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Oncology Clinical Protocol CICL670FIC05 / NCT02993224

Open-label, multicenter, single arm, phase II study assessing treatment patient preference for new deferasirox formulation (film-coated tablet) compared to the reference deferasirox dispersible tablet formulation

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Table of contents

Table of contents 2
List of tables 6
List of abbreviations 7
Glossary of terms 9
Protocol summary: 10
Amendment 1 (12-Feb-2019) 14
1 Background 16
1.1 Overview of disease pathogenesis, epidemiology and current treatment 16
1.2 Introduction to investigational treatment(s) and other study treatment(s) 17
1.2.1 Overview of deferasirox dispersible tablet: 17
1.2.2 Overview of deferasirox film-coated tablet 19
2 Rationale 20
2.1 Study rationale and purpose 20
2.2 Rationale for the study design 20
2.3 Rationale for dose and regimen selection 20
2.4 Rationale for choice of combination drugs 21
2.5 Rationale for choice of comparators drugs 21
3 Objectives and endpoints 21
4 Study design 24
4.1 Description of study design 24
4.2 Switching of treatments 25
4.3 Timing of interim analyses 26
4.4 Definition of end of study 26
4.5 Definition of patient completed 26
4.6 Definition of early study termination 26
5 Population 26
5.1 Patient population 26
5.2 Inclusion criteria 27
5.3 Exclusion criteria 27
6 Treatment 29
6.1 Study treatment 29
6.1.1 Dosing regimen 29
6.1.2 Ancillary treatments 32
6.1.3 Rescue medication 32
6.1.4 Treatment duration 32

[redacted]

6.2 Dose modifications 32
6.2.1 Dose modification and dose delay 32
6.2.2 Treatment interruption and treatment discontinuation 35
6.2.3 Follow-up for toxicities 36
6.3 Prior and Concomitant medications 36
6.3.1 Permitted concomitant therapy 36
6.3.2 Prohibited concomitant therapy 37
6.4 Patient numbering, treatment assignment 37
6.4.1 Patient numbering 37
6.4.2 Treatment assignment 37
6.4.3 Treatment blinding 37
6.5 Study drug preparation and dispensation 37
6.5.1 Study treatment packaging and labeling 38
6.5.2 Drug supply and storage 38
6.5.3 Study drug compliance and accountability 38
6.5.4 Disposal and destruction 39
7 Visit schedule and assessments 39
7.1 Study flow and visit schedule 39
7.1.1 Screening 48
7.1.2 Treatment period 49
7.1.3 Study Evaluation Completion visit including premature withdrawal 50
7.1.4 Follow up period 51
7.2 Assessment types 52
7.2.1 Efficacy assessments 52
7.2.2 Safety and tolerability assessments 52
7.2.3 Other assessments 56
7.3 Patient reported outcomes 56
7.3.1 Preference Questionnaire 56
7.3.2 mSICT – patients greater or equal to 10 years old 57
7.3.3 Observer Reported mSICT – patients less than 10 years old 58
7.3.4 GI Symptoms – patients greater or equal to 10 years old 59
7.3.5 Observer Reported GI Symptoms – patients less than 10 years old 59
7.3.6 Palatability – patients greater or equal to 10 years old 59
7.3.7 Observer Reported Palatability – patients less than 10 years old 60
8 Safety monitoring and reporting 61
8.1 Adverse events 61

[redacted]

8.1.1 Definitions and reporting 61
8.1.2 Laboratory test abnormalities 62
8.2 Serious adverse events 62
8.2.1 Definitions 62
8.2.2 Reporting 63
8.3 Emergency unblinding of treatment assignment 63
8.4 Pregnancies 64
8.5 Warnings and precautions 64
8.6 Data Monitoring Committee 64
8.7 Steering Committee 64
9 Data collection and management 64
9.1 Data confidentiality 64
9.2 Site monitoring 65
9.3 Data collection 65
9.4 Database management and quality control 66
10 Statistical methods and data analysis 66
10.1 Analysis sets 66
10.2 Patient demographics/other baseline characteristics 67
10.2.1 Demographics and baseline characteristics 67
10.2.2 Medical history 67
10.3 Treatments (study treatment, concomitant therapies, compliance) 68
10.3.1 Study Treatment 68
10.3.2 Prior and concomitant medication 68
10.4 Primary objective 69
10.4.1 Variable 69
10.4.2 Statistical hypothesis, model, and method of analysis 69
10.4.3 Handling of missing values/censoring/discontinuations 70
10.4.4 Supportive and Sensitivity analyses 70
10.5 Secondary objectives 70
10.5.1 Key secondary objective(s) 70
10.5.2 Other secondary efficacy objectives 70
10.5.3 Safety objectives 72
10.5.4 Pharmacokinetics 75
10.5.5 Biomarkers 75
10.5.6 Patient-reported outcomes 75
10.6 Exploratory objectives 77

[redacted]

10.7 Interim analysis 77
10.8 Sample size calculation 77
10.9 Power for analysis of key secondary variables 77
11 Ethical considerations and administrative procedures 78
11.1 Regulatory and ethical compliance 78
11.2 Responsibilities of the investigator and IRB/IEC/REB 78
11.3 Informed consent procedures 78
11.4 Discontinuation of the study 79
11.5 Publication of study protocol and results 79
11.6 Study documentation, record keeping and retention of documents 79
11.7 Confidentiality of study documents and patient records 80
11.8 Audits and inspections 80
11.9 Financial disclosures 80
12 Protocol adherence 80
12.1 Amendments to the protocol 80
13 References (available upon request) 81
14 Appendices 83
14.1 Dosing tables (Deferasirox DT, Deferasirox FCT) 83
14.2 Examples of light meal 96
14.3 Algorithm for Preference questionnaire completion 98

[redacted]

List of tables

Table 3-1 Objectives and related endpoints 22
Table 6-1 Equivalent FCT starting dose at Week 25 29
Table 6-2 Dose and treatment schedule 31
Table 6-3 Daily dose of study drug based on serum ferritin level 31
Table 7-1 Visit Evaluation Schedule - Core Phase 40
Table 7-2 Visit Evaluation Schedule - Extension Phase 44
Table 7-3 Equivalent dose to be used: Deferasirox DT vs Deferasirox FCT 49
Table 7-4 Central Clinical laboratory parameters collection plan 54
Table 7-5 Scoring Matrix 60
Table 10-1 Definition of notable/extended ranges for laboratory test 74
Table 10-2 Definition of notable ranges for vital signs and weight 75
Table 14-1 Deferasirox DT dosing table for 5 mg/kg/day 83
Table 14-2 Deferasirox DT dosing table for 10 mg/kg/day 83
Table 14-3 Deferasirox DT dosing table for 15 mg/kg/day 84
Table 14-4 Deferasirox DT dosing table for 20 mg/kg/day 84
Table 14-5 Deferasirox DT dosing table for 25 mg/kg/day 85
Table 14-6 Deferasirox DT dosing table for 30 mg/kg/day 85
Table 14-7 Deferasirox DT dosing table for 35 mg/kg/day 87
Table 14-8 Deferasirox DT dosing table for 40 mg/kg/day 88
Table 14-9 Deferasirox FCT dosing table for 3.5 mg/kg/day 89
Table 14-10 Deferasirox FCT dosing table for 7 mg/kg/day 89
Table 14-11 Deferasirox FCT dosing table for 10.5 mg/kg/day 89
Table 14-12 Deferasirox FCT dosing table for 14 mg/kg/day 90
Table 14-13 Deferasirox FCT dosing table for 17.5 mg/kg/day 90
Table 14-14 Deferasirox FCT dosing table for 21 mg/kg/day 91
Table 14-15 Deferasirox FCT dosing table for 24.5 mg/kg/day 92
Table 14-16 Deferasirox FCT dosing table for 28 mg/kg/day 93
Table 14-17 Dose Regimen based on Serum Ferritin level 94
Table 14-18 Patients pre-treated with Deferoxamine 95

[redacted]

List of abbreviations

AE	Adverse Event
AML	Acute Myeloid Leukemia
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume-1) after single dose
AUCtau	The AUC calculated to the end of a dosing interval (tau) at steady-state (amount x time x volume-1)
b.i.d.	bis in diem/twice a day
C2hr	Post-dose 2 hr plasma concentration
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass x volume-1)
CRO	Contract Research Organization
Ctrough	Pre-dose plasma concentration
CSR	Clinical study report
DFO	Deferoxamine
DFP	Deferiprone
DS&E	Drug Safety and Epidemiology
DT	Dispersible Tablet
eCRF	Electronic Case Report/Record Form
ECG	Electrocardiogram
EOS	End Of Study
i.v.	intravenous(ly)
FAS	Full Analysis Set
FCT	Film-coated tablet
GI	Gastrointestinal
ICH	International Conference on Harmonization
ICT	Iron chelation therapy
IEC	Independent Ethics Committee
IO	Iron Overload
IPSS-R	Revised International Prognostic Scoring System
IRB	Institutional Review Board
IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
LC-MS/MS	Liquid Chromatography-Mass Spectrometry/Mass Spectrometry
LIC	Liver Iron Concentration
MDS	Myelodysplastic syndrome
o.d.	*omnia die*/once a day
NCCN	National Comprehensive Cancer Network
NOAELs	No-adverse-effect-levels
PAS	PK Anaylisis Set
p.o.	*per os*/by mouth/orally
PHI	Protected Health Information

[redacted]

PRO	Patient Reported Outcome
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
RBC	Red Blood Cell
REB	Research Ethics Board
SAE	Serious Adverse Event
SEC	Study Evaluation Completion
SOP	Standard Operating Procedure
QoL	Quality of Life
VES	Visit Evaluation Schedule

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Dose level	The dose of drug given to the patient (total daily or weekly etc.).
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
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
Patient Number (Patient No.)	A unique identifying number assigned to each patient who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, except End of Treatment scheduled assessments.
Stop study participation	Point/time at which the patient came in for a final evaluation visit (study evaluation schedule) 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
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 from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data

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Protocol summary:

Protocol Number	CICL670FIC05
Title	Open-label, multicenter, single arm, phase II study assessing treatment patient preference for new deferasirox formulation (film-coated tablet) compared to the reference deferasirox dispersible tablet formulation
Brief title	Study to assess patient preference of deferasirox DT (dispersible tablet) or deferasirox FCT (film-coated tablet) in thalassemia patients.
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of the present study is to: • evaluate patient's preference of deferasirox DT or deferasirox FCT formulations in patients with transfusion-dependent thalassemia or non-transfusion-dependent thalassemia as measured by preference questionnaire at Week 48 • evaluate patient's preference of deferasirox DT or deferasirox FCT formulations or previous iron chelation in patients with transfusion-dependent thalassemia or non- transfusion-dependent thalassemia as measured by preference questionnaire at Week 4, Week 24 and Week 28. • evaluate patient's palatability, GI symptom and satisfaction of deferasirox DT or deferasirox FCT formulations or previous iron chelation in patients with transfusion-dependent thalassemia or non- transfusion-dependent thalassemia as measured by PRO questionnaire at Screening Visit, Week 4, Week 24, Week 28 and Week 48. • evaluate any difference of preference and other assessments between each subgroup, i.e., patients with transfusion-dependent or non-transfusion-dependent thalassemia. • evaluate the overall safety of deferasirox DT compared with deferasirox FCT formulations in patients with transfusion-dependent thalassemia or non- transfusion-dependent thalassemia as measured by frequency and severity of adverse events and changes in laboratory values of interest during deferasirox FCT (Week 25 to 48) compared with deferasirox DT (Baseline day 1 to 24) • assess compliance based on pill-countevaluate efficacy of deferasirox (both DT and FCT) in decreasing serum ferritin levels
Primary Objective	• To evaluate patient preference of deferasirox FCT or deferasirox DT in patient with transfusion –dependent thalassemia or non-transfusion – dependent thalassemia as measured by preference questionnaire at Week 48
Secondary Objectives	• To evaluate patient's palatability, GI symptom and satisfaction of deferasirox FCT or deferasirox DT or previous iron chelation based on Patient Reported Outcomes (PRO) • To evaluate patient preference of deferasirox FCT or deferasirox DT or previous iron chelation • To evaluate the reason behind preference for deferasirox FCT versus deferasirox DT

[redacted]

	• To evaluate the effect of deferasirox FCT compared with deferasirox DT on patient compliance using pill count • To evaluate the overall safety of deferasirox FCT compared with deferasirox DT • To evaluate efficacy of deferasirox (both formulations DT and FCT) in decreasing serum ferritin levels
Study design	This is a an open-label, multicenter, single arm, phase II study aimed at collecting data on preference for iron chelation therapy in patients with transfusion-dependent thalassemia (TDT) or non-transfusion-dependent thalassemia (NTDT) throughout a 48 week treatment period. The study is divided into 2 phases: - Core Phase: • Screening period (visit number 1): which last up to 4 weeks to determine the patient eligibility, followed by, • Period 1: from Baseline visit Day 1 to Week 24: • TDT patients: Deferasirox DT starting at 20 mg/Kg/day to maximum dose: 40 mg/Kg/day • NTDT patients: Deferasirox DT starting at 10 mg/Kg/day to maximum dose: 20 mg/Kg/day • Period 2: from Week 25 to Week 48: • TDT patients: Deferasirox FCT starting at 14 mg/Kg/day to maximum dose: 28 mg/Kg/day • NTDT patients: Deferasirox FCT starting at 7 mg/Kg/day to maximum dose: 14 mg/Kg/day - Extension Phase: • Deferasirox FCT: from Week 49 until Study Evaluation Completion (SEC - visit number 777) or until at least one of the End of Study criterion is met, whichever comes first: • TDT patients: Deferasirox FCT starting at 14 mg/Kg/day to maximum dose: 28 mg/Kg/day • NTDT patients: Deferasirox FCT starting at 7 mg/Kg/day to maximum dose: 14 mg/Kg/day.
Population	Approximately 145 patients aged ≥ 2 years, male or female with transfusion-dependent thalassemia or non-transfusion-dependent thalassemia requiring chelation therapy due to iron overload will be included in this study. Patients may have been previously treated with iron chelators for at least 6 months (other than Deferasirox) or be chelation naïve. In the case of a pre-treated patient, the patient must be continuously treated by other chelators for at least 6 months. 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.
Key Inclusion criteria	• Written informed consent/assent must be provided. For pediatric patients, consent will be obtained from parent(s) or legal patient's representative. • Male and female patient aged ≥ 2 years • Deferasirox naïve patient or chelation naive patient or treated by other chelators for at least 6 months continuously, such as: • Deferiprone/ DFP

[redacted]

	• Deferoxamine /DFO • Combination (DFO + DFP) • Subject is willing to discontinue current iron chelation therapy at least 5 days prior to the day 1 and for the duration of the study • Patients with transfusion-dependent thalassemia with transfusional iron overload as shown by: • a serum ferritin level of > 1000 ng/ml at screening and if available, LIC > 3 mg Fe/g dw within 6 months prior to screening • Patients with non-transfusion-dependent thalassemia with iron overload as shown by: • a serum ferritin level of ≥ 800 ng/ml at screening and if available, LIC ≥ 5 mg Fe/g dw within 6 months prior to screening.
Key Exclusion criteria	• Male and female patient aged < 2 years • Creatinine clearance below the contraindication limit in the locally approved prescribing information. • Serum creatinine level > 1.5 x ULN (upper limit of normal) • AST (SGOT) / ALT (SGPT) > 5xULN, unless LIC is confirmed as >10 mg Fe/dw within 6 months prior to screening visit. • Significant proteinuria as indicated by a urinary protein/creatinine ratio > 0.5 mg/mg in a non-first void urine sample. • Patients with significant impaired gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral deferasirox (e.g. ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection). • Clinical or laboratory evidence of active Hepatitis B (HBsAg in the absence of HBsAb) or Hepatitis C (HCV Ab positive with HCV RNA positive). • Patients participating in another clinical trial or receiving an investigational drug
Investigational and reference therapy	Deferasirox (ICL670) dispersible tablets as per label (Exjade®) Deferasirox (ICL670) film- coated tablets as per label
Efficacy assessments	Efficacy of Deferasirox DT and FCT will be evaluated based on changes in Serum ferritin levels from Day 1 baseline
Safety assessments	• Safety will be monitored by assessing the following parameters: • Adverse events and in particular specific gastrointestinal events, up to at least 30 days following last dose of study drug • Hematology, blood chemistry (including renal and hepatic parameters) and urinalysis • Vitals signs, • Physical examinations • Ocular examinations • Auditory examinations • Chest X-Ray • ECGs
Other assessments	• The study will include four Patient Reported Outcome (PRO) measurements: patient preference questionnaire, patient palatability

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	questionnaires, GI symptoms and the mSITC (modified Satisfaction with iron chelation therapy) questionnaires • The compliance will be measured by pill count
Data analyses	• The primary analysis is based on patient preference of FCT over DT at Week 48, based on preference questionnaire. • The null hypothesis is that there is no difference in the proportion of patients preferring FCT or DT at Week 48. The alternative hypothesis is that there is a difference in the proportion of patients preferring FCT or DT at Week 48. • The primary analysis will be tested based on McNemar's test and Odd's Ratio (OR) and 95% Confidence Interval (CI) will also be provided for comparing the proportions of preferences over FCT and DT.
Key words	New formulation, deferasirox, chelation, iron overload, compliance, satisfaction, palatability, PRO, preference, safety

[redacted]

Amendment 1 (12-Feb-2019)

Amendment rationale

The purpose of this amendment is to provide additional clarity to the study Investigators in relation to dosing of deferasirox for patients with non-transfusion dependent thalassemia (NTDT), those patients changing therapy from deferiprone, and those patients with body weight lower than 20 kg; to provide additional guidance in relation to the ocular and auditory assessments; to revise the underlying assumptions used to calculate the sample size of the study; to clarify the inclusion criterion that relates to prior therapy; to correct inconsistencies and typos; and to update withdrawal of consent language.

At the time of this amendment, 132 patients have been enrolled in the study.

The protocol has been amended to provide clearer guidance on dose titration and delineate more clearly the maximum permitted dose of deferasirox for patients with non-transfusion dependent thalassemia. In general, these patients require lower doses of iron chelation therapy than patients with transfusion dependent thalassemia and therefore additional guidance in relation to deferasirox dosing specifically for this patient group was required. The results of the THETIS study [Taher AT et al, 2016] demonstrated that doses of up to 30 mg/kg/day of deferasirox in patients with NTDT was effective (at week 52, mean LIC ± SD decreased significantly from 15.13 ± 10.72 mg Fe/g dw at baseline to 8.46 ± 6.25 mg Fe/g dw [absolute change from baseline, −6.68 ± 7.02 mg Fe/g dw [95% CI: −7.91, −5.45]; P b 0.0001]). In addition, the safety profile of deferasirox in this study was consistent with the already established one. The THETIS study based dose adjustments on Liver Iron Concentration [LIC] results. In this trial, dose adjustments are based on serum ferritin levels. The relationship between LIC and serum ferritin in patients with NTDT and the derivation of corresponding clinically relevant thresholds were established by Taher AT et al [2015] using data from the THALASSA trial. These thresholds have been implemented in this amendment.

Table 14-16, which guided Investigators on the dose of deferasirox patients who had received prior deferiprone should be initiated on, has been removed due to a lack of supporting evidence. Rather, the starting dose of deferasirox will henceforth be based on the patient's serum ferritin level, consistent with clinical practice and the dosing guidance throughout the protocol. An additional change made in Appendix 14 was the inclusion of dosing guidance for children weighing less than 20 kg.

The minimum requirements for ocular and auditory assessments in pediatric patients have been clarified based on queries raised by the participating Investigators to ensure the consistency of required safety information.

Recently, additional analyses regarding patient preference with respect to deferasirox DT and deferasirox FCT from the ECLIPSE study have been published (Taher AT et al, 2018). In the ECLIPSE study, patients only received one formulation of deferasirox (either DT or FCT). Patients were asked to complete a preference questionnaire that included all possible formulations of iron chelation therapy. The preference for the FCT formulation ranged between 41-60% of patients, the preference for DT ranged between <5 – 18% and no preference (excluding missing assessments) did not exceed 10%. Based on this recent data, the assumptions underlying the sample size of this study have been updated, resulting in a reduction in the

number of patients required to enrol in the study (25 fewer) without impacting the power of the study.

The final substantial clarification made in this amendment is to specify that all patients must be deferasirox naive rather than Exjade naive given the availability of generic formulations of deferasirox in many of the countries participating in the study.

As of October 22, 2018, 92 patients have been enrolled in this trial.Protocol changes: The main changes in this amendment are:

- Clarify inclusion criteria number 3, by replacing Exjade naïve patient with Deferasirox naïve patient
- Clarify requirements for ocular and auditory assessments
- Add the withdrawal of informed consent section
- Provide additional dosing guidance for patients who have been treated with deferiprone
- Provide additional dosing guidance for NTDT patients
- Update Appendix 14.1: Deferasirox DT and FCT dosing table starting from a body weight of 10 kg
- Revise the sample size calculation
- Correct inconsistencies, typographical and other errors detected in the protocol
- Add Appendix 14.3 Algorithm for Preference questionnaire completion

IRBs/IECs

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

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

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

Overview β-thalassemia

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

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

The total annual incidence of symptomatic individuals is estimated at 1 in 100,000 throughout the world and 1 in 10,000 people in the European Union. However accurate data on carrier rates in many populations are lacking.

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

The therapeutic concept of iron chelation has been established with more than 50 years of clinical experience with Desferal®, deferoxamine mesylate, (DFO). However, poor oral bioavailability and short plasma half-life ($t_{1/2}$) has necessitated its application as slow subcutaneous (s.c.) or intravenous (i.v.) infusion. Iron-chelation therapy with DFO is extremely demanding however, and many patients experience considerable discomfort from administration of the drug, as well as a significant negative impact on their Quality of Life (QoL) (Arboretti et al, 2001) thus resulting in poor compliance. The lack of compliance with DFO

[redacted]

administration in patients who have serious blood disorders has necessitated recognition for the need of an effective iron chelator which can be given via the more convenient oral route.

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

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

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

1.2.1 Overview of deferasirox dispersible tablet:

The orally available tridentate iron chelator deferasirox (company research code ICL670) was first approved for the treatment of chronic iron overload due to blood transfusions in adults and pediatric patients aged 2 years and older in the United States in November 2005 and is currently approved for this indication in more than 100 countries. Deferasirox has also been approved in more than 60 countries for the treatment of chronic iron overload in patients with non-transfusion dependent thalassemia aged 10 years and older.

Deferasirox dispersible tablet (DT) is currently marketed as Exjade® in three dosing strengths (125, 250, and 500 mg) and is dosed based on body weight. The currently approved dose range is up to 40 mg/kg/day; the approved starting dose is 20 mg/kg/day. Initial daily doses of 10 or 30 mg/kg may be considered depending on treatment aim and transfusion intensity. Deferasirox DT is to be taken once daily on an empty stomach, at least 30 minutes before the next meal. Administration requires dispersion of the tablets in a glass of water, orange juice or apple juice, which takes approximately 3 minutes.

1.2.1.1 Non-clinical experience

Deferasirox is an N-substituted bis-hydroxyphenyl-triazole, a class of tridentate iron chelators. It is available as a dispersible tablet containing 125, 250, or 500 mg of drug substance. In certain countries, deferasirox is available as dispersible tablet containing 100 or 400 mg of drug substance. In addition, new formulations, such as swallowable film-coated tablets containing 90, 180 or 360 mg of drug substance and as oral granules corresponding to an amount equivalent to 90, 180 and 360 mg of drug substance, have also been produced.

The potent, specific ability of deferasirox to mobilize and promote the excretion of tissue iron has been demonstrated in animal models; it was twice as effective as parenteral deferoxamine (Desferal®, DFO) and 5-fold more effective than deferiprone (Ferriprox®) in iron-loaded rats, and more than 10-fold as effective as deferiprone at equimolar doses in iron-loaded marmosets.

Deferasirox has been tested *in vitro* and *in vivo* in animal toxicology, carcinogenicity, and safety pharmacology studies. The compound was generally well tolerated and prohibitive toxicities

[redacted]

were not observed in rodent (rat) and non-rodent (marmoset) species. Many of the observed effects, particularly to the kidney, are considered to be a result of iron deprivation. No-adverse-effect-levels (NOAELs) in 4-week studies were 10mg/kg in rats (standard diet) and 65 and 130 mg/kg in male and female marmosets, respectively. The NOAELs in chronic studies were 30 mg/kg in rats (diet supplemented with iron) and 40 mg/kg in marmosets. Deferasirox had no effect on animal fertility and is not teratogenic. In rats and transgenic mice, no relevant carcinogenic potential has been observed.

1.2.1.2 Clinical experience

Orally administered deferasirox is rapidly and well absorbed in mice, rats, marmosets and dogs and metabolism is mainly by glucuronidation. Deferasirox and its iron complex are highly bound (>98%) to plasma proteins, and distribution is mainly intravascular. Key elimination processes are hepatic metabolism and hepato-biliary elimination ultimately into the feces. Mrp2-mediated active transport processes may be involved in the excretion of deferasirox and metabolites. No notable retention of 14C radioactivity was observed in the tissues of rats following [14C] deferasirox administration. The placental barrier was passed only to a low extent; however, because deferasirox and/or its metabolites can be transferred into milk, women are advised not to breast feed.

In β-thalassemia patients, peak plasma concentrations of deferasirox were achieved with a median Tmax at between 1-4 hours at steady state and the mean terminal elimination half-life was in the range of 7-16 hours which support once daily administration. Following oral administration, the steady-state PK of deferasirox was dose-proportional over the dose range of 10-40 mg/kg (dispersible tablets). Clinical studies demonstrated a dose-dependent increase in iron excretion.

Metabolism is primarily by glucuronidation and elimination is mainly via the biliary/fecal route.

In clinical drug-drug interaction studies, deferasirox inhibited metabolism of the CYP2C8 substrate, repaglinide, and CYP1A2 substrate theophylline. No inhibitory effect on the CY3A4 substrate midazolam was observed. The potent inducer of UGT and CYP isoenzymes, rifampicin led to a marked decrease of deferasirox exposure in humans. The absence of a drug interaction with digoxin was confirmed in humans.

Deferasirox dispersible tablet facilitates administration of the appropriate quantity of drug substance to pediatric and adult patients. Bioavailability studies with deferasirox dispersible tablets indicated that absorption is increased with food, and this is dependent on the fat content and the timing of food intake. Deferasirox dispersible tablet was taken on an empty stomach at least 30 minutes prior to food in clinical studies; this is also the recommendation in the label.

Deferasirox bioavailability was increased with the newly developed formulations (film-coated tablet and granule); therefore, equivalent deferasirox AUC was achieved at a lower dose with the new formulations (e.g., 1080 mg film-coated tablets vs. 1080 mg granules vs. 1500 mg dispersible tablets) although C_{max} was higher with the new formulations compared to the current formulation (dispersible tablets). The absence of a substantial food effect with the new formulations allowed patients to take the drug either on an empty stomach or with a light meal [ICL670F2101].

[redacted]

Results of a retrospective exposure-response analysis suggested that safety and efficacy of deferasirox are largely driven by overall exposure (AUC) and changes in C_{max} are unlikely to result in worsening renal laboratory values.

1.2.2 Overview of deferasirox film-coated tablet

Based on the chronic nature of chelation therapy and the importance of patient compliance, an improved deferasirox formulation for oral administration is being developed (company research code ICL670). The film-coated tablet (FCT) to be used in this study contains the same active substance but has been strength-adjusted to achieve comparable exposure to the currently approved dispersible tablet. The film-coated tablet (FCT) will be available in three dose strengths (90 mg, 180 mg and 360 mg) and is dosed based on body weight. The film-coated tablets can be taken with or without a light meal.

Deferasirox film-coated tablet (FCT) is already marketed in some countries like USA or Canada, as Jadenu®.

Pharmacokinetics

Deferasirox film-coated tablets are a strength-adjusted formulation of deferasirox with higher bioavailability compared to the Exjade® dispersible tablet formulation. After strength-adjustment, the film-coated tablet formulation (360 mg strength) was equivalent to Exjade® dispersible tablets (500 mg strength) with respect to the mean area under the plasma concentration time curve (AUC) under fasting conditions [74]. The Cmax was increased by 30% (90% CI: 20.3% - 40.0%); however a clinical exposure/response analysis has revealed no evidence of clinically relevant effects of such an increase.

Absorption

Deferasirox (dispersible tablet formulation) is absorbed following oral administration with a median time to maximum plasma concentration (tmax) of about 1.5 to 4 hours. The absolute bioavailability (AUC) of deferasirox (dispersible tablet formulation) was about 70% compared to an intravenous dose. The absolute bioavailability of the film-coated tablet formulation has not been determined. Bioavailability of deferasirox film-coated tablets was 36% greater than that with Exjade® dispersible tablets.

A food-effect study involving administration of the film-coated tablets to healthy volunteers under fasting conditions and with a low-fat (fat content <10% of calories) or high-fat (fat content >50% of calories) meal indicated that the AUC and Cmax were slightly decreased after a low-fat meal (by 11% and 16%, respectively). After a high-fat meal, AUC and Cmax were increased (by 18% and 29%, respectively). The increases in Cmax due to the change in formulation and due to the effect of a high-fat meal may be additive and therefore, it is recommended that Deferasirox FCT should be taken either on an empty stomach or with a light meal

2 Rationale

2.1 Study rationale and purpose

The availability of deferasirox DT (Exjade®) as a once-daily oral chelation treatment provided patients with a treatment that was a significant improvement over parenteral deferoxamine therapy. This was confirmed in studies that measured satisfaction and quality of life of oral vs. parenteral chelation (Cappellini et al 2007, Osborne et al 2007)

Novartis has developed a film-coated tablet (FCT) with the same active substance as deferasirox DT but with modified excipients.

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

The purpose of the present study is fully described on Table 3-1.

2.2 Rationale for the study design

This is an open-label, multicenter, single arm, phase II study which will enroll patients with transfusion-dependent thalassemia and non-transfusion-dependent thalassemia.

Patient preference is the primary objective of this study and will be addressed by measuring the proportion of patient claimed preference of deferasirox FCT over deferasirox DT assessed by a preference questionnaire at Week 48

Patients previously treated with iron chelators for at least 6 months continuously (excluding deferasirox) or who are chelator naïve will be eligible to participate in this study.

The study consists of two phases. The treatment duration for the core phase of 48 weeks is considered sufficient to assess the patient preference, safety, compliance and PRO profiles of the two formulations. Previous studies of pediatric and adolescent patients have demonstrated differences in iron chelation medication compliance within this time period (Jordan 2012, Alvarez 2009). The extension phase permits patients to continue receiving deferasirox FCT for a maximum of 12 months after completion of the core phase, or until one of the end of study criterion is met, whichever comes first.

Patient preference for different ICTs, satisfaction, palatability and GI symptoms will be assessed via validated questionnaires; overall safety, efficacy of deferasirox (both DT and FCT) and pill count will be assessed as secondary objectives. The subgroups of interest are the patients with transfusion-dependent or non-transfusion-dependent thalassemia, as well as ethnicity.

2.3 Rationale for dose and regimen selection

Deferasirox is available in three dosing strengths: 125, 250 and 500 mg for dispersible tablets and 90, 180 and 360 mg for film-coated tablets.

[redacted]

For each patient, the dose is calculated by the physician based on the patient's weight, and then rounded up or down to the nearest tablet configuration, which can result in a variance between the calculated and actual dose of up to 15%. This dosing paradigm is consistent with how deferasirox DT (Exjade®) has been developed with regard to safety and efficacy.

All Deferasirox naïve patient or chelation naive patients or patients who have been treated by other chelators such as Deferiprone(DFP) / Deferoxamine (DFO) or Combination (DFO + DFP) for at least 6 months continuously, at the study entry will use a starting dose of:

- Deferasirox DT of 20 mg/kg/day in transfusion-dependent thalassemia (TDT)
- Deferasirox DT of 10 mg/kg/day in non-transfusion-dependent thalassemia (NTDT),

The equivalent FCT starting dose is:

- Deferasirox FCT of 14 mg/kg/day in transfusion-dependent thalassemia (TDT)
- Deferasirox FCT of 7 mg/kg/day in non-transfusion-dependent thalassemia (NTDT).

For patients with difficulties in swallowing Deferasirox FCT, it is allowed to crush the film-coated tablets. It should be administered by sprinkling the full dose on soft food like yogurt or apple sauce (apple puree). For further instructions, refer to the Appendix 14.

Dose adjustments are permitted as follows:

- Patients receiving the DT formulation: ± 5-10 mg/kg/day; maximum daily dose: 40 mg/kg/day for TDT patients; 20 mg/kg/day for NTDT patients
- Patients receiving the FCT formulation: ± 3.5-7 mg/kg/day; maximum daily dose: 28 mg/kg/day for TDT patients; 14 mg/kg/day for NTDT patients.

For ICT naïve patients at study entry the dose can be adjusted after 4 weeks of study treatment and for ICT pre-treated patients, the dose should be adjusted if necessary every 3 months based on serum ferritin levels

2.4 Rationale for choice of combination drugs

Not applicable

2.5 Rationale for choice of comparators drugs

Not applicable

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 evaluate patient preference between deferasirox FCT and deferasirox DT	Proportion of patient claimed preference of deferasirox FCT over deferasirox DT as measured by preference questionnaire at Week 48	
Secondary		Refer to Section 10.5.1
To evaluate patient preference of deferasirox FCT or deferasirox DT or previous iron chelation	Proportion of patient claimed preference of deferasirox FCT, deferasirox DT, and previous iron chelation as measured by preference questionnaire at Week 28	
To evaluate patient preference of deferasirox DT or previous iron chelation	Proportion of patient claimed preference of deferasirox DT, over previous iron chelation as measured by preference questionnaire at Week 4 and Week 24	
To evaluate the reason behind preference for deferasirox FCT or deferasirox DT	Proportion of preference reasons for deferasirox FCT over deferasirox DT as measured by preference questionnaire at Week 28 and Week 48	
To evaluate the effect of deferasirox FCT compared with deferasirox DT on patient compliance using pill count	Relative consumed pill count during deferasirox FCT (Week 25 to 48) compared with deferasirox DT (Baseline day 1 to Week 24)	
To evaluate the effect of deferasirox FCT compared with deferasirox DT or previous iron chelation on patient palatability using PRO	Absolute and relative change in domain scores of palatability questionnaire over time during deferasirox FCT (Week 28 to 48) compared with deferasirox DT (Week 4 to 24) or previous iron chelation (Screening)	
To evaluate the effect of deferasirox FCT compared with deferasirox DT or previous iron chelation on patient satisfaction using PRO	Absolute and relative change in domain scores of SICT questionnaire over time during deferasirox FCT (Week 28 to 48) compared with deferasirox DT (Week 4 to 24) or previous iron chelation (Screening)	
To evaluate the effect of deferasirox FCT compared with deferasirox DT or previous iron chelation on patient GI symptom using PRO	Absolute and relative change in domain scores of SICT questionnaire over time during deferasirox FCT (Week 28 to 48) compared with deferasirox DT (Week 4 to 24) or previous iron chelation (Screening)	

Objective	Endpoint	Analysis
To evaluate the overall safety of deferasirox FCT compared with deferasirox DT	Overall safety, as measured by frequency and severity of adverse events and changes in laboratory values of interest during deferasirox FCT (Week 25 to 48) compared with deferasirox DT (Baseline day 1 to Week 24)	
To evaluate efficacy of deferasirox (both DT and FCT) in decreasing serum ferritin levels	Absolute and relative change from baseline (Day 1) in serum ferritin on monthly basis	

4 Study design

4.1 Description of study design

This is an open-label, multicenter, single arm, phase II study aimed at collecting data on preference for iron chelation therapy in patients with transfusion-dependent thalassemia (TDT) or non-transfusion-dependent thalassemia (NTDT) throughout a 48 week treatment period.

It is a pre-requisite for the patient to provide written consent for participation in this study. This must be in place prior to performing any study-related procedures or assessments, including those described at the screening visit (please refer to Table 7-1 and Table 7-2

Patients will undergo up to 4 weeks of screening and if deemed eligible, will receive deferasirox dispersible tablet (DT) formulation for 24 weeks. At the completion of 24 weeks patients will be transitioned on Week 25 to an equivalent dose of the deferasirox film coated tablet (FCT) formulation and continue treatment until Week 48 (EOT of Core Phase).

Patients can then continue deferasirox FCT formulation as per the judgment of the investigator, through an extension phase for a maximum of 12 months from the last dose of deferasirox FCT received at the end of period 2 in the Core Phase.

If one of the end of study criterion is met at any time during the study, the patient must discontinue from the study and should complete the Study Evaluation Completion (SEC - visit number 777). Please refer to Section 4.4 .

Patients must be followed up for 30 days after the last dose of study drug for safety evaluation (safety follow up visit).

- Core Phase:
  - Screening phase which lasts for a maximum of 4 weeks to determine patient eligibility followed by
  - Baseline visit (day 1)
  - Period 1: deferasirox DT as 20-40 mg/kg/day dose regimen of dispersible tablet formulation for 24 weeks followed by
  - Period 2: deferasirox FCT as 14-28 mg/kg/day dose regimen of film- coated tablet for 24 weeks.
- Extension Phase:
  Deferasirox FCT as 14-28 mg/kg/day dose regimen of film-coated tablet.
- PRO Validation Sub-study:
  - Patients in Egypt and Thailand may participate in this optional sub-study [sub-study protocol will only be submitted in the participating countries]

Participation in the extension phase is optional. Please refer to Section 4.4 for EOS criteria.

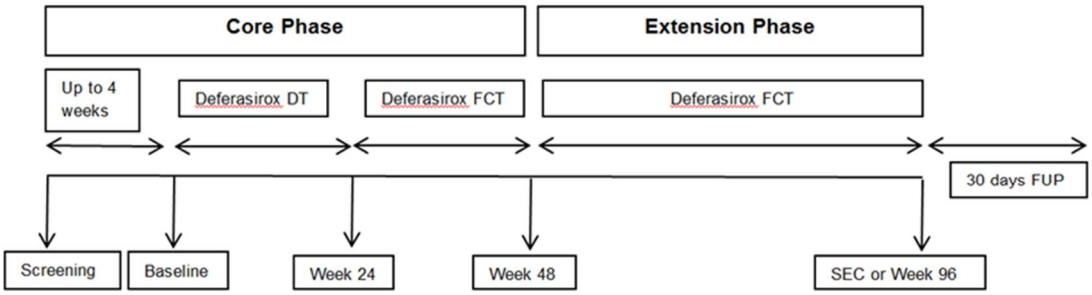
Study treatment should be administered by the patient once per day. Patients will return to the site every 2 weeks until Week 4 (V4) and then every 4 weeks for study medication and study assessments as specified in -Table 7-1 and Table 7-2.

[redacted]

Serious adverse events, regardless of causality, occurring after the subject has provided consent until 30 days following the last administration of study treatment must be reported to the Novartis drug safety team within 24 hours of the investigator learning of its occurrence.

Patients who discontinue study treatment early before completing the study (regardless if the discontinuation occurs at core or extension phase) should be scheduled for a visit as soon as possible, at which time all of the assessments listed for SEC (visit 777) must be performed.

Figure 4-1 Study design



4.2 Switching of treatments

At the discretion of the investigator, patients can switch from deferasirox DT to deferasirox FCT at any time during Period 1 of the Core phase, and vice versa, from deferasirox FCT to deferasirox DT at any time during Period 2 of the Core phase.

This change and the rationale of the switch must be recorded in the CRF. Also the investigator must provide the preference questionnaire to the patient at the immediate next visit and then keep following the schedule of questionnaires pre-planned on Table 7-1 and Table 7-2 (for example; if the investigator decides to switch from deferasirox DT to deferasirox FCT at Week 12, the preference questionnaire must be provided to the patient on the next visit, Week 16, and the rest of the preference questionnaires as per regular schedule: Week 24, Week 28 and Week 48). Please refer to 14 Appendices for further information on preference questionnaire completion.

The investigator can decide in the best interest of the patient to switch from one formulation to the other with the agreement of the patient if an adverse event *(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)* grade ≥ 2 (GI symptoms, skin rash, laboratory abnormalities) occurred with deferasirox DT or deferasirox FCT.

Re-switching treatments is not allowed within each period in this study, which means that a patient cannot switch from Deferasirox DT to Deferasirox FCT and the switch back to Deferasirox DT, and viceversa (Deferasirox FCT to Deferasirox DT, and then back to Deferasirox FCT).

[redacted]

4.3 Timing of interim analyses

One interim analysis is planned in this study.An interim analysis will be performed when all enrolled patients complete Week 48 (Visit 15) to assess the patient preference after 6 months with deferasirox FCT treatment in comparison to deferasirox DT.

Refer to Section 2.2 and Section 10

4.4 Definition of end of study

All patients must remain within the study until Week 48 (last visit on Core Phase) unless one of the criteria defined in Section 7.1.3 (definition of premature patient withdrawal) is met, in which case, the patient must discontinue from the study and complete the Study Evaluation Completion Visit (SEC - visit number 777) within 7 days of discontinuing treatment. A patient will be considered as having "completed the study" if all the visits have been performed from Screening (visit number 1) to Week 48 (visit number 15).

The end of study is defined as the earliest occurrence of one of the following:

- The patient has reached Week 96 at Extension phase.
- Deferasirox FCT is locally reimbursed for this indication (only applicable in Extension phase)
- Another clinical study or post-trial access program becomes available that can continue to provide deferasirox FCT in this patient population and all patients ongoing are eligible to be transferred to that clinical study

The investigator will be responsible for informing IRBs and/or EC.

Patients will perform a safety follow up visit 30 days after the last dose of study drug.

4.5 Definition of patient completed

A patient will be considered as having "completed the study" if the patient has completed the core phase of the study, i.e., Week 48."

4.6 Definition of early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in Section 7 for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

5 Population

5.1 Patient population

Approximately 145 patients aged $\geq$ 2 years, male or female with transfusion-dependent thalassemia or non-transfusion-dependent thalassemia requiring chelation therapy due to iron

[redacted]

overload will be included in this study. Patients may have been previously treated with iron chelators (excluding deferasirox) for at least 6 months or be chelation naïve.

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

5.2 Inclusion criteria

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

1. Prior to any screening procedures being performed, written informed consent/assent must be provided. For pediatric patients, consent will be obtained from the parent(s) or the patient's legal representative. Investigators will also obtain assent of patients according to local, regional or national guidelines.
2. Male and female patients aged ≥ 2 years
3. Deferasirox naïve patient or a chelation naive patient or a patient treated by other chelators for at least 6 months continuously, such as:
   a. Deferiprone (DFP)
   b. Deferoxamine (DFO)
   c. Combination (DFO + DFP)
4. Subject is willing to discontinue current iron chelation therapy at least 5 days prior to the Study day 1 and for the duration of the study
5. Patients with transfusion-dependent thalassemia (independent of underlying condition) with transfusional iron overload as shown by:
   - a serum ferritin level of > 1000 ng/ml at screening and if available, LIC > 3 mg Fe/g dw within 6 months prior to screening
6. Patients with non-transfusion-dependent thalassemia with iron overload as shown by:
   - a serum ferritin level of ≥ 800 ng/ml at screening and if available, LIC ≥ 5 mg Fe/g dw within 6 months prior to screening

5.3 Exclusion criteria

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

1. Creatinine clearance below the contraindication limit in the locally approved prescribing information.
2. Serum creatinine level > 1.5 x ULN (upper limit of normal)
3. AST (SGOT) /ALT (SGPT) > 5 x ULN, unless LIC confirmed as >10 mg Fe/dw within 6 months prior to screening visit.
4. Significant proteinuria as indicated by a urinary protein/creatinine ratio > 0.5 mg/mg in a non-first void urine sample.
5. Patients with significant impaired gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral deferasirox (e.g. ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).
6. Clinical or laboratory evidence of active Hepatitis B or Hepatitis C (HBsAg in the absence of HBsAb OR HCV Ab positive with HCV RNA positive).

[redacted]

7. Patients with psychiatric or addictive disorders which prevent them from giving their informed consent or undergoing any of the treatment options or patients unwilling or unable to comply with the protocol.
8. Patients with a known history of HIV seropositivity (Elisa or Western blot).
9. History of malignancy of any organ system, treated or untreated, within the past 5 years whether or not there is evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin.
10. Patients participating in another clinical trial or receiving an investigational drug. Patients who have recently completed treatment with an investigational product must have ceased this treatment for at least five times the half-life of the investigational product.
11. History of hypersensitivity to any of the study drug or excipients.
12. Significant medical condition interfering with the ability to partake in this study (e.g. systemic uncontrolled hypertension, unstable cardiac disease not controlled by standard medical therapy, systemic disease (cardiovascular, renal, hepatic, etc.).
13. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using effective methods of contraception during dosing of study treatment. Effective contraception methods include:
    - Total abstinence, when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
    - Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient.
    - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository.
    - Placement of an intrauterine device (IUD) or intrauterine system (IUS).
    - Please note that deferasirox may reduce the efficacy of hormonal contraception thus it is recommended to use alternative methods of contraception as described above.
14. Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.
15. Sexually active males unless they use a condom during intercourse while taking drug and for 28 days after stopping study medication and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.

[redacted]

For prohibited medication please refer to Section 6.3.2.

Eligibility criteria must be reviewed prior any study treatment is given.

6 Treatment

6.1 Study treatment

The sponsor will provide the following open label study medication:

- Deferasirox DT will be provided as 125 mg, 250 mg and 500 mg dispersible tablets for oral use.
- The strengths provided in an individual country may differ and will reflect the strengths available commercially in each country
- Deferasirox FCT will be provided as 90 mg, 180 mg and 360 mg film-coated tablets for oral use.

Once a patient meets one of the end of study criterion (see Section 4.4), he/she will be discontinued from the study, a SEC visit will be completed and will be followed up for safety purposes 30 days after the last dose of study drug. If the patient is to continue on Deferasirox FCT after discontinuing from the study, this will be using commercially available deferasirox FCT (Jadenu®) as 90 mg, 180 mg and 360 mg film-coated tablets for oral use.

For this study, the terms "investigational drug", "study drug" and "study treatment" refer to deferasirox FCT as well as deferasirox DT.

6.1.1 Dosing regimen

Having completed the screening period (including the 5-day wash-out period for patients previously treated with Deferiprone/DFP or Deferoxamine/DFO), eligible patients will start the core phase and be switched on the Day 1 visit to deferasirox DT for 24 weeks followed by deferasirox FCT for 24 weeks duration. Upon completion of Week 48 (Core Phase), the patient can still be treated with deferasirox FCT for a maximum of another 48 weeks or until one of the end of study criteria defined is met, whichever comes first.

The starting dose on Baseline Day 1 would be as following:

- Deferasirox DT of 20 mg/kg/day in transfusion-dependent thalassemia (TDT)
- Deferasirox DT of 10 mg/kg/day in non- transfusion-dependent thalassemia (NTDT),

Table 6-1 Equivalent FCT starting dose at Week 25

Equivalent dose to be used	
Deferasirox DT (mg/kg/day)	**Deferasirox FCT (mg/kg/day)**
5	3.5
10	7
15	10.5
20	14
25	17.5
30	21

[redacted]

Equivalent dose to be used	
Deferasirox DT (mg/kg/day)	**Deferasirox FCT (mg/kg/day)**
35	24.5
40	28

All iron chelation pre-treated patients who had received treatment with deferoxamine (DFO) and deferiprone (DFP) will be initiated on deferasirox DT. The dose of deferiprone will be determined by their serum ferritin and the dose of deferoxamine by using the equivalent deferasirox DT dose (see Appendix 14.2).

Dose adjustment for better treatment effects, based on serum ferritin levels and investigator's judgment, will be allowed for ICT naïve patients after 4 weeks of study treatment and for ICT pre-treated patients every 3 months. The dose adjustments will be performed in steps of 5-10 mg/kg/day for deferasirox DT or in steps of 3.5-7 mg/kg/day for deferasirox FCT.

For each patient the daily dose is calculated by the physician based on the patient's actual body weight, and then rounded up or down to the nearest whole tablet according to the available strengths of deferasirox tablets (125 mg, 250 mg and 500 mg for the DT and 90 mg, 180 mg and 360 mg for the FCT, see Appendix 14.1).

The investigator should instruct the patient (or legal patient's representative in the case of pediatric patients) to take the study drug as prescribed. All doses planned and prescribed to the patient and all dose changes including reasons for change during the study must be recorded in the eCRF.

During the regular study visits, the investigator or pharmacist will dispense to the patient or the patient's legal representative, an appropriate number of deferasirox tablets depending on the patients calculated dose. The number of tablets of each strength dispensed will be recorded in the Subject IMP dispensing and accountability log. Each time the deferasirox study drug is dispensed to the patient and/or legal patient's representative, the investigator will provide detailed instructions on how to prepare and administer the dose. Patients or the patient's legal representative will be instructed to take/administer the assigned amount of study drug and will be obliged to return all unused study medication every 4 weeks. Study medication returned by the patient or the patient's legal representative will be counted and unused study medication will be recorded by the investigator or pharmacist involved in the study. Drug accountability will be verified by the field monitor during site visits and at the completion of the trial.

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

Patients on deferasirox DT period will take the deferasirox DT every day (not later than 12:00 PM) on an empty stomach, at least 30 minutes before the next meal. The patient will disperse the required number of deferasirox DT in a glass of water, apple juice or orange juice. Gentle stirring should be applied and continued until the tablets are fully disintegrated, which takes approximately 1 to 3 minutes. Immediately, after full disintegration of the tablets, the entire content of the glass should be swallowed.

[redacted]

Patients on deferasirox FCT will swallow the required number of deferasirox FCT every day (not later than 12:00 PM) with or without a light meal. For patients with difficulties in swallowing Deferasirox FCT, it is allowed to crush the film-coated tablets. They should be administered by sprinkling the full dose on soft food like yogurt or apple sauce (apple puree).

All patients should take their deferasirox dose (DT or FCT) before 12:00 PM (noon).

Dose adjustments based on safety are allowed at any time point in the study and will be in increments of 5-10 mg/kg/day for deferasirox DT or 3.5-7 mg/kg/day for deferasirox FCT. Dose adjustments based on efficacy are permitted. For ICT naïve patients at study entry dose adjustments are allowed after 4 weeks of study treatment based on serum ferritin levels and investigator's judgement. For ICT pre-treated patients, the dose of deferasirox should be adjusted if necessary every 3 months based on the trends in serum ferritin and investigator's judgement. For more details please refer to Table 6.2 – Dose of study drug based on serum ferritin level.

Table 6-2 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Starting Dose* (weeks 1-4)	Dose adjustment (after week 4)	Max dose	Frequency and/or Regimen
Deferasirox DT – TDT patients	Dispersible tablets, p.o.	20 mg/kg/day	+ 5 - 10 mg/kg/day	40 mg/kg/day	Once daily
Deferasirox DT – NTDT patients	Dispersible tablets, p.o.	10 mg/kg/day	+ 5 - 10 mg/kg/day	20 mg/kg/day	Once daily
Deferasirox FCT – TDT patients	Film-coated tablets, p.o.	14mg/kg/day	+ 3.5 - 7 mg/kg/day	28 mg/kg/day	Once daily
Deferasirox FCT – NTDT patients	Film-coated tablets, p.o.	7 mg/kg/day	+ 3.5 - 7 mg/kg/day	14 mg/kg/day	Once daily

*Iron chelation naïve patients. All iron chelation pre-treated patients see Section 6.1.1 and Appendix 14.2 for guidance.

Table 6-3 Daily dose of study drug based on serum ferritin level

Dose Regimen of Drug for TDT patients	Serum ferritin level
20 mg/Kg Deferasirox DT 14 mg/Kg Deferasirox FCT	1000-1500 ng/ml
30 mg/Kg Deferasirox DT 21 mg/Kg Deferasirox FCT	>1500-2000 ng/ml
40 mg/Kg Deferasirox DT 28 mg/Kg Deferasirox FCT	>2000 ng/ml
Dose Regimen of Drug for NTDT patients	**Serum ferritin level**
5 mg/Kg Deferasirox DT 3.5 mg/Kg Deferasirox FCT	300-799 ng/ml
10 mg/Kg Deferasirox DT	800-2000 ng/ml

[redacted]

Dose Regimen of Drug for TDT patients	Serum ferritin level
7 mg/Kg Deferasirox FCT	
20 mg/Kg Deferasirox DT 14 mg/Kg Deferasirox FCT	>2000 – 4000 ng/ml
30mg/Kg Deferasirox DT 21mg/Kg Deferasirox FCT	>4000ng/mL

Serum ferritin level will be measured monthly to evaluate the study drug response

6.1.2 Ancillary treatments

Not applicable

6.1.3 Rescue medication

Not applicable

6.1.4 Treatment duration

The planned treatment duration of the core phase is 48 weeks and the planned treatment period for the extension phase is another 48 weeks.

The total duration of the study is approximately 104 weeks (including the Screening, Treatment, Study Evaluation Completion and Safety Follow-up visits).

6.2 Dose modifications

6.2.1 Dose modification and dose delay

For patients who are unable to tolerate the protocol-specified dosing schedule, dose reductions are permitted in order to keep the patient on study drug. These changes must be recorded on the dosage administration record in the eCRF.

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 the 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.

6.2.1.1 Change in patient's weight

The dose of study medication will be adapted using the Dosing Table (provided in Appendix 14.1) during the study in case the change (increase or decrease) in body weight exceeds 10% of the body weight compared to Visit 2 or the last dose adjustment due to a change in the patient's body weight.

6.2.1.2 Elevations in serum creatinine

Serum creatinine should be monitored during the study as stated in the Table 7-1 and Table 7-2.

[redacted]

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

Deferasirox dose reduction by 10 mg/kg/day for the DT formulation and by 7 mg/kg/day for the FCT formulation should be performed if there is a rise in serum creatinine by 33% above baseline value resulting in a serum creatinine above the ULN on two consecutive visits (a minimum of 7 days apart).

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

After a treatment interruption, if serum creatinine falls below the age appropriate upper limit of normal range 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).

6.2.1.3 Changes in Serum Ferritin

Serum ferritin should be monitored monthly during the study as stated in the Visit Evaluation Schedule Table 7-1 and Table 7-2.

For ICT pre-treated patients, the dose of deferasirox DT should be adjusted if necessary every 3 months based on the trends in serum ferritin and investigator's judgement. Table 6.2 provides additional guidance on suggested doses.

Dose adjustments should be made in steps of 5-10 mg/kg/day for deferasirox DT and of 3.5-7 mg/kg/day for deferasirox FCT and are to be tailored to the individual patient's response and therapeutic goals (maintenance or reduction of iron burden).

For TDT patients not adequately controlled with:

- Deferasirox DT doses of 30 mg/kg/day, doses of up to 40 mg/kg/day may be considered. Doses above 40 mg/kg/day are not permitted.
- Deferasirox FCT doses of 21 mg/kg/day, doses of up to 28 mg/kg/day may be considered. Doses above 28 mg/kg/day are not permitted.

For NTDT patients not adequately controlled with:

- Deferasirox DT doses of 15 mg/kg/day, doses of up to 20 mg/kg/day may be considered. Doses above 20 mg/kg/day are not permitted.
- Deferasirox FCT doses of 10.5 mg/kg/day, doses of up to 14 mg/kg/day may be considered. Doses above 14 mg/kg/day are not permitted.

In patients whose serum ferritin level has reached the target (usually between 500 and 1000 ng/mL for TDT patients or between 300-800 ng/mL for NTDT patients), dose reductions in steps of 5-10 mg/kg/day for deferasirox DT and of 3.5-7 mg/kg/day for deferasirox FCT should be considered to maintain serum ferritin levels within the target range.

If serum ferritin falls below 500 ng/mL for TDT patients and 300 ng/mL for NTDT patients, an interruption of study treatment should be considered until serum ferritin rises above 500 ng/mL or 300 ng/mL respectively.

[redacted]

6.2.1.4 Changes in urine protein/creatinine ratio

Proteinuria should be monitored during the study as stated in Table 7-1 and Table 7-2.

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

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

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

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

Dose adjustment will be based on local laboratory results.

6.2.1.5 Skin Rash

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 the dose back to 100% of the patient's last 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 the patient's last 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 5 mg/kg/day for deferasirox DT and of 3.5 mg/kg/day for deferasirox FCT every 2 weeks until the patient's last dose is achieved.

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

6.2.1.6 Increased liver enzyme levels (ALT/AST)

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

[redacted]

6.2.1.7 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 and ophthalmic testing (including fundoscopy) must be performed before the start of deferasirox treatment and at regular intervals thereafter (every 12 months). If disturbances are noted, dose reduction or interruption may be considered and a repeated testing performed as per investigator's judgement.

6.2.1.8 Dose modification criteria for hypersensitivity reactions

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

6.2.1.9 Dose modification criteria for cytopenias

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

6.2.1.10 Gastrointestinal disturbances

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

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

Remind patient to discontinue any laxative preparations or stool softeners they may be taking.

Eat small, frequent meals. Determine if the patient is lactose intolerant. Deferasirox DT contains lactose in the formulation so supplemental lactase may benefit the patient. As a reminder, the deferasirox FCT does not contain lactose. Remind the patient to drink 8 to 10 glasses of clear liquid per day. Suggest that the patient take their deferasirox DT with water, not with orange juice or apple juice until the diarrhea resolves.

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

6.2.2 Treatment interruption and treatment discontinuation

Patients who permanently discontinue study drug before completing the study should be scheduled for an End of Treatment visit (SEC – visit number 777) within 7 days from the last dose, at which time all of the assessments listed for the End of treatment (SEC – visit number 777) visit will be performed. The Study Evaluation Completion eCRF page must be completed,

[redacted]

documenting the date and reason for stopping study treatment. Any safety finding that leads to discontinuation of study drug should be captured on the AE eCRF.

All patients who discontinue study drug, including those who refuse to return for an End of treatment visit (SEC), will be contacted by the investigational site for safety evaluations 30 days after the last dose of study drug.

Patients who discontinue study drug should be considered withdrawn from the study after the final visit assessments are performed or when it is clear that the patient will not return for these assessments.

All patients must be followed for AEs and SAEs for 30 days after the last dose of study treatment. Patients lost to follow up should be recorded as such on the eCRF. For patients who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

The investigator can decide in the best interest of the patient to switch from one formulation to the other with the agreement of the patient if an adverse event grade ≥ 2 (GI symptoms, skin rash, laboratory abnormalities) occurred with deferasirox DT or deferasirox FCT.

6.2.3 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or abnormal laboratory value must be followed at least for 4 weeks, from the last treatment dose received or until the adverse event is resolved or the laboratory value is considered to be clinically insignificant.

6.3 Prior and Concomitant medications

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

6.3.1 Permitted concomitant therapy

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

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

- Patients are able to continue blood transfusions during the study protocol according to the regimen that they had been receiving prior to enrollment that could allow maintaining a hemoglobin level $\geq$ 9g/dL.
- 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 NSAIDs, corticosteroids, or oral bisphosphonates, and use of deferasirox in patients receiving anticoagulants may increase the risk of gastrointestinal irritation and bleeding

[redacted]

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

6.3.2 Prohibited concomitant therapy

- Aluminium 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
- Any iron chelation therapy other than the study drug

6.4 Patient numbering, treatment assignment

6.4.1 Patient numbering

Each patient is identified in the study by a Patient Number (Patient 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 Patient 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 patient is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Patient No.

Once assigned, the Patient No. must not be reused for any other patient. If the patient fails to start the treatment for any reason, the reason will be entered into the Screening Log.

Re-screening is not allowed in the study.

6.4.2 Treatment assignment

This is an open label study. Patients will be assigned as described in (Section 4.1 and Section 6.1)

All patients who fulfill all inclusion/exclusion criteria and complete the core phase, are eligible to roll over to the extension phase and receive the FCT formulation until one of the End of Study criteria is met (Section 4.4).

6.4.3 Treatment blinding

Not applicable as this is an open label study.

6.5 Study drug preparation and dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study drug(s) will be dispensed to the patient by authorized site personnel only.

[redacted]

All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

6.5.1 Study treatment packaging and labeling

Site personnel will add the patient number on the medication label. Immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the packaging and affix it to the Subject IMP dispensing and accountability log for that patient's unique patient number.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug.

6.5.2 Drug supply and storage

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

6.5.3 Study drug compliance and accountability

6.5.3.1 Study drug compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the source documents at each patient visit and Subject IMP dispensing and accountability log.. Patient compliance with study treatment will be evaluated using the pill count.

6.5.3.2 Study drug accountability

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

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor so the final drug reconciliation can be documented accordingly.

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

Details are described in the monitoring plan.

[redacted]

6.5.4 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, third party or at site level only if permitted by local regulations and authorized by Novartis in a prior agreement, as appropriate.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 and Table 7-2 list all of the assessments and indicate with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation.

No CRF will be used as a source document.

Patients should be seen for all visits to perform the scheduled assessments on the designated day, or as close to it as possible, i.e., not exceeding ± 2 days for all assessments scheduled in Visits 1 to 7 and ± 7 days for all other visits till Visit 26. Study visits must be anchored (calculated) based on the baseline visit.

All Baseline assessments indicated in Table 7-1 and Table 7-2 must be completed prior to initiating Deferasirox DT treatment.

Study evaluation completion (SEC / Visit 777) should be performed as follows:

- For discontinuers or completers of the core phase, who do not roll over to the extension phase, SEC has to done within 7 days of discontinuing treatment.
- For completers of the extension phase, the SEC needs to be performed after receiving 96 weeks of treatment. The Study Evaluation Completion (777) and W96 visit will occur on the same visit and same date.

In this clinical trial, a week is 7 calendar days.

All data obtained from these assessments must be supported in the patient's source documentation. The table indicates which data are entered into the database (D) or remain in source documents only (S) (column category).

[redacted]

Table 7-1 Visit Evaluation Schedule - Core Phase

	Category	Protocol Section 7.2	Screening	Baseline	CORE PHASE treatment[4]												
Visit Number			1	2[12]	3	4	5	6	7	8	9	10	11	12	13	14	15[6]
Study Week			Up to 28days prior to Baseline	**D1**	**W2**	**W4 (M1)**	**W8 (M2)**	**W12 (M3)**	**W16 (M4)**	**W20 (M5)**	**W24 (M6)**	**W28(M7)**	**W32 (M8)**	**W36 (M9)**	**W40 (M10)**	**W44 (M11)**	**W48 (M12)**
Informed consent	(D)	7.1.1	X														
Inclusion/ exclusion criteria	(D)	7.1.1.1	X	X													
History of disease	(D)	7.1.1.3	X														
Demography[13]	(D)	7.1.1.3	X														
Relevant medical history/current medical conditions	(D)	7.1.1.3	X														
Prior chelation therapy[1]	(D)	7.1.1.3	X														
Transfusion/RBC History	(D)	7.1.1.3	X														X
Transfusions received	(D)	7.1.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam	(S)	7.2.2.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	(D)	7.2.2.3	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	(D)	7.2.2.3	X														X
Vital signs	(D)	7.2.2.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ocular exam	(D)	7.2.2.5	X														X
Audiometry	(D)	7.2.2.5	X														X

[redacted]

	Category	Protocol Section 7.2	Screening	Baseline	CORE PHASE treatment[4]												
Visit Number			1	2[12]	3	4	5	6	7	8	9	10	11	12	13	14	15[6]
Study Week			Up to 28days prior to Baseline	**D1**	**W2**	**W4 (M1)**	**W8 (M2)**	**W12 (M3)**	**W16 (M4)**	**W20 (M5)**	**W24 (M6)**	**W28(M7)**	**W32 (M8)**	**W36 (M9)**	**W40 (M10)**	**W44 (M11)**	**W48 (M12)**
ECG	(D)	7.2.2.7.1	X														X
Chest X-ray (if clinically indicated)	(D)	7.2.2.4	X														X
Prior and Concomitant medications	(D)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	(D)	7.2.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory assessments-Blood																	
Hematology	(D)	7.2.2.6.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Biochemistry	(D)	7.2.2.6.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum ferritin	(D)	7.2.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum creatinine	(D)	7.2.2.6.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Creatinine clearance	(D)	7.2.2.6.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hepatitis testing	(D)	7.2.2.6.5	X														X
Serum pregnancy test[3]	(D)	7.2.2.6.4	X														X
Laboratory assessments-Urine																	
Urine dipstick	(D)	7.2.2.6.3	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Microscopic urine	(D)	7.2.2.6.3	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[redacted]

	Category	Protocol Section 7.2	Screening	Baseline	CORE PHASE treatment[4]												
Visit Number			1	2[12]	3	4	5	6	7	8	9	10	11	12	13	14	15[6]
Study Week			Up to 28days prior to Baseline	**D1**	**W2**	**W4 (M1)**	**W8 (M2)**	**W12 (M3)**	**W16 (M4)**	**W20 (M5)**	**W24 (M6)**	**W28(M7)**	**W32 (M8)**	**W36 (M9)**	**W40 (M10)**	**W44 (M11)**	**W48 (M12)**
Proteinuria (urine protein/ creatinine ratio)	(D)	7.2.2.6.3	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test	(D)	7.2.2.6.4		X													
Other assessments																	
Deferasirox DT drug administration	(D)			X	X	X	X	X	X	X	X						
Deferasirox FCT drug administration	(D)											X	X	X	X	X	X
Dispensed/ returned DT/FCT count	(D)	7.2.4		X	X	X	X	X	X	X	X[5]	X	X	X	X	X	X
PRO[7,8]																	
Preference	(D)					X					X	X					X
SICT	(D)		X[9,10]			X					X	X					X
GI symptoms	(D)		X[9,10]			X					X	X					X
Palatability	(D)		X[9,10, 11]			X					X	X					X
End of Core Phase																	X

[1] Includes 5-day washout period from previous iron chelation therapy.

[2] Study Evaluation Completion visit will be undertaken for all patients completing the study or discontinuing earlier for any reason. Please refer to Section 7 (except for further information.

[3] A serum pregnancy test can also be carried out at any time if deemed necessary by the investigator.

[redacted]

[4] The study will last until one of the patient withdrawal criteria is met (Section 7.1.3.1). At that time, the patient needs to complete the Study Evaluation Completion (SEC / 777) visit, and then FUP visit 30 days after last dose of study drug.

[5] Last dose of deferasirox DT will be dispensed on Week 24, and taken by the patient until Week 24 day 7. At the Week 24 visit, the site will also dispense deferasirox FCT. The patient will take the first dose on Week 25 day 1.

[6] Week 48 Visit (visit number 15) is a combined visit as it is the last visit of the Core Phase and the Baseline visit for the extension phase

[7] If the patient switches treatment, the investigator must provide the preference questionnaire to the patient in the immediate next visit. Please refer to Appendix 14.3 for further information.

[8] "PROs" include observer reports for patients 2-9 years old

[9] Palatability, satisfaction and GI symptoms questionnaires will be provided to the patient on Screening (visit number 1), during the 5 days of wash-out period from previous iron chelators therapies

[10] Completion of PRO questionnaires at screening visit for ICT naïve patient or patients who did not take any ICT treatment within the 6 months prior to screening is not required

[11] Completion of palatability questionnaires at screening visit for patients who received Deferoxamine as prior chelation therapy is not required

[12] All Baseline assessments indicated in Table 7-1 and Table 7-2 must be completed prior to initiating Deferasirox DT treatment.

[13] The investigators will have to re-assess, every 6 months, the childbearing potential of female patients aged 13 and older who are pre-menarche at the time of enrolling in the study. Once patient is able to bear children, they will need to undergo a urine pregnancy test in the next consecutive visit and then follow the VES for the urine and serum pregnancy tests.

Table 7-2 Visit Evaluation Schedule - Extension Phase

	Category	Protocol Section 7.2	Baseline EXT	EXTENSION PHASE treatment[4]											Study Evaluation Completion[2]	Safety Follow up
Visit Number			**15[5]**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**777**	**501**
Study Week			**W48 (M12)**	**W52 (M13)**	**W56 (M14)**	**W60 (M15)**	**W64 (M16)**	**W68 (M17)**	**W72 (M18)**	**W76 (M19)**	**W80 (M20)**	**W84 (M21)**	**W88 (M22)**	**W92 (M23)**	**W96 (M24)**	**30 days after last dose of study drug received**
Informed consent	(D)	7.1.1														
Inclusion/ exclusion criteria	(D)	7.1.1.1														
History of disease	(D)	7.1.1.3														
Demography	(D)	7.1.1.3														
Relevant medical history/current medical conditions	(D)	7.1.1.3														
Prior chelation therapy[1]	(D)	7.1.1.3														
Transfusion/RBC History	(D)	7.1.1.3														
Transfusions received	(D)	7.1.2	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical exam	(S)	7.2.2.1	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weight	(D)	7.2.2.3	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height	(D)	7.2.2.3	X													

[redacted]

	Category	Protocol Section 7.2	Baseline EXT	EXTENSION PHASE treatment[4]											Study Evaluation Completion[2]	Safety Follow up
Visit Number			**15[5]**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**777**	**501**
Study Week			**W48 (M12)**	**W52 (M13)**	**W56 (M14)**	**W60 (M15)**	**W64 (M16)**	**W68 (M17)**	**W72 (M18)**	**W76 (M19)**	**W80 (M20)**	**W84 (M21)**	**W88 (M22)**	**W92 (M23)**	**W96 (M24)**	**30 days after last dose of study drug received**
Vital signs	(D)	7.2.2.2	X	X	X	X	X	X	X	X	X	X	X	X	X	
Ocular exam	(D)	7.2.2.5	X													
Audiometry	(D)	7.2.2.5	X													
ECG	(D)	7.2.2.7.1	X													
Chest X-ray (if clinically indicated)	(D)	7.2.2.4	X													
Prior and Concomitant medications	(D)		X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events	(D)	7.2.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory assessments-Blood																
Hematology	(D)	7.2.2.6.1	X	X	X	X	X	X	X	X	X	X	X	X	X	
Biochemistry	(D)	7.2.2.6.2	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum ferritin	(D)	7.2.1	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum creatinine	(D)	7.2.2.6.2	X	X	X	X	X	X	X	X	X	X	X	X	X	
Creatinine clearance	(D)	7.2.2.6.2	X	X	X	X	X	X	X	X	X	X	X	X	X	

[redacted]

	Category	Protocol Section 7.2	Baseline EXT	EXTENSION PHASE treatment[4]											Study Evaluation Completion[2]	Safety Follow up
Visit Number			**15[5]**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**777**	**501**
Study Week			**W48 (M12)**	**W52 (M13)**	**W56 (M14)**	**W60 (M15)**	**W64 (M16)**	**W68 (M17)**	**W72 (M18)**	**W76 (M19)**	**W80 (M20)**	**W84 (M21)**	**W88 (M22)**	**W92 (M23)**	**W96 (M24)**	**30 days after last dose of study drug received**
Serum/ urine pregnancy test[3, 6]	(D)	7.2.2.6.4	X													
Laboratory assessments- Urine																
Urine dipstick	(D)	7.2.2.6.3	X	X	X	X	X	X	X	X	X	X	X	X	X	
Microscopic urine	(D)	7.2.2.6.3	X	X	X	X	X	X	X	X	X	X	X	X	X	
Proteinuria (urine protein/ creatinine ratio)	(D)	7.2.2.6.3	X	X	X	X	X	X	X	X	X	X	X	X	X	
Other assessments																
Deferasirox FCT drug administration	(D)		X	X	X	X	X	X	X	X	X	X	X	X	-	
Dispensed/ returned FCT count	(D)	7.2.4	X	X	X	X	X	X	X	X	X	X	X	X	X	

[1] Includes 5-day washout period from previous iron chelation therapy.

[2] Study Evaluation Completion visit will be undertaken for all patients completing the study or discontinuing earlier for any reason. Please refer to Section 7.1 for further information.

[redacted]

[3] A serum pregnancy test can also be carried out at any time if deemed necessary by the investigator.

[4] The study will last until one of the EOS criteria is met (Section 4.4). At that time, the patient needs to complete the Study Evaluation Completion (SEC) visit, and then FUP visit 30 days after last dose of study drug.

[5] Week 48 Visit (visit number 15) is a combined visit as it's being identified as the last visit of the Core Phase and the Baseline visit for the extension phase (if none of the End Of Study criteria is met)

[6]The investigators will have to re-assess, every 6 months, the childbearing potential of female patients aged 13 and older who are pre-menarche at the time of enrolling in the study. Once a patient is able to bear children, they will need to undergo a urine pregnancy test at the next consecutive visit and then follow the VES for the urine and serum pregnancy tests thereafter.

7.1.1 Screening

Prior to commencement of the screening examination, the patient must have given full informed consent and have completed the study Informed Consent form. Once this has been signed and dated by the patient or the patient's legal representative, then the investigator can undertake the required assessments to confirm the patient's eligibility for the study.

Ocular and Audiometry examinations must be performed at screening. In the case that the examination(s) had already been performed 6 months prior to screening, then the examination(s) do not need to be repeated. The examination(s) can be performed at any time at the investigators discretion if symptomatically/clinically indicated.

Serum ferritin, serum creatinine and proteinuria (urine protein/ creatinine ratio) will be measured during the screening visit for eligibility criteria.

The serum ferritin samples should be obtained in the absence of known infection.

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

The full list of assessments to be performed during the screening period (including the 5-day wash out period for patients previously treated with deferiprone (DFP) or deferoxamine (DFO)) is detailed in Table 7-1.

See Section 7.1.1.2 to get information on how to process screen failures.

Patients that do not meet the eligibility criteria are not allowed to be re-screened.

7.1.1.1 Eligibility screening

Following registration for screening, patient eligibility will be checked once all screening procedures are completed, and before study drug is provided to the patient.

7.1.1.2 Information to be collected on screening failures

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure. The reason for not being started on treatment will be entered on the Screening Log.

The demographic information, informed consent, inclusion/exclusion evaluation and Screening log pages in the eCRF must also be completed for Screen Failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a Serious Adverse Event (SAE) during the Screening Phase (see Section 8 for SAE reporting details).

7.1.1.3 Patient demographics and other baseline characteristics

Data will be collected on patient characteristics including demographic information (age, sex, ethnicity, etc.) and other background or relevant medical history/ current medical condition, transfusion history, disease history, prior chelation history, serum pregnancy test, vital signs at Screening visit.

[redacted]

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

Other assessments include chest x-ray (if clinically indicated), ocular exam, audiometry and ECG.

Specifics are given on Table 7-1 and Table 7-2. Patients who meet all the inclusion/exclusion criteria at screening will be admitted for baseline evaluations. All baseline results for safety evaluations must be available prior to dosing on Day 1.

At baseline visit (day 1), a verification of eligibility will be performed prior to performing any baseline assessments and administering the study drug.

7.1.2 Treatment period

The duration of core phase treatment is 48 weeks. Patient visits will occur every 2 weeks during the first month of treatment and then every 4 weeks thereafter until Visit 777 (SEC).

Having completed the screening period (including the 5-day wash out period for patients previously treated with deferiprone (DFO) or deferoxamine (DFP)), patients who are eligible will be enrolled to receive deferasirox DT during 24 weeks then switch to deferasirox FCT for 24 weeks. Daily dose is calculated by the physician based on the patient's actual body weight.

At the start of treatment, iron chelation naïve patients will receive deferasirox DT 10 mg/kg (NTDT patients) or 20 mg/kg (TDT patients) once daily then will transition to the equivalent FCT dose as outlined in the following table.

Table 7-3 Equivalent dose to be used: Deferasirox DT vs Deferasirox FCT

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

All iron chelation pre-treated patients will follow the below guidance:

Patients who were taking deferoxamine (DFO), will need to take the deferosirox DT equivalent deferasirox. For deferiprone (DFP) the dose of deferosirox DT will be based on their serum ferritin. Please refer to Table 6-2.

[redacted]

At the Week 48 visit, patients will roll over to the extension phase in the case that none of the End of Study criteria is met at that time. The patient will receive deferasirox FCT following the same dose regulations and adjustments as per the core phase.

The treatment period of the extension study is approximately 52 weeks (including treatment period (48 weeks), Study Evaluation Completion and 4 weeks Safety Follow-up visits)

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

For details of assessments, see Table 7-1 and Table 7-2.

7.1.3 Study Evaluation Completion visit including premature withdrawal

At the time patients discontinue study treatment; a visit should be scheduled at which time all of the assessments listed for the Study Evaluation Completion (SEC) visit will be performed. A Study Evaluation Completion eCRF page should be completed, giving the date and reason for stopping the study treatment, within 7 days following the last dose of study treatment.

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 30 days after the last dose of study treatment.

Patients who discontinue study treatment should be considered withdrawn from the study after the SEC visit assessments are performed or when it is clear that the patient will not return for these assessments.

If a study withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the Study Evaluation Completion eCRF page.

Patients who complete the extension phase will have to complete the SEC after receiving 96 weeks of treatment. The Study Evaluation Completion (777) and W96 visit will occur on the same visit and same date.

For criteria for premature withdrawal refer to Section 7.1.3.1. For criteria on End of Study refer to Section 4.3.

7.1.3.1 Criteria for premature patient withdrawal

Patients may voluntarily withdraw from the study or be dropped from it at the discretion of the investigator/Sponsor at any time. Patients may be withdrawn from the study if any of the following occur unless the investigator decides in the best interest of the patient to switch from deferasirox DT to deferasirox FCT:

- Pregnancy (not applicable for the switch)
- Unwillingness to comply with procedures as outlined in the study protocol, including unwillingness to comply with the prescribed study treatment
- Discovery of patient ineligibility (not applicable for the switch)
- Intake of prohibited medications (not applicable for the switch)
- Adverse event(s)
- Abnormal lab value(s)

[redacted]

- Unsatisfactory therapeutic effect
- Protocol violation (not applicable for the switch)
- Subject withdrew consent (not applicable for the switch)
- Lost to follow-up (not applicable for the switch)
- Administrative problems (not applicable for the switch)
- Death (not applicable for the switch)
- Decision of the Sponsor
- Unacceptable toxicity in the opinion of the investigator/Sponsor

If such withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the Study Evaluation Completion eCRF.

7.1.3.2 Withdrawal of informed consent section

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

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

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

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

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

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

All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

7.1.4 Follow up period

All patients must have a safety evaluation 30 days after the last dose of study treatment (regardless if that situation occurs during core or extension phase).

For patients who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

[redacted]

7.2 Assessment types

7.2.1 Efficacy assessments

Serum ferritin testing will be performed in both phases every month. The baseline serum ferritin value will be defined during the screening period.

7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing physical examination, vital signs, height and weight, ECG, Chest X-ray, Ocular and Auditory examinations, laboratory evaluations as well as collecting of the adverse events at every visit. For details on AE collection and reporting, refer to Section 8 (in the core and extension phase).

7.2.2.1 Physical examination

A physical examination will be performed at all study visits (refer to Table 7-1 and Table 7-2). The physical examination on Day 1, will serve as the Baseline physical examination for the entire study. The exam will entail an examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities and nervous system.

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

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

7.2.2.2 Vital signs

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

Young children may be placed on their parent's / caregivers' lap for the measurement of the vital signs.

7.2.2.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes will be measured. For specifications refer to Table 7-1 and Table 7-2.

[redacted]

7.2.2.4 Chest x-ray section

Chest x-ray will be performed at screening visit (if clinically indicated). If any chest x-ray has been performed 3 months prior to study entry the last available result will be collected.

7.2.2.5 Auditory and ocular examination

Patients will undergo auditory and ocular examinations at screening, Week 48 and at unscheduled visits (if needed). For specifications refer to Table 7-1 and Table 7-2

The auditory examination includes the following assessments:

- Comprehensive audiometry threshold examination
- Speech recognition

The ophthalmologic examination includes the following assessments:

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

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

Please follow the guidance below for children aged 2 to 5. It can also be applied for children aged 5 to 7 who cannot complete the aforementioned ocular tests:

- Sedation is not requested nor required.
- The ophthalmologist of each site must decide what is age-appropriate ocular testing without the use of sedation. If any aspect of the ocular testing listed above cannot be completed, please document this in the CRF (which assessments and the reason).
- Once the site has determined which assessment can be performed for a given patient in the screening visit, then these assessments must be repeated consistently at subsequent visits
- It is critical to collect the visual acuity results. Please collect 'best corrected' visual acuity for all patients (for example: do with glasses if done with glasses before).
- The preferred method of collection for tonometry is applanation tonometry. If not possible, then do an age-appropriate procure (without sedation).

For children aged 2 to 5 and older who do not cooperate, speech audiometry should be performed. If not possible, then the speech recognition test will be suffice.

7.2.2.6 Laboratory evaluations

All analyses will be performed by the local lab. Please refer to Table 7-4 for detailed laboratory parameters.

[redacted]

Table 7-4 Central Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, MCH, MCHC, MCV, Platelets, Red blood cells, White blood cells (WBC) count with differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils), RBC Morphology
Biochemistry	Albumin, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Bicarbonate, Calcium, Chloride, Creatinine, Creatine kinase, glucose, inorganic phosphorus, potassium; sodium Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, LDL, HDL, Lactate dehydrogenase (LDH), Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, C-reactive protein (CRP)
Urinalysis	Microscopic Panel (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells) Macroscopic Panel (Dipstick) (Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen)
Hepatitis markers	HbsAg, HbsAb, HCV Ab, HCV RNA, PCR (quantitative)
Additional tests	Serum ferritin, creatinine clearance, urine protein/creatinine ratio, serum pregnancy test, urine pregnancy test

7.2.2.6.1 Hematology

Hematology samples will be collected as described in Table 7-1 and Table 7-2, following local standard practice.

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

7.2.2.6.2 Clinical chemistry

Clinical chemistry samples will be collected as described in Table 7-1 and Table 7-2 following local standard practice.

Parameters to be measured will include: albumin, alkaline phosphatase, ALT (SGPT), AST (SGOT), bicarbonate, calcium, chloride, serum creatinine, creatine kinase, glucose, inorganic phosphorus, potassium, sodium, total bilirubin (direct and indirect bilirubin only required if total bilirubin is > 1.5 ULN) total cholesterol, LDL, HDL, lactate dehydrogenase (LDH), total protein, triglycerides, blood urea nitrogen (BUN) or urea, uric acid, C-reactive protein (CRP).

In addition, serum creatinine will be measured every 2 weeks during the first four weeks after first study drug administration and then monthly. Refer to Table 7-1 and Table 7-2 for specifics.

Creatinine clearance will be estimated using the Cockcroft-Gault equation for adult patients and Schwartz formula for pediatric patients. This estimate will be provided each time serum creatinine is collected. The formula should be consistently used throughout the study for a particular patient.

Use the following reference source for calculation of creatinine clearance:

- https//reference.medscape.com/calculator/creatinine-clearance-cockcroft-gault
- http//wwwusers.med.cornell.edu/~spon/picu/calc/crclsch2.htm

[redacted]

Serum ferritin test will also be performed at the screening visit to assess the eligibility of the patient. Serum ferritin testing will also be performed as described on Table 7-1 and Table 7-2.

7.2.2.6.3 Urinalysis

Urinalysis samples will be collected as described on Table 7-1 and Table 7-2, following local standard practice.

A midstream, second voided morning urine sample will be obtained. Bilirubin, blood, glucose, ketones, leukocytes esterase, nitrite, pH, protein, specific gravity, urobilinogen will be assessed. Microscopic analysis will be performed only in case of positive dipstick.

At the screening visit, a urine sample (at least 15 ml) will be collected for urinary protein/creatinine ratio to assess the eligibility of the patient. First morning void samples must not be used for this analysis.

For patients who develop proteinuria or a worsening of pre-existing proteinuria (assessed by a dipstick) at any visit, please refer to Section 6.2.1.4. Threshold values for proteinuria should be provided.

7.2.2.6.4 Pregnancy and assessments of fertility

All female patients capable of becoming pregnant will have a pregnancy test (serum β-HCG) at the screening visit and visit 15. An urine pregnancy text will be performed as described in Table 7-1 and Table 7-2. The results of the test must be available prior to initiating treatment with any study medication. Positive pregnancy tests will exclude a patient from participating in this trial.

Pregnancy must be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the local Novartis Clinical Safety & Epidemiology Department. Pregnancy follow-up must be recorded on the same form and must include an assessment of the possible relationship to the Novartis study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

7.2.2.6.5 Hepatitis Viral tests

Hepatitis viral testing consists of the following items: Hepatitis B surface Antigen (HBsAg), Hepatitis B Surface Antibody (Anti-HBs), Hepatitis C Antibody (Anti-HCV), HCV PCR (Quantitative). Hepatitis viral testing will be conducted at Screening Visit 1 to assess trial eligibility and visit 15.

7.2.2.7 Cardiac assessments

7.2.2.7.1 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed

- at screening visit
- week 48

Interpretation of the tracing must be made by a qualified physician and documented on the ECG eCRF page. Each ECG tracing should be labeled with the study number, patient number, date, and kept in the source documents at the study site. Clinically significant abnormalities present

[redacted]

when the patient signed informed consent should be reported on the Medical History eCRF page. Clinically significant findings must be discussed with Novartis prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events eCRF page.

7.2.3 Other assessments

Patient compliance with study treatment will be evaluated using pill count.

Pill count will be measured as per assessments mentioned in Table 7-1 and Table 7-2. The number of tablets of study medication of each strength (125 mg, 250 mg and 500 mg for the DT and 90 mg, 180 mg and 360 mg for the FCT) dispensed will be recorded during the study in the source documents using a subject IMP dispensing log and accountability log and in the Drug Accountability eCRF. Empty bottles and unused medication will be returned by the patient to the study site. Unused study medication tablets will be counted and recorded by the investigator/pharmacist/study staff involved in the study.

7.3 Patient reported outcomes

Please see guidance below on PRO completion:

- In case of treatment switch, the investigator must provide the preference questionnaire to the patient at the immediate next visit and then keep following the schedule of questionnaires pre-planned on Table 7-1 and Table 7-2. Please refer to Appendix 14.3 for further information.
- Completion of PRO questionnaires at screening visit for ICT naïve patient or patients who did not take any ICT treatment within the 6 months prior to screening visit is not required as patient never took any ICT thus they cannot answer to the questionnaire related to palatability, satisfaction and AEs to ICT.
- Completion of palatability questionnaires at screening visit for patients who received Deferoxamine as prior chelation therapy is not required

In case the patient's parents/legal representative and/or the patient are illiterate, the nurse / study coordinator should read each question and the response options to the parent / legal representative. The answer provided verbally by the parent / legal representative can be recorded on the PRO questionnaire by the nurse / study coordinator. In this case, the nurse/ study coordinator must not prompt or in any way try to help the parent / legal representative select an answer. This process needs to be carefully document in the source notes.

7.3.1 Preference Questionnaire

The preference questionnaire is a four item questionnaire. There are four separate versions depending on the week(s) that the questionnaire is administered.

For week 48 (primary endpoint) the first item asks the patients (or parents of young patients from 2 to 9 years old) which medicine they are currently taking with the response options: "Tablet to dissolve in liquid", "Film coated tablet ", "Sprinkle powder on food" and "I don't know". The second item asks which of the medicines did the patient "Like best" with the same response options as that of the first item. Finally, the third item asks the patient why he/she preferred the medicine they chose.

[redacted]

For week 28 the first item asks patients to choose from the following medicines: "Tablet to dissolve in liquid", "Film coated tablet (taken once a day)", "Tablet (taken 3 times a day)", "Sprinkle powder on food", "Injection" and "I don't know". The second items remain the same asking which medicine the patients like the best (out of the above response options). Similarly the third item remains the same.

For weeks 4 and 24 the first item asks patients to choose from the following medicines: "Tablet to dissolve in liquid", "Tablet (taken 3 times a day)", "Injection" and "I don't know". The second items remain the same asking which medicine the patients like the best (out of the above response options). Similarly the third item remains the same.

The following preference attributes are provided:

- Taste
- Aftertaste (taste left in your mouth after you swallow)
- Convenience (it's not a problem to take your medicine - administration)
- Number of pills
- No/Less side effects
- Can correctly prepare the medicine
- Easier to remember to take the medicine
- Number of times you have to take the medicine
- No/Less pain on the injection site
- Gain my personal time with family and friends
- Other_____

The questionnaire is administered at week 4, week 24, week 28 and week 48. No total score is calculated on the preference questionnaire. Each item will be scored as the proportion of patients who select each response option.

7.3.2 mSICT – patients greater or equal to 10 years old

The Modified SICT (mSICT) questionnaire consists of 15 items that represent 3 domains; Adherence, Preference and Concerns.

The adherence domain consists of 7 items, 6 of which are measured using a 5 point response scale.

Items 4, 5 and 6 use the response format 1 "Never"", 2 "Rarely" 3 "Sometimes" 4 " Most of the time", 3 "Sometimes", 4 "Rarely", and 5 "Never; Item 8 uses the response format 1 "Very easy", 2 "Easy", 3 "Neither easy nor hard", 4 "Hard" and 5 "Very hard"; Items 9 and 10 use the response format 1 "Very bothered", 2 "Quite bothered", 3 "Moderately bothered", 4 "A little bothered" and 5 "Not bothered at all". An Adherence domain score will be calculated by summing these 6 items and as a result a higher score will indicate worse adherence.

Item 7 captures the reasons that the patient did not always take their medication as instructed and is only asked for patients who, at Item 6, indicated that they did not "Always" take their medication as instructed. These patients are instructed to choose all reasons that apply. Each response category will be coded as a binary item, for example taste will be an item with the

[redacted]

response format 0 “Not endorsed”, 1 “Endorsed”. For the “other” option, if there is a common response (>10%) it will be included as an additional binary response category in the analysis, otherwise other will be treated as Other 0 “Not endorsed”, 1 “Endorsed”. This item will be used as a standalone item to better understand the overall Adherence domain.

Satisfaction/preference domain consists of 3 items, 2 assess the patients’ satisfaction with the medication and are measured using a 5 point response scale with the response format: 1 “Very satisfied”, 2 “Satisfied”, 3 “Neither satisfied nor dissatisfied”, 4 “Dissatisfied”, 5 “Very dissatisfied”. A Satisfaction domain score will be calculated by summing these two items. Higher scores will indicate worse satisfaction.

The third item asks the patients to assess which medication for iron overload they prefer; this item will be used as a standalone item in the clinical trial.

Concerns domain consists of 3 items to address any concerns and worries the patient has with their medication. All 3 items are measured on a 5 point response scale with the response format 1 “Always”, 2 “Most of the time”, 3 “Sometimes”, 4 “Rarely” and 5 “Never”. A Concerns domain score will be calculated by summing these 3 items. Higher scores will indicate fewer concerns.

Two additional items (items 14 and 15) will also be scored as standalone items. Item 14 asks patients to choose attributes pertaining to why they chose to prefer a certain medication. Item 15 asks patients to “rank order” the medicines they have taken.

Adherence, satisfaction/preference and concerns domain scores and items will be summarized using standard descriptive statistics (Screening, week 4, week 24, week 28 and week 48).

7.3.3 Observer Reported mSICT – patients less than 10 years old

Similar to the mSICT for patients greater than 10 years old, an observer reported mSICT will be administered to those patients who are 2-9 years old. Parents or caregivers of these patients will complete the mSICT for behaviors that are observed. The items are similar to the original mSICT however item 15 (the ranking exercise) is not included. In addition, there are 7 items asking the parent to respond from their perspective regarding:

- Feeling worried
- How often medication was given for iron over load
- Thinking to stop giving medication for iron overload
- Following the doctor’s instructions
- Reasons why not always giving medication
- Ease of administrating medication
- Bothered by time it took to administer medication

Adherence, satisfaction/preference and concerns domain scores (which are the same as above) and items will be summarized using standard descriptive statistics (Screening, week 4, week 24, week 28 and week 48).

[redacted]

7.3.4 GI Symptoms – patients greater or equal to 10 years old

The GI symptom questionnaire consists of 6 items, 5 of which are scored using a 0 – 10 rating scale with item appropriate end anchors to rate the symptom, for example Pain in your belly 0 = no pain and 10 = worst pain, with the numbers 1-9 labeled in between. The sixth item assesses bowel movement frequency during the past 24 hours, using 7 response options 0 = 0 (none), 1 = 1, 2 = 2, 3 = 3, 4 = 4, 5 = 5 – 10 and 6 = 11 or more.

A GI summary score will be created using the 10 point response scale items (5 items), Item 6 will be excluded from the calculation of the GI symptom summary score and used in the analysis as a standalone item. Overall, higher scores on the GI symptom diary items and the summary score will indicate worse symptoms.

Weekly GI diary symptoms summary scores as well as item 6 (bowel movement) will be summarized using descriptive statistics at Screening, week 4, week 24, week 28 and week 48.

7.3.5 Observer Reported GI Symptoms – patients less than 10 years old

An observer GI symptoms questionnaire will be administered to those patients who are 2-9 years old. All items will be completed by the parents of the patients. All items are the same and the scoring algorithm remains the same.

Weekly GI diary symptoms summary scores as well as item 6 (bowel movement) will be summarized using descriptive statistics at Screening, week 4, week 24, week 28 and week 48.

7.3.6 Palatability – patients greater or equal to 10 years old

The palatability questionnaire consists of 4 items. Two items measure the taste and aftertaste of the medication and are scored on a 5 point response scale with the response format 1 “Very good”, 2 “Good”, 3 “Neither good nor bad”, 4 “Bad” and 5 “Very bad”. The aftertaste item offers an additional response option of “no aftertaste”. This response option will be recoded such that all patients have a response, for example, patients who choose this option will be coded 0 and patients who rated the aftertaste will be coded 1. This will result in binary (yes/no) aftertaste item.

The remaining palatability items refer to whether the medication was taken (i.e., swallowed or vomited) and how the patient perceived the amount of medication to be taken.

A summary of Items 1, 3 and 4 leading to the palatability summary score will be constructed using the following rules:

Recode Item 1 “Very good”, “Good” & “Not good or bad” =1

“Bad” & “Very bad” = 2

Recode Item 2 “Swallowed ALL of the medicine” =1

“Spat out SOME of the medicine” & “Spat out ALL of the medicine” & “Swallowed none” =2

“Vomited within 30 minutes after swallowing the medicine” = 3

Recode Item 3 “Not enough liquid” & “Too much liquid” = 1

“Just enough liquid” = 2

[redacted]

No missing data will be imputed when calculating the palatability summary score.

The Table 7-5 presents the Items 1, 3 and 4 scoring matrix leading to the palatability summary score:

Table 7-5 Scoring Matrix

Palatability Score	Item1 – taste	Item3 – what happened	Item4 – amount	Definition
0	Bad & Very bad; 2	Vomited < 30 min; 3	Not enough & too much; 1	Worst palatability
1	Bad & Very bad; 2	Vomited < 30 min; 3	Just enough: 2	1
2	Bad & Very bad; 2	Spat some/ all out; 2	Not enough & too much; 1	2
3	Bad & Very bad; 2	Spat some/ all out; 2	Just enough: 2	3
4	Bad & Very bad; 2	Swallowed all: 1	Just enough: 2	4
5	Bad & Very bad; 2	Swallowed all: 1	Not enough & too much; 1	5
6	V. good, Good & Not good/bad; 1	Vomited < 30 min; 3	Not enough & too much; 1	6
7	V. good, Good & Not good/bad; 1	Vomited < 30 min; 3	Just enough: 2	7
8	V. good, Good & Not good/bad; 1	Spat some/ all out; 2	Not enough & too much; 1	8
9	V. good, Good & Not good/bad; 1	Spat some/ all out; 2	Just enough: 2	9
10	V. good, Good & Not good/bad; 1	Swallowed all: 1	Not enough & too much; 1	10
11	V. good, Good & Not good/bad; 1	Swallowed all: 1	Just enough: 2	Best palatability

The palatability summary score will be summarized using descriptive statistics by treatment arm and week (Screening, week 4, week 24, week 28 and week 48).

7.3.7 Observer Reported Palatability – patients less than 10 years old

An observer palatability questionnaire will be administered to those patients who are 2-9 years old. All items will be completed by the parents of the patients. All items are the same and the scoring algorithm remains the same as outlined in Section 7.3.6.

The palatability summary score will be summarized using descriptive statistics by treatment arm and week (Screening, week 4, week 24, week 28 and week 48).

[redacted]

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).

Except for screening failures, adverse events that begin or worsen after informed consent should be recorded in the Adverse Events eCRF. Conditions that were already present at the time of informed consent should be recorded in the Relevant Medical History/Current Medical Conditions eCRF page. Adverse event monitoring should be continued for at least 30 days (or 5 half-lives, whichever is longer) following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Severity of adverse events will be assessed as mild, moderate, or severe. Information about deaths will be collected though an SEC form.

The occurrence of adverse events should be sought by non-directive questioning of the patient 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 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. The severity grade (mild, moderate, or severe)
2. Its duration (Start and end dates or Ongoing at End of Study)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: suspected vs non-suspected)
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

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 eCRF.

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)

[redacted]

of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant by investigator, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events eCRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for 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.

8.2 Serious adverse events

8.2.1 Definitions

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

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

[redacted]

8.2.2 Reporting

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

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the oncology Novartis Drug Safety and Epidemiology (DS&E) department.

The telephone and telefax number of the contact persons in the local department of Drug Safety and Epidemiology (DS&E), specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original 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 Drug Safety and Epidemiology (DS&E) 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, this is an open-label treatment study.

[redacted]

8.4 Pregnancies

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

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Drug Safety and Epidemiology Department (DS&E). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

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

A Steering Committee (SC), comprising 2 principal investigators from the study, will be formed plus two Novartis members (regional medical head and a statistician). The purpose of this study management committee is to provide overall guidance regarding the conduct and execution of the trial to include (and not limited to) rationale of the study, accrual and contribution to scientific input for publications.

The details of the role of the Steering Committee will be defined in a Steering Committee charter.

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

[redacted]

- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI

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

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

9.2 Site monitoring

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

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on eCRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

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

9.3 Data collection

This study will use 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.

[redacted]

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

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 staffs are required to respond promptly to queries and to make any necessary changes to the data.

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

The site staff will transcribe data from the paper questionnaires into the EDC system.

The occurrence of any protocol deviations will be determined. After these actions have been completed and the data has been verified to be complete and accurate, the database will be declared locked and made available for data analysis. Authorization is required prior to making any database changes to locked data, by joint written agreement between the Medical Advisor or Equivalent, Head of Biostatistics PLSS, Global/ Head Data Sciences PLSS; prior authorizing the database un-lock, a CTT meeting will be hosted, to discuss the issues leading to database unlock and update. For EDC studies, after database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

10 Statistical methods and data analysis

Summary statistics for continuous variables will generally include the number of patients (N), minimum, lower quartile, mean, median, upper quartile, and maximum. For categorical or binary variables, the number and percent of patients in each category will be presented. P-values presented will be 2-sided unless otherwise specified.

Inferential efficacy comparisons will be done on the first 4, 24, 28 and 48 weeks of treatment.

All data analyses will be presented by treatment group (wherever applicable) and by transfusion or non-transfusion dependence thalassemia. Efficacy and safety data for the core and extension phases will also be presented by the above groups. Patients will be included in more than 1 treatment group for some analyses (e.g. exposure-adjusted AEs over the entire treatment period).

The analysis will be conducted on all patient data at Week 4, 24, 28, 48, and at the time the trial (both phases) ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

10.1 Analysis sets

The following analysis sets will be used in this trial.

[redacted]

Enrolled Set

The Enrolled Set comprises of all patients enrolled in this study.

Full Analysis Set

The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned and who received at least one dose of each study treatment (DT and FCT). Patients will be analyzed according to the treatment they have been assigned to.

Safety set

The Safety Set includes all patients who received at least one dose of either study treatment (DT or FCT), and at least one safety assessment on or after Day 1.

Patients will be analyzed according to the study treatment received, where treatment received is defined as the assigned treatment if the patient took at least one dose of that treatment or the first treatment received if the assigned treatment was never received.

Per-Protocol set

The Per-Protocol Set (PPS) consists of a subset of the patients in the FAS who are compliant with requirements of the CSP (clinical study protocol) without any major protocol deviation.

The major protocol deviations that will lead to exclusion of patients from the PPS will be detailed in the SAP.

Pharmacokinetic analysis set

Not applicable

10.2 Patient demographics/other baseline characteristics

10.2.1 Demographics and baseline characteristics

Summary statistics will be presented for continuous demographic and baseline characteristic variables the subgroup of interest and for all patients in the Enrolled Set. The number and percentage of patients in each category will be presented for categorical variables for each treatment group and all patients.

Demographic and baseline disease characteristics will be summarized for the variables listed in Section 7.1.1.3.

10.2.2 Medical history

Any significant prior or active medical condition at the time of signing informed consent will be coded using the MedDRA dictionary. These medical conditions will be summarized by primary system organ class and preferred term.

[redacted]

10.3 Treatments (study treatment, concomitant therapies, compliance)

10.3.1 Study Treatment

The following variables will be summarized descriptively for each study treatment based on the Safety Set. Summaries will be presented overall and on prior intake of iron chelation status (naïve or pre-treated) and thalassemia transfusion status (transfusion or non-transfusion), separately for Core and Extension phases.

The number of medications (pills) received for each dosing regimen; the duration of exposure (in weeks) and in categories (<4 weeks, 4-<12 weeks, 12-<24 weeks, >=24 weeks); average planned (mg/kg/day) and average actual daily dose; cumulative planned (mg/kg) and cumulative total actual dose (mg/kg); percentage of planned dose taken; dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure); and relative dose intensity (computed as the ratio of dose intensity and planned dose intensity).

The number of patients with dose adjustments (reductions, interruption, or permanent discontinuation) and the reasons will be summarized for all patients and by treatment group. Dose adjustments for auditory, hypersensitivity reactions and cytopenias will also be summarized.

The number of patients with 'switching' from one treatment to another at any treatment period along with the reasons of switching will also be summarized.

The duration of exposure is defined as the number of weeks between the start and end of study medication. The exposure calculation will be based on the actual date of switch from one treatment to another. The end of study medication day is the last day with a non-zero actual dose of study medication as recorded on the drug administration pages.

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

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

10.3.2 Prior and concomitant medication

Prior and concomitant medications will be summarized in separate tables by treatment group.

Prior medications are defined as treatments taken and stopped prior to first dose of study treatment. Any medication given at least once between the day of first dose of randomized study treatment and the date of the last study visit will be a concomitant medication, including those which were started pre-baseline and continued into the period where study treatment is administered.

Medications will be presented in alphabetical order, by Anatomical Therapeutic Classification (ATC) codes and grouped by anatomical main group.

[redacted]

Tables will show the overall number and percentage of patients receiving at least one treatment of a particular ATC code and at least one treatment in a particular anatomical main group.

Significant prior and concomitant non-drug therapies and procedures will be summarized using WHO Drug Reference List.

The number and percentage of patients receiving prior iron chelation treatments will be presented by treatment group as well as the reasons for stopping their and the total duration of exposure to chelation therapies previously.

10.4 Primary objective

The primary objective is to evaluate patient preference of deferasirox DT or deferasirox FCT formulations in patients with transfusion-dependent thalassemia or non-transfusion dependent thalassemia as measured by the preference questionnaire at Week 48.

10.4.1 Variable

The primary variable is proportion and percentage (%) of patients claimed preference of deferasirox FCT over deferasirox DT as measured by preference questionnaire at Week 48.

The analysis of primary variable will be based on the FAS.

10.4.2 Statistical hypothesis, model, and method of analysis

The null hypothesis is that there is no difference in the proportion of patients preferring FCT or DT at Week 48. The alternative hypothesis is that there is a difference in the proportion of patients preferring FCT or DT at Week 48

Let $p_{.1}$ denotes the proportion of patients with preference (discordance) or no-preference (concordance) of DT and $p_{1.}$ denotes the proportion of patients with preference or no-preference of FCT, at Week 48.

In statistical terms, the following hypothesis will be tested for primary objective:

H_1: $p_{1.} = p_{.1}$, versus H_{A1}: $p_{1.} \neq p_{.1}$

This is equivalent to test: H_1: $p_{12} = p_{21}$, versus H_{A1}: $p_{12} \neq p_{21}$,

where p_{12} and p_{21} denotes the proportion of patients with preference of FCT over DT and vice versa.

In other words,

H_1: Deferasirox FCT is not different from deferasirox DT with respect to patient preference at Week 48

versus

H_{A1}: Deferasirox FCT is different from deferasirox DT with respect to patient preference at Week 48

The primary analyses of testing patient preference of FCT over DT will be conducted via Mc Nemar's test. Both exact and asymptotic p-values will be presented for Mc Nemar's test for matched pairs.

[redacted]

Along with p-values, the estimates of proportions of patient preferences and non-preferences for each study treatment will also be presented along with 95% CI (if required).

The family-wise error will be set to 2-sided α=5% or 1-sided α=2.5%.

Please refer to Section 10.8 for sample size calculation.

10.4.3 Handling of missing values/censoring/discontinuations

There will be no imputation for missing data. Wherever appropriate, available data will be summarized over specified intervals using suitable summary statistics. Details will be provided in SAP.

10.4.4 Supportive and Sensitivity analyses

Sensitivity analyses and supportive analyses will be conducted in order to provide evidence that the results seen from the primary analysis are robust.

In order to support the Mc Nemar's test for matched pair, the Odd's Ratio (OR) of patient preference (i.e., $OR=p_{12}/p_{21}$), 95% confidence interval (CI) and p-values may also be presented, if appropriate. Conditional logistic model for matched pair analyses may also be fitted if required.

The above primary analyses will also be performed for each subgroup of stratification factor, i.e., on patients with transfusion dependent or non-transfusion dependent thalassemia. Also, the primary analyses may be performed based on prior treatment status of iron chelation.

In case of switching, the primary analyses will be performed separately for patients with or without switching before Week 48. Further details will be presented in SAP.

The primary analysis will also be provided for PPS.

10.5 Secondary objectives

The secondary objectives and endpoints are described in protocol Section 3. The analyses will be based on FAS population.

10.5.1 Key secondary objective(s)

Not applicable

10.5.2 Other secondary efficacy objectives

The following secondary analyses will be performed:

Patient preference of FCT, DT, and iron chelation at Week 28

Proportion and percentage, % (and 95% CI) of patients with preference and non-preference of FCT over DT, FCT over iron chelation, and DT over iron chelation will be summarized separately at Week 28.

Homogeneity test (Cochran's Q test) may be performed to check the homogeneity of the three preferences. Exact and asymptotic p-values of Mc Nemar's test will also be presented as analogous to primary analysis, for each pair of treatment comparison. For comparison of FCT

[redacted]

and DT with iron-chelation, only patients who are pre-treated with iron chelation will be selected.

Patient preference of DT and iron chelation at Week 4 and Week 24

Proportion and percentage, % (and 95% CI) of patients with preference and non-preference of DT over iron chelation will be summarized at Week 4 and Week 24. Exact and asymptotic p-values of Mc Nemar's test will also be presented as analogous to primary analysis. Only patients who are pre-treated with iron-chelation will be considered.

Reasons of patient preference

The reasons or factors influencing behind patient preference of FCT over DT will be summarized at Week 28 and 48. Proportions of patients for selecting each reason will be presented for each study treatment. Further summary of reasons behind non-preference of each study treatment will also be presented.

Compliance using pill count

Compliance is measured by pill /tablet count based on amount of medication dispensed, returned and reported as lost/wasted by the patient or caregiver. Compliance will be calculated for each treatment (FCT: Week 25- Week 48, DT: Baseline day 1 – Week 24) as the ratio of total count consumed to total count prescribed, where

total count consumed is derived from cumulative dispensed, returned and lost/wasted counts;

- total count prescribed is cumulative prescribed count

Analysis of covariance (ANCOVA) will be performed for comparison between both treatment groups (FCT and DT). The ANCOVA model for compliance endpoint will include treatment group and age group ((2 to <6 years, 6 to<10 years, 10 to <18 years, and >=18 years) and thalassemia transfusion dependence (transfusion and non-transfusion dependent) as factors. Least squares estimates, 95% CI and p-value will be presented for each treatment and difference between treatments.

Summary statistics of number of pills (and percentages) will also be presented overall and by treatment and subgroups. Refer to Section 10.5.6 for further details.

Serum Ferritin for monthly visits from Day 1 baseline up to Week 48

Summary statistics of change from baseline (absolute and difference, and 95% CI) will presented by treatment and subgroups and difference between treatments. Further details will be mentioned in SAP.

Palatability

Refer to PRO Section 10.5.6 for details.

mSICT

Refer to PRO Section 10.5.6 for details.

[redacted]

GI symptoms

Refer to PRO Section 10.5.6 for details.

10.5.3 Safety objectives

The overall safety will be measured by frequency and severity of AEs and changes in laboratory values of interest during the two treatment period (DT and FCT). The analyses are described below in respective sections.

10.5.3.1 Analysis set and grouping for the analyses

For all safety analyses, the Safety set will be used. All listings and tables will be presented by treatment group (wherever applicable) and by transfusion or non-transfusion dependence thalassemia. The safety analyses will also be presented separately for core and extension phases of the study.

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
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

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 AEs will be summarized separately and compared for two treatment groups FCT (Week 25 to 48) and DT (Baseline Day 1 to Week 24).

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on on mild, moderate, severe, life threatening, death), type of adverse event, relation to study treatment. If a patient reported more than one AE with the same preferred term, the AE with the greatest severity will be presented. If a patient reported more than one AE within the same primary system organ class, the patient will be counted only once with the greatest severity at the system organ class level, where applicable.

Serious adverse events, non-serious adverse events and adverse events of special interest (AESI) which are specific gastrointestinal events during the on-treatment period will be tabulated.

Separate summaries will be provided for death, SAE, other significant AEs leading to discontinuation and AEs leading to dose adjustment (including study treatment discontinuation).

As appropriate, the incidence of AEs will be presented per 100 patient years of exposure.

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.

[redacted]

A graphical display of relative frequencies within system organ classes and relative risks, as appropriate, may be presented is required.

For AEs of special interest, time-to-event analysis will be performed, as appropriate and as described in the statistical analysis plan. Results will be tabulated and the Kaplan-Meier estimates for the cumulative rate will be plotted.

10.5.3.3 Laboratory abnormalities

The summary of laboratory evaluations will be presented for different groups of laboratory tests (hematology, serum chemistry, serum ferritin, serum creatinine, and urinalysis). Descriptive summary statistics for the change from baseline to each study visit will be presented. These descriptive summaries will be presented by test group, laboratory test and treatment group. Change from baseline will only be summarized for patients with both baseline and post-baseline. The laboratory evaluations will be summarized separately and compared for two treatment groups FCT (Week 25 to 48) and DT (Baseline Day 1 to Week 24).

For each parameter, the maximum change from baseline within each study period will be evaluated analogously.

In addition, shift tables will be provided for all parameters to compare a patient's baseline laboratory evaluation relative to the visit's observed value. For the shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value was normal, low, or high for each visit value relative to whether or not the baseline value was normal, low, or high. These summaries will be presented by laboratory test and treatment group. Shifts will be presented by visit as well as for most extreme values post-baseline.

Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.3. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE v4.3, results will be categorized as low/normal/high based on laboratory normal ranges.

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

- Listing of all laboratory data with values flagged to show the corresponding CTCAE v4.3 grades if applicable and the classifications relative to the laboratory normal ranges (Table 10-1)
- For laboratory tests where grades are defined by CTCAE v4.3
- Worst post-baseline CTCAE grade (regardless of the baseline status). Each patient will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE v4.3 grades to compare baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE v4.3,

- Shift tables using the low/normal/high/ (low and high)

[redacted]

- Classification to compare baseline to the worst on-treatment value.

Apart from the above laboratories summaries, summaries of Hepatitis Viral tests will also be performed.

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

Laboratory test	Criteria for notable ranges
Platelet count	< 100 x 10^9/L (extended range <50×10^9/L)
Absolute neutrophils	< 1.5 x 10^9/L (extended range <0.5×10^9/L)
Serum creatinine	> 33% increase from baseline and > ULN at two consecutive measurements at least 7 days apart
Creatinine clearance*	<60 mL/min at two consecutive measurements at least 7 days apart (extended range <40 mL/min at two consecutive measurements at least 7 days apart)
Urinary protein/urinary creatinine ratio	≥ 1.0 (mg/mg) at two consecutive measurements at least 7 days apart
ALT and AST	>5 x ULN and >2 x baseline value (extended range >10×ULN and >2×baseline value)
* Creatinine clearance will be estimated using the Schwartz formula	

10.5.3.4 Other safety data

Data from vital signs, body weight, ECG, ocular, and auditory examinations will be listed and summarized with descriptive statistics as appropriate separately for the Safety Set. All new or worsened abnormalities will be recorded on the AE eCRF page.

ECG

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

Vital signs

Measurements of vital signs and body weight done more than 30 days after discontinuation of study medication, will be excluded from the analysis but will be listed.

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

A listing will be provided for all vital signs and weight. Notable vital signs and weight values are flagged. The criteria for notably abnormal vital signs and weight are displayed in Table 10-2.

[redacted]

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

Systolic blood pressure	≥180 mmHg / ≤90 mmHg with increase / decrease from baseline of ≥20 mmHg
Diastolic blood pressure	≥105 mmHg / ≤50 mmHg with increase / decrease from baseline of ≥15 mmHg
Pulse rate	≥120 bpm / ≤50 bpm with increase / decrease from baseline of ≥15 bpm
Weight	≥7% increase or decrease from baseline weight

Auditory, chest x-ray and ocular assessment evaluations

Auditory evaluations, chest x-ray and ocular examinations will be performed at baseline and at 12 months visit. Any abnormalities at baseline will be summarized. Abnormalities will be reported together with an overall interpretation of the findings. All new or worsened abnormalities will be recorded on the AE eCRF page. All findings of patients with new or worsened clinically significant abnormalities will be listed.

10.5.3.5 Supportive analyses for secondary objectives

Similar to the supportive analyses for primary objective as mentioned in section 4.4

10.5.3.6 Tolerability

Not applicable

10.5.4 Pharmacokinetics

Not applicable

10.5.5 Biomarkers

Not applicable

10.5.6 Patient-reported outcomes

The following PROs will be summarized using FAS.

Preference questionnaire

The preference questionnaire is a three item questionnaire. There are three separate versions depending on the week(s) that the questionnaire is administered. For week 48 (primary endpoint) the first item asks the patients on which medicine they are currently taking with the response options: “Tablet to dissolve in liquid”, “Film coated tablet (taken once a day)”, “Sprinkle powder on food” or, “I don’t know”. The second item asks which of the medicines did the patient “Like best” with the same response options as that of the first item. Finally, the third item asks the patient why he/she preferred the medicine they chose.

For week 28 the first item asks patients to choose from the following medicines: “Tablet to dissolve in liquid”, “Film coated tablet”, “Tablet (taken 3 times a day)”, “Sprinkle powder on food”, “Injection” and “I don’t know”. The second items remain the same asking what patients like the best (out of the above response options. Similarly the third item remains the same.

[redacted]

For weeks 4 and 24 the first item asks patients to choose from the following medicines: “Tablet to dissolve in liquid”, “Tablet (taken 3 times a day)”, “Injection” and “I don’t know”. The second items remain the same asking what patients like the best (out of the above response options. Similarly the third item remains the same.

Summaries of the preference questionnaires will be performed at Visits 4, 24, 28 and 48 in Core phase of the study and additionally from the data collected at the time of immediate next visit based on patients who had treatment switching.

The analysis of preference data has been explained in protocol Section 10.4 and Section 10.5.2.

Palatability

The palatability questionnaire consists of 4 items. Two items measure the taste and aftertaste of the medication and are scored on a 5 point response scale with the response format 1 “Very good”, 2 “Good”, 3 “Neither good nor bad”, 4 “Bad’ and 5 “Very bad”. The remaining palatability items refer to whether the medication was taken (i.e., swallowed or vomited) and how the patient perceived the amount of medication to be taken.

For the palatability questionnaire the overall score will be constructed using a scoring matrix from the score of items. Standard descriptive analyses including absolute and relative changes will be performed for both formulations (DT/FCT) for the overall score at Week 4, Week 24, Week 28 and Week 48 and overall score at Screening for iron chelators. The baseline data for treatment period 1 and 2 will be Week 4 and Week 24 data respectively, only one assessment is observed at Screening period.

The standard descriptive analyses include: n, mean, standard deviation, minimum, median and maximum. The 95% confidence interval for the absolute and relative (or difference) change from baseline of the overall score will also be presented for the treatments. In addition to that, summaries will also be performed from the data collected at the time of immediate next visit based on patients who had treatment switching.

Details about scoring and further analyses will be included in the SAP.

mSICT

The Modified SICT (mSICT) questionnaire consists of 15 items that represent 3 domains; Adherence, Preference and Concerns.

For the SICT questionnaire, 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 both formulations (DT/FCT) for each domain score at Week 4, Week 24, Week 28 and Week 48 and at Screening for iron chelators. The baseline data for treatment period 1 and 2 will be Week 4 and Week 24 data respectively, only one assessment is observed at Screening period.

The standard descriptive analyses include: n, mean, standard deviation, minimum, median and maximum. The 95% confidence intervals for the absolute and relative (or difference) changes from baseline in all domains will be presented for the treatments. In addition to that, summaries will also be performed from the data collected at the time of immediate next visit based on patients who had treatment switching. .

Details about scoring and further analyses will be included in the SAP.

[redacted]

GI symptoms

The GI symptom consists of 6 items, 5 of which are scored using a 0 – 10 rating scale with item appropriate end anchors to rate the symptom, The sixth item assesses bowel movement frequency during the past 24 hours, using 7 response options.

The GI symptoms will be summarized as analogous to the above questionnaires. Details about scoring and further analyses will be included in the SAP.

10.6 Exploratory objectives

Not applicable

10.7 Interim analysis

One interim analysis is contemplated in this study.

The interim analysis will be performed after all patients complete Week 48 to assess the patient preference after 6 months with deferasirox FCT treatment in comparison to deferasirox DT. The primary analysis to evaluate the patient preference of FCT over DT will be performed at this interim.

10.8 Sample size calculation

Based on data from the ECLIPSE study [Taher et al, 2018], the following assumptions have been made at Week 48, the patient preference for deferasirox FCT (formulation) is 45% and preference for deferasirox DT (formulation) is 25% and no preference to either of the formulations is 30%. This means the discordant pairs is 70 % (i.e. 70% preferred one formulation over another,45 %) and concordant pairs= 30% (assuming same preference for each formulation, 15%).

At least 130 patients are needed at Week 48 to have 80% power to detect the difference of patient preference of 20% (i.e., 45% preference of FCT over DT and 25% preference of DT over FCT) at a two sided significance level of 0.05 using McNemar's test for matched pairs.

To allow for roughly 10% of subjects with missing measurement, a total of approximately 145 evaluable patients aged ≥2 years male or female with transfusion-dependent thalassemia or non-transfusion-dependent thalassemia requiring chelation therapy due to iron overload, need to be enrolled. Patients may have been previously treated with iron chelators (outside Deferasirox DT) or be chelation naïve.

EAST 6.0 is used to calculate the sample size.

10.9 Power for analysis of key secondary variables

Not applicable

[redacted]

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 or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their eCRFs.

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

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

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 assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

11.6 Study documentation, record keeping and retention of documents

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

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

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

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

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written

permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

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

11.9 Financial disclosures

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

12 Protocol adherence

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

12.1 Amendments to the protocol

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

[redacted]

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14 Appendices

14.1 Dosing tables (Deferasirox DT, Deferasirox FCT)

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

- For a patient whose body weight is 46 kg, and whose planned deferasirox DT dose is 20 mg/kg/day, the calculated deferasirox DT daily dose would be 920 mg. So taking into account the available strengths of 125, 250 & 500 mg deferasirox DT tablets, the patient should receive the closest daily dose of 875 mg which can be easily constituted by taking 1 x 125 mg + 1 x 250 mg + 1 x 500 mg deferasirox DT tablets = 3 tablets.
- For a patient whose body weight is 46 kg, and whose planned deferasirox FCT dose is 14 mg/kg/day, the calculated deferasirox FCT daily dose would be 644 mg. So taking into account the available strengths of 90, 180 & 360 mg deferasirox FCT tablets, the patient should receive the closest daily dose of 630 mg which can be easily constituted by taking 1 x 90 mg + 1 x 180 mg + 1 x 360 mg deferasirox FCT tablets = 3 tablets.

The dosing tables below have been constructed with cut-offs for lower and upper body weights being 20 and 143 kg respectively depending on the dose administered. This is taking into account that the study will enroll male or female patients ≥ 2 years.

Table 14-1 Deferasirox DT dosing table for 5 mg/kg/day

Pt Weight in kg	Closest Dose	125 mg	250 mg	500 mg
10 – 19.9	Please consult the Novartis Medical Lead for advice			
20 – 37.5	125	1	0	0
37.6 - 62.5	250	0	1	0
62.5 - 87.5	375	3	0	0
87.6 - 112.5	500	0	0	1
112.6 - 137.5	625	1	0	1

Table 14-2 Deferasirox DT dosing table for 10 mg/kg/day

Pt Weight in kg	Closest Dose	125 mg	250 mg	500 mg
10 – 19.9	125	1	0	0
20 – 31.3	250	0	1	0
31.4 – 43.8	375	3	0	0
43.9 – 56.3	500	0	0	1
56.4 – 68.8	625	1	0	1
68.9 – 81.3	750	0	1	1
81.4 – 93.8	875	3	0	1

[redacted]

Pt Weight in kg	Closest Dose	125 mg	250 mg	500 mg
93.9 – 106.3	1000	0	0	2
106.4 – 118.8	1125	1	0	2

Table 14-3 Deferasirox DT dosing table for 15 mg/kg/day

Pt Weight in Kg	Closest Dose	125 mg	250 mg	500 mg
10 – 13.9	125	1	0	0
14 - 20.8	250	0	1	0
20.9 – 29.2	375	3	0	0
29.3 – 37.5	500	0	0	1
37.6 – 45.8	625	1	0	1
45.9 – 54.2	750	0	1	1
54.3 – 62.5	875	3	0	1
62.6 – 70.8	1000	0	0	2
70.9 – 79.2	1125	1	0	2
79.3 – 87.5	1250	0	1	2
87.6 – 95.8	1375	3	0	2
95.9 – 104.2	1500	0	0	3
104.3 – 112.5	1625	1	0	3
112.6 – 120.8	1750	0	1	3

Table 14-4 Deferasirox DT dosing table for 20 mg/kg/day

Pt Weight in Kg	Closest dose	125 mg	250 mg	500 mg
10 – 15.9	250	0	1	0
16.0 – 21.9	375	3	0	0
22.0 – 28.1	500	0	0	1
28.2 – 34.4	625	1	0	1
34.5 – 40.6	750	0	1	1
40.7 – 46.9	875	3	0	1
47.0 – 53.1	1000	0	0	2
53.2 – 59.4	1125	1	0	2
59.5 – 65.6	1250	0	1	2
65.7 – 71.9	1375	3	0	2
72.0 – 78.1	1500	0	0	3
78.2 – 84.4	1625	1	0	3
84.5 – 90.6	1750	0	1	3
90.7 – 96.9	1875	3	0	3
97.0 – 103.1	2000	0	0	4
103.2 – 109.4	2125	1	0	4

[redacted]

Pt Weight in Kg	Closest dose	125 mg	250 mg	500 mg
109.5 – 115.6	2250	0	1	4
115.7 – 121.9	2375	3	0	4

Table 14-5 Deferasirox DT dosing table for 25 mg/kg/day

Pt Weight in Kg	Closest dose	125 mg	250 mg	500 mg
10 – 13.9	250	0	1	0
14.0 – 16.9	375	3	0	0
17..0 – 22.5	500	0	0	1
22.6 – 27.5	625	1	0	1
27.6 – 32.5	750	0	2	1
32.6 – 37.5	875	3	0	1
37.6 – 42.5	1000	0	0	2
42.6 – 47.5	1125	1	0	2
47.6 – 52.5	1250	0	1	2
52.6 – 57.5	1375	3	0	2
57.6 – 62.5	1500	0	0	3
62.6 – 67.5	1625	1	0	3
67.6 – 72.5	1750	0	1	3
72.6 – 77.5	1875	3	0	3
77.6 – 82.5	2000	0	0	4
82.6 – 87.5	2125	1	0	4
87.6 – 92.5	2250	0	1	4
92.6 – 97.5	2375	3	0	4
97.6 – 102.5	2500	0	0	5
102.6 – 107.5	2625	1	0	5
107.6 – 112.5	2750	0	1	5
112.6 – 117.5	2875	3	0	5
117.6 – 122.5	3000	0	0	6

Table 14-6 Deferasirox DT dosing table for 30 mg/kg/day

Pt Weight in Kg	Closest Dose	125mg	250 mg	500 mg
10 – 14.9	375	3	0	0
15.0 – 18.9	500	0	0	1
19..0 – 22.9	625	1	0	1
23.0 – 27.1	750	0	1	1
27.2 – 31.3	875	3	0	1
31.4 – 35.4	1000	0	0	2
35.5 – 39.6	1125	1	0	2

[redacted]

39.7 – 43.8	1250	0	1	1
43.9 – 47.9	1375	3	0	2
48.0 – 52.1	1500	0	0	3
52.2 – 56.3	1625	1	0	3
56.4 – 60.4	1750	0	1	3
60.5 – 64.6	1875	3	0	3
64.7 – 68.8	2000	0	0	4
68.9 – 72.9	2125	1	0	4
73.0 – 77.1	2250	0	1	4
77.2 – 81.3	2375	3	0	4
81.4 – 85.4	2500	0	0	5
85.5 – 89.6	2625	1	0	5
89.7 – 93.8	2750	0	1	5
93.9 – 97.9	2875	3	0	5
98.0 – 102.1	3000	0	0	6
102.2 – 106.3	3125	1	0	6
106.4 – 110.4	3250	0	1	6
110.5 – 114.6	3375	3	0	6
114.7 – 118.8	3500	0	0	7

[redacted]

Table 14-7 Deferasirox DT dosing table for 35 mg/kg/day

Pt Weight in Kg	Closest Dose	125 mg	250 mg	500 mg
10 – 13.9	375	3	0	0
14.0-19.9	500	0	0	1
20.0-26.5	875	1	1	1
26.6-30.1	1000	0	0	2
30.2-33.6	1125	1	0	2
33.7-37.2	1250	0	1	2
37.3-40.8	1375	1	1	2
40.9-44.4	1500			3
44.5-47.9	1625	1		3
48.0-51.5	1750		1	3
51.6-55.1	1875	1	1	3
55.2-58.6	2000			4
58.7-62.2	2125	1		4
62.3-65.8	2250		1	4
65.9-69.4	2375	1	1	4
69.5-72.9	2500			5
73.0-76.5	2625	1		5
76.6-80.1	2750		1	5
80.2-83.6	2875	1	1	5
83.7-87.2	3000			6
87.3-90.8	3125	1		6
90.9-94.4	3250		1	6
94.5-97.9	3375	1	1	6
98.0-101.5	3500			7
101.6-105.1	3625	1		7
105.2-108.6	3750		1	7
108.7-11.2	3875	1	1	7
112.3-115.8	4000			8
115.9-119.4	4125	1		8
119.5-122.9	4250		1	8
123.0-126.5	4375	1	1	8
126.6-130.1	4500			9
130.2-133.6	4625	1		9
133.7-137.2	4750		1	9
137.3-140.8	4875	1	1	9
140.9-144.4	5000			10

[redacted]

Table 14-8 Deferasirox DT dosing table for 40 mg/kg/day

Pt Weight in Kg	Closest Dose	125mg	250 mg	500 mg
10.0 – 11.9	375	3	0	0
12.0 – 13.9	500	0	0	1
14.0 – 16.9	625	1	0	1
17.0 – 20.3	750	0	1	1
20.4 – 23.4	875	1	1	1
23.5 – 26.6	1000	0	0	1
26.7 – 29.7	1125	1	0	2
29.8 – 32.8	1250	0	1	2
32.9 – 35.9	1375	1	1	2
36.0 – 39.1	1500	0	0	3
39.2 – 42.2	1625	1	0	3
42.3 – 45.3	1750	0	1	3
45.4 – 45.3	1875	1	1	3
48.5 – 51.6	2000	0	0	4
51.7 – 54.7	2125	1	0	4
54.8 – 57.8	2250	0	1	4
57.9 – 60.9	2375	1	1	4
61.0 – 64.1	2500	0	0	5
64.2 – 67.2	2625	1	0	5
67.3 – 70.3	2750	0	1	5
70.4 – 73.4	2875	1	1	5
73.5 – 76.6	3000	0	0	6
76.7 – 79.7	3125	1	0	6
79.8 – 82.8	3250	0	1	6
82.9 – 85.9	3375	1	1	6
86.0 – 89.1	3500	0	0	7
89.2 – 92.2	3625	1	0	7
92.3 – 95.3	3750	0	1	7
95.4 – 98.4	3875	1	1	7
98.5 – 101.6	4000	0	0	8
101.7 – 104.7	4125	1	0	8
104.8 – 107.8	4250	0	1	8
107.9 – 110.9	4370	1	1	8
111.0 – 114.1	4500	0	0	9

[redacted]

Table 14-9 Deferasirox FCT dosing table for 3.5 mg/kg/day

Pt Weight in kg	Closest Dose (mg)	90 mg	180 mg	360 mg
10 – 19.9	Please consult the Novartis Medical Lead for advice			
20 - 38	90	1		
39 - 64	180		1	
65 - 89	270	1	1	
90 - 115	360			1
116 - 141	450	1		1

Table 14-10 Deferasirox FCT dosing table for 7 mg/kg/day

Pt Weight in kg	Closest Dose (mg)	90 mg	180 mg	360 mg
10 – 19.9	90	1	0	0
20 - 32	180		1	
33 - 44	270	1	1	
45 - 57	360			1
58 - 70	450	1		1
71 - 83	540		1	1
84 - 96	630	1	1	1
97 - 109	720			2
110 - 122	810	1		2
123 - 134	900		1	2
135 - 147	990	1	1	2

Table 14-11 Deferasirox FCT dosing table for 10.5 mg/kg/day

Pt Weight in kg	Closest Dose (mg)	90 mg	180 mg	360 mg
10 – 13.9	90	1	0	0
14 - 21	180		1	
22 - 29	270	1	1	
30 - 38	360			1
39 - 46	450	1		1
47 - 55	540		1	1
56 - 64	630	1	1	1
65 - 72	720			2
73 - 81	810	1		2
82 - 89	900		1	2
90 - 98	990	1	1	2
99 - 106	1080			3

[redacted]

Pt Weight in kg	Closest Dose (mg)	90 mg	180 mg	360 mg
107 - 115	1170	1		3
116 - 124	1260		1	3
125 - 132	1350	1	1	3
133 - 141	1440			4

Table 14-12 Deferasirox FCT dosing table for 14 mg/kg/day

Pt Weight in kg	Closest Dose (mg)	90 mg	180 mg	360 mg
10 – 15.9	180	0	1	0
16 - 22	270	1	1	
23 - 28	360			1
29 - 35	450	1		1
36 - 41	540		1	1
42 - 47	630	1	1	1
48 - 54	720			2
55 - 60	810	1		2
61 - 67	900		1	2
68 - 73	990	1	1	2
74 - 80	1080			3
81 - 86	1170	1		3
87 - 92	1260		1	3
93 - 99	1350	1	1	3
100 - 105	1440			4
106 - 112	1530	1		4
113 - 118	1620		1	4
119 - 125	1710	1	1	4
126 - 131	1800			5
132 - 137	1890	1		5
138 - 144	1980		1	5

Table 14-13 Deferasirox FCT dosing table for 17.5 mg/kg/day

Pt Weight in kg	Closest Dose (mg)	90 mg	180 mg	360 mg
10 – 17.9	180	0	1	0
18 - 23	360			1
24 - 28	450	1		1
29 - 33	540		1	1
34 - 38	630	1	1	1
39 - 43	720			2

[redacted]

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

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

Pt Weight in kg	Closest Dose (mg)	90 mg	180 mg	360 mg
10 – 13.9	270	1	1	0
14 – 19.9	360	0	0	1
20 - 23	450	1		1
24 - 27	540		1	1
28 - 31	630	1	1	1
32 - 36	720			2
37 - 40	810	1		2
41 - 44	900		1	2
45 - 48	990	1	1	2
49 - 53	1080			3
54 - 57	1170	1		3
58 - 61	1260		1	3
62 - 66	1350	1	1	3
67 - 70	1440			4
71 - 74	1530	1		4
75 - 78	1620		1	4

[redacted]

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

Table 14-15 Deferasirox FCT dosing table for 24.5 mg/kg/day

Pt Weight in kg	Closest Dose (mg)	90 mg	180 mg	360 mg
10 – 11.9	270	1	1	0
12 – 15.9	360	0	0	1
16 – 19.9	450	1	0	1
20 - 23	540		1	1
24 - 27	630	1	1	1
28 - 30	720			2
31 - 34	810	1		2
35 - 38	900		1	2
39 - 41	990	1	1	2
42 - 45	1080			3
46 - 49	1170	1		3
50 - 52	1260		1	3
53 - 56	1350	1	1	3
57 - 60	1440			4
61 - 63	1530	1		4
65 - 67	1620		1	4
68 - 71	1710	1	1	4
72 - 74	1800			5
75 - 78	1890	1		5
79 - 82	1980		1	5

[redacted]

Pt Weight in kg	Closest Dose (mg)	90 mg	180 mg	360 mg
83 - 85	2070	1	1	5
86 - 89	2160			6
90 - 93	2250	1		6
94 - 97	2340		1	6
98 - 100	2430	1	1	6
101 - 104	2520			7
105 - 108	2610	1		7
109 - 111	2700		1	7
112 - 115	2790	1	1	7
116 - 119	2880			8
120 - 122	2970	1		8
123 - 126	3060		1	8
127 - 130	3150	1	1	8
131 - 133	3240			9
134 - 137	3330	1		9
138 - 141	3420		1	9

Table 14-16 Deferasirox FCT dosing table for 28 mg/kg/day

Pt Weight in kg	Closest Dose (mg)	90 mg	180 mg	360 mg
10 – 11.9	270	1	1	0
12 – 13.9	360	0	0	1
14 – 17.9	450	1	0	1
18 – 19.9	540	0	1	1
21 - 24	630	1	1	1
25 - 27	720			2
28 - 30	810	1		2
31 - 33	900		1	2
34 - 36	990	1	1	2
37 - 40	1080			3
41 - 43	1170	1		3
44 - 46	1260		1	3
47 - 49	1350	1	1	3
50 - 52	1440			4
53 - 56	1530	1		4
57 - 59	1620		1	4
60 - 62	1710	1	1	4
63 - 65	1800			5
66 - 69	1890	1		5

[redacted]

Pt Weight in kg	Closest Dose (mg)	90 mg	180 mg	360 mg
70 - 72	1980		1	5
73 - 75	2070	1	1	5
76 - 78	2160			6
79 - 81	2250	1		6
82 - 85	2340		1	6
86 - 88	2430	1	1	6
89 - 91	2520			7
92 - 94	2610	1		7
95 - 97	2700		1	7
98 - 101	2790	1	1	7
102 - 104	2880			8
105 - 107	2970	1		8
108 - 110	3060		1	8
111 - 114	3150	1	1	8
115 - 117	3240			9
118 - 120	3330	1		9
121 - 123	3420		1	9
124 - 126	3510	1	1	9
127 - 130	3600			10
131 - 133	3690	1		10
134 - 136	3780		1	10
137 - 139	3870	1	1	10
140 - 142	3960			11

Equivalent dose guidance

For patients pre-treated with deferoxamine, a starting dose of DT or an equivalent FCT dose that is numerically half that of the deferoxamine dose (e.g. a patient receiving 40 mg/kg/day of deferoxamine for 5 days per week (or equivalent) could be transferred to a starting daily dose of 20 mg/kg/day of DT or 14 mg/kg/day of FCT) see Table 14-17.

For patients pre-treated with deferiprone (DFP), please base the patient's required dose on their serum ferritin level.

Table 14-17 Dose Regimen based on Serum Ferritin level

Dose Regimen of Drug for TDT patients	Serum ferritin level
20 mg/Kg Deferasirox DT 14 mg/Kg Deferasirox FCT	1000-1500 ng/ml
30 mg/Kg Deferasirox DT 21 mg/Kg Deferasirox FCT	>1500-2000 ng/ml
40 mg/Kg Deferasirox DT 28 mg/Kg Deferasirox FCT	>2000 ng/ml

[redacted]

Dose Regimen of Drug for NTDT patients	Serum ferritin level
5 mg/Kg Deferasirox DT 3.5 mg/Kg Deferasirox FCT	300-799 ng/ml
10 mg/Kg Deferasirox DT 7 mg/Kg Deferasirox FCT	800-2000 ng/ml
20 mg/Kg Deferasirox DT 14 mg/Kg Deferasirox FCT	>2000- 4000 ng/ml
30 mg/Kg Deferasirox DT 21 mg/Kg Deferasirox FCT	>4000 ng/ml

Please see the table belowfor guidance:

Table 14-18 Patients pre-treated with Deferoxamine

Previous dose	Equivalent dose to be used	
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
60	30	21
70	35	24.5
80	40	28

[redacted]

14.2 Examples of light meal

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

Example 2:	**amount**	**kcal**	**g total fats**
Pita Bread	1 medium (5.25" across) pita	124	1
hummus or deli chicken/turkey	1 Tablespoon humuus 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**

Example 5:			
egg whites, cooked, no fat added	2 large egg whites	32	0
salsa, red, cooked	6 Tablespoons	26	0
Wheat Bread or Toast	2 slices	138	2
jams, preserves, all flavors	1 Tablespoon	109	0
orange juice	1 cup	114	0

[redacted]

skim milk	1 cup	83	0
	Total:	**502**	**2**

Example 6:

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

[redacted]

14.3 Algorithm for Preference questionnaire completion

In case of treatment switch during the Core Phase of the study, the investigator must provide the preference questionnaire to the patient in the immediate next visit and then keep following the schedule of questionnaires pre-planned on Table 7-1 and Table 7-2.

Please see below the preference questionnaire version to be completed, based on treatment switch (yes/no) and when it occurred.

- Scenario 1 – Patient does NOT switch treatment

STUDY VISIT	QUESTIONNAIRE VERSION
Visit 4 (week 4)	Questionnaire vs. week 4 and 24
Visit 9 (week 24)	Questionnaire vs. week 4 and 24
Visit 10 (week 28)	Questionnaire vs. week 28
Visit 15 (week 48)	Questionnaire vs. week 48

- Scenario 2 – **Treatment switch** happens **V3**

STUDY VISIT	QUESTIONNAIRE VERSION
Visit 4 (week 4)	Questionnaire vs. week 28
Visit 9 (week 24)	Questionnaire vs. week 28
Visit 10 (week 28)	Questionnaire vs. week 28
Visit 15 (week 48)	Questionnaire vs. week 48

- Scenario 3 – Treatment switch happens between Visit 4 to Visit 7

STUDY VISIT	QUESTIONNAIRE VERSION
Visit 4 (week 4)	Questionnaire vs. week 4 and 24
Unplanned – next study visit after treatment switch	Questionnaire vs. week 28 eCRF: Summary page -
Visit 9 (week 24)	Questionnaire vs. week 28
Visit 10 (week 28)	Questionnaire vs. week 28
Visit 15 (week 48)	Questionnaire vs. week 48

[redacted]

- Scenario 4 – **Treatment switch** happens at **visit 8**

STUDY VISIT	QUESTIONNAIRE VERSION
Visit 4 (week 4)	Questionnaire vs. week 4 and 24
Visit 9 (week 24)	Questionnaire vs. week 28
Visit 10 (week 28)	Questionnaire vs. week 28
Visit 15 (week 48)	Questionnaire vs. week 48

- Scenario 5 – **Treatment switch** happens at **visit 9**

STUDY VISIT	QUESTIONNAIRE VERSION
Visit 4 (week 4)	Questionnaire vs. week 4 and 24
Visit 9 (week 24)	Questionnaire vs. week 4 and 24
Visit 10 (week 28)	Questionnaire vs. week 28
Visit 15 (week 48)	Questionnaire vs. week 48

- Scenario 6 – **Treatment switch** happens at visit 10 to 13

STUDY VISIT	QUESTIONNAIRE VERSION
Visit 4 (week 4)	Questionnaire vs. week 4 and 24
Visit 9 (week 24)	Questionnaire vs. week 4 and 24
Visit 10 (week 28)	Questionnaire vs. week 28
Unplanned – next study visit after treatment switch	Questionnaire vs. week 48 eCRF: Summary page -
Visit 15 (week 48)	Questionnaire vs. week 48

[redacted]

- Scenario 7 – **Treatment switch** happens at **visit 14**

STUDY VISIT	QUESTIONNAIRE VERSION
Visit 4 (week 4)	Questionnaire vs. week 4 and 24
Visit 9 (week 24)	Questionnaire vs. week 4 and 24
Visit 10 (week 28)	Questionnaire vs. week 28
Visit 15 (week 48)	Questionnaire vs. week 48

[redacted]