/kg/day for FCT or 50% of previous dose, whichever is less.

While monitoring continues, the dose may be increased by 3.5 mg/kg/day for FCT every 2 weeks to a maximum of 50% of the patient's previous dose if the investigator determines that dose increase is in the best interest of the patient.

[redacted]

In subjects who develop severe hepatic impairment (Child-Pugh Class C) during the study, deferasirox must be discontinued.

6.3.1.9 Dose modification criteria for auditory (decreased hearing) and ocular (lens opacities) disturbances

Auditory (decreased hearing) and ocular (lens opacities) disturbances have been reported with deferasirox treatment. Auditory testing will be performed at screening visit 1 before the start of deferasirox treatment and at end of treatment and is permitted through the remainder of the study at the discretion of the Investigator based on subject's reporting of symptoms. Ocular testing will be performed at screening before the start of deferasirox treatment and at end of treatment and is permitted through the remainder of the study at the discretion of the Investigator based on the subject's reporting of symptoms. If auditory or ocular disturbances are noted, dose reduction or interruption may be considered and a repeated testing performed as per investigator's judgement.

6.3.1.10 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 must be discontinued. Deferasirox must not be reintroduced in patients who have experienced previous hypersensitivity reactions on deferasirox due to the risk of anaphylactic shock.

6.3.1.11 Dose modification criteria for cytopenias

There have been reports (both post-marketing 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 cytopenias. Reintroduction of therapy with deferasirox may be considered once the cause of cytopenia has been identified.

6.3.1.12 Gastrointestinal disturbances

Some basic recommendations, based on practical experience, can be made to guide investigators in managing subjects who experience diarrhea.

At the first sign of diarrhea, consider anti-diarrhea medication such as loperamide.

Remind the subject to discontinue any laxative preparations or stool softeners.

Eat small, frequent meals. Determine if the subject is lactose intolerant. Note that deferasirox FCT does not contain lactose. Remind the subject to drink an adequate amount of clear liquid per day.

Patients with GI symptoms (including abdominal pain, nausea, vomiting, and diarrhea) and/or patients who are unable to tolerate once a day study drug dosing, the following treatment management steps are recommended in the order specified below:

[redacted]

- Change the timing of study drug administration from morning to evening, and in addition, try using an anti-diarrheal agent for 2 days in case of diarrhea
- If symptoms still continue, try administering the daily dose as a split dose twice daily.

Once symptoms resolve, twice daily dosing should be switched back to once daily.

Do not split dose if only prescribing one tablet per day.

- Should the GI issues persist, study drug may be discontinued if the investigator believes it is in the best interest of the patient.

Table 6-4 Criteria for dose reduction / interruption and re-initiation of deferasirox treatment for adverse drug reactions

Recommended dose modifications for deferasirox	
Body weight	
Increase/decrease of weight by >10% compared to baseline weight or body weight at last dose adjustment due to change in patient's body weight	Dose of study medication needs to be adapted using Deferasirox FCT Weight Dose Table Dose adjustment needed for Weight changes >10% compared to baseline weight or if there is a change in patient's body weight since last dose adjustment. Smaller variations in body weight (<10%) during study, do not require dose adjustments. In this case, baseline body weight can be used to calculate correct dose.
Investigations (Renal)	
Serum creatinine and/or creatinine clearance	
Single increase in serum creatinine ≥33%	Maintain dose level and repeat the assessment at next visit as clinically indicated
Single serum creatinine increase ≥33% above baseline value and >ULN	Deferasirox dose reduction by 7 mg/kg/day for the FCT is necessary. If after dose reduction, resolution of serum creatinine occurs (<33%) and within normal limits, dose can be re-escalated to 100% of the last dose. If increase in serum creatinine recurs again within 2 months according to guidelines above, therapy needs to be reduced to 50% of the last dose After 2 months, if the serum creatinine increase does not recur, study medication may be re-escalated to 100% of the last dose depending on the clinical judgement of the investigator. If after an initial dose reduction, a progressive increase in serum creatinine beyond the ULN is observed, or SCr increases re-occur repeatedly at adequate dose, a treatment interruption is recommended. After a treatment interruption, if serum creatinine falls below the age-appropriate ULN on two 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) depending on the clinical judgement of the investigator.
Patients who met the eligibility criteria and who experience a renal function decrease < LLN (CrCl < 90ml/min) at 2 consecutive visits	If decrease cannot be attributed to other causes, DFX must be dose reduced by 7mg/kg/day. If after dose reduction the renal function increases >

[redacted]

[redacted]

Recommended dose modifications for deferasirox	
	LLN (CrCl >90ml/min), dose may be re-escalated to the last daily dose prior dose reduction depending on the clinical judgement of the investigator. If after dose reduction the renal function remains <LLN (CrCl <90ml/min), treatment must be interrupted. Treatment may be reinitiated depending on the clinical judgement of the investigator. If creatinine clearance falls below 60ml/min study treatment must be discontinued.
Investigations (Hepatic)	
Isolated direct (conjugated) Bilirubin elevation	
> ULN – 1.5 x ULN	Maintain dose level
> 1.5 - 3.0 x ULN	Omit dose with weekly monitoring of LFTs, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN. If resolved in ≤ 14 days, then maintain dose level If resolved in > 14 days, then dose reduction of 3.5 or 7 mg/kg/day for deferasirox FCT.
> 3.0 - 10.0 x ULN	Omit dose with weekly monitoring of LFTs, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN. If resolved in ≤ 14 days, then dose reduction of 3.5 or 7 mg/kg/day for deferasirox FCT If resolved in > 14 days, then discontinue patient from study drug treatment. The patient needs to be monitored weekly (including LFTs), or more frequently if clinically indicated until TBIL have resolved to baseline or stabilization. Please refer to section 6.3.3 for additional details on follow-up.
> 10.0 x ULN*	Discontinue patient from study drug treatment The patient needs to be monitored weekly (including LFTs), or more frequently if clinically indicated, until TBIL have resolved to baseline or stabilization. Please refer to section 6.3.3 for additional details on follow-up.
AST or ALT elevation	
> ULN - 3.0 x ULN	Maintain dose level
> 3.0 - 5.0 x ULN (For patients with baseline value ≤ 3.0 x ULN)	(For patients with baseline value > 3.0 -5.0 x ULN)
> 5.0 - 10.0 x ULN (For patients with baseline value > 3.0 -5.0 x ULN)	
> 5.0 - 10.0 x ULN (For patients with baseline value ≤ 3.0 x ULN)	
> 10.0 - 20.0 x ULN	

[redacted]

	Maintain dose level. Repeat LFTs as soon as possible, preferably within 48- 72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN. Please refer to section 6.3.3 for additional details on follow-up.
	Maintain dose level.
	Omit dose. Repeat LFTs as soon as possible, preferably within 48- 72 hours from awareness of the abnormal results; monitor LFTs weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN If resolved in ≤ 14 days, maintain dose level If resolved in > 14 days, then dose reduction of 3.5 or 7 mg/kg/day for deferasirox FCT.
	Omit dose. Repeat LFTs as soon as possible, preferably within 48-

[redacted]

Recommended dose modifications for deferasirox	
	72 hours from awareness of the abnormal results; monitor LFTs weekly, or more frequently if clinically indicated, until resolved to ≤ baseline. Then dose reduction of 3.5 or 7 mg/kg/day for deferasirox FCT.
> 20.0 x ULN (For patients with baseline value > 3.0 -5.0 x ULN)	Discontinue patient from study drug treatment Repeat LFTs as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs weekly, or more frequently if clinically indicated, until resolved to baseline or stabilization. Please refer to section 6.3.3 for additional details on follow-up of toxicities.
Combined elevations of AST or ALT and total bilirubin	
For patients with normal baseline ALT or AST or total bilirubin value: AST or ALT >3.0xULN combined with total bilirubin >2.0 x ULN without evidence of cholestasis OR [AST or ALT>2x baseline AND > 3.0 xULN] OR [AST or ALT > 8.0 xULN], whichever is lower, combined with [total bilirubin >2x baseline AND >2.0 xULN	Interrupt study treatment. Permanently discontinue patient from study drug treatment if no other plausible explanation can be found for the combined increase. Repeat as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTs, or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilization. Please refer to section 6.3.3 for additional details on follow-up of toxicities.
Hepatic impairment	
Moderate hepatic impairment (Child- Pugh Class B	The study medication will be interrupted and patient monitored. If liver disease prognosis improves, deferasirox can be reintroduced at 7 mg/kg/day for FCT or 50% of previous dose, whichever is less. While monitoring continues, dose may be increased by 3.5 mg/kg/day for FCT every 2 weeks, to a maximum of 50% of patient's previous dose if the investigator determines that dose increase is in the best interest of the patient. Study medication must be used with caution in such patients.
In patients who develop severe hepatic impairment (Child-Pugh Class C) during the study	Study medication must be discontinued.
Other recommended dose modifications **Changes in Serum Ferritin**	
500 – 1000 ng/mL	The dose of deferasirox FCT should be adjusted as necessary every 3 months based on the trends in serum ferritin and investigator's judgement. ICT naïve patients can adapt dose after 4 weeks on study. Dose adjustments for deferasirox FCT 3.5 mg or 7 mg/kg/day are to be tailored to the individual patient's response and the therapeutic goal of (reduction 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. The starting dose and the dose adjustment considerations must take into account that the therapeutic goal is reduction of iron burden (as opposed to maintenance of iron burden). Doses above 28 mg for deferasirox FCT

[redacted]

ria not allowed.
Dose reductions in steps of 3.5 or 7 mg/kg/day for
6 Protocol No.

[redacted]

Recommended dose modifications for deferasirox	
	deferasirox FCT are required to maintain serum ferritin levels within the target range.
< 500 ng/ml	Interruption of study treatment is required until serum ferritin rises above 500 ng/mL
Changes in urine protein/creatinine ratio	
> 0.5 (mg/mg) in two consecutive non- first void urine samples (a minimum of 48h apart), if all other causes of proteinuria have been excluded.	For patients who develop proteinuria or a worsening of pre-existing proteinuria at any visit, urine samples should be collected and assessed by the laboratory. In case of a single increase of the urinary protein/creatinine ratio the assessment should be repeated at the next visit. Deferasirox FCT dose reduction by 50% When resolution of UPCR (<0.5mg/mg) at the next study visit, dose can be resumed again at 100% If increase in UPCR >0.5mg/mg recurs again within 2 months after initial increase, therapy needs to be reduced to 50% of the last dose. If increase in UPCR does not recur after 2 months at reduced dose (50%), study medication can be returned to 100% of the last dose.
> 1.0 (mg/mg) in one single non-first void urine samples.	Interrupt study treatment. When resolution of increase in UPCR (<0.5mg/mg) at the next study visit, dose can be resumed again at 50% of the last dose. If increase in UPCR does not recur after 1 month at reduced dose (50%), study medication can be returned to 100% of the last dose. 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 laboratory results.
Severe skin reactions	
Severe skin reactions, including Stevens-Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN), DRESS	Must be reported if occurs during Exjade therapy. If SJS ,TEN, DRESS is suspected, study treatment must be immediately discontinued and not be reintroduced
Skin Rash (other than SJS, TEN, DRESS)	
For skin rash of mild/moderate severity (defined as those causing minimal symptoms which require no 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, resume study drug at 50% of patient's last dose. If the rash does not recur, increase dose back to 100% of patients dose after 2 weeks.
Severe rash (distressing symptoms requiring discontinuation and/or systemic steroids)	Discontinue treatment until resolution of rash. Once the rash has resolved, resume at 50% of 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, increase by steps of 3.5 mg/kg/day for deferasirox FCT every 2 weeks until 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

[redacted]

Recommended dose modifications for deferasirox	
	of the patient. Novartis may be contacted by the investigator to discuss dosing options if the investigator so desires
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 is required before the start of deferasirox treatment. If disturbances are noted dose reduction or interruption may be considered and a repeated testing performed as per investigator's judgment.
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. Deferasirox should not be reintroduced in patients who have experienced previous hypersensitivity reactions on deferasirox due to the risk of anaphylactic shock
Dose modification criteria for cytopenias	
Unexpected 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.
Gastrointestinal disturbances	
Gastrointestinal issues (including diarrhea, constipation, nausea, vomiting and abdominal pain)	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 the patient to discontinue any laxative preparations or stool softeners they may be taking and to eat small, frequent meals. Determine if the patient is lactose intolerant. Monitor fluid intake and adapt as necessary according to body weight. Should the gastrointestinal issues (including diarrhea, constipation, nausea, vomiting and abdominal pain) persist, 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 Dose adjustments for QTcF prolongation

Not applicable

[redacted]

6.3.3 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or abnormal laboratory value must be followed for at least 30 days. All unresolved toxicities should be followed by the investigator until CTCAE Grade ≤1, return to baseline, stabilization or the subject is lost to follow-up.

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

Patients with transaminase increase combined with TBIL increase may be indicative of potential DILI, and should be considered as clinically important events.

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

- For patients with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN
- For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as ALP elevation > 2.0 x ULN with R value < 2 in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis.

Note: (The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤ 2), hepatocellular (R ≥ 5), or mixed (R >2 and < 5) liver injury).

In the absence of cholestasis, these patients should be immediately discontinued from study drug treatment, and repeat LFT testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc. Data and test results must be entered in the hepatotoxicity follow up test procedures eCRFs available in the clinical database.

1. Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR and alkaline phosphatase.
2. A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.
3. Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.
4. Obtain PK sample, as close as possible to last dose of study drug, if PK analysis is performed in the study.
5. Additional testing for other hepatotropic viral infection (CMV, EBV or HSV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

[redacted]

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified should be considered as "medically significant", thus, met the definition of SAE (Section 8.2.1) and reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

6.3.4 Anticipated risks and safety concerns of the study drug

Appropriate eligibility criteria, as well as specific dose modification and stopping rules are included in this protocol. Recommended guidelines for prophylactic or supportive treatment for expected toxicities, including management of study-drug induced AEs i.e., gastrointestinal, skin toxicity and diarrhea are provided in Table 6-4. Refer to preclinical toxicity and or clinical data found in the Investigator's Brochure.

6.4 Concomitant medications

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 and herbal/natural medications) administered during the study must be listed on the Concomitant Medications or the Procedures and Significant Non-Drug Therapies CRF. Blood transfusions must be entered on the Blood Component Transfusion CRF

6.4.1 Blood transfusion

History of blood transfusions within the period of 3 months prior to Screening visit 1 must be recorded on Blood Component Transfusion CRF page. Additionally, record of blood transfusion during the study must collected (see Table 7-1) and entered on the Blood Component Transfusion CRF page.

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 any adverse consequences.

Aluminum containing antacid therapies should be avoided because they may bind to deferasirox.

The concomitant use of deferasirox with potent UGT inducers (e.g. rifampicin, phenytoin, phenobarbital, ritonavir) may result in a decrease in deferasirox efficacy.

Concomitant use of any iron chelation therapy other than the study drug, investigational agents or bile acid sequestrants is not allowed.

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

- Concomitant administration of deferasirox with drugs that have known ulcerogenic potential such as non-steroidal anti-inflammatory drugs, corticosteroids, or oral bisphosphonates, and use of deferasirox in patients receiving anticoagulants my increase the risk of gastrointestinal irritation

[redacted]

- Deferasirox, as a weak CYP3A4 inducer, may potential increase serum levels of substances metabolized through CYP3A4 (e.g. cyclosporine, simvastatin, hormonal contraceptive agents)
- Deferasirox is a moderate inhibitor of CYP2C8 and therefore, may increase serum concentrations of substances metabolized through CYP2C8 (e.g. repaglinide, pa paclitaxel)

6.4.3 Prohibited concomitant therapy

Concomitant use of bile acid sequestrants decreases deferasirox systemic exposure. Avoid the concomitant use of bile acid sequestrants (e.g. cholestyramine, colesevelam, colestipol) with deferasirox

- Any iron chelation therapy other than study drug
- Any investigational drug other than the study medication

6.4.4 Use of Bisphosphonates (or other concomitant agents)

Not applicable

6.4.4.1 Proposed language for other concomitant medications

Not applicable

6.5 Patient numbering, treatment assignment or randomization

6.5.1 Patient numbering

Each patient is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Subject No. 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 subject is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Subject No. available to the investigator through the Oracle Clinical RDC interface.

6.5.2 Treatment assignment or randomization

This is a single-arm, non-randomized, interventional, open- label, global multi-center study.

6.5.3 Treatment blinding

This is an open-label study and therefore, patients, investigators, study site staff and study field monitors are not blinded to study treatment.

6.6 Study drug preparation and dispensation

The investigator or responsible site personnel will contact the IRT system to register the patient by providing the required information into the IRT system. All drug dispensation will be registered in IRT. Countries with commercially available deferasirox will register only the quantity dispensed as there are no unique kit numbers on commercial drugs.

[redacted]

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 CRF. Crushing deferasirox FCT is mandatory for this trial. Do not split dose if only prescribing one tablet per day. Caregiver will receive instructions from the site study personnel on study drug preparation.

Table 6-5 Preparation and dispensing

Study Treatments	Dispensing	Preparation
Crushed Deferasirox FCT	Tablets, including instructions for crushing and administration, are dispensed by study personnel on an outpatient basis. Patients will be provided with adequate supply of study treatment for self-administration at home until at least their next scheduled study visit.	All doses of deferasirox FCT must be crushed in the home environment. Crushing the deferasirox FCT is mandatory. One example of a crushing method is to place the film-coated tablets between two pieces of wax paper and roll over the wax paper with a rolling pin until the tablets become a fine powder, then funnel the wax paper crushed FCT powder contents into a bowl and mix with a soft food.

6.6.1 Study treatment packaging and labeling

6.6.1.1 Countries where Deferasirox FCT is not commercially available

The study drug will be supplied centrally by Novartis to countries where Deferasirox FCT is not commercially available.

Study medication labels will be in the local language and will comply with the legal requirements of the respective country and will include storage conditions and a unique medication number.

. Responsible site personnel will identify the study treatment dosage(s) to dispense to the patient. Site personnel will add the patient number on the label. Immediately before dispensing the package to the patient, site personnel will record study drug dosage amounts and quantity dispensed in the source document (Drug Label Form) for that patient. If the label has 2-parts (base plus tear-off label), immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the package and affix it to the patient's source document.

6.6.1.2 Countries where Deferasirox FCT is commercially available

Countries where Deferasirox FCT is commercially available will use commercially available Deferasirox FCT as study drug and will follow their local process for using commercial product for clinical trials.

[redacted]

Table 6-6 Packaging and labeling

Study treatments	Packaging	Labeling (and dosing frequency)
Deferasirox FCT	Local Commercial (for countries where Deferasirox FCT is marketed)	Labeled as Deferasirox FCT
ICL670	Non-commercial (for countries where Deferasirox FCT is not marketed)	Labeled as ICL670

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.

Sites in countries where Deferasirox FCT is not commercially available will be supplied centrally with study drug (ICL670) by Novartis. Upon receipt, the investigator or designee will confirm study drug receipt in IRT and store study drug according to the instructions specified on the drug labels and in the Investigator's Brochure.

The sites in the countries where Deferasirox FCT is commercially available will use commercially available Deferasirox FCT (as study drug) supplied by the local Novartis affiliate. Upon receipt, the investigator or designee will store study drug according to the instructions specified on the drug label.

Table 6-7 Supply and storage of study treatments

Study treatments	Supply	Storage
Deferasirox FCT	Locally supplied by Novartis for countries where Deferasirox FCT is marketed	Refer to study treatment label
ICL760	Centrally supplied by Novartis (labeled medication) for countries where Deferasirox FCT is not marketed.	Refer to study treatment label

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug compliance

Compliance will be assessed by the investigator and/or study site personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit

6.6.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. All drug dispensation will be registered in IRT. 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.

[redacted]

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

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. All data obtained from these assessments must be supported in the patient’s source documentation. All data obtained from these assessments and noted with an “S” in the category column must be supported in the patient’s source documentation. The “D” in the category column must be supported in Novartis eCRF database.

No CRF will be used as a source document.

[redacted]

Table 7-1 Visit evaluation schedule

	Category	Protocol Section	Screening Visit 1 Day -14 to -8	Screening Visit 2 Day -7 to -1 (Newly Initiated DFX patients	Baseline								End of study treatment (EoT) Week 24 ± 7 days	30 day safety follow-up
Visit Name			**SV1**	**SV2***	**Week 1 Day 1**	**Week 2 ± 3 days**	**Week 3 ± 3 days**	**Week 4 ± 3 days**	**Week 8 ± 7 days**	**Week 12 ± 7 days**	**Week 16 ± 7 days**	**Week 20 ± 7 days**		
Obtain Informed Consent	D	11.3	X											
IRT(IWRS)	S	7.1.2.1	X	X	X	X	X	X	X	X	X	X	X	
Patient History														
Demography	D	7.1.2.3	X											
Inclusion/exclusion criteria	D	5.2, 5.3	X	X										
Medical History	D	7.1.2.3	X											
Transfusion Therapy[1]	D	6.4	X Continuous – up to 30 days after last dose											
Prior and Concomitant Medications/Prior Chelation	D	6.4	X Continuous – up to 30 days after last dose											
Surgical and Medical Procedures	D	6.4	X Continuous – up to 30 days after last dose											
Physical Examination														
Physical Examination	S	7.2.2.1	X	X	X	X	X	X	X	X	X	X	X	
Height	D	7.2.2.3	X										X	
Weight	D	7.2.2.3	X	X	X			X	X	X	X	X	X	
Vital signs	D	7.2.2.2	X	X	X	X	X	X	X	X	X	X	X	

[redacted]

Visit Name	Category	Protocol Section	Screening Visit 1 Day -14 to -8 SV1	Screening Visit 2 Day -7 to -1 (Newly Initiated DFX patients SV2*	Baseline Week 1 Day 1	Week 2 ± 3 days	Week 3 ± 3 days	Week 4 ± 3 days	Week 8 ± 7 days	Week 12 ± 7 days	Week 16 ± 7 days	Week 20 ± 7 days	End of study treatment (EoT) Week 24 ± 7 days	30 day safety follow-up
Laboratory Assessments														
Hematology	D	7.2.2.5.1	X		X			X	X	X	X	X	X	
Chemistry	D	7.2.2.5.2	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis (Dipstick)	D	7.2.2.5.3	X		X			X	X	X	X	X	X	
Urinalysis (Urinary protein/creatinine ratio)	D	7.2.2.5.3	X		X			X	X	X	X	X	X	
Urinalysis (Microscopic)	D	7.2.2.5.3	As clinically indicated											
Hepatitis markers	D	7.1.2.3	X	As clinically indicated										
Cardiac Assessments														
ECG	D	7.2.2.10.1	X	As clinically indicated										
Safety														
Adverse events	D	8.1	X Continuous – up to 30 days after last dose											
Hepatotoxicity Follow-up testing procedures	D	6.3.3.1	As clinically indicated											
Ocular assessments[2]	D	7.2.2.6	X	As clinically indicated									X	
Auditory assessments[2]	D	7.2.2.7	X	As clinically indicated									X	
Observer Reported Outcomes														

[redacted]

	Category	Protocol Section	Screening Visit 1 Day -14 to -8	Screening Visit 2 Day -7 to -1 (Newly Initiated DFX patients	Baseline								End of study treatment (EoT) Week 24 ± 7 days	30 day safety follow-up
Visit Name			SV1	SV2*	Week 1 Day 1	Week 2 ± 3 days	Week 3 ± 3 days	Week 4 ± 3 days	Week 8 ± 7 days	Week 12 ± 7 days	Week 16 ± 7 days	Week 20 ± 7 days		
mSICT	D	7.2.8	X[3]					X		X			X	
Palatability questionnaire	D	7.2.8	X[3]					X		X			X	
GI symptom questionnaire	D	7.2.8	X[3]			X	X	X	X	X	X	X	X	
Study drug dispensation	D	6.3.1			X			X	X	X	X	X		
End of phase disposition	D		X	X									X	
Safety follow-up	D	4.1												X

* SV2 is applicable only to patients who are chelation naïve or are currently treated with chelation therapy other than deferasirox. Patients on prior deferasirox will NOT be subject to SV2

[1] History of prior transfusion up to 3 months prior to Screening visit 1 (SV1) must be collected at SV1. Additionally, record of transfusion during the study must be collected.

[2] The choice of method for ocular and auditory assessments will be at the discretion of the investigators. Best efforts should be made to perform these assessments in all subjects, although feasibility in very young children will be at the discretion of the investigator.

[3] Chelation naïve patients and patients treated with chelation therapy other than deferasirox who stopped chelation treatment more than 7 days prior to Screening visit 1 (SV1) will not complete questionnaires at SV1.

[redacted]

7.1.1 Molecular pre-screening

Not applicable

7.1.2 Screening

Prior to commencement of the screening examination, the patient and their caregiver(s) must have given full informed consent and have completed the study Informed Consent Form. Once this has been signed and dated by the patient's legal guardian then the investigator can take the patients through the study inclusion and exclusion criteria to make sure the patient is fully eligible to participate. The investigator or responsible site personnel will register Screening visit 1 in IRT.

The full list of assessments to be performed during the screening period (Day -14 to Day 1) is detailed in Table 7-1. Two Screening visits at least 7 days apart are needed to perform key safety parameters prior to the first dose administration in patients who are chelation naïve or are currently treated with a chelation therapy other than deferasirox.

For patients that are chelation naïve or currently treated with other chelators, the investigator or responsible site personnel will register Screening visit 2 in IRT. Patients on prior deferasirox will be subject to only screening visit 1 and baseline visit can be scheduled after eligibility is established.

Re-screening for patients who screen-failed is permissible on a case by case basis. Please contact Novartis for guidance to get information on how to process screen failures. Re-screening visits will be registered in IRT.

7.1.2.1 Eligibility screening

Patient eligibility will be checked after screening procedures have been completed. .

7.1.2.2 Information to be collected on screening failures

Patients or their caregivers 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 Site Screening Log. Data for screen failure patients will be collected on the following eCRFs:

- Demography
- Informed consent
- Inclusion/exclusion
- Screening phase disposition
- Adverse events (only if SAE occurred)
- Death (if applicable)
- Withdrawal of consent (if applicable)

[redacted]

7.1.2.3 Patient demographics and other baseline characteristics

At screening visit 1 data will be collected on patient characteristics including demographics (age, sex, ethnicity, etc.), medical history (including current medical conditions and history of disease), transfusion history, physical examination, laboratory assessments, and vital signs.

To determine eligibility to be enrolled in the study, patients will also undergo assessments as per the inclusion and exclusion criteria which include hematology and chemistry evaluations, hepatitis viral history evaluation, serum ferritin, serum creatinine, creatinine clearance, liver function enzymes (ALT/AST), direct/total bilirubin, ALP, a known history of HIV positive test result (ELISA or Western blot) which is documented in the source documents, history of active Hepatitis B and/or C, UPCR, and urinalysis. Patients will also undergo a standard ophthalmologic evaluation, audiometry, and ECG.

7.1.3 Run-in period

Any current iron chelation therapy except deferasirox will be discontinued to undergo a 5-day washout period prior to commencing the 24-week treatment period with crushed deferasirox FCT.

A second screening visit will occur for chelation naïve and patients treated with iron chelation therapy other than deferasirox as detailed in Table 7-1.

7.1.4 Treatment period

Having completed the screening period, patients will be enrolled and eligibility registered in IRT. The patient will then begin therapy with crushed deferasirox FCT as per study protocol.

The treatment duration is 24 weeks. Study treatment is defined as crushed deferasirox FCT applied according to study protocol. Study-mandated evaluations and safety assessments will be performed every week for the first month and monthly thereafter in alignment with the visit schedule, see Table 7-1.

7.1.5 Discontinuation of study treatment

Patients or their caregivers may voluntarily discontinue from the study for any reason at any time. If a patient decides to discontinue from the study, 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 CRF 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 otherreason.

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

Patients who discontinue deferasirox FCT should NOT be considered withdrawn from the study. They should return for the assessments indicated in Section 7.2.1. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, email, letter) should be made to contact them as specified in Section 7.1.8.

Study treatment may be discontinued under the following circumstances:

[redacted]

- Adverse Event
- Death
- Lack of Efficacy
- Withdrawal of informed Consent
- Protocol Deviation
- Study terminated by sponsor
- Technical Problem
- Lost to follow-up
- Physicians decision
- Subject/guardian decision

Patients who discontinue deferasirox FCT should undergo an end of treatment visit within 7 days followed by a 30 day safety follow-up.

The Investigator or responsible site personnel must contact the IRT to register the patient's discontinuation.

7.1.5.1 Replacement policy

Patients who discontinue or are withdrawn will not be replaced on study.

7.1.6 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 prior to withdrawal of consent in order to guarantee the validity of the study.

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.

7.1.7 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 Adverse Events, Prior and Concomitant Medications, and Surgical and Medical procedures eCRFs. All unresolved adverse events should be followed by the investigator until the events are resolved, or the subject is lost to follow-up.

[redacted]

7.1.8 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents 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 CRF.

7.1.9 Unscheduled visits

Unscheduled safety assessments may be performed as clinically indicated at the discretion of the investigator at any time during the study.

7.2 Assessment types

7.2.1 Efficacy assessments

The efficacy variable will be the change in serum ferritin from baseline to end of treatment.

Serum ferritin will be performed at screening visit 1 to assess the eligibility of the patient. Serum ferritin will be assessed at week 1 /day 1 and monthly during the treatment period. Additional assessment of serum ferritin assessments may be performed more frequently if needed in accordance with the clinical judgment of the investigator.

7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing frequency and severity of adverse events as well as physical examination, vital signs, hematology, blood chemistry, urinalysis, ECG, ocular, and auditory assessments and laboratory parameters as detailed in Table 7-1. Additional details can be found in Section 7.5.1.7.

For details on AE collection and reporting, refer to Section 8.

7.2.2.1 Physical examination

A complete physical examination will be performed at screening visit 1 and each visit as detailed in Table 7-1.

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, and extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, and pelvic exams will be performed.

Information about the physical examination must be present in the source documents 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 patient's CRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's CRF.

[redacted]

7.2.2.2 Vital signs

Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, and body temperature will be measured at screening visit 1, screening visit 2 and at all visits including end of treatment as detailed in Table 7-1.

7.2.2.3 Height and weight

Standing height will be assessed at screening visit 1 and end of treatment. Weight will be assessed at screening visits 1 and 2, week 1/day 1, monthly visits, week 4 through week 20 and end of treatment as detailed in Table 7-1.

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured.

7.2.2.4 Performance status

Not applicable

7.2.2.5 Laboratory evaluations

Clinical laboratory parameters will be assessed as detailed in Table 7-2.

Table 7-2 Local Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, MCH, MCHC, MCV, Platelets, Red blood cells, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)
Chemistry	Alkaline phosphatase, ALT , AST, Creatinine, Creatinine clearance, Direct Bilirubin, Total Bilirubin, Blood Urea Nitrogen (BUN) or Urea, Uric acid, Total protein, Bicarbonate, Albumin, Chloride, Glucose, Inorganic phosphate, Potassium, Sodium, Calcium and Magnesium.
Urinalysis	Microscopic Panel (Red Blood Cells, White Blood Cells, Casts, Bacterial casts Macroscopic Panel (Dipstick): Color, Bilirubin, WBCs, Blood, Glucose, Ketones, Nitrite, pH, Protein, Specific Gravity, Urobilinogen Urinalysis: Urine protein/creatinine ratio
Hepatitis markers	HBsAg, Anti-HCV, Anti-HBs, HCV RNA-PCR quantitative (screening visit 1)

Analysis of all laboratory specimens including urinary dipstick analysis will be performed by a local laboratory.

7.2.2.5.1 Hematology

Complete blood cell count with differential samples will be collected at screening visit 1, week 1 and monthly at weeks 4 through 24 as detailed in Table 7-1.

Parameters to be measured will include: Hemoglobin, Hematocrit, Red Blood Cell Count, Mean Corpuscular Volume, Mean Corpuscular Hemoglobin, Mean Corpuscular Hemoglobin Concentration, White Blood Cell Count, White Blood Cell Differential, and Platelet Count

7.2.2.5.2 Clinical chemistry

Clinical chemistry samples will be collected at screening visit 1 and screening visit 2 and at visits as detailed in Table 7-1.

[redacted]

The parameters to be measured at screening visits and at specific timepoints in the study are as follows:

Screening Visit 1 -All patients:

Parameters to be measured include serum creatinine, creatinine clearance, blood urea nitrogen or urea, total bilirubin, direct bilirubin, ALT, AST, alkaline phosphatase, uric acid, total protein, bicarbonate, albumin, chloride, glucose, inorganic phosphate, potassium, sodium, calcium, magnesium and serum ferritin.

Screening Visit 2 - (Only patients who are chelation naïve or treated with iron chelation other than deferasirox):

Parameters to be measured include serum creatinine, creatinine clearance and serum ferritin.

Study Visit Baseline (Week 1) – All patients:

Parameters to be measured include serum creatinine, creatinine clearance, blood urea nitrogen or urea, total bilirubin, direct bilirubin, ALT, AST, alkaline phosphatase uric acid, total protein, bicarbonate, albumin, chloride, glucose, inorganic phosphate, potassium, sodium, calcium, magnesium and serum ferritin.

Study Visit Week 2 – All patients:

Parameters to be measured include serum creatinine and creatinine clearance

Study Visit Week 3 – All patients:

Parameters to be measured include serum creatinine, creatinine clearance, total bilirubin, direct bilirubin, ALT, AST, uric acid, total protein, bicarbonate, albumin, chloride, glucose, inorganic phosphate, potassium, sodium, calcium, magnesium and alkaline phosphatase.

Study Visit Weeks 4, 8, 12, 16, 20 and end of treatment – All patients:

Parameters to be measured include serum creatinine, creatinine clearance, blood urea nitrogen or urea, total bilirubin, direct bilirubin, ALT, AST, alkaline phosphatase, uric acid, total protein, bicarbonate, albumin, chloride, glucose, inorganic phosphate, potassium, sodium, calcium, magnesium and serum ferritin.

Renal parameters are monitored weekly to establish a reliable pretreatment baseline and hepatic parameters are monitored biweekly for safety at the initiation of treatment.

For calculated CrCl from local labs where the enzymatic method is used to determine creatinine clearance the modified Schwartz formula will be used for analysis. This estimate will be provided each time serum creatinine is collected.

For calculated CrCl from local labs where Jaffe method is used we will use the Schwartz formula. This estimate will be provided each time serum creatinine is collected.

All clinical chemistry samples will be sent to local laboratories.

7.2.2.5.3 Urinalysis

Urinalysis samples will be collected at screening visit 1, week 1/day 1, and at monthly visits from week 4 through end of treatment as detailed in Table 7-1. A midstream second voided

[redacted]

morning sample will be obtained. Dipstick measurements for specific gravity, pH, blood, white blood cells, glucose, protein, bilirubin, color, nitrite, urobilinogen and ketones will be assessed at the local site. Microscopic analysis will be performed only in case of a positive dipstick result for protein. Dipsticks will be supplied by a local laboratory. Any significant findings on dipstick will be followed up with a microscopic evaluation where WBC and RBC sediments will also be measured. If ketones are positive, measurement of hemoglobin A1C and/or fasting pre-prandial glucose may be performed by the local laboratory at the request of the Investigator.

At screening visit 1 and in addition to the dipstick measurement, a urine sample (at least 15 mL) will be collected and sent to a local laboratory for urinary protein/creatinine ratio to assess the eligibility of the patient. In addition, urine samples for urinary protein/creatinine ratios will be collected at week 1/day 1 and at monthly visits, weeks 4 through end of treatment. First morning void samples must not be used for this analysis. Significant protein is indicated by a urinary protein/creatinine ratio >0.5 mg/mg.

For patients who develop proteinuria or worsening of pre-existing proteinuria (assessed by dipstick) at any visit, microscopic analysis must performed by the local laboratory.

All urinalysis samples will be sent to a local laboratory.

7.2.2.6 Ocular assessments

Ocular assessments will be performed at screening visit 1 and at end of treatment according to the local (institution's) clinical practice. The choice of method for ocular assessments will be at the discretion of the investigators. Best efforts should be made to perform these assessments in all subjects, although feasibility in very young children will be at the discretion of the investigator. Additional ocular assessment is permitted at the discretion of the Investigator based on patient reporting of symptoms.

7.2.2.7 Auditory assessments

Auditory assessments will be performed at screening visit 1 and at end of treatment according to local (institution's) clinical practice. The choice of method for auditory assessments will be at the discretion of the investigators. Best efforts should be made to perform these assessments in all subjects, although feasibility in very young children will be at the discretion of the investigator. Additional auditory assessment is permitted at the discretion of the Investigator based on patient reporting of symptoms.

7.2.2.8 Pregnancy and assessments of fertility

Not applicable

7.2.2.9 Radiological examinations

Not applicable

7.2.2.10 Cardiac assessments

Not applicable

[redacted]

7.2.2.10.1 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed at screening visit 1.

Interpretation of the tracing must be made by a qualified physician and documented on the ECG CRF 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 CRF 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 Adverse Events CRF page.

Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated. Local cardiologist ECG assessment may also be performed at any time during the study at the discretion of the investigator.

7.2.2.10.2 Cardiac imaging - MRA (magnetic resonance angiography), MUGA (multiple gated acquisition) scan or echocardiogram

Not applicable

7.2.2.10.3 Cardiac enzymes

Not applicable

7.2.2.11 Tolerability

Patients and/or their caregivers will complete an electronic palatability questionnaire as detailed in Table 7-1 and provided in the Appendix 14.1.

7.2.3 Limitations of the study

Novartis will carefully ensure that the PASS will not interfere/modify the local medical practices. The sites will be selected based on their transfusional hemosiderosis treatment experience and patients will be enrolled even if they already started chelation for this indication. Novartis will interact with local networks to ensure targeting the best representation as possible. Therefore, no limitation of potential selection bias is expected in this trial.

The limitations of the research may be a small sample size.

7.2.4 Pharmacokinetics

Not applicable

7.2.4.1 Analytical method

Not applicable

7.2.5 Biomarkers

Not applicable

[redacted]

7.2.5.1 Additional biomarker assessments

Not applicable

7.2.5.1.1 Optional additional exploratory biomarker assessments using remaining biomarker samples

Not applicable

7.2.6 Other assessments

No additional tests will be performed on patients entered into this study.

7.2.7 Resource utilization

Not applicable

7.2.8 Patient reported outcomes

As detailed in Table 7-1 and provided in Appendix 14.1. patients or their caregivers will complete a series of ObsRO questionnaires at the study site (during study visits) as follows:

- palatability and mSCIT of crushed FCT, at SV1 and at the following visits: week 4, week 12 and at end of treatment
- gastrointestinal symptoms of crushed FCT at SV1 and at the following visits: week 2, week3, week4 , week 8, week 12, week 16, week 20 and at end of treatment

Note: Chelation naïve patients and patients treated with chelation therapy who stopped treatment more than 7 days prior to Screening visit 1 will not complete questionnaires at screening.

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

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

Abnormal laboratory values or test results occurring after informed consent constitute adverse events 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).

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF. Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis

[redacted]

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 Adverse Event.

Adverse events will be assessed according to severity: mild, moderate or severe. Information about any deaths (related to an Adverse Event or not) will also be collected through a Death form.

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

1. Severity (Mild, moderate or severe)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study or investigational 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 serious adverse event (SAE) is defined as in Section 8.2.1 and which seriousness criteria have been met
7. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown).

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For moderate and severe events, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

Once an adverse event 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. Follow up will continue up to 30 days after study drug discontinuation.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event 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 Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low

[redacted]

hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events 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 adverse event, 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 adverse event, should not be reported as adverse events. 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 lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

8.1.3 Adverse events of special interest

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are 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.

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

Selected AEs, especially related to disturbances of the gastrointestinal tract, will be collected and assessed for severity: esophagitis, stomatitis, mouth ulceration, gastric ulcers, hemorrhage, abdominal pain, diarrhea, nausea, and vomiting.

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

[redacted]

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

Any SAEs experienced after the 30 day safety evaluation follow-up period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

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.

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, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Chief Medical Office and Patient Safety (CMO&PS) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE 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

8.4 Pregnancies

Not applicable

[redacted]

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 Investigator Brochure. 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

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.

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

[redacted]

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 CRFs 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 CRFs, 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, audiology and ocular exams, and the results of any other tests or assessments. All information recorded on CRFs 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 CRF 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 CRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

For sites using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (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 sites 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 and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

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

[redacted]

All IRT assigned kits (study drug) will be tracked using an Interactive Response Technology system. The system will be supplied by a vendor, who will also manage the database.

10 Statistical methods and data analysis

The study employs a prospective, multi-center trial design to monitor and assess the safety profile of the crushed deferasirox FCT in pediatric patients age ≥2 to <6 years with transfusional hemosiderosis over 24 weeks. The study will enroll at least 40 patients worldwide.

The data will be analyzed by Novartis and/or a designated Clinical Research Organization (CRO).

Continuous variables will be summarized by number of patients, mean, standard deviation, minimum, median, and maximum. For selected parameters, 25th and 75th percentiles will also be presented.

Categorical variables will be summarized by frequencies and percentages.

In addition to the statistical methods outlined below, further details and any additional exploratory analyses that may be performed will be described in the Statistical Analysis Plan (SAP).

10.1 Analysis sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients who received at least one dose of deferasirox FCT during the study.

10.1.2 Safety set

The Safety Set includes all patients who received at least one dose of deferasirox FCT during the study.

The Safety Set and the FAS will be the same for this single arm phase IV study.

10.1.3 Per-Protocol set

Not applicable

10.1.4 Dose-determining analysis set

Not applicable

10.1.5 Pharmacokinetic analysis set

Not applicable

10.1.6 Other analysis sets

Not applicable

[redacted]

10.1.6.1 Efficacy/evaluable set

Not applicable

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively using the FAS. The baseline visit will be the study visit in which dosing of deferasirox FCT is initiated.

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

Relevant medical histories and current medical history at baseline will be summarized by system organ class and preferred term.

10.3 Treatments (study treatment, concomitant therapies, compliance)

Descriptive statistics (n, mean, standard deviation, minimum, median, and maximum) will be used to summarize continuous variables (e.g., laboratory assessments), and frequency counts and percentages will be provided for categorical variables.

The duration of exposure to deferasirox FCT as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) will be summarized by means of descriptive statistics.

The number of patients with dose adjustments (reductions, interruption, or permanent discontinuation) and the reasons will be summarized and all dosing data will be listed.

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

10.4 Primary objective

The primary objective of the study is to assess the safety of crushed deferasirox FCT with respect to selected gastrointestinal (GI) disorders. Details regarding the analysis of AEs are described in Section 10.5.3.2.

10.4.1 Variable

The primary endpoint is the number and percentage of patients with selected gastrointestinal disorders (esophagitis, stomatitis, mouth ulceration, gastric ulcers, hemorrhage, abdominal pain, diarrhea, nausea, and vomiting) up to 24 weeks including 30 days safety follow-up.

10.4.2 Statistical hypothesis, model, and method of analysis

Proportion of patients with selected GI disorders will be provided together with the 95% confidence interval using the Clopper-Pearson exact method for this proportion.

[redacted]

10.4.3 Handling of missing values/censoring/discontinuations

Not applicable

10.4.4 Supportive and Sensitivity analyses

Not applicable

10.5 Secondary objectives

Evaluate AEs suspected to be related to the crushed deferasirox FCT:

- Number and percentage of patients who experienced AEs suspected to be related to the study drug up to 24 weeks including 30 day safety follow-up overall and by SOC.

To assess the overall safety of crushed deferasirox FCT:

- Number and percentage of patients with any AEs, SAEs, and AEs leading to discontinuation together with their severity up to 24 weeks including 30 days safety follow-up will be provided. Details regarding the analysis of AEs are described in Section 10.5.3.2.
- Absolute change from baseline over time as box plots for serum creatinine, creatinine clearance, UPCR, total bilirubin, ALP, ALT, AST will be provided. Furthermore, shift tables using low/normal/high classification will be provided. Details regarding lab abnormalities are described in Section 10.5.3.3.
- Other safety data (e.g., ECGs, vital signs, ocular, auditory examinations) will be descriptively summarized.

To assess the efficacy of deferasirox FCT treatment:

- Absolute change from baseline over time in SF values up to 24 weeks of treatment will be provided

To evaluate patient treatment satisfaction, palatability and GI symptoms with ObsROs

- Please refer to Section 10.5.7.

10.5.1 Key secondary objective(s)

Not applicable

10.5.2 Other secondary efficacy objectives

Not applicable

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used. The overall observation period will be divided into three mutually exclusive segments:

1. Pre-treatment period: from day of patient's informed consent to the day before first dose of study medication

[redacted]

2. On-treatment period: from day of first dose of study medication to 30 days after last dose of study medication
3. Post-treatment period: starting at day 30+1 after last dose of study medication.

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.

10.5.3.2 Adverse events (AEs)

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

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity, type of adverse event, relation to study treatment.

Serious adverse events and non-serious adverse events and adverse events of special interest (AESI: including esophagitis, stomatitis, mouth ulceration, gastric ulcers, hemorrhage, abdominal pain, diarrhea, nausea and vomiting) during the on-treatment period will be tabulated. The number and frequency of overall AEs and gastrointestinal AEs will be summarized for naïve (no ICT prior to enrollment) and non-naïve patients.

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

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

10.5.3.3 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.

The following summaries will be generated separately for chemistry, urinalysis assessments:

- Shift tables using normal/notable/extended ranges to compare baseline to the worst on-treatment value (where applicable)
- Listing of all laboratory data with values flagged to show the corresponding normal/notable/extended ranges

For selected lab assessments such as hematology parameters, observed values (and changes from baseline) will be summarized by descriptive statistics (n, mean, standard deviation, minimum, lower quartile, median, upper quartile, and maximum).

Creatinine clearance will be estimated using the (modified) Schwartz formula and the change from baseline will be provided.

10.5.3.4 Other safety data

Data on ECG, vital signs, height, weight, ocular and auditory findings will be listed, summarized and flagged as appropriate. Any significant findings after the start of the study will be documented as AEs and reported as such.

[redacted]

Summary statistics of the number of transfusions, average amount RBC (in mL/kg/day) transfused per patient, as well as the average iron intake (in mg/kg/day) will be provided.

10.5.3.5 Supportive analyses for secondary objectives

Not applicable

10.5.3.6 Tolerability

Tolerability of crushed deferasirox FCT will be assessed by AEs, SAEs, AEs leading to discontinuation and observer reported outcomes.

10.5.4 Pharmacokinetics

Not applicable

10.5.4.1 Data handling principles

Not applicable

10.5.5 Biomarkers

Not applicable

10.5.5.1 Outline of the data analysis

Not applicable

10.5.5.2 Data handling principles

Not applicable

10.5.5.3 Data analysis principles

Not applicable

10.5.6 Resource utilization

Not applicable

10.5.7 Patient-reported outcomes

The questionnaires for patients aged ≥ 2 years and <6 years have been designed as observations made by caregivers such as the parent or legal guardian.

Three questionnaires were developed to evaluate crushed deferasirox FCT: the modified Satisfaction with Iron Chelation therapy (mSICT), a palatability questionnaire, and a GI symptom questionnaire. All questions will be translated into the patient/caregiver's native language.

All patients or caregivers will complete the ObsRO questions via electronic questionnaires at the site and the site study personnel will review and ensure all relevant observations with parent or legal guardian are recorded before submission.

[redacted]

The mSICT and palatability questionnaire will be completed at screening visit 1 (chelation pre-treated patients), week 4, week 12, and end of treatment. The screening visit 1 mSICT and palatability questionnaire responses will be considered as baseline. No mSICT and palatability questionnaire will be evaluated at the screening visit for chelation naïve patients and for patients who completed a course of chelation therapy more than 7 days prior to screening visit.

The GI symptoms questionnaire will be completed at screening visit 1 and at the following visits: week 2, week3, week4 , week 8, week 12, week 16, week 20 and at end of treatment. The screening visit 1 GI symptom questionnaire responses will be considered as baseline. No GI symptoms questionnaire will be evaluated at the screening visit for chelation naïve patients and for patients who completed a course of chelation therapy more than 7 days prior to screening visit

For the mSICT and palatability questionnaires, the score for each domain will be the mean of the score of items included in the corresponding domain. Standard descriptive analyses will be performed for each domain score at screening visit 1, week 4, week 12, and end of treatment visits, as well as their absolute changes at week 4, week 12, and end of treatment from screening visit 1 for chelation pre-treated patients.

For the chelation naïve patients, only descriptive statistics by visit will be provided. The standard descriptive analyses include: n, mean, standard deviation, minimum, median, and maximum. The 95% confidence intervals for the absolute mean changes in all domains at week 4 and week 12 and end of treatment from screening visit 1 will be presented for pre-treated chelation patients only.

GI symptoms will be summarized over time by descriptive statistics for all visits and for all patients (i.e. either chelation naïve or pre-treated with chelation therapy). Descriptive statistics and the 95% confidence intervals for the absolute mean changes by visit will be provided for chelation pre-treated patients. The standard descriptive analyses include: n, mean, standard deviation, minimum, median, and maximum. Details about scoring and analyses will be included in the Statistical Analysis Plan.

10.6 Exploratory objectives

Not applicable

10.7 Interim analysis

No formal interim analysis is planned for this study.

10.7.1 Progression free survival (PFS)

Not applicable

10.7.2 Key secondary endpoint: Overall survival (OS)

Not applicable

[redacted]

10.8 Sample size calculation

This study is designed to enroll a minimum of 40 patients. Statistical computations were performed (see table below) to evaluate probabilities to observe at least one patient with an AE given 40 patients and different scenarios of AE incidence rates (Hanely and Lippman- Hand 1983). This table shows a reasonable chance to observe AE events occurring with an incidence of 3% or higher together with the 95% Clopper-Pearson confidence interval (CI) for the incidence rate.

Table 10-1 Clopper-Pearson 95% CI for different incidence of AEs and the corresponding probability to observe at least one AE

Incidence of AE	Clopper-Pearson 95% CI for the incidence rate	Probability that at least one patient out of 40 experiences that AE
3%	(0.00, 0.14)	0.70
4%	(0.00, 0.15)	0.80
5%	(0.01, 0.17)	0.87
6%	(0.01, 0.18)	0.92
7%	(0.01, 0.20)	0.95
10%	(0.03, 0.24)	0.99
15%	(0.06, 0.30)	1.00
20%	(0.09, 0.36)	1.00
25%	(0.13, 0.41)	1.00
30%	(0.17, 0.47)	1.00

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 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

[redacted]

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.

Additional consent form

Additional assent consent form will be provided in accordance with local regulations in each applicable country.

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.

[redacted]

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 (CRF) 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 CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

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.

[redacted]

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]

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[redacted]

14 Appendices

14.1 mSICT (Modified Satisfaction with Iron Chelation Therapy) - crushed FCT

Directions

The following questions are about the medicine your child takes for iron overload (too much iron in the body) in the past week (past 7 days). Please read each one and answer by yourself. There are no right or wrong answers. All of your answers will remain confidential. Choose only one answer.

Items

1. Over the past week, how often did your child's medicine for iron overload limit his/her usual activities?
   - □ Always
   - □ Most of the time
   - □ Sometimes
   - □ Rarely
   - □ Never

2. Over the past week, how often was your child upset about the side effects of his/her medicine for iron overload?
   - □ Always
   - □ Most of the time
   - □ Sometimes
   - □ Rarely
   - □ Never

3. Over the past week, how often did your child take his/her medicine for iron overload?
   - □ Always
   - □ Most of the time
   - □ Sometimes
   - □ Rarely
   - □ Never

[redacted]

4. Over the past week, how often did your child express that he/she wanted to stop taking medicine for iron overload?
   - □ Always
   - □ Most of the time
   - □ Sometimes
   - □ Rarely
   - □ Never

5. Over the past week, how often did your child follow the doctor's instructions for taking his/her medicine for iron overload?
   - □ Always
   - □ Most of the time
   - □ Sometimes
   - □ Rarely
   - □ Never

6. What are the reasons expressed by your child for not always taking his/her medicine for iron overload as instructed by the doctor? (Choose all that apply)
   - □ Taste
   - □ Aftertaste (taste left in your child's mouth after swallowing his/her medicine)
   - □ Inconvenience (for child)
   - □ Prepared the medicine incorrectly (took the whole tablet without crushing)
   - □ Trouble of crushing the tablet
   - □ Other _____

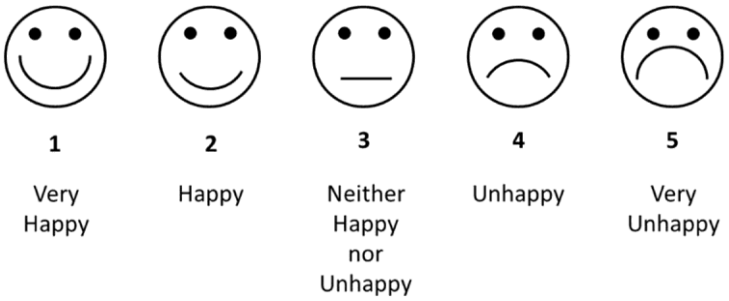
7. Over the past week, how easy or hard did your child tell you it was to take his/her medicine for iron overload?
   - □ Very easy
   - □ Easy
   - □ Neither easy nor hard
   - □ Hard
   - □ Very hard

8. Over the past week, how bothered did your child express that he/she was by the amount of time he/she had to wait to eat food after taking medicine for iron overload?
   - □ Very bothered
   - □ Quite bothered
   - □ Moderately bothered
   - □ A little bothered

[redacted]

□ Not bothered at all

9. Please choose the face that best describes how happy or unhappy your child appeared with his/her medicine for iron overload over the past week.



10. Which type of medicine did your child say he/she liked best?
    □ Tablet to dissolve in liquid
    □ Tablet (taken once a day)
    □ Tablet (taken 3 times a day)
    □ Tablet crushed
    □ Sprinkle powder on food
    □ Injection
    □ I don't know

11. What are the reasons that your child preferred the "crushed medicine" for iron overload? (Choose all that apply)
    □ Taste
    □ Aftertaste (taste left in the child's mouth after he/she swallows)
    □ Convenience (it's not a problem to take the medicine – administration)
    □ Number of pills
    □ No/Less side effects
    □ Can correctly prepare the medicine
    □ Easier to remember to take the medicine
    □ Number of times he/she has to take the medicine
    □ No/Less pain on the injection site
    □ Gain personal time with their family and friends
    □ Other _____

Directions

The following questions are about YOUR experiences with the medicine your child takes for iron overload **in the past week (past 7 days)**. Please read each one and answer by yourself.

[redacted]

There are no right or wrong answers. All of your answers will remain confidential. Choose only one answer.

12. Over the past week, how often did you feel worried that your child was not swallowing enough of his/her medicine for iron overload?
    - □ Always
    - □ Most of the time
    - □ Sometimes
    - □ Rarely
    - □ Never

13. Over the past week, how often did you give your child his/her medicine for iron overload?
    - □ Always
    - □ Most of the time
    - □ Sometimes
    - □ Rarely
    - □ Never

14. Over the past week, how often did you think to stop giving your child his/her medicine for iron overload?
    - □ Always
    - □ Most of the time
    - □ Sometimes
    - □ Rarely
    - □ Never

15. Over the past week, how often did you follow the doctor's instructions for giving your child his/her medicine for iron overload?
    - □ Always
    - □ Most of the time
    - □ Sometimes
    - □ Rarely
    - □ Never

16. Based on doctor's instructions, how easy or hard was it for you to crush the tablet for iron overload?
    - □ Very easy
    - □ Easy
    - □ Neither easy nor hard
    - □ Hard

[redacted]

□ Very hard

17. What are the reasons that you did not always give your child his/her medicine for iron overload as instructed by the doctor? (Choose all that apply)
    □ Child refused to take
    □ Forgot to give the medicine
    □ Inconvenient for you or your child
    □ Side effects (for child)
    □ Did not prepare the medicine according to the doctor's instructions
    □ Did not give the full amount of the prepared medicine
    □ Other _____

18. Over the past week, how easy or hard was it for you to give your child his/her medicine for iron overload?
    □ Very easy
    □ Easy
    □ Neither easy nor hard
    □ Hard
    □ Very hard

19. Over the past week, how bothered were you by the amount of time it took to prepare your child's medicine for iron overload?
    □ Very bothered
    □ Quite bothered
    □ Moderately bothered
    □ A little bothered
    □ Not bothered at all

20. Please rank order the following medicines based on what your children most prefers to what he/she least prefers.

Medicine	**Rank (1= most prefer and 6= least prefer)**
Tablet to dissolve in liquid	
Tablet (taken once a day)	
Tablet (taken 3 times a day)	
Tablet crushed	
Sprinkle powder on food	
Injection	

[redacted]

14.2 Palatability (taste and ability to consume medicine) Questionnaire

Directions

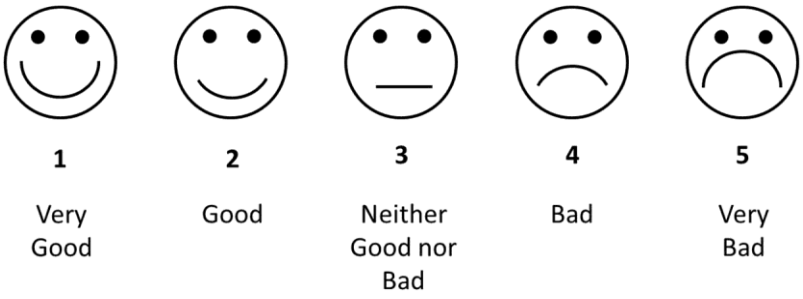
The following questions are about the medicine your child takes for iron overload (too much iron in the body). Please read each one and answer by yourself. There is no right or wrong answer. All of your answers will remain confidential.

Please answer each question about the medicine your child took for iron overload **in the past week**:

Items

1. Please choose the face that best describes your child's reaction to the taste of the medicine for iron overload immediately after putting it in his/her mouth in the past week.

2. Please choose the face that best describes your child's reaction to the aftertaste of the medicine after swallowing his/her medicine for iron overload in the past week.



3. Using the answers listed below, which answer best, describes what happened after your child took his/her medicine for iron overload in the past week?
   - □ Swallowed and retained ALL of the medicine
   - □ Spat out SOME of the medicine
   - □ Spat out ALL of the medicine and swallowed none of it
   - □ Vomited within 30 minutes after swallowing the medicine

4. How would you describe the amount of liquid that your child took with his/her medicine for iron overload in the past week?

[redacted]

□ Not enough liquid
□ Just enough liquid
□ Too much liquid

14.3 GI Symptom Questionnaire

Directions

Please read each symptom carefully. Indicate how often your child had each symptom **over the past week.**

Please answer all of the following questions about your child's GI symptoms after taking his/her medication for iron overload.

Items

1. Pain in his/her belly
   □ Always
   □ Most of the time
   □ Sometimes
   □ Rarely
   □ Never

2. Nausea (feeling like he/she might throw up)
   □ Always
   □ Most of the time
   □ Sometimes
   □ Rarely
   □ Never

3. Vomiting (throwing up)
   □ Always
   □ Most of the time
   □ Sometimes
   □ Rarely
   □ Never

4. Constipation
   □ Always
   □ Most of the time
   □ Sometimes
   □ Rarely
   □ Never

[redacted]

5. Diarrhea
   - □ Always
   - □ Most of the time
   - □ Sometimes
   - □ Rarely
   - □ Never

6. How many bowel movements did your child have in the past week?
   - □ 0 (none)
   - □ 1
   - □ 2
   - □ 3
   - □ 4
   - □ 5-10
   - □ 11 or more

[redacted]

14.4 Deferasirox FCT Weight Dose Table

Body weight ranges per dosing group (kg)								# of Tablets to dispense		
3.5 mg/kg/day [kg]	**7 mg/kg/day [kg]**	**10.5 mg/kg/day [kg]**	**14 mg/kg/day [kg]**	**17.5 mg/kg/day [kg]**	**21 mg/kg/day [kg]**	**24.5 mg/kg/day [kg]**	**28 mg/kg/day [kg]**	**90 mg**	**180 mg**	**360 mg**
19 - 38	10 - 19	7 - 12	5 – 9	5 - 7	5 - 6	5		1		
39 - 64	20 - 32	13 - 21	10 - 16	8 - 12	7 - 10	6 - 9	5 - 8		1	
65 - 90	33 - 45	22 - 30	17 - 22	13 - 18	11 - 15	10 - 12	9 - 11	1	1	
91 - 115	46 - 57	31 - 38	23 - 28	19 - 23	16 - 19	13 - 16	12 - 14			1
116 - 140	58 - 70	39 - 47	29 - 35	24 - 28	20 - 23	17 - 20	15 - 17	1		1
	71 - 83	48 - 55	36 - 41	29 - 33	24 - 27	21 - 23	18 - 20		1	1
	84 - 96	56 - 64	42 - 48	34 - 38	28 - 32	24 - 27	21 -24	1	1	1
	97 - 109	65 - 72	49 - 54	39 - 43	33 - 36	28 - 31	25 - 27			2
	110 - 122	73 - 81	55 - 61	44 - 48	37 - 40	32 - 34	28 - 30	1		2
	123 - 135	82 - 90	62 - 67	49 - 54	41 - 45	35 - 38	31 - 33		1	2
	136 - 140	91 - 98	68 - 73	55 - 59	46 - 49	39 - 42	34 - 36	1	1	2
		99 - 107	74 - 80	60 - 64	50 - 53	43 - 45	37 - 40			3
		108 - 115	81 - 86	65 - 69	54 - 57	46 - 49	41 - 43	1		3
		116 - 124	87 - 93	70 - 74	58 - 62	50 - 53	44 - 46		1	3
		125 - 132	94 - 99	75 - 79	63 - 66	54 - 56	47 - 49	1	1	3
		133 - 140	100 - 106	80 - 84	67 - 70	57 - 60	50 - 52			4
			107 - 112	85 - 90	71 - 75	61 - 64	53 - 56	1		4
			113 - 118	91 - 95	76 - 79	65 - 67	57 - 59		1	4
			119 - 125	96 - 100	80 - 83	68 - 71	60 - 62	1	1	4
			126 - 131	101 - 105	84 - 87	72 - 75	63 - 65			5
			132 - 138	106 - 110	88 - 92	76 - 78	66 - 69	1		5
			139 - 140	111 - 115	93 - 96	79 - 82	70 - 72		1	5
				116 - 120	97 - 100	83 - 86	73 - 75	1	1	5
				121 - 126	101 - 105	87 - 90	76 - 78			6
				127 - 131	106 -109	91 - 93	79 - 81	1		6
				132 - 136	110 - 113	94 - 97	82 - 85		1	6
				137 - 140	114 - 117	98 - 101	86 - 88	1	1	6
					118 - 122	102 - 104	89 - 91			7
					123 - 126	105 -108	92 - 94	1		7
					127 - 130	109 -112	95 - 98		1	7
					131 - 135	113 - 115	99 - 101	1	1	7
					136 - 139	116 - 119	102 - 104			8
					140	120 - 123	105 - 107	1		8
						124 - 126	108 - 110		1	8
						127 - 130	111 - 114	1	1	8
						131 - 134	115 - 117			9
						135 - 137	118 - 120	1		9
						138 - 140	121 - 123		1	9
							124 - 126	1	1	9
							127 - 130			10
							131 - 133	1		10
							134 - 136		1	10
							137 -139	1	1	10
							140			11

These dosing tables have been constructed for each dosing group using lower and upper body weight limits of 5 and 140 kg, respectively. This is taking into account that the study will

[redacted]

enroll male or female children, ≥ 2 and < 6 years. For patients with a low body weight (e.g. below 19 kg in the 5 mg/kg/day dosing group) the dosing requirements given will not allow for the use of the smallest strength available. In such cases a written request will be sent to Novartis, to advise on the individual patient enrolment / dose adjustments options.

14.5 Examples of light meals with soft foods

Table 14-1 Examples of light meals with soft foods

Example 1	Amount	kcal	g total fats
Wheat Bread or Toast	2 slices	138	2
jams, preserves, all flavors	1 Tablespoon	109	0
Banana	Medium (7-7 7/8" long)	105	0
Orange juice	1 cup	114	0
Skim milk	1 cup	83	0
	Total:	**549**	**2**

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

Example 3	Amount	kcal	g total fats
Yogurt, fruit, low-fat	6 oz.	173	2
Banana	Medium (7-7 7/8" long)	105	0
Orange juice	1 cup	114	0
Skim milk	1 cup	83	0
	Total:	**475**	**2**

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

[redacted]

Example 5	Amount	kcal	g total fats
Egg whites, cooked, no fat added	2 large egg whites	32	0
Salsa, red, cooked	6 Tablespoons	26	0
Wheat Bread or Toast	2 slices	138	2
Jams, preserves, all flavors	1 Tablespoon	109	0
Orange juice	1 cup	114	0
Skim milk	1 cup	83	0
	Total:	**502**	**2**

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

Post-Authorization Safety Study (PASS)

Is this a PASS study - If yes, follow instructions below	☒ Yes ☐ No

[redacted]