NOVARTIS

Novartis Research and Development

ICL670, deferasirox

Protocol CICL670F2202 / NCT02435212

A randomized, open-label, multicenter, two arm, phase II study to evaluate treatment compliance, efficacy and safety of an improved deferasirox formulation (granules) in pediatric patients with iron overload

Document type:	Amended Protocol Version
EUDRACT number:	2013-004739-55
Version number:	06 (Clean)
Development phase:	II
Document status:	Final
Release date:	24-Jun-2021

[redacted]

[redacted]

Table of contents

[redacted]

[redacted]

List of figures

List of tables

[redacted]

[redacted]

List of abbreviations

AE	Adverse Event
AESI	Adverse Events of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
AUC	Area Under Curve
AV	Atrioventricular
CMV	Cytomegalovirus
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
COVID-19	Coronavirus disease 2019
CSR	Clinical study report
CV	Coefficient of Variation
DAR	Dose Administration Record
DFO	Deferoxamine
DS&E	Drug Safety and Epidemiology
DT	Dispersible Tablet
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
eCRS	Electronic Case Retrieval Strategy
ELISA	Enzyme-Linked Immunosorbent Assay
EOT	End Of Treatment
FAS	Full Analysis Set
FCT	Film-coated tablet
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
HCV	Hepatitis C Virus
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
HSV	Herpes Simplex Virus
IA	Interim Analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
ICT	Iron chelation therapy
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology that includes Interactive Voice Response System (IVRS) and Interactive Web Response System (IWRS)
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
LFTs	Liver Function Tests
MCH	Mean cell Hemoglobin

[redacted]

MCHC	Mean cell Hemoglobin Concentration
MCV	Mean cell Volume
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
ObsRO	Observer Reported Outcomes
p.o.	*per os*/by mouth/orally
PAS	Pharmacokinetics Analysis Set
PD	Pharmacodynamic
PHI	Protected Health Information
PK	Pharmacokinetics
PPS	Per Protocol Set
PRBC	Pack Red Blood Cells
PRO	Patient Reported Outcome
RBC	Red Blood Cell
REB	Research Ethics Board
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCD	Sickle Cell Disease
SD	Standard Deviation
SICT	Satisfaction Iron Chelation Therapy
SJS	Stevens-Johnson syndrome
SOC	System Organ Class
TBIL	Total Bilirubin
ULN	Upper Limit of Normal range
UPCR	Urine Protein Creatinine Ratio
WBC	White Blood Cells
WHO ATC	Anatomical Therapeutic Chemical classification system

[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
New formulation	Granules or film-coated tablets (FCT) – both are of the same qualitative and quantitative composition, using the same active ingredients at the same doses, and the same excipients (with exception of the film-coating ingredients only used in the FCT). In the context of this study, the new formulation is provided by means of Granules.
Patient Number	A unique identifying number assigned to each patient who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned.
Randomization number	A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stick pack	Aluminum foil pouches, or sachets used to package the deferasirox granules.
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient as part of the required study procedures, including placebo and active drug run-ins.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Treatment group	A treatment group defines the dose and regimen or the combination, and may consist of 1 or more cohorts. Cohorts are not expanded, new cohorts are enrolled.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points

[redacted]

Protocol summary:

Protocol number	CICL670F2202
Title	A randomized, open-label, multicenter, two arm, phase II study to evaluate treatment compliance, efficacy and safety of an improved deferasirox formulation (granules) in pediatric patients with iron overload
Brief title	Study to evaluate treatment compliance, efficacy and safety of an improved deferasirox formulation (granules) in pediatric patients (2-<18 years old) with iron overload
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of the present study is to: • assess the compliance of the granule and the dispersible tablet (DT) formulations in pediatric patients with iron overload over 24 weeks and 48 weeks of treatment, using stick pack/tablet count and pre-dose pharmacokinetic (PK) concentrations and a PRO questionnaire. • assess the clinical benefit due to improved compliance of the new formulation by measurements of serum ferritin levels for both formulations, after 24 and 48 weeks of treatment. • assess Patient / Observer Reported Outcomes (PRO/ObsRO) on palatability and treatment satisfaction • assess the safety of both formulations • examine the pre- and post-dose concentrations of both formulations using sparse PK sampling • explore exposure-response (PK/PD) relationships for measures of safety and effectiveness • assess long term safety of granules formulation via an optional extension phase consisting of up to 5 years for those who complete 48 weeks of core treatment phase and choose to continue in the extension phase
Primary Objective(s)	To evaluate patient compliance (using stick pack or tablet counts) and change in serum ferritin over time for both formulations of deferasirox, i.e., granules and dispersible tablet (DT) in iron chelation therapy (ICT) naïve patients in the first 24 weeks of treatment during the core phase.
Secondary Objectives	• To evaluate both formulations on patient compliance (using stick pack or tablet counts) and change in serum ferritin in ICT naïve patients, after 48 weeks of treatment • To evaluate both formulations on change in serum ferritin in ICT naïve and pretreated patients, after 24 weeks and 48 weeks of treatment • To evaluate both formulations on patient satisfaction and palatability using PRO/ObsRO questionnaires • To evaluate both formulations on overall safety • To evaluate compliance using a daily PRO/ObsRO questionnaire • To evaluate pre-dose PK data to support the assessment of compliance • To obtain pre- and post-dose concentrations to explore exposure-response relationships • To assess long-term safety of the granules formulation during the optional extension phase for patients who choose to continue

[redacted]

Study design	This is a randomized, open-label, multicenter, two arm, phase II study to evaluate treatment compliance and change in serum ferritin of a deferasirox granule formulation and a deferasirox DT formulation in children and adolescents aged ≥ 2 and < 18 years at enrollment with any transfusion-dependent anemia requiring chelation therapy due to iron overload, to demonstrate the effect of improved compliance on iron burden. Randomization will be stratified by age groups (2 to <10 years, 10 to <18 years) and prior iron chelation therapy (Yes/ No). There will be two study phases which include a 1 year core phase where patients will be randomized to a 48 week treatment period to either Deferasirox DT or granules, and an optional extension phase where all patients will receive the granules up to 5 years from entering extension phase. Patients who demonstrated benefit to granules or DT in the core phase, and/or express the wish to continue in the optional extension phase on granules, will be offered this possibility until there is local access to the new formulation (granules or FCT) or up to 5 years from entering extension phase, whichever occurs first. One interim analysis has been added to allow for early analysis of the core phase data if requested by the health authority. All patients randomized in the study and who have completed a minimum of 12 weeks of treatment exposure or discontinued from treatment core phase at the time of the cutoff date will be included in the interim analysis.
Population	Up to 216 naïve and pre-treated (96 ICT naïve and up to 120 pre-treated) male and female children and adolescents aged ≥ 2 and < 18 years at enrollment with any transfusion-dependent anemia requiring chelation therapy due to iron overload, and a treatment goal to reduce iron burden will be included in this study. At least 96 (48 per treatment arm) patients should be iron chelation naïve. The optional extension phase will give the patients who have participated and completed the 48 weeks core treatment phase as per protocol, the possibility to extend treatment with granules for a maximum of 5 years after completing the core treatment phase or until there is local access to new formulation (granules or FCT), whichever occurs first. All patients who choose to continue in the extension phase will receive granules during the optional extension phase. There will be two study phases which include a 1 year core phase where patients will be randomized to a 48 week treatment period to either Deferasirox DT or granules, and an optional extension phase where all patients will receive the granules up to 5 years from entering extension phase. Patients who demonstrated benefit to granules or DT in the core phase, and/or express the wish to continue in the optional extension phase on granules, will be offered this possibility until there is local access to the new formulation (granules or FCT) or up to 5 years from entering extension phase, whichever occurs first.
Inclusion criteria	• Written informed consent/assent before any study-specific procedures. Consent will be obtained from patients, parent(s) or legal guardians. Investigators will also obtain consent/assent of patients according to local guidelines. • Male and female children and adolescents aged ≥ 2 and < 18 years.* [France: Male and female children and adolescents aged ≥ 2 and < 18 years, however children aged ≥ 2 and ≤ 6 years can be enrolled only when deferoxamine treatment is contraindicated or inadequate in these patients as per investigator decision] *Applicable to core phase only. Once in the core phase patients can turn 18 years and still be considered eligible, also for participation in the optional extension phase. • Any transfusion-dependent anemia associated with iron overload requiring iron chelation therapy and with a history of transfusion of approximately 20 PRBC units, and a treatment goal of reduction, not maintenance of iron burden as measured by serum ferritin. • Serum ferritin > 1000 ng/mL, measured at screening Visit 1 and screening Visit 2 (the mean value will be used for eligibility criteria).

[redacted]

	• Completion of core phase per protocol (For the optional extension phase criteria only).
Exclusion criteria	• Creatinine clearance below the contraindication limit in the locally approved prescribing information. Creatinine clearance will be estimated from serum creatinine (using the Schwartz formula) at screening Visit 1 or screening Visit 2. • Serum creatinine > 1.5 xULN at screening Visit 1 or screening Visit 2. • ALT or AST >3.0 x ULN at screening visit 1 or screening visit 2. • Direct (conjugated) bilirubin >2 x ULN at screening visit 1 or screening visit 2. • (Criterion no longer applicable, removed as part of Amendment 1): ~~Prior iron chelation therapy~~ • Liver disease with severity of Child-Pugh class B or C. • Significant proteinuria as indicated by a urinary protein/creatinine ratio >0.5 mg/mg in a second morning urine sample at screening Visit 1 or screening Visit 2. • 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 or Hepatitis C (HBsAg in the absence of HBsAb OR HCV Ab positive with HCV RNA positive). • Patients with psychiatric or addictive disorders which prevent them from giving their informed consent/assent or undergoing any of the treatment options or patients unwilling or unable to comply with the protocol (including use of electronic devices for ePRO). • Local access to new formulation (granules or FCT) is available for the patient (For the optional extension phase criteria only).
Investigational and reference therapy	• Patients will be randomized to either Deferasirox granules or Deferasirox DT (Exjade) in the core phase. • All patients who choose to continue in the extension phase will receive deferasirox granules in the extension phase.
Efficacy assessments	The co-primary efficacy endpoints assessed during the core phase will be: • Compliance measured by stick pack/tablet count over 24 weeks of treatment (i.e. assessed at week 25 visit). • Change from baseline in serum ferritin after 24 weeks of treatment (i.e. Serum Ferritin at week 25 visit).
Primary endpoint assessments	• Compliance will be measured by stick pack/tablet count over 24 weeks of treatment (i.e. assessed at week 25 visit): it will be performed by study personnel every 4 weeks (weeks 5, 9, 13, 17, 21, 25 and End of Treatment (EOT) (core)/777 visits) during the core phase based on the amount of medication dispensed, returned and reported as lost/wasted by the patient / caregiver • Serum ferritin test will be performed at Screening Visits 1 and 2 and every 4 weeks from week 5 till after 24 weeks of treatment (i.e. assessed at week 25 visit)..
Secondary endpoint assessments	**Core phase:** • Compliance will be measured by stick pack/tablet count over 48 weeks of treatment: it will be performed by study personnel every 4 weeks (weeks 5, 9, 13, 17, 21, 25 29, 33, 37, 41, 45, and EOT(core)/777 visits) during the core phase based on the amount of medication dispensed, returned and reported as lost/wasted by the patient / caregiver • Serum ferritin test will be performed at Screening Visits 1 and 2 and every 4 weeks from week 5 till end of treatment visit.

[redacted]

	• The study will include the use of a Satisfaction with Iron Chelation Therapy questionnaire, a Palatability questionnaire and a compliance diary to evaluate both formulations on these patient / observer reported outcomes. • Safety will be monitored by assessing the following parameters: • Hematology, chemistry (including renal and hepatic parameters), urinalysis • Adverse events; including renal toxicity (including renal failure), hepatic toxicity (including hepatic failure) and gastrointestinal hemorrhage, which will be actively monitored until symptom resolution or until the condition stabilizes • Vital signs • Physical examinations • Ocular examinations • Auditory examinations • Cardiac examinations (ECG and echocardiogram) • Growth parameters and development parameters • Deferasirox concentrations will be measured in plasma at predefined time points on all patients. [Egypt: PK samples will not be collected due to restriction on sample exportation] • Pharmacokinetic samples collected by sparse PK sampling in all patients [Egypt: PK samples will not be collected] will be analyzed using modeling approaches to explore PK/PD (safety and efficacy) relationships. **Optional Extension phase:** • Long term safety of granules in the optional extension phase: • Overall safety, as measured by frequency and severity of adverse events (including active monitoring for renal toxicity; including renal failure, hepatic toxicity; including hepatic failure, and gastrointestinal hemorrhage), and changes in laboratory values from baseline (serum creatinine, creatinine clearance, ALT, AST, RBC and WBC). In addition, vital signs, physical, ophthalmological, audiometric, and growth and development evaluations will be assessed.
Other assessments	Daily questionnaire on study treatment compliance completed through core phase only.
Data analysis	**Analysis sets:** The Full Analysis Set 1 (FAS-1) comprises all ICT naïve patients to whom study treatment has been assigned by randomization. The Full Analysis Set 2 (FAS-2) comprises all ICT pre-treated patients to whom study treatment has been assigned by randomization. The Full Analysis Set 3 (FAS-3) comprises all ICT pre-treated and naïve patients to whom study treatment has been assigned by randomization. According to the intent to treat principle, patients will be analyzed according to the treatment and stratification factors they have been assigned to during the randomization procedure. The Safety Set 1 includes all ICT naïve patients who received at least one dose of study medication. The Safety Set 2 includes all ICT pre-treated patients who received at least one dose of study medication. The Safety Set 3 includes all ICT pre-treated and naïve patients who received at least one dose of study medication. The Safety Set 4 will consist of all patients who received at least one dose of granules formulation during the core or extension phase. Patients will be analyzed according to the study treatment they actually received. The Per Protocol Set consists of all ICT naïve patients from the FAS-1 without any major protocol deviation. The major protocol deviations that will lead to exclusion of patients from the PPS will be detailed in the Statistical Analysis Plan (SAP). The Pharmacokinetic Analysis Set (PAS) consists of all patients who have at

[redacted]

	least one evaluable pre or post-dose PK concentration (deferasirox). More details are provided in Section 10.1.4. **Statistical Analyses:** **Primary efficacy endpoints:** All analyses for the primary objective will be performed based on core period and on the FAS-1 and presented by treatment group: deferasirox DT and deferasirox granule formulation. The co-primary efficacy variables are: • Compliance measured by stick pack /tablet count based on amount of medication dispensed, returned and reported as lost/wasted by the patient or caregiver over 24 weeks of treatment (i.e. assessed at week 25 visit). Compliance will be calculated 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 over 24 weeks of treatment (i.e. assessed at week 25 visit); • total count prescribed is cumulative prescribed count over 24 weeks of treatment (i.e. assessed at week 25 visit). • Change from baseline in serum ferritin after 24 weeks of treatment (i.e. serum ferritin assessment at week 25 visit). The primary efficacy analysis will be the comparison of means between the two treatment arms of change from baseline after 24 weeks of treatment in SF and mean relative consumed stick pack /tablet count over 24 weeks of treatment. Analysis of covariance (ANCOVA) will be performed for comparison between treatment groups at a one-sided 5% level of significance. The ANCOVA model for compliance endpoint will include treatment group and age group (2 to<10 years, 10 to <18 years), as factors. The model for serum ferritin endpoint will also include the serum ferritin value at baseline as covariate. The trial will be claimed successful if the superiority of granule formulation relative to DT formulation could be demonstrated with regard to both endpoints. Therefore, no adjustment of the type I error (alpha) is required. **Sample size calculation:** The primary objective is to evaluate patient compliance (using stick packs or tablets counts) and change in serum ferritin (SF) over time for both formulations of deferasirox in pediatric ICT naïve patients with iron overload after 24 weeks of treatment. The sample size was calculated to show superiority of the granule formulation relative to DT formulation with regard to both co-primary endpoints. The assumptions made for this study were as follows: • For serum ferritin: An expected improvement between both formulations in SF change from baseline after 24 weeks of treatment of −450 ng/mL with a standard deviation (SD) of 900 ng/mL based on results from study CICL670A0107 in pediatric patients treated with Exjade on ≥25 mg/kg/day after 24 weeks of treatment. • For compliance over 24 weeks of treatment using stick packs or tablets counts: An expected improvement between both formulations in mean relative consumed tablet count of 10% with a SD equal to 17.625% based on the pooled analysis on pediatric patients (77) from Exjade studies [ICL670A2206] (39), [ICL670A2204] (24) and [ICL670A2214] (14). The sample size driven by the calculation for serum ferritin, has been determined to obtain 76% power at one-sided 5% level of significance for showing superiority of granule formulation over DT formulation with respect to change from baseline after 24 weeks of treatment in serum ferritin, assuming a dropout rate of 5%. A sample size of 48 in each group will have 76% power to detect a difference in means of 400.0 ng/mL assuming that the common SD is 800.0 ng/mL using a

[redacted]

two group t-test with a 0.050 one-sided significance level. With 48 patients per arm, the power to detect a 10% difference in mean compliance is about 84%.

In addition, the clinical trial will enroll patients previously treated with iron chelation. Considering that a direct comparison of granule and DT formulations in terms of efficacy is not foreseen in previously chelated patients, the required sample size is not based on power calculations as usual. The selection of number of patients is based on the precision in the estimate of SF change at 48 weeks of treatment and on practical considerations.

A maximum of 120 patients (60 patients will be in each formulation group) previously chelated patients will be enrolled. Sixty patients will provide an estimate of SF change with precision (half-width of 95% confidence interval) equal to 303.6.

The table below lists the precisions in the estimates of SF change for different numbers of patients using the estimated SD obtained from the CICL670A0107 study results in pediatric patients treated with Exjade on ≥25 mg/kg/day at week 48 of treatment.

Precision in the estimate of the serum ferritin change

Number of patients	Half-width of 95% confidence interval in the estimate of the SF change
40	371.8
45	350.6
50	332.6
55	317.1
60	303.6

The total required sample size for this clinical trial is up to 108 patients for each treatment group (up to 216 patients in total), including 48 iron chelation naive patients per group (96 patients in total).

Safety: The assessment of safety will be based mainly on the frequency and severity of AEs and changes in laboratory values. Other safety data (e.g., ECGs, vital signs, echocardiogram, ocular, auditory examinations) will also be summarized. For all safety analyses, the safety set will be used.

Pharmacokinetics:
Pre- and post-dose concentrations will be summarized descriptively and graphically presented.
The analyses will be based on the PAS.

To explore PKPD relationship:
Serum ferritin change from baseline will be fitted by a linear mixed effect model with log- transformed matching pre-dose concentrations as covariates and subject as random effect.
Serum creatinine change from baseline, serum creatinine clearance change from baseline and urine protein creatinine ratio change from baseline will be fitted by a linear mixed effect model with log-transformed matching pre-dose concentrations and post-dose concentrations respectively as covariates and subject as random effect. Incidence of notable serum creatinine events will be analyzed by a logistic regression fitted by GEE methods as appropriate including matching log-transformed pre-dose concentrations and post-dose concentrations respectively.
Incidence of notable serum creatinine clearance events will be analyzed by a logistic regression fitted by GEE methods as appropriate including matching log-transformed pre-dose concentrations post-dose concentrations respectively.
For all statistical models other covariates such as demographic characteristics may be included if appropriate.
All analyses will be based on the Safety Set or FAS of the core phase.

[redacted]

	Interim analysis: All the analyses included in the interim analysis will be descriptive. Testing of hypotheses will not be performed and no decisions regarding the future course of the trial is anticipated at the time of the IA and the trial will continue. Therefore adjustment for multiplicity is not performed. Descriptive statistics will be provided by treatment arm on the primary endpoints (i.e. change from baseline in serum ferritin and compliance measured by stick pack /tablet count) and key safety data.
Key words	New formulation, deferasirox, chelation, iron overload, compliance, satisfaction, palatability, PRO, PK, safety, PK/PD

[redacted]

Amendment 6 (24-Jun-2021)

Amendment rationale

As of 24-Jun-2021, 67 patients are ongoing in the extension phase of the study. All patients had completed the Core phase of the study by 18-Dec-2018. The primary analysis for this study was completed on 07-Dec-2018 (data cut-off date 31-May-2018).

The main purpose of this amendment is to introduce the requirement for central collection and assessment of photographs from ocular examinations (lens photographs and wide angle fundus photographs) collected during the study by a Novartis designated imaging Contract Research Organization (CRO). This change is in response to a Health Authority request to submit CALYPSO ophthalmic data (for up to 2 years of follow up) to support the ocular safety evaluation of deferasirox.

Clarification was also added to state that for patients who need correction, the best corrected visual acuity should be tested when performing the distance visual acuity test and that the corrected visual acuity should be documented in the source records.

In addition, mitigation procedures have been implemented throughout the protocol to ensure participant safety and trial integrity during a Public Health emergency, as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster.

Finally, assessment of the study Risk/Benefit in light of the ongoing coronavirus disease 2019 (COVID-19) pandemic at the time of this protocol amendment concluded that there are no additional risks related to COVID-19 for this study. Patient with cytopenias are more susceptible to infections in general, compared to patients without cytopenias. There have been postmarketing reports of cytopenias in patients treated with deferasirox and patients with cytopenias may be at higher risk of COVID-19 with a poorer prognosis. The periodic monitoring of blood counts and interruption of study treatment in patients who develop unexplained cytopenia, as defined in the protocol, are expected to mitigate this risk.

Changes to the protocol

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

- List of Abbreviations (LOA) and Protocol summary (data analysis): Aligned with updates in the protocol.
- Section 4.5: New section added, describing the rationale for public health emergency mitigation procedures.
- Section 6.5: Included public health emergency mitigation guidelines, regarding the delivery of IMP directly to the participant's home at the discretion of the Investigator.
- Section 7.1: Updated to add a ± 30-day window for yearly assessments, i.e. audiometry, ocular, and growth and development examinations, in the extension phase, to allow more flexibility for the sites.

[redacted]

- Section 7.1: Included public health emergency mitigation guidelines, regarding alternative methods of providing continued care, such as phone calls and virtual contacts, to replace on-site study visits for the duration of the disruption.
- Table 7-1 and Table 7-2: Separated Audiometry and Ocular sections and updated protocol section numbers.
- Section 7.2.4: Included public health emergency mitigation guidelines, regarding the inclusion of phone or virtual calls for safety monitoring and discussion of the participant's health status for the duration of the disruption.
- Section 7.2.4.4: Removed the reference to ocular examinations from this section as a new section (7.2.4.5) was added to clarify more detail about central imaging assessments.
- Section 7.2.4.5, Table 7-3: New section and table added for ocular examinations and central imaging assessments. This section was included to introduce the requirement for central collection and assessment by an imaging CRO.
- Section 7.2.4.6: Included public health emergency mitigation guidelines, regarding the use of a local laboratory if the subject is unable to conduct safety laboratory assessments at the site.
- Section 8.4: Updated the duration for pregnancy reporting after the estimated date of delivery.
- Section 9.3: Included ocular examination photographs as an additional component of data collection.
- Section 9.4: Included ocular examination photographs as an additional component of data being collected and processed centrally.
- Section 10: Added public health emergency mitigation guidelines regarding statistical methods and data analysis.
- Section 10, Section 10.1.2, Section 10.1.3, Section 10.4.4, Section 10.5.3, Section 10.5.4.2, Section 10.5.5: Changed RAP to SAP
- Section 10.2: Removed Safety Set 4 demographic and other background data summary, as these are already presented in FAS-3 summary.
- Section 10.3: Corrected the definition of average daily dose calculation and updated the concomitant medication definition to align text with the SAP.
- Section 10.4.4, Section 10.5.1: Changed the term 'sensitivity analysis' to 'supplementary analysis'.
- Section 10.5.4.1: Updated AESI maintenance and retrieval to align with the current Novartis internal process.
- Section 10.6.1.2, Table 10-2: The normal ranges for pulse rate and weight were updated for pediatric patients. Notable ranges for systolic and diastolic blood pressure were removed.

[redacted]

- Section 11.3: Included public health emergency mitigation guidelines, regarding the inclusion of remote informed consent discussion due to limits that prevent an on-site visit.
- Section 13: Added a new reference.

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 protocol amendment.

[redacted]

Amendment 5 (06-Dec-2017)

Amendment rationale

As of 06-Dec-2017, 210 patients have been randomized (94 chelation naïve and 116 pre-treated patients). The pre-treatment arm is fully accrued.

The purpose of this amendment is to modify the assessment timepoint for the primary analysis (currently change from baseline for serum ferritin and compliance after 48 weeks of treatment), and to reduce the sample size for the chelation naive patients , following recent interaction with Health Authorities. The eligibility criteria for the extension phase have been modified.

Amendment rationales are as follows:

1. The assessment timepoint for the primary analysis will be modified for serum ferritin and compliance to 24 weeks of treatment (as assessed at week 25 visit), in lieu of 48 weeks. A linear relationship between changes from baseline at 24 and 48 weeks of treatment has been established based on a pool of representative randomized studies (CICL670A0105, CICL670A0107, CICL670A0109 and CICL670A2206) with serum ferritin available at 6 and 12 months for deferoxamine and deferasirox arms. The model fits well in the set of observations and showed that the treatment effect at 6 and 12 months are correlated, with a slightly more pronounced effect at 12 months. This finding supports the use of the 6 months time-point as reliable surrogate for the 12 months time-point (Novartis data on file). Primary endpoints based on changes from baseline after 24 weeks of treatment will allow an earlier disclosure of primary analysis. The compliance (using drug count) has been evaluated in pediatric patients over 6 months and 12 months for deferoxamine and deferasirox arms in the ICL670A2206 study. The observed treatment effect over 6 months vs. 12 months is similar. This suggests compliance over 6 months is accurate at predicting compliance over 12 months. Furthermore data comparing deferoxamine and deferasirox suggest a self-reported adherence to deferasirox DT of 97% after one year. Therefore it can be assumed that the 6 month reported adherence will be very similar and can serve as a surrogate (Trachtenberg 2011)The rationale is also based on the demonstrated relationship of efficacy as assessed by serum ferritin with deferasirox dose, iron burden and continuous iron intake (Cappellini et al 2006).
2. The recruitment of chelation of naïve patients has been much slower than anticipated due to the global availability of chelation therapies in these indications. Through recent interactions with Health Authorities, it has been discussed and agreed that the sample size for chelation naïve patients has been reduced to reflect the modification of primary endpoints. At least of 96 chelation naive patients are planned to be enrolled instead of 120 patients. This lower sample size will allow to obtain 76% power at a one-sided 5% level of significance for showing superiority of granule formulation over DT formulation with respect to change from baseline after 24 weeks of treatment in serum ferritin, assuming a dropout rate of 5%. This power is considered adequate to demonstrate targeted treatment effect, and will allow an earlier full recruitment of chelation naïve patients in the study, and therefore an earlier disclosure of primary analysis.
3. Eligibility criteria for the extension phase are being updated in order to allow patients who have participated and completed 48 weeks of treatment in the core phase and for whom

[redacted]

new formulation is not yet available, to continue in the extension phase if they derive clinical benefit from the study drug, as confirmed by Investigator. The current criteria are too stringent and would unnecessarily exclude patients who are benefiting from the study drug. During the extension phase patients will continue to follow the protocol including any dose modification guidelines and early withdrawal/discontinuation guidelines as they did in the core phase of the study.

Changes to the protocol

- Protocol Summary section - Purpose and rationale has been updated to assess compliance at 24 weeks and 48 weeks of treatment. Population requirements reduced from 240 to 216 naive and pre-treated patients, and 120 naive patients has been reduced to 96. Number of patients per treatment arm has been reduced from 60 to 48 patients. Inclusion/exclusion criteria have been updated for the extension phase. Primary endpoint assessments have been modified from 48 to after 24 weeks of treatment, i.e. at Week 25 visit. Secondary endpoint assessments have been confirmed in light of the new primary endpoint assessments. Data analysis section has been updated to reflect new primary endpoints and sample size.
- Duration of extension phase has been clarified throughout protocol.
- EOT/777 refer to the end of treatment core visit. This has been updated to reference the EOT core visit throughout protocol.
- For clarification any reference to Week 25 is designated as 'Week 25 visit' and any reference to 24 weeks of treatment is designated as '24 weeks of treatment' throughout protocol.
- Rationale for modifying primary endpoints to 24 weeks of treatment has been added to Sections 2.1.
- Primary endpoints have been updated throughout protocol (Sections 2.1, 2.2, Table 3-1, Sections 4.2, 10.4.1, 10.4.2, 10.4.4 and 10.8)
- Definition of end of study has been updated to indicate when primary and final analyses will occur (Section 4.3).
- Section "Handling of missing values/discontinuations" for the primary endpoint has been added (Section 10.4.3)
- Sample size has been updated throughout protocol (Sections 2.2, 5.1 and 10.8)
- Secondary objectives/endpoints have been updated throughout protocol (Table 3-1, Sections 10.5, 10.5.1 and 10.5.2)
- Re-aligned the criteria for re-starting dose after omission due to increase in direct (conjugated) bilirubin. Currently re-starting criteria (1.5 x ULN) are not aligned with dose modification criteria (2.0 x ULN).
- Eligibility criteria for extension phase has been updated throughout protocol (Sections 5.2, 5.3, Table 7-2, Sections 7.1.1, 7.2.2 and 7.2.4.5)
- Section 7.2.5.2: Updated PK analytical method and provider to allow for a new PK lab to be used, as [redacted]. is no longer the only lab participating in PK analysis for the study.
- Sections 10.2 and 10.6.1.5: Changed FAS-4 to Safety Set as FAS-4 has been removed.

[redacted]

- Sections 10.4.3 to 10.4.4 and 10.5.1 to 10.5.5 re-numbered to align with rest of protocol.
- Section 13: Addition of references to support change in primary endpoints.
- Minor editorial changes have been made throughout protocol.

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

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 protocol amendment.

[redacted]

Amendment 4 (15-Jun-2017)

Amendment rationale

As of 15-Jun-2017, 178 patients have been randomized (60 chelation naïve and 118 pre-treated patients). The pre-treatment arm is fully accrued.

The purpose of this amendment is to include an interim analysis, allow for paper PRO completion, and clarify various points to improve site understanding and consistency in implementation of the protocol.

Amendment rationales are as follows:

1. With this amendment, one interim analysis has been added to allow for early analysis of the data if requested by the health authority.
2. To allow for paper PRO questionnaires use in case of technical issue or malfunctioning of the electronic device.
3. To clarify the completion of the ObsPRO questionnaires for patients who turn 10 years will continue to be completed by the caregiver.
4. To clarify the inclusion/exclusion criteria for the optional extension phase.
5. To clarify that when either TBIL or direct bilirubin are increased and > 2 x ULN, it always needs to be checked whether there is also an increase of ALT/AST that meets the definition of DILI.
6. To modify the dose modification and exclusion criteria for direct bilirubin to enhance enrolment and reduce the amount of study drug interruptions without compromising safety. Many transfusion-dependent anemia patients have higher baseline level of direct bilirubin due to hemolysis. Implementation of these less strict exclusion and dose modification criteria will not have any impact on capturing patients with Drug induced liver injury as this only occurs in case of increase of direct bilirubin > 2x ULN.
7. To include dose modifications in case of Toxic epidermal necrosis (TEN) on Table 6-2 as per latest IB update.
8. To correct height and weight to monthly in the optional extension phase to align with the CRF and collection requirements.
9. To re-define Safety Set 4. At the end of the study, safety data for the optional extension phase data will be analyzed considering core and extension phases for patients who received granule formulation. The Safety Set 4 will be used and the FAS-4 has been removed.
10. Baseline categories for serum creatinine, creatinine clearance, ALT, AST and urine protein/creatinine ratio have been re-defined to align with the protocol exclusion and dose modification criteria.
11. To clarify the endpoint for PK/PD analyses: notable serum creatinine/creatinine clearance ‘values’ replaced with ‘events’ as two consecutives lab values need to be above/below the range to be considered as notable.
12. To clarify the level of blinding of Sponsor and the procedure to minimize the potential impact of treatment knowledge.

[redacted]

13. Clarified and corrected VES for optional extension phase (Table 7-2).
14. For the ObsRo/PRO data analyses, the term "Baseline" has been removed as the first assessment done at Week 2 after the randomization will not be considered as a baseline assessment.
15. PK analyses have been clarified to be aligned and consistent with the study objectives

Changes to the protocol

- Cover page: Author update from [redacted] to [redacted] and from [redacted] to [redacted] due to change in Study Lead and Medical Lead, respectively.
- List of Abbreviations – Added abbreviations used in protocol but previously not included in list.
- Added details of interim analysis to Protocol Summary section and Sections 4.1, 4.2 and 10.7.
- Added consent of patients throughout protocol as patients may be expected to become age of consent during course of study.
- Added clarification of the inclusion/exclusion criteria for the optional extension phase throughout protocol.
- Modified the dose modification and exclusion criteria for direct bilirubin in Protocol Summary section, Section 5.3 and Table 6-2.
- Clarified that when either TBIL or direct bilirubin are increased and > 2 x ULN, it always needs to be checked whether there is also an increase of ALT/AST that meets the definition of DILI (Table 6-2).
- Included dose modifications in case of Toxic epidermal necrosis (TEN). (Table 6-2).
- Added procedure to minimize the potential impact of treatment knowledge (Section 6.4.3).
- Updated Visit Evaluation Schedule for Extension phase to include monthly height and weight (Table 7-2 and Section 7.2.4.3).
- Removed Full Analysis Set 4 (FAS-4) from Protocol Summary section and Section 10.1.1.
- Redefined Safety Set 4 in Protocol Summary section and Section 10.1.2.
- Added urine protein creatinine ratio change from baseline to explore exposure-response relationships in Protocol Summary section, Table 3-1 and Section 10.5.5.3.
- Notable serum creatinine 'values' has been replaced with 'events' in Protocol Summary section, Table 3-1 and Section 10.5.5.3.
- Clarified starting dose as compared to pre-washout dose (Sections 2.3, 4.1 and 6.1.1).
- Section 6.1.1: Clarified need to return empty stick packs and bottles.
- Section 6.4.3: Updated language for treatment blinding.
- Table 7-2: Clarified VES for ECG and echocardiogram assessments. Added Urine pregnancy test at EOT visit.
- Section 7.2.2: Clarified timing of serum ferritin testing for optional extension phase eligibility.

[redacted]

- Section 7.2.3: Updated section to allow for paper ObsRO/PRO questionnaires use. Clarified the completion of the ObsPRO questionnaires for patient after turn 10. Clarified compliance diary will no longer be collected during the optional extension phase.
- Section 7.2.4.3: Updated height and weight to align with Exjade prescribing information.
- Section 7.2.4.6.2: Clarified schedule for echocardiogram assessments.
- Section 8.2.2: Updated SAE reporting contact details.
- Section 8.4: Updated pregnancy reporting contact details.
- Section 9.4: Updated section to allow for paper PRO questionnaires use.
- Section 10.2: Redefined baseline categories for serum creatinine, creatinine clearance, ALT, AST and urine protein/creatinine ratio
- Sections 10.5.2: Removal of the term "Baseline for ObsRO/PRO data analyses.
- Sections 10.5.5, 10.5.5.1 and 10.5.5.2 and Protocol Summary section: Clarified PK/PD and PK parameters analyses.
- Section 14.3: Clarified dosing based on patient's body weight.
- In addition, clarifications were added to correct typographical errors and inconsistencies in different sections throughout protocol.

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

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 protocol amendment.

[redacted]

Amendment 3 (24-Aug-2016)

Amendment rationale

At the time of this amendment thirty nine patients have been randomized.

The purpose of this amendment is as follows:

1. To add an optional extension phase to the existing study. This optional extension phase will give the patients who have participated and completed the 48 weeks core treatment phase as per protocol and do not have access to the new formulation (granules or FCT) the possibility to extend treatment with deferasirox granules for a maximum of 5 years after completing the core treatment phase or until there is local access to new formulation (granules or FCT) whichever occurs first. Patients must have demonstrated benefit to granules or DT in the core phase, and/or express the wish to continue in the optional extension phase on granules in order to start the optional extension phase.

2. To sharpen the clarification of the eligibility criteria related to renal criteria in order to promote better Investigator understanding, leading to better adherence and improved renal safety.

3. To provide the investigators with further clarified dose modification guidance for renal monitoring with regards to creatinine clearance, increased serum creatinine and proteinuria. Clear guidance on how to reinitiate treatment after required dose interruption has also been included in order to improve patient safety.

In addition, clarifications were added to correct typographical errors and inconsistencies in different sections.

Changes to the protocol

- List of Abbreviations: Added FCT (Film-coated tablet)
- Glossary of Terms: Defined new formulation and stickpack.
- Protocol Summary: Made distinctions between core phase and the optional extension phases in Primary Objectives, Study design, Inclusion criteria, Efficacy assessments, Primary endpoint assessments, Secondary endpoint assessments, and Other assessments Sections.
- Protocol Summary: Added details of the optional extension phase to Purpose and rationale, Secondary Objectives, Population, Inclusion criteria, Exclusion criteria, Investigational and reference therapy, and Secondary endpoint assessments Sections.
- Protocol Summary: Further clarified laboratory exclusion criteria
- Protocol Summary: Clarified extended FAS, made distinction between core phase and the optional extension phase, and added extension phase details in Data analysis Section.
- Section 1.2.2: Added description of stick pack and film-coated tablets. Added warm porridge as a vehicle for granule administration.
- Section 2.1: Provided rationale for giving all patients granule formulation in the optional extension phase. Added extension phase purpose.

[redacted]

- Section 2.2: Distinguished between the two phases of study treatment (core and optional extension). Provided rationale for including the optional extension phase.
- Section 2.3: Distinguished between core and optional extension phases.
- Table 3-1: Added Objective of the optional extension phase.
- Section 4.1: Added the optional extension phase design. Updated end of treatment visit timelines.
- Figure 4-1: Updated Study schema.
- Section 4.3: Updated definition of end of study.
- Section 5.2: Updated inclusion criteria for the optional extension phase.
- Section 5.3: Further clarified laboratory exclusion criteria. Added the optional extension phase exclusion criteria.
- Section 6.1: Distinguished study treatment between core and the optional extension phases.
- Section 6.1.1: Further clarified dosing regimen based on lab values and prior dosing in core phase. Added dose adjustment guidelines for optional extension phase. Added warm porridge as vehicle for granule administration.
- Table 6-1: Further clarified starting dose.
- Section 6.1.2: Updated treatment duration to include the optional extension phase.
- Section 6.2.1: Dose adjustment outside or protocol sections now require a written request from Investigator.
- Table 6-2: Further clarified dose modifications based on changes in body weight, serum creatinine and/or creatinine clearance, isolated direct (conjugated) bilirubin elevation, serum ferritin, urine protein/creatinine ratio, as well as auditory and ocular disturbances, and hypersensitivity reactions.
- Section 6.2.2: Added end of treatment guidance for the optional extension phase. Added SEC eCRF completion requirement.
- Section 6.2.3: Updated follow-up for patients permanently discontinuing due to adverse event or abnormal laboratory value.
- Section 6.3: Updated conmed reporting by patient.
- Section 6.3.1: Clarified timing of PK vs transfusions.
- Section 6.3.2: Clarified language for use of other iron chelators.
- Section 6.4.2: Made distinction between core and optional extension phases. Added the optional extension phase details.
- Section 7.1: Made distinction between core and optional extension phases. Added the optional extension phase details and updates to assessments during the optional extension phase throughout Section 7.1.
- Table 7-1: Renamed Visits 777 and 778 and specified table for core phase of study.
- Table 7-2: Created Table 7-2 to include the optional extension phase visits and assessments. Tables 7-3 through 7-5 numbering updated.
- Section 7.1.5: Added collection of death details during follow-up period.

[redacted]

- Section 7.2: Assessment updates for the optional extension phase have been added, including removal of stick pack count, removal of ePRO assessments and updated schedules for the assessments per Table 7-2. Patients transitioning from being on DT in the core will require additional renal safety labs per Section 7.2.4.5.2.
- Section 7.2.4.5: Clarified pregnancy testing schedule
- Table 7-4: PK collections no longer required were removed for clarity.
- Table 7-5: Added 'taken pre-dose' and 'taken post-dose' for clarity.
- Section 8: Added collection of death details during follow-up period.
- Section 8.4: Updated pregnancy section for the optional extension phase.
- Section 10: Clarified study purpose. Clarified extended FAS and added FAS-4 for the optional extension phase throughout section. Clarified extended Safety Set and added Safety Set-4 for the optional extension phase throughout section.
- Section 10.3: Added duration of exposure in weeks for core phase. The optional extension phase will be in months. Clarified prior and concomitant meds.
- Section 10.4: Clarified primary objective for core phase.
- Section 10.5: Added the optional extension Visit 17. Made distinction between core and optional extension phases where needed. Added 'Summary tables for AEs will be repeated for the optional extension phase on the Safety Set 4. Lab abnormalities will be described for the optional extension phase on the Safety Set 4. Added 'matching' to log-transformed pre- and post-dose concentrations in Section 10.5.5.3.
- Table 10-2: Updated definition of notable weight ranges.
- Section 10.6: Updated 'Other safety data' section. Distinguished between assessments for core and optional extension phases.
- Section 10.6.1.5: Serum ferritin during the optional extension phase added.
- Table 14-3: Corrected body weight ranges.
- Table 14-4: Corrected body weight ranges.
- In addition, clarifications were added to correct typographical errors and inconsistencies in different sections.

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

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 protocol amendment.

[redacted]

Amendment 2 (15-Jun-2016)

Amendment rationale

At the time of this amendment 13 patients have been randomized.

The purpose of this amendment is:

1. To allow the sites in Egypt to use a local laboratory instead of central laboratory for the analysis of safety required in this trial and to exempt patients' enrolled in Egypt from the collection of PK samples. This exemption is granted to Egypt due to national restriction on export of any biological samples out of Egypt.
2. To clarify the inclusion criteria #2 for France concerning children aged from 2 to 6 years old as per Exjade prescribing information.

In addition, clarifications were added to correct typographical errors and inconsistencies in different sections.

Changes to the protocol

- Protocol Summary: inclusion criteria and secondary endpoint assessments.
- Section 2.2: added exemption to collect PK samples in Egypt.
- Section 5.2: Clarify inclusion criteria # 2 for France.
- Table 6-2: Added laboratory testing will be done in a local laboratory for Egypt.
- Section 7.1.1.3: Added laboratory testing will be done in a local laboratory for Egypt.
- Section 7.2.2: Added laboratory testing will be done in a local laboratory for Egypt.
- Section 7.2.4.5: Added local laboratory will be used in Egypt for hematology, clinical chemistry and urinalysis.
- Section 7.2.5.1: added exemption to collect PK samples in Egypt.
- Section 9.3: added only safety samples will be collected in Egypt.
- Section 9.4: added data for laboratories sampling will be processed locally sites in Egypt.

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

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 are non-substantial and do not require IRB/IEC approval prior to implementation.

Amendment 1 (01-Dec-2015)

Amendment rationale

At the time of this amendment one patient has been randomized.

The purpose of this amendment is as follows:

1. Expand the study population by revising the inclusion criteria to allow for the enrollment of up to 120 patients who have prior history of iron chelation treatment in addition to the 120 chelation naïve patients originally planned, which would allow the continuation of the study if the recruitment of chelation naïve patients becomes challenging to complete in a reasonable timeframe.
2. Modify the secondary objectives:
   a. Revised sparse PK sampling schedule to reduce required blood draws and extensive/overnight hospital stays in this pediatric population to improve feasibility of study.
   b. Addition of new objective to evaluate the change in serum ferritin in both populations (chelation naïve and pre-treated chelation patients)
3. In order to optimize the patient safety and the toxicity monitoring, eligibility criteria and the management guidelines for cardiac and hepatic toxicity have been revised. In addition pregnant and nursing (lactating) women have been included as exclusion criteria in alignment with the prescribing Exjade information.
4. The amendment also provides the investigators with modified dose modification rules for hepatic toxicity management guidelines. Specific work-up guidelines for potential Drug Induced Liver Injury (DILI) cases has been added to the protocol, the dose modification rules as well as the follow-up evaluations for hepatic toxicities have also been updated accordingly.
5. ePRO assessment schedule has been updated.
6. Clarification to the concomitant medications and contraception as detailed below:
   a. Guidance was updated on the use of contraception, the sentence included in the exclusion criteria section regarding the definition of “not of child-bearing potential” has been removed as it was not appropriate to pediatric population but to menopause or post-sterilization women.
   b. Guidance was updated regarding the concomitant administration of deferasirox with CYP3A4, CYP1A2 and CYP1A2 substrates that have a narrow therapeutic index in alignment with the prescribing Exjade information
7. Statistical methods and data analysis section has been updated in alignment with the updated PK sampling and the inclusion of ICT pre-treated patients.
8. Additional guidance for iron chelation pre-treated patients starting dose has been added as Appendix 14.1.
9. Definition of a light meal added as Appendix 14.2.

In addition, clarifications were added to correct typographical errors and inconsistencies in different sections.

[redacted]

Changes to the protocol

Changes to List of Tables

- Renumbered Table 10-4 to Table 10-2 to be aligned with protocol updates

Changes to List of Abbreviations

- Updated to follow abbreviations used in protocol

Changes to Protocol summary

- Purpose and rationale, primary and secondary objectives, study design, population, inclusion and exclusion criteria, secondary endpoint assessments, other assessments and data analysis updated

Changes to Section 1.2.2 Overview of deferasirox granules

- Reference to Appendix 14.2 added

Changes to Section 2.1 Study rational and purpose

- Purpose of the study updated

Changes to Section 2.2 Rationale for the study design

- Iron chelation pre-treated patient population included
- Stratification updated

Changes to Section 2.3 Rationale for dose and regime selection

- Guidance for the study starting dose for the different population (naïve versus iron chelation pre-treated patients) included and allowed dose adjustments included

Changes to Section 3 Objectives and Endpoint

- Primary and Secondary objectives and endpoints updated

Changes to Section 4 Study Design.1 Description of study design

- Inclusion of a washout period during screening period for those iron chelation pre-treated patients.
- Stratification updated
- Guidance for the study starting dose for the different population (naïve versus iron chelation pre-treated patient) included

Changes to Section 5.1 Patient population

- Removing the sentence: Patient must be iron-chelation naïve.
- Iron chelation pre-treated patient population included

Changes to Section 5.2 Inclusion criteria

- Criterion #2 has been updated to include Iron chelation pre-treated patient population
- Criterion #3 has been updated to include PRBC clarification for pediatric population

Changes to Section 5.3 Exclusion criteria

- Criterion # 3 has been updated to exclude alanine/aspartate transaminase (ALT/AST) > 3.0 x ULN,
- Criterion #4 is no longer applicable to be aligned with the updated patient population

[redacted]

- Criterion #15 has been updated to clarify the definition of females of child bearing, and effective contraception language has been moved to Section 7.2.4.5.4.
- Added criterion #17 to exclude pregnant and nursing (lactating) women.
- Added criterion #18 to exclude patients with direct (conjugated) bilirubin >1.5 x ULN
- Added criterion #19 to exclude any patient with history or current diagnosis of cardiac disease

Changes to Section 6.1 Dosing regimen

- Inclusion of a washout period during screening period for those iron chelation pre-treated patients.
- Guidance for the study starting dose for the different population (naïve versus iron chelation pre-treated patient) and dose adjustment allowances added

Changes to Section 6.2 Dose modifications

- Inclusion of a dose adjustment guideline Table 6-2 instead of text. In addition, inclusion of hepatic dose modification wording in the table.

Added new Section 6.2.4 Follow up on potential drug-induced liver injury (DILI) cases

Added new Section 6.2.5 Anticipate risk and safety concerns of the study drug

Changes to Section 6.3 Prior and Concomitant medications

- Removed guidance to report blood transfusions on concomitant medication CRF (separate blood transfusion CRF page available).

Changes to Section 6.3.1 Permitted concomitant therapy requiring caution and/or action

- Guidance added related to the use of concomitant administration of deferasirox with CYP3A4, CYP1A2 and CYP1A2.

Changes to Section 6.3.2 Prohibited concomitant therapy

- Updated as per Exjade prescribing info.

Changes to Section 6.4.2 Treatment assignment or randomization

- Stratification updated

Changes to Section 6.4.3 Treatment blinding

- Removed blinding details

Changes to Table 7-1

- Include prior chelation assessment
- Assessment schedule updated for the SICT and palatability questionnaires.

Assessment schedule updated for the PK post-sampling. Changes to Section 7.1.1 Screening

- Ocular and Audiometry assessments guidance updated.

Changes to Section 7.1.2 Treatment period

- Guidance for the study starting dose for the different population (naïve versus iron chelation pre-treated patient) included.

[redacted]

Changes to Section 7.1.3 End of treatment visit including study completion and premature withdrawal

- Section removed and new Section 7.1.4 Withdrawal of consent added to provide additional guidance to patients withdrawal

Changes to Section 7.1.3.1 Criteria of premature patient withdrawal

- Section removed and new Section 7.1.3 Discontinuation of study treatment added to provide additional guidance to patients who discontinued study treatment

Section 7.1.3.2 PK Replacement Policy

- Section removed

Changes to Section 7.2.3 Patient/Observer Reported Outcomes

- Visits schedule updated for the SICT and palatability questionnaires.

Changes to Section 7.2.4.4 auditory and ocular examination

- Ocular and Audiometry assessments guidance updated.

Changes to Section 7.2.4.5.2 Clinical chemistry

- Creatinine clearance calculation clarified for patients who turn 18 years old during the study.

Changes to Section 7.2.4.5.4 Pregnancy and assessments of fertility

- Guidelines for pregnancy prevention updated
- Breastfeeding included as criteria for exclusion.

Changes to Section 7.2.4.6.1 Electrocardiogram (ECG)

- Documentation, labeling and storage of ECGs during the study have been updated.

Changes to Section 7.2.4.6.2 Echocardiography

- Documentation, labeling and storage of echocardiography during the study have been updated.

Changes to Section 7.2.5.1 PK blood sample collection and handling

- PK sampling time points updated

Remove of Section 7.2.5.3 PK parameters in alignment to the updated PK objective

Changes to Section 7.2.7 Resource utilization

- Sentence removed in alignment with the new PK sampling.
- Added Not Applicable to this section.

Changes to Section 8.1.1 Definitions and reporting

- Severity of adverse events used in this trial has been clarified.

Changes to Section 8.1.2.1 Definitions and reporting

- Clarification of severe event.

Changes to Section 8.4 Pregnancies

- Pregnancy reporting and management updated

[redacted]

Changes to Section 10.1.1 Full Analysis set

- Full Analysis set updated to include only ICT naïve patient
- Extended Full Analysis set added to include ICT pre-treated and naïve patients
- Updated stratification

Changes to Section 10.1.2 Safety set

- Safety set updated to include only ICT naïve patient
- Extended Safety set added to include ICT pre-treated and naïve patients

Changes to Section 10.1.3 Per Protocol set

- Per protocol set updated to include only ICT naïve patient

Changes to Section 10.1.4 Pharmacokinetics Analysis set

- Pharmacokinetics Analysis set updated in alignment with the updated PK sampling

Changes to Section 10.2 Patient demographics/other baseline characteristics

- Other background data updated to include prior chelation therapy and prior deferasirox chelation therapy

Changes to Section 10.3 Treatment (duration of exposure, concomitant therapies, percentage of planned dose taken)

- Section updated to include extended Safety set

Changes to Section 10.4 Primary objective

- Primary objective modified to include only ICT naïve patient

Changes to Section 10.4.1 Variables and analysis set

- Updated FAS to FAS-1

Changes to Section 10.4.2 Statistical methods of analysis

- Updated FAS to FAS-1
- Stratification factor updated

Changes to Section 10.4.3 Supportive analysis

- Primary analysis updated to include extended full analysis set

Changes to Section 10.5.1 To evaluate both formulations on patients' satisfaction and palatability using PRO/ObsPRO questionnaires

- Extended Full Analysis set included
- Scheduled of assessment for the SICT and Palatability questionnaires updated

Changes to Section 10.5.2 To evaluate both formulations on overall safety, measured by frequency and severity of adverse events and changes in laboratory values

- Extended Safety set included
- Clarified scoring of palatability questionnaire

Changes to Section 10.5.3 To evaluate compliance using a daily PRO/ObsPRO questionnaire

- Extended Full Analysis set included

[redacted]

- Removed handling of on-treatment AE section
- Updated standard descriptive analysis section

Changes to Section 10.5.3.1 Adverse Events (AEs)

- Added summary of type of AEs to be presented
- Added how incidence of AESI will be summarized

Changes to Section 10.5.4 Pharmacokinetics

- Section updated to include description of and compliance assessment Cmin and Cmax

Changes to Section 10.5.5.1 To evaluate pre-dose PK data to support the assessment of compliance

- Section updated

Remove of Section 10.4.7.2 Derivation PK parameters in alignment to the updated PK objective.

Changes to Section 10.5.5.2 Description of individual PK concentrations and parameters

- Section updated

Changes to Section 10.5.5.3 to explore PK/PD relationship

- Section updated

Remove of Section 10.4.7.5 Derivation of optimal PK sampling and trial simulation in alignment to the updated PK objective.

Changes to Section 10.6.1 Other safety data

- Extended Safety set included

Changes to Section 10.6.1.2 Vital signs and body weight

- Added vital signs and weight
- Renumbered Table 10-4 to Table 10-2 to align with protocol updates

Changes to Section 10.6.1.3 Auditory and Ocular assessment evaluations

- Added ‘Week’.

Changes to Section 10.7 sample size calculation

- Section updated to include the ICT pre-treated patients
- Renumbered Table 10-2 to Table 10-3 to be aligned with protocol updates.

Changes to Section 13 References (Available upon request)

- Updated references to align with protocol updates

Changes to Section 14.1 equivalent dose guidance

- Guidance added for starting dose for iron pre-treated patient
- Examples of light meal added

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

[redacted]

IRB/IEC/REB Approval

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

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

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

[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Transfusion-dependent hemoglobinopathies, such as thalassemia and sickle cell disease (SCD) represent a major global health burden, with > 300 000 infants born with SCD or thalassemia annually and iron overload is an inevitable clinical consequence for patients with transfusion-dependent anemias. Iron chelation therapy (ICT) is, therefore, an important and integral part of their supportive care.

Deferoxamine (DFO) was the only iron chelator available in the United States between 1962 and 2005. DFO is used as a subcutaneous infusion over 8 to 10 hours, 5 to 7 days a week, usually overnight. Many patients find DFO inconvenient and therefore adherence to this treatment is suboptimal. Deferasirox (Exjade®) became commercially available in the US in November 2005. As the first oral iron chelator, Exjade represented a substantial advancement in chelation treatment with many benefits over parenteral therapy, especially for pediatric patients and their families. Adherence to prescribed iron chelation is crucial to reduce or prevent iron overload and has been correlated with improved patient survival (Kushner et al 2001; Borgna-Pignatti et al 2004, Gabutti and Piga 1996). The goal of chelation is to maintain a serum ferritin of less than 1000 ng/ml, however most patients live with significantly higher serum ferritins due to compliance issues with their chelation therapy (Standard of Care Guidelines for Thalassemia 2012). Pediatric patients who are not adequately chelated risk delayed sexual maturation, retarded growth, progressive liver and heart disease, and a reduced life expectancy (Vichinsky 2008).

1.1.1 Overview of beta-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.

[redacted]

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 2008a).

1.1.2 Overview of sickle cell disease

Sickle cell disease is a multisystem disease, associated with episodes of acute illness and progressive organ damage, and is one of the most common severe monogenic disorders worldwide (Weatherall 2010). It is caused by the sickle mutation affecting the β-globin chain of hemoglobin. Erythrocytes containing hemoglobin S have irregular morphology and under low oxygen conditions, hemoglobin S polymerizes leading to 'sickled' cells. The pathogenesis of SCD relates to the shortened lifespan of the sickled erythrocytes (16 to 20 days in contrast to a lifespan of 120 days for normal erythrocytes) and adhesion of the sickled erythrocytes to the microvascular endothelium.

Transfusion of red blood cells on a chronic or intermittent basis is therefore important in the management of SCD. There is increasing evidence of the value of transfusions particularly in reducing the risk of stroke, vaso-occlusive events, acute chest syndrome, and growth failure in pediatric patients with SCD.

However, progressive iron loading and tissue injury is an inevitable result of frequent blood transfusions, although the pattern of hemosiderosis seems different to that described in thalassemia. In particular, most iron loading occurs in the liver, with little cardiac iron deposition.

Assessment of SCD-specific populations has demonstrated that elevated iron levels are associated with an increased frequency of acute events, hospitalizations, and death (Inati et al 2011).

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, and then rounded up or down to the nearest whole tablet according to the available strengths. The currently approved dose range is up to 40 mg/kg/day; the approved starting dose in US is 20 mg/kg/day. Outside the US 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

[redacted]

before the next meal. Administration requires dispersion of the tablets in an appropriate amount of water, orange juice or apple juice, which takes approximately 3 minutes.

Detailed information on preclinical and clinical evaluation of deferasirox DT is provided in the current [Investigators' Brochure].

1.2.2 Overview of deferasirox granules

Because of the chronic nature of chelation therapy and the importance of patient compliance, an improved deferasirox formulation for oral administration is being developed. The granule formulation to be used in this study contains the same active substance but has been strength-adjusted to achieve comparable exposure to the currently approved DT formulation. In addition several excipients have been modified. The granule formulation is packaged in aluminum foil pouches (alternatively referred to as stick packs or sachets). The stick packs will be available in three dosing strengths (90, 180 and 360 mg) and is dosed based on body weight, and then rounded up or down to the nearest whole stick pack according to the available strengths.

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

The granules should be administered by sprinkling the full dose on a soft food (e.g., yogurt, applesauce or warm porridge). The dose should be immediately and completely consumed, and not stored for future use. The granules should be taken once a day, preferably at the same time each day, and may be taken on an empty stomach or with a light meal, (please refer to Appendix 14.2).

2 Rationale

2.1 Study rationale and purpose

The availability of deferasirox DT 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 2006; Osborne et al 2007).

Since its approval, oral chelation with deferasirox DT has become well established, with many children never experiencing parenteral therapy. However prescribers, patients and their care-givers report limitations related to the convenience, palatability and GI tolerability of the current DT formulation, all factors that can play a significant role in the appropriate administration and compliance with chelation treatment, especially in children. (Haghpanah et al 2014) reported that 30% of adult patients treated with deferasirox DT complain about its undesirable taste. In the pediatric population, undesirable taste is expected to have even more impact on compliance then in the adult population. In a survey of more than 800 pediatricians on the perceived barriers to treatment completion in the pediatric population with chronic illnesses, the most frequent issues were 1. Frequency of dosing (91%), 2. Side effects of medication (88%) and 3. Unpleasant taste (84%) (Tuleu C 2011). Depending on the degree of palatability, compliance rates in the pediatric population can range from 11% to 93% (Tuleu C 2011).

[redacted]

As it is well established that long-term compliance to chelation therapy impacts outcome in thalassemia and other congenital anemias (Mednick et al 2010); improvements in convenience, palatability and tolerability of the formulation can bring substantial therapeutic benefit to patients.

Novartis has developed a new deferasirox formulation of granules and FCT with the same active substance as the deferasirox DT but with modified excipients.

After strength-adjustment, the granule formulation was shown to achieve the same overall exposure (AUClast and AUCinf) as the currently approved DT formulation in single-dose healthy volunteer studies; the peak serum concentrations (Cmax) were approximately 18% higher ([CICL670F2104]). In addition, a food effect study ([CICL670F2106]) indicated that the granule formulation can be taken either with or without a light meal.

The granule formulation of deferasirox, with its improved pharmaceutical properties and changes in composition, offers an opportunity to provide pediatric patients significant improvements such as:

- the freedom to take deferasirox with food (due to the absence of a substantial food effect as shown in ([CICL670F2106]) which obviates the requirement to take the drug on an empty stomach at least 30 minutes before food and therefore allows patients more convenience and flexibility in the scheduling and administration of their daily dose;
- a better tolerability profile as the exclusion of lactose and sodium lauryl sulfate in the new formulations alleviates concerns with use in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, glucose-galactose malabsorption or severe lactase deficiency and may improve the gastrointestinal tolerability of deferasirox;
- and overall, better convenience/palatability as a granule formulation.

It is for these reasons that Novartis will be providing all patients in the optional extension phase of the study with the granule formulation of deferasirox. Those on DT formulation in the core phase will switch to the granules in the optional extension phase. The purpose of the study is to:

- assess the compliance of the granule and the DT formulations in pediatric patients with iron overload treated over 24 and 48 weeks using stick pack/tablet count, pre-dose pharmacokinetic (PK) concentrations and a PRO/ObsRO questionnaire
- assess the clinical benefit due to improved compliance of the new formulation by measurements of serum ferritin levels for both formulations after 24 and 48 weeks of treatment.
- assess Patient / Observer Reported Outcomes (PRO/ObsRO) on palatability and treatment satisfaction, both factors influencing patient compliance and adherence.
- assess the safety of both formulations; renal toxicity (including renal failure), hepatic toxicity (including hepatic failure) and gastrointestinal hemorrhage will be actively monitored
- examine the pre-and post-dose concentrations of both formulations using sparse PK sampling.
- explore exposure-response (PK/PD) relationships for measures of safety and effectiveness

[redacted]

- assess long term safety of granules formulation during the optional extension phase consisting of up to 5 years for those who complete 48 weeks of core treatment phase

2.2 Rationale for the study design

This is an open-label, randomized, multicenter, two arm, phase II study. Female and male children and adolescents aged ≥ 2 and < 18 years at enrollment with any transfusion-dependent anemia requiring chelation therapy due to iron overload, and a treatment goal to reduce iron burden will be enrolled in this study.

Children and adolescents who are chelation naïve (sample size of at least96 patients) and those previously treated with iron chelators (maximum sample size of 120 patients) can participate in this study. The addition of the previously chelated patients will allow for an assessment of safety and efficacy between the two populations.

A washout period of 5 days prior to randomization is required for previously treated patients.

The randomization will be stratified by age groups and by prior ICT to ensure a balanced distribution of patients to the two treatment arms on stratifying factors: age groups (2 to <10 years (using ObsRO questionnaires) and 10 to <18 years (using PRO questionnaires) and prior ICT (Yes/No), as described in Section 4.1.

The core treatment duration of 48 weeks is considered sufficient to assess the compliance, serum ferritin, safety and patient / observer reported outcome (PRO/ObsRO) profiles of the two formulations.

The primary objective is to evaluate the impact in ICT naïve patients of these new pharmaceutical properties and changes in composition of the granule formulation on patient compliance and change in serum ferritin with study treatment during the core phase, after 24 weeks of treatment. It is well documented that compliance to chelation therapy is associated with clinical outcome (Standards of Care Guidelines for Thalassemia 2012). There are both direct and indirect methods to assess patient compliance, each method has advantages and disadvantages. Directly observed therapy, measurement of concentrations of drug or its metabolites in blood or urine, and detection or measurement in blood of a biologic marker are examples of direct methods of measures. Indirect methods include asking the patients about how easy it is for them to take prescribed medication, performing pill counts, collecting patient questionnaires, and assessing children's adherence by asking help of a caregiver (Osterberg and Blaschke 2005). In the absence of a preferred standard of measurement, multiple measures are often used to best assess this behavior (Partridge et al 2002).

In the core phase, treatment compliance of a pediatric population will be assessed using both direct and indirect methods:

- Adherence to the quantity of prescribed medication will be estimated via stick pack/tablet counts (known more generally throughout literature as "pill counts") in the core phase. Pill counts are known to overestimate adherence and obscure short-term variability in behavior within and between subjects, even in a population selected for high levels of compliance. The Hawthorne Effect has been observed in studies where patients are aware that a specific behavior is being monitored (Partridge, et al 2002). This phenomenon, in which subjects alter a behavior because they are aware that they are under observation, may be heightened

[redacted]

during pill counts performed during clinic visits. Such an effect may lead to pill dumping or similar activities by subjects to obscure lapses in their medication adherence (Rudd, et al 1989).

- Pre-dose PK levels will be measured in all patients at start of treatment and at regular intervals during the study period in the core phase to support the assessment of compliance. [Egypt: no PK samples will be collected due to restriction on export of samples]
- Adherence with medication regimen instructions will also be recorded via a patient daily questionnaire in the core phase. Requiring daily entries documenting medication behavior decreases recall bias from less frequent recording, but may also overestimate adherence behavior as patients tend to answer in a way they judge to be desirable to clinic staff. Asking medication consumption questions in a way that normalizes non-adherence can help mitigate some of this bias (Osterberg and Blaschke 2005). This method may also be subject to less of a Hawthorne Effect, particularly as patients become normalized to completing daily diary entries, which include questions about medication consumption.

The clinical benefit related to improved compliance will be assessed by changes in serum ferritin over time. The starting dose and the dose adjustment considerations in this study will take into account that the therapeutic goal is reduction of iron burden (as opposed to maintenance of iron burden). In clinical practice it is recommended to dose adjust for efficacy after 3 months of treatment based on trends in serum ferritin. A treatment duration of 48 weeks; with dose regimens aimed to reduce iron burden provides sufficient time to determine if improved compliance to treatment is leading to greater reduction in serum ferritin from baseline. A linear relationship between changes from baseline at 24 and 48 weeks of treatment has been established based on a pool of representative randomized studies (CICL670A0105, CICL670A0107, CICL670A0109 and CICL670A2206) with Serum ferritin available at 6 and 12 months for deferoxamine and deferasirox arms and is supportive of the primary analysis at 24 weeks of treatment. Furthermore data comparing deferoxamine and deferasirox suggest a self-reported adherence to deferasirox DT of 97% after one year. Therefore it can be assumed that the 6 month reported adherence will be very similar and can serve as a surrogate (Trachtenberg 2011). The rationale is also based on the demonstrated relationship of efficacy as assessed by serum ferritin with deferasirox dose, iron burden and continuous iron intake (Cappellini et al 2006).

In addition treatment satisfaction and palatability will be measured via age adapted validated questionnaires in the core phase.

Overall safety will be addressed by measuring the frequency and severity of adverse events, including renal toxicity, hepatic toxicity, and gastrointestinal hemorrhage; which will be actively monitored and changes in laboratory values. Additional safety assessments will include vital signs, physical exam, ophthalmological, audiometric, cardiac, and growth and development evaluations. Time points for assessing laboratory values have been chosen based on the current labeling information of deferasirox DT (Exjade®) in order to be as close as possible to the daily practice in administering the study treatment. The rationale to include the optional extension phase is to collect additional safety data about the new formulation and to provide access to the new deferasirox formulation (granules) to patients for continuity of treatment. This optional extension phase will give the patients who have participated and completed the 48 weeks core treatment phase as per protocol and do not have access to the new

[redacted]

formulation (granules or FCT) the possibility to extend treatment with deferasirox granules until there is local access to the new formulation (granules or FCT) or up to 5 years from entering extension phase, whichever occurs first. Patients must have demonstrated benefit to granules or DT in the core phase, and/or express the wish to continue in the optional extension phase on granules in order to start the optional extension phase.

2.3 Rationale for dose and regimen selection

Deferasirox is available in three dosing strengths (125, 250 and 500 mg for DT and 90, 180 and 360 mg for the granule formulation). 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/stick pack configuration. This dosing paradigm is consistent with how deferasirox DT (Exjade®) has been developed with regard to safety and efficacy.

Children and adolescents aged ≥ 2 and < 18 years at enrollment in the core phase with any transfusion-dependent anemia requiring chelation therapy due to iron overload will be randomized to either the DT or the granules treatment arm in a 1:1 ratio.

All ICT naïve patients randomized to the study will use either the DT starting dose of 20 mg/kg/day; which is the only approved starting dose in the US, and the commonly recommended starting dose in other countries, or the equivalent strength-adjusted granules starting dose of 14 mg/kg/day.

The deferasirox granules dose is strength-adjusted due to a higher bioavailability of this formulation compared to the dispersible tablets.

All ICT pre-treated patients will use a deferasirox DT or an equivalent strength-adjusted granules starting dose corresponding to their closest pre-washout dose, please refer to Appendix 14.1. Further dose adjustment, based on serum ferritin levels, safety parameters and investigator's judgment, will be allowed. 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.

In the optional extension phase, all patients will be provided the deferasirox formulation (granules). Patients on DT formulation during the core phase will receive the equivalent strength-adjusted granules dose corresponding to the last DT dose in the core phase taking dose adjustment guidelines into account (please refer to Table 6-2 and Appendix 14.1). Patients in granules during the core phase will continue on the same dose as was given at the end of the core phase taking dose adjustment guidelines into account. Please refer to Table 6-2 as 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		
• To evaluate both formulations on patient compliance, using stick pack/tablet count over 24 weeks of treatment in ICT naïve patients during core phase	• Compliance measured by stick pack/tablet count over 24 weeks of treatment (i.e. assessed at week 25 visit)	Refer to Section 10.4
• To evaluate the change from baseline in serum ferritin after 24 weeks of treatment for both formulations in ICT naïve patients during the core phase	• Change from baseline in serum ferritin after 24 weeks of treatment (i.e. serum ferritin at week 25 visit)	Refer to Section 10.4
Secondary (Core phase)		
To evaluate both formulations on change in serum ferritin and compliance in ICT naive patients, after 48 weeks of treatment	• Compliance measured by stick pack/tablet count after 48 weeks of treatment • Change from baseline in serum ferritin after 48 weeks of treatment	Refer to Section 10.5.1
To evaluate both formulations on change in serum ferritin after 24 weeks and 48 weeks of treatment in ICT naïve and pre-treated patients	Change from baseline in serum ferritin after 24 weeks (i.e. assessed at week 25 visit) and 48 weeks of treatment	Refer to Section 10.5.2
To evaluate both formulations on patient satisfaction and palatability using Patient / Observer Reported Outcomes (PRO/ObsRO) questionnaires	Domain scores of treatment satisfaction and palatability over time	Refer to Section 10.5.3
To evaluate both formulations on overall safety	Overall safety, as measured by frequency and severity of adverse events (including active monitoring for renal toxicity; including renal failure, hepatic toxicity; including hepatic failure, and gastrointestinal hemorrhage), and changes in laboratory values from baseline (serum creatinine, creatinine clearance, ALT, AST, RBC and WBC). In addition, vital signs, physical, ophthalmological, audiometric, cardiac, and growth and development evaluations will be assessed.	Refer to Section 10.5.4
To evaluate compliance using a daily PRO/ObsRO questionnaire	Rate of dosing instructions deviations (doses missed / not taken at the same time every day)	Refer to Section 10.5.5

Objective	Endpoint	Analysis
To evaluate pre-dose PK data to support the assessment of compliance	Pre-dose deferasirox concentrations in all patients [except Egypt] at Weeks 1, 3, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41 and 45 visits(13 samples)	Refer to Section 10.5.6.1
Post-dose data to be analyzed along with pre-dose PK data	Post-dose deferasirox concentrations between 2 and 4 hours post-dose at Weeks 5 and 9 (2 samples)	Refer to Section 10.5.6.2
To explore exposure-response relationships for measures of safety and effectiveness	Serum creatinine change from baseline, notable serum creatinine event, serum creatinine clearance change from baseline and notable serum creatinine clearance events, urine protein creatinine ratio change from baseline and serum ferritin change from baseline, in relationship to pre- and post-dose deferasirox concentrations.	Refer to Section 10.5.6.3
Secondary (Optional Extension phase)		
To assess additional safety data about new formulation (granules) in pediatric population	Overall safety, as measured by frequency and severity of adverse events (including active monitoring for renal toxicity; including renal failure, hepatic toxicity; including hepatic failure, and gastrointestinal hemorrhage), and changes in laboratory values from baseline (serum creatinine, creatinine clearance, ALT, AST, RBC and WBC). In addition, vital signs, physical, ophthalmological, audiometric, and growth and development evaluations will be assessed.	Refer to Section 10.5.4 and Section 10.6.1

[redacted]

4 Study design

4.1 Description of study design

This is a randomized, open-label, multicenter, two arm, phase II study to evaluate treatment compliance and change in serum ferritin over time of a deferasirox granule formulation and a deferasirox DT formulation in children and adolescents aged ≥ 2 and < 18 years at enrollment with any transfusion-dependent anemia requiring chelation therapy due to iron overload, and having a treatment goal to reduce iron burden as measured by serum ferritin.

It is a pre-requisite for the patient to provide written consent/assent to participate in this study. Consent will be obtained from patients, parent(s) or legal guardians. Investigators will also obtain patient's consent/assent according to local guidelines. This must be in place prior to performing any study-related procedures or assessments, including those described at the screening visits (Table 7-1).

As described in Figure 4-1, a screening period (from Day -21) will be used to assess eligibility of patients and will consist of two visits at least 7 days apart. All inclusion and exclusion criteria must be evaluated and documented in the source documents as being met and the results of all screening assessments must be available and reviewed by the investigator. Patients whose eligibility is confirmed will be enrolled and any current chelation therapy will be discontinued to undergo a 5-day chelation washout period (only applicable to patients previously treated with iron chelation therapy) prior to commencing a 48-week randomized treatment period with either deferasirox DT (taken as per local label) or deferasirox granule formulation (taken with or without a light meal) beginning on Day 1.

All participants who have completed the core study as per protocol and who do not have local access to the new formulation (granules or FCT) have the option to continue to the optional extension phase of the study where they will be provided with granules until there is local access to the new formulation (granules or FCT) or up to 5 years from beginning extension phase, whichever occurs first. Patients on DT in the core phase will switch to granules in the optional extension, whereas those on granules in the core phase will remain on granules in the optional extension phase. Patients must have demonstrated benefit to granules or DT in the core phase, and/or express the wish to continue in the optional extension phase on granules in order to start the optional extension phase.

An end of treatment visit (EOT) will occur within 7 days of last dose of study drug and a Safety Follow-up 30 days following the last dose of study drug.

- For patients participating in the optional extension phase, end of study and safety follow-up will be performed within 30 days last dose was given in the optional extension phase.
- For patients not participating in the optional extension phase, end of study and safety follow up will occur within 30 days last dose was given in the core phase.

Randomization will be stratified using an interactive voice/web response system (IVRS/IWRS). The stratification will be defined by age groups (2 to <10 years, 10 to <18 years) and by prior ICT (Yes/No). Details on stratification will be outlined in the study manual provided by the IVRS vendor.

[redacted]

At the start of treatment, ICT naïve patients will receive either deferasirox DT 20 mg/kg once daily or deferasirox granules 14 mg/kg once daily.

All ICT pre-treated patients will use a deferasirox DT or an equivalent strength-adjusted granules starting dose corresponding to their closest pre-washout dose, please refer to Appendix 14.1.

Study treatment should be administered by the patient once per day and the PRO questionnaires be completed by all patients aged between 10 and <18 years as per instructions provided by the investigator. During the 48 weeks treatment period, patients will return to the site for study assessments weekly for the first 3 weeks and then every 4 weeks starting from week 5 until the end of treatment visit, as specified in Table 7-1.

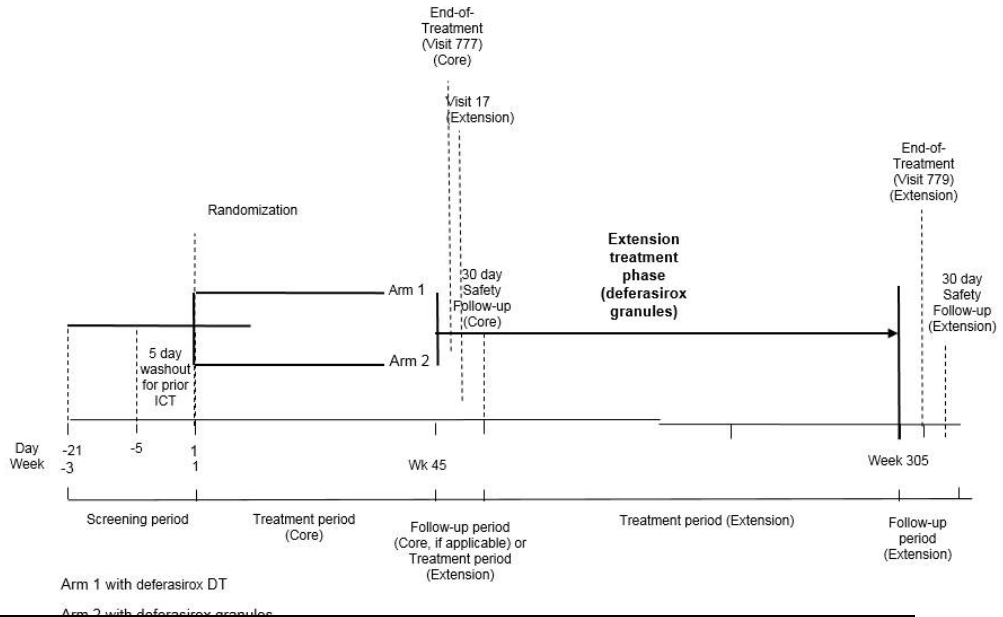
In the optional extension phase, all patients will be provided with the granules. Patients on DT formulation during the core phase will receive the equivalent strength-adjusted granules dose corresponding to the last DT dose in the core phase taking dose adjustment guidelines into account (please refer to Table 6-2 and Appendix 14.1). Patients in granules during the core phase will continue on the same dose as was given at the end of the core phase taking dose adjustment guidelines into account. Please refer to Table 6-2 as applicable.

Patients who discontinue study treatment before completing the core or optional extension phase should be scheduled for an end of treatment visit within 7 days of the last dose of study treatment, at which time all of the assessments listed for the end of treatment (Visit 777 (for the core) or Visit 779 (for the optional extension)) will be performed.

All patients, regardless if they discontinue the study treatment early or per protocol, will be contacted for safety evaluations for 30 days after the last dose of study treatment.

One interim analysis has been added to allow for early analysis of the core phase data if requested by the health authority.

Figure 4-1 Study schema



[redacted]

4.2 Timing of interim analyses and design adaptations

One interim analysis has been added to allow for early analysis of the data if requested by the health authority. All the analyses included in the interim analysis will be descriptive. The IA will be performed by the Novartis study team. No decisions regarding the future course of the trial is anticipated at the time of the IA and the trial will continue.

All patients randomized in the study and who have completed a minimum of 12 weeks of treatment exposure or discontinued from treatment core phase at the time of the cut-off date will be included in the interim analysis (Section 10.7).

The cut-off for the primary analysis will be 24 weeks after approximately 96 ICT naive patients have been randomized.

The core data analysis is planned when all patients have completed their 48 week study treatment in the core phase including safety follow-up (if applicable).

4.3 Definition of end of the study

Completion of this study as a whole will occur upon the availability and accuracy verification of the last data point required for statistical analysis of the optional extension phase. Data collection will terminate and End of Study will be declared after all patients have completed the treatment phase of the optional extension phase (up to 305 weeks) including the safety follow-up period (30 days after treatment discontinuation).

4.4 Early study termination

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

4.5 Rationale for Public Health Emergency mitigation procedures

During a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, mitigation procedures to ensure participant safety and trial integrity are listed in relevant sections. Notification of the Public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

5 Population

5.1 Patient population

Up to 216 ICT naïve and pre-treated (at least 96 ICT naïve and up to 120 pre-treated) male and female children and adolescents aged ≥ 2 and < 18 years at enrollment with any transfusion-dependent anemia requiring chelation therapy due to iron overload, and a treatment goal to

[redacted]

reduce iron burden will be included in this study. At least 96 (48 per treatment arm) patients should be iron 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 enrollment in the study.

5.2 Inclusion criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria at screening Visit 1 and 2 unless otherwise specified:

1. Written informed consent/assent before any study-specific procedures. Consent will be obtained from parent(s) or legal guardians. Investigators will also obtain consent/assent of patients according to local guidelines.
2. Male and female children and adolescents aged ≥ 2 and < 18 years. **[France: Male and female children and adolescent aged ≥ 2 and < 18 years old, however children aged ≥ 2 and ≤ 6years can be enrolled only when deferoxamine treatment is contraindicated or inadequate in these patients as per investigator decision**. Applicable to core phase only. Once in the core phase patients can turn 18 years and still be considered eligible, also for participation in the optional extension phase.
3. Any transfusion-dependent anemia associated with iron overload requiring iron chelation therapy and with a history of transfusion of approximately 20 PRBC units and a treatment goal to reduce iron burden (300mL PRBC = 1 unit in adults whereas 4 ml/kg PRBC is considered 1 unit for children).
4. Serum ferritin > 1000 ng/mL, measured at screening Visit 1 and screening Visit 2 (the mean will be used for eligibility criteria).
5. Patient has to have participated and completed the 48 weeks core phase treatment as per protocol (For optional extension phase eligibility only).

5.3 Exclusion criteria

1. Creatinine clearance below the contraindication limit in the locally approved prescribing information (using Schwartz formula) at screening visit 1 or screening visit 2.
2. Serum creatinine > 1.5 xULN at screening Visit 1 or screening Visit 2.
3. ALT and/or AST > 3.0 x ULN at screening visit 1 or screening visit 2.
4. **(Criterion no longer applicable, removed as part of Amendment 1):** ~~Prior iron chelation therapy~~
5. Liver disease with severity of Child-Pugh class B or C.
6. Significant proteinuria as indicated by a urinary protein/creatinine ratio > 0.5 mg/mg in a second morning urine sample at screening Visit 1 or screening Visit 2.
7. 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).
8. 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]

9. 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.
10. Patients with a known history of HIV seropositivity (Elisa or Western blot).
11. 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 or squamous cell carcinoma of the skin.
12. Patients participating in another clinical trial or receiving an investigational drug.
13. History of hypersensitivity to any of the study drug or excipients.
14. 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.).
15. Female patients of childbearing potential (e.g. are menstruating) who do not agree to abstinence or, if sexually active, do not agree to the use of contraception as defined in Section 7.2.4.6.4.
16. For prohibited medication please refer to Section 6.3.2
17. Pregnant or nursing (lactating) women
18. Direct (conjugated) bilirubin >2 x ULN at screening visit 1 or screening visit 2.
19. History or current diagnosis of cardiac disease indicating significant risk of safety for patients participating in the study such as uncontrolled or significant cardiac disease, including any of the following:
    - Clinically significant (symptomatic) cardiac arrhythmias (e.g., sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker).
20. Local access to new formulation (granules or FCT) is available (For optional extension phase eligibility only).

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 (during core phase).
- Deferasirox granules will be provided as stick packs containing 90 mg, 180 mg and 360 mg granules for oral use (during core and optional extension phase).

6.1.1 Dosing regimen

Having completed the Screening period (including the 5-day chelation washout period for patients previously treated with iron chelators), eligible patients for the core phase will be randomized to one of the following Treatment Arms in a ratio of 1:1:

- Treatment Arm 1 with deferasirox DT
- Treatment Arm 2 with deferasirox granules

[redacted]

At the start of treatment, ICT naïve patients will receive either deferasirox DT 20 mg/kg once daily or deferasirox granules 14 mg/kg once daily. All ICT pre-treated patients will use a deferasirox DT or an equivalent strength-adjusted granules starting dose corresponding to their closest pre-washout dose, please refer to Appendix 14.1.

When creatinine clearance at study start is ≥40ml/min and <60 ml/min (where locally applicable), starting dose needs to be reduced by 50%. This means for treatment naive patients that they will need to start at 10 mg/kg for DT and 7 mg/kg for granules. For pretreated patients, they will need to start at 50% of the pre-washout dose when creatinine clearance ≥40ml/min and <60 ml/min during at least one screening visit. For patients with an already existing reduced creatinine clearance (≥40ml/min and <60 ml/min before study start), a dose reduction of 50% is only necessary when this was not already performed.

In the optional extension phase, all patients will be provided with the granules at visit 17. Patients on DT formulation during the core phase will receive the equivalent strength-adjusted granules dose corresponding to the last DT dose in the core phase taking dose adjustment guidelines into account (please refer to Table 6-2 and Appendix 14.1). Patients in granules during the core phase will continue on the same dose as was given at the end of the core phase taking dose adjustment guidelines into account. Please refer to Table 6-2 as applicable.

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/stick pack according to the available strengths of deferasirox formulations (125 mg, 250 mg and 500 mg for the DT and 90 mg, 180 mg and 360 mg for the granules, see Appendix 14.1).

Recommended 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 - 7.0 mg/kg/day for deferasirox granules.

During the optional extension phase, dose adjustments in steps of 3.5 to 7.0 mg/kg for deferasirox granules are also only allowed every 3 months.

Dose adjustments based on safety are allowed at any time point in the study. The maximum dose of deferasirox DT will be 40 mg/kg/day and the maximum dose of deferasirox granules will be 28 mg/kg/day.

The starting dose and the dose adjustment considerations must take into account that the therapeutic goal is reduction of iron burden (as opposed to maintenance of iron burden).

The investigator should instruct the patient and/or the legal patient's representative to take the study treatment as prescribed. All doses planned and prescribed to the patient and all dose changes, including the reasons for change, during the study must be recorded in the electronic Case Report Form (eCRF).

During the regular study visits, the investigator or pharmacist will dispense to the patient and/or legal patient's representative, an appropriate number of deferasirox tablets / stick packs depending on the patients calculated dose and Treatment Arm assignment. The number of tablets / stick packs of each strength dispensed will be recorded in the Study Drug Dosing Log. Each time the deferasirox study treatment is dispensed to the patient and/or legal patient's

[redacted]

representative, the investigator will provide detailed instructions on how to prepare and administer the dose. Patients / caregivers will be instructed to take / to administer the assigned amount of study drug and to return all unused study medication including empty stick packs and bottles at their next visit. Study medication returned at each visit will be counted and unused study medication will be recorded by the investigator/ pharmacist involved in the study. Drug accountability will be noted by the field monitor during site visits and at the completion of the trial.

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 randomized to Treatment arm 1 will take the deferasirox DT every day on an empty stomach, at least 30 minutes before the next meal. The patient will disperse the required number of deferasirox tablets in an appropriate amount 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.

Patients randomized to Treatment arm 2 should administer the granules by sprinkling the full dose on a soft food (e.g., yogurt, applesauce or warm porridge). The dose should be immediately and completely consumed, and not stored for future use. The granules should be taken once a day, preferably at the same time each day, and may be taken on an empty stomach or with a light meal.

It is recommended that the doses be timed such that they occur at almost the same time each day. For example, if the patient took the study medication at 8:00AM on first day of treatment, the subsequent dose would also be taken at approximately 8:00AM on the next day, and so on.

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Starting Dose*	Dose adjustment steps	Maximum dose	Frequency
Deferasirox DT	Dispersible tablets, p.o.	20 mg/kg/day (10 mg/kg/day when creatinine clearance ≥ 40 and <60 ml/min)	+/- 5-10 mg/kg/day	40 mg/kg/day	Once daily
Deferasirox granules	Granules, p.o.	14 mg/kg/day (7 mg/kg/day when creatinine clearance ≥ 40 and <60 ml/min)	+/- 3.5-7.0 mg/kg/day	28 mg/kg/day	Once daily

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

[redacted]

6.1.2 Treatment duration

The total duration of study treatment during the core phase is 48 weeks. The total duration of the core phase is approximately 55 weeks (including the Screening, Treatment and Safety Follow-up visits).

The maximum duration of the optional extension phase will be 5 years. This optional extension phase will give the patients who have participated and completed the 48 weeks core treatment phase as per protocol and do not have access to the new formulation (granules or FCT) the possibility to extend treatment with deferasirox granules until there is local access to the new formulation (granules or FCT) or up to 5 years from entering extension phase, whichever occurs first. Patients must have demonstrated benefit to granules or DT in the core phase, and/or express the wish to continue in the optional extension phase on granules in order to start the optional extension phase.

6.2 Dose modifications

6.2.1 Permitted study drug adjustments

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.

For all cases where a dose adjustment is considered necessary but is not covered in the following sections, the investigator must 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.

Any dose-adjustments for any reason, specified by the protocol (such as safety, efficacy, other) or not, must be recorded on the dosage administration record eCRF together with the reason for each dose-adjustment. It is important to keep accurate dose-adjustment records to enable an adequate evaluation of the co-primary endpoint of compliance.

A summary of dose adjustment guidelines is presented in Table 6-2.

[redacted]

Table 6-2 Criteria for interruption and re-initiation of Deferasirox treatment

Dose modifications for deferasirox	
Body weight	
Increase/decrease of weight by >10% compared to Visit 3 (baseline weight) or body weight at last dose adjustment due to change in patient's body weight	Dose of study medication needs to be adapted using Dosing Table (provided in Appendix 14.2). Only when weight changes with >10% compared to baseline weight or body weight at last dose adjustment due to change in patient's body weight, dose needs to be adapted. Smaller variations in body weight (<10%) during study, does not require adjustments in dose. In this case, baseline body weight can be used to calculate correct dose.
Investigations (Renal)	
Serum creatinine and/or creatinine clearance	
Single increase in serum creatinine ≥33%	Maintain dose level and repeat the assessment at next visit as clinically indicated
For pediatric patients: - Single increase ≥33% above baseline value (visit 3/week1) and >ULN For adult patients: - Increases by 33% or more above the baseline (visit 3/week1) measurement, repeat the serum creatinine within 1 week, and if still elevated by 33% or more	Deferasirox dose reduction by 10 mg/kg/day for the DT and by 7 mg/kg/day for the granules is necessary.
	If after a dose reduction, a progressive increase in serum creatinine beyond the ULN is observed, a treatment interruption is mandated. If after dose reduction/interruption, resolution of serum creatinine occurs (<33%) at the next study visit and within normal limits, dose can be resumed again at 100%. If increase in serum creatinine reoccurs again within 2 months according to guidelines above, therapy needs to be reduced to 50% of the last dose. After 2 months, if the serum creatinine increase does not recur, study medication can be returned to 100% of the last dose.
Creatinine clearance between 40 and less 60 mL/min	Reduce dose with 50%. If after dose reduction, resolution of creatinine clearance occurs (>60 ml/min), dose can be resumed again at 100%.
Creatinine clearance < 40 mL/min or serum creatinine increases > 2 times the age-appropriate ULN	Deferasirox therapy must be discontinued

[redacted]

Dose modifications for deferasirox	
Investigations (Hepatic)	
Isolated direct (conjugated) Bilirubin elevation	
> ULN – 2 x ULN	Maintain dose level
> 2 - 3.0 x ULN	Omit dose with weekly monitoring of LFTs[a], or more frequently if clinically indicated, until resolved to ≤ 2.0 x ULN: If resolved in ≤ 14 days, then maintain dose level If resolved in > 14 days, then dose reduction of 5 or 10 mg/kg/day for deferasirox DT and of 3.5 or 7 mg/kg/day for deferasirox granules.
> 3.0 - 10.0 x ULN*	Omit dose with weekly monitoring of LFTs[a], or more frequently if clinically indicated, until resolved to ≤ 2.0 x ULN: If resolved in ≤ 14 days, then dose reduction of 5 or 10 mg/kg/day for deferasirox DT and of 3.5 or 7 mg/kg/day for deferasirox granules. If resolved in > 14 days, then discontinue patient from study drug treatment. The patient needs to be monitored weekly (including LFTs[a]), or more frequently if clinically indicated, until direct (conjugated) bilirubin have resolved to baseline or stabilization over 4 weeks.
> 10.0 x ULN*	Discontinue patient from study drug treatment The patient needs to be monitored weekly (including LFTs[a]), or more frequently if clinically indicated, until direct (conjugated) bilirubin have resolved to baseline or stabilization over 4 weeks.
Isolated AST or ALT elevation	
> ULN - 3.0 x ULN	Maintain dose level
> 3.0 - 5.0 x ULN For patients with baseline value ≤ 3.0 x ULN	Maintain dose level. Repeat LFTs[a] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs[a] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN
For patients with baseline value > 3.0 -5.0 x ULN	Maintain dose level

[redacted]

Dose modifications for deferasirox	
> 5.0 - 10.0 x ULN For patients with baseline value ≤ 3.0 x ULN	Omit dose. Repeat LFTs[a] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[a] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN If resolved in ≤ 14 days, maintain dose level If resolved in > 14 days, then dose reduction of 5 or 10 mg/kg/day for deferasirox DT and of 3.5 or 7 mg/kg/day for deferasirox granules.
For patients with baseline value > 3.0 -5.0 x ULN	Maintain dose level. Repeat LFTs[a] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs[a], weekly, or more frequently if clinically indicated, until resolved to ≤ 5.0 x ULN
> 10.0 - 20.0 x ULN	Omit dose. Repeat LFTs[a] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[a] weekly, or more frequently if clinically indicated, until resolved to ≤ baseline. Then dose reduction of 5 or 10 mg/kg/day for deferasirox DT and of 3.5 or 7 mg/kg/day for deferasirox granules.
> 20.0 x ULN	Discontinue patient from study drug treatment Repeat LFTs[a] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[a] weekly, or more frequently if clinically indicated, until resolved to baseline or stabilization over 4 weeks.
Combined [b] elevations of AST or ALT and bilirubin (direct (conjugated) and/or total)	
For patients with normal baseline ALT or AST or direct (conjugated) bilirubin value: AST or ALT >3.0xULN combined with direct (conjugated) bilirubin >2.0 x ULN without evidence of cholestasis[c] OR (Note to study team: If supported by available data) For patients with elevated baseline AST or ALT or direct (conjugated)bilirubin value [AST or ALT>2x baseline AND > 3.0 xULN] OR [AST or ALT > 8.0 xULN], whichever is lower, combined with [direct (conjugated) bilirubin >2x baseline AND >2.0 xULN	Permanently discontinue patient from study drug treatment. Repeat as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTs[a]), or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilization over 4 weeks. Refer to Section 6.3.2 for additional follow-up evaluations as applicable.

[redacted]

Dose modifications for deferasirox	
For patients with normal baseline ALT or AST or total bilirubin value: AST or ALT >3.0xULN combined with total bilirubin >2.0xULN without evidence of cholestasis[c] OR (Note to study team: If supported by available data) For patients with elevated baseline AST or ALT or total bilirubin value [AST or ALT>2x baseline AND >3.0xULN] OR [AST or ALT>8.0 ULN], whichever is lower, combined with total bilirubin >2x baseline AND >2.0xULN	Permanently discontinue patient from study drug treatment. Repeat as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTs[a]), or more frequently if clinically indicated until AST, ALT, or bilirubin have resolved to baseline or stabilization over 4 weeks. Refer to Section 6.3.2 for additional follow-up evaluations as applicable.
Hepatic impairment	
Moderate hepatic impairment (Child-Pugh Class B)	The study medication will be interrupted and patient monitored. If liver disease prognosis improves, deferasirox can be reintroduced at 10 mg/kg/day for DT and at 7 mg/kg/day for granules or 50% of previous dose, whichever is less. While monitoring continues, dose may be increased by 5 mg/kg/day for DT and by 3.5 mg/kg/day for granules every 2 weeks, to a maximum of 50% of patient's previous dose if the investigator determines that dose increase is in the best interest of the patient. Study medication must be used with caution in such patients.
In patients who develop severe hepatic impairment (Child-Pugh Class C) during the study	Study medication must be discontinued.
Other dose modifications	
Changes in Serum Ferritin	
	The dose of deferasirox DT or granules should be adjusted if necessary every 3 months based on the trends in serum ferritin and investigator's judgement. ICT naïve patients can adapt dose after 4 weeks. Dose adjustments need to be made in steps of 5 or 10 mg/kg/day for deferasirox DT and of 3.5 or 7 mg/kg/day for deferasirox granules and are to be tailored to the individual patient's response and the therapeutic goal of (reduction of iron burden). In patients not adequately controlled with deferasirox DT doses of 30 mg/kg/day, doses of up to 40 mg/kg/day may be considered. In patients not adequately controlled with deferasirox granules doses of 21 mg/kg/day, doses of up to 28 mg/kg/day may be considered. The starting dose and the dose adjustment considerations must take into account that the therapeutic goal is reduction of iron burden (as opposed to maintenance of iron burden). Doses above 40 mg/kg/day for deferasirox DT and above 28 mg for deferasirox granules are not allowed.

[redacted]

Dose modifications for deferasirox	
500 – 1000 ng/mL	Dose reductions in steps of 5 to 10 mg/kg/day for deferasirox DT and of 3.5 or 7 mg/kg/day for deferasirox granules is required to maintain serum ferritin levels within the target range.
< 500 ng/ml	Interruption of study treatment is required until serum ferritin rises above 500 ng/mL
Changes in urine protein/creatinine ratio	
For patients who develop proteinuria or a worsening of pre-existing proteinuria (assessed by a dipstick) at any visit, urine samples should be collected and assessed by the central laboratory. [Egypt: Local laboratory] In case of a single increase of the urinary protein/creatinine ratio the assessment should be repeated at the next visit.	
> 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 dose reduction by 50% When resolution of UPCR (<0.5mg/mg) at the next study visit, dose can be resumed again at 100% If increase in UPCR >0.5mg/mg recurs again within 2 months after initial increase, therapy needs to be reduced to 50% of the last dose. If increase in UPCR does not recur after 2 months at reduced dose (50%) , study medication can be returned to 100% of the last dose
> 1.0 (mg/mg) in one single second-void urine samples.	Interrupt study treatment. When resolution of increase in UPCR (<0.5mg/mg) at the next study visit, dose can be resumed again at 50% of the last dose. If increase in UPCR does not recur after 1 month at reduced dose (50%), study medication can be returned to 100% of the last dose.
In case of persistent proteinuria	Study treatment may be discontinued if the investigator believes it is in the best interest of the patient. Novartis may be contacted by the investigator to discuss dosing options if the investigator so desires. Dose adjustment will be based on laboratory results. [Egypt: Local laboratory]
Severe skin reactions	
Severe skin reactions, including Stevens-Johnson syndrome (SJS) and Toxic epidermal necrosis (TEN)	Have to be reported during Exjade therapy. If SJS or TEN are suspected, study treatment must be immediately discontinued and not be reintroduced
Skin Rash (other than SJS)	
For skin rash of mild/moderate severity (defined as those causing minimal symptoms which require no or minimal supportive treatment)	Study drug should be continued without dose adjustment. The skin rash may resolve spontaneously without further intervention. If the rash persists for >1 week or becomes more severe, treatment with study drug will be interrupted. After the rash resolves, resume study drug at 50% of patient's last dose. If the rash does not recur, increase dose back to 100% of patients dose after 2 weeks.

[redacted]

Dose modifications for deferasirox	
Severe rash (distressing symptoms requiring discontinuation and/or systemic steroids)	Discontinue treatment until resolution of rash. Once the rash has resolved, resume at 50% of patient's dose. If necessary, a brief course of oral steroids may be given concurrently with resumption of study drug. If the rash does not recur, increase by steps of 5 mg/kg/day for deferasirox DT and of 3.5 mg/kg/day for deferasirox granules every 2 weeks until patient's last dose is achieved. If the rash recurs, study treatment may be discontinued if the investigator believes that it is in the best interest of the patient. Novartis may be contacted by the investigator to discuss dosing options if the investigator so desires
Dose modification criteria for auditory and ocular disturbances	
Auditory (decreased hearing) and ocular (lens opacities) disturbances have been reported with deferasirox treatment.	Auditory and ophthalmic testing (including fundoscopy) is required before the start of deferasirox treatment. If disturbances are noted dose reduction or interruption may be considered and a repeated testing performed as per investigator's judgement.
Dose modification criteria for hypersensitivity reactions	
Cases of serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been reported in patients receiving deferasirox, with the onset of the reaction occurring in the majority of cases within the first month of treatment.	If reactions are severe, deferasirox should be discontinued and appropriate medical intervention instituted. Deferasirox should not be reintroduced in patients who have experienced previous hypersensitivity reactions on Exjade due to the risk of anaphylactic shock
Dose modification criteria for cytopenias	
Unexpected Cytopenias	There have been post-marketing reports (both spontaneous and from clinical trials) of cytopenias in patients treated with deferasirox. Most of these patients had pre-existing hematological disorders that are frequently associated with bone marrow failure. The relationship of these episodes to treatment with deferasirox is uncertain. In line with the standard clinical management of such hematological disorders, blood counts should be monitored regularly. Dose interruption of treatment with deferasirox should be considered in patients who develop unexplained cytopenia. Reintroduction of therapy with deferasirox may be considered (as per investigator decision), once the cause of the cytopenia has been identified.

[redacted]

Dose modifications for deferasirox	
Gastrointestinal disturbances	
Gastrointestinal issues (including diarrhea, constipation, nausea, vomiting and abdominal pain)	Some basic recommendations, based on practical experience, can be made to guide physicians in managing patients who experience diarrhea. At the first sign of diarrhea, consider anti-diarrheal medication such as loperamide. Remind the patient to discontinue any laxative preparations or stool softeners they may be taking and to eat small, frequent meals. Determine if the patient is lactose intolerant. Deferasirox DT contains lactose in the formulation so supplemental lactase may benefit the patient; however the deferasirox granules do 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. Should the gastrointestinal issues (including diarrhea, constipation, nausea, vomiting and abdominal pain) persist, study drug may be discontinued if the investigator believes it is in the best interest of the patient. Novartis may be contacted by the investigator to discuss dosing options if the investigator so desires.
All dose modifications should be based on the worst preceding toxicity. [a] Core LFTs consist of ALT, AST, GGT, total bilirubin (fractionated [direct and indirect], if direct (conjugated) bilirubin > 2.0 x ULN), and alkaline phosphatase (fractionated [quantification of isoforms], if alkaline phosphatase > 2.0 x ULN.) [b] "Combined" defined as direct (conjugated) bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold If combined elevations of AST or ALT and direct (conjugated) bilirubin do not meet the defined thresholds, please follow the instructions for isolated elevation of direct (conjugated) bilirubin and isolated elevation of AST/ALT, and take a conservative action based on the degree of the elevations (e.g. discontinue treatment at the situation when omit dose is needed for one parameter and discontinue treatment is required for another parameter). After all elevations resolve to the defined thresholds that allow treatment re-initiation, re-start the treatment either at the same dose or at one dose lower if meeting a criterion for dose reduction [c] "Cholestasis" defined as ALP elevation (>2.0 xULN and R value <2) in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes the relative pattern of ALT and/or ALP elevation is due to cholestatic or hepatocellular liver injury * Note: If total bilirubin > 3.0 x ULN is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then dose reduction of 5 or 10 mg/kg/day for deferasirox DT and of 3.5 or 7 mg/kg/day for deferasirox granules and continue treatment at the discretion of the investigator.	

[redacted]

6.2.2 Treatment interruption and treatment discontinuation

Patients who permanently discontinue study drug before completing the core phase should be scheduled for an End of Treatment visit within 7 days from last dose, at which time all of the assessments listed for the End of treatment visit will be performed. Patients discontinuing the optional extension phase at any time need to be scheduled for an End of Treatment visit within 7 days of the last dose. The End of Treatment eCRF should be completed for all patients at the end of both the core and the optional extension treatment phases, documenting the date and reason for stopping randomized study treatment. For the core phase the patient will be asked if they are continuing on to the optional extension phase. 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, will be contacted by the investigational site for safety evaluations during the 30 days following the last dose of study drug and the Study Evaluation Completion eCRF should be completed.

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.

6.2.3 Follow-up for toxicities

All patients will be followed for at least 30 days following their last dose of treatment. Patients whose treatment is interrupted due to an adverse event or abnormal laboratory value must be followed at least once a week for 4 weeks, and subsequently at 4 week intervals, until resolution or stabilization of the event, whichever comes first. Patients whose treatment is permanently discontinued due to an adverse event or abnormal laboratory value must be followed (for adverse events and serious adverse events) for at least 30 days following the last dose of treatment.

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

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

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

[redacted]

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

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

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

In the absence of cholestasis, these patients should be immediately discontinued from study drug treatment, and repeat LFT testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

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

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

6.2.5 Anticipated risks and safety concerns of the study drug

Appropriate eligibility criteria as well as specific dose modification rules are included in this protocol. Guidelines for prophylactic or supportive treatment for expected toxicities, including management of study-drug induced adverse events, i.e., please refer to Section 6.2.1 (Table 6-2).

Refer to preclinical toxicity and or clinical data found in the [Investigator’s Brochure].

[redacted]

6.3 Prior and Concomitant medications

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

6.3.1 Permitted concomitant therapy requiring caution and/or action

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

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

Patients were also to continue blood transfusions during the study protocol according to the regimen that they had been receiving prior to enrollment that could allow maintaining a hemoglobin level of ≥ 9 g/dL. If transfusion needs to be performed on a PK sampling day, PK sampling must occur prior to the transfusion.

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.
- Deferasirox, as a weak CYP3A4 inducer, may potentially decrease serum levels of substances metabolized through CYP3A4 (e.g. alfentanil, aprepitant, budesonide, buspirone, conivaptan, cyclosporine, darifenacin, darunavir, dasatinib, dihydroergotamine, dronedarone, eletriptan, eplerenone, everolimus, felodipine, fentanyl, hormonal contraceptive agents, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, pimozide, quetiapine, quinidine, saquinavir, sildenafil, simvastatin, sirolimus, tacrolimus, tolvaptan, tipranavir, triazolam, ticagrelor, and vardenafil).
- Deferasirox is a moderate inhibitor of CYP2C8 and therefore it may increase serum concentrations of substances metabolized through CYP2C8 (e.g. repaglinide, paclitaxel).
- Deferasirox can potentially increase the exposure of the concomitantly administered CYP1A2 substrates (e.g. theophylline, clozapine, tizanidine). When deferasirox and theophylline are used concomitantly, monitoring of theophylline concentration and theophylline dose reduction should be considered.
- The concomitant use of deferasirox with potent UGT inducers (e.g. rifampicin, phenytoin, phenobarbital, ritonavir) may result in a decrease in deferasirox efficacy due to a possible decrease in deferasirox concentration.

[redacted]

6.3.2 Prohibited concomitant therapy

- Aluminium containing antacid therapies should be avoided because they may bind to deferasirox.
- Concomitant use of bile acid sequestrants decreases deferasirox systemic exposure. Avoid the concomitant use of bile acid sequestrants (e.g., cholestyramine, colesevelam, colestipol) with deferasirox.
- Concomitant use of any other iron chelation therapy (deferoxamine, deferiprone, deferasirox) during study treatment phases are not allowed.
- Any investigational drug other than study medication.

6.4 Patient numbering, treatment assignment or randomization

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.

The investigator or designated staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. Once assigned, the Patient No. must not be reused for any other patient and the Patient No. for that individual must not be changed, even if the patient is re-screened. If the patient fails to be randomized or start treatment for any reason, the reason will be entered into the Screening Log.

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

6.4.2 Treatment assignment or randomization

Patients will be assigned to one of the 2 treatment arms, deferasirox DT or granules (Section 4.1 and Section 6.1) in a ratio of 1:1 during the core phase.

Randomization will be stratified by age groups (2 to <10 years, 10 to <18 years) and by prior ICT (Yes/No). The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the Interactive Response Technology (IRT) provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication randomization list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to medication packs containing each of the study treatments.

Prior to dosing, all patients who fulfill all inclusion/exclusion criteria will be randomized via IRT to one of the treatment arms. The investigator or his/her delegate will call or log on to the IRT and confirm that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign

[redacted]

a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the patient. The randomization number will not be communicated to the caller.

During optional extension phase, all patients will be provided with new deferasirox formulation (granules). No randomization will be done.

6.4.3 Treatment blinding

This is an open-label study and patients, investigators, study site staff and sponsor will have full knowledge of treatment allocation.

In order to minimize the potential impact of treatment knowledge, until the primary analysis is conducted, no aggregated statistical analysis (efficacy or safety) will be performed by treatment, other than the analyses specified in the protocol (Section 4.2).

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

As per Section 4.5, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, delivery of Investigational Medicinal Product (IMP) directly to a participant's home may be permitted (if allowed by Local or Regional Health Authorities and Ethics Committees as appropriate) in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. The dispatch of IMP from the site to the participant's home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of 1 month's supply. In this case, regular phone calls or virtual contacts (every 4 weeks or more frequently if needed) will occur between the site and the participant for instructional purposes, safety monitoring, drug accountability, investigation of any adverse events, ensuring participants continue to benefit from treatment and discussion of the participant´s health status until the participants can resume visits at the study site.

6.5.1 Study drug packaging and labeling

The study medication packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the treatment arms. Responsible site personnel will identify the study treatment package(s) to dispense to the patient by using the IRT and obtaining the medication number(s). Site personnel will add the patient number on the label. Immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique patient number.

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.

[redacted]

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

Patient compliance with study treatment, the co-primary variable in this study, will be evaluated using the stick pack/tablet count (for detailed information please refer to Section 7.2.1)

Compliance will be assessed by the investigator and/or study personnel every 4 weeks and information provided by the patient and/or caregiver will be captured in the Drug Accountability Log. This information must be captured in the source document at each patient visit.

6.5.3.2 Study drug accountability

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

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

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

6.5.4 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments for the core phase and Table 7-2 lists all of the assessments for the optional extension phase and both indicate with an “X”, the visits when they are performed. Patients in the core phase who complete Visit 16 and decide to proceed to the optional extension phase will begin following all the assessments included in the visit 777 in Table 7-1 and then follow the optional extension assessment visit 17 listed in Table 7-2 on the

[redacted]

same day so as to avoid a gap in treatment. Patients who were on the DT arm during core phase of study who have switched to granules at Visit 17 as part of the optional extension phase will need to return weekly (Visits 18, 19 and 20) for the first month after beginning the optional extension phase (granules) for serum creatinine and creatinine clearance. Thereafter they will follow the same schedule as patients who were on granules arm during the core phase. Visit 778 should not be completed by patients who continue into the optional extension phase. Should a patient discontinue the core phase at or prior to Visit 16, they should perform Visits 777 and 778 including safety follow up as per Table 7-1.

Patients in the optional extension phase will complete Visit 779 and 780 at the end of the study or in case of earlier discontinuation.

Patients should be seen for all visits to perform the scheduled assessments on the designated day, or as close to is as possible, i.e., for the core phase not exceeding ± 2 days for assessments scheduled in Visits 1 to 6 and ± 7 days for all other visits until End of Treatment Visit 777. For the optional extension phase, not exceeding ± 7 days for all visits until End of Treatment Visit 779. In this clinical trial, a week is 7 calendar days. For yearly assessments in extension phase, i.e. audiometry, ocular and growth and development examinations, ± 30day window is allowed.

All visits should be scheduled respective to the randomization date (Visit 3) for the core phase, rather than in relation to the previous visits. For the optional extension phase, all visits should be scheduled respective to Visit 17.

All data obtained from these assessments must be supported in the patient's source documentation. No eCRF pages will be used as a source document.

As per Section 4.5, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowed by local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

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

Study Procedure	Category	Protocol Section	Screening (2 visits at least 7days apart)		Core Treatment Phase										End of CoreTreatment (continue to Visit 17 in Table 7-2 if going into extension phase)	Study Evaluation Completion (Core phase) including Safety Follow up if not continuing to optional extension phase
Visit:			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12, 13, 14, 15 &16**	**777**	**778**
Week:			**-3 Weeks**		**1**	**2**	**3**	**5**	**9**	**13**	**17**	**21**	**25**	**29, 33, 37, 41 & 45 (monthly)**	**Within 7 days of last dose for patients not participating in extension phase. (Week 49 if going into extension phase.)**	**30 days after last dose**
Obtain Informed Consent (and assent per local guidelines)	(D)	7.1.1	X													
Randomization	(D)	6.4			X											
Inclusion/exclusion criteria	(D)	7.1.1.3	X	X												
Demography	(D)	7.1.1.3	X													
Relevant medical history/current medical conditions	(D)	7.1.1.3	X													
Prior chelation therapy	(D)	7.1.1.3	X													
Disease history	(D)	7.1.1.3	X													

[redacted]

Study Procedure	Category	Protocol Section	Screening (2 visits at least 7days apart)		Core Treatment Phase										End of CoreTreatment (continue to Visit 17 in Table 7-2 if going into extension phase)	Study Evaluation Completion (Core phase) including Safety Follow up if not continuing to optional extension phase
Visit:			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12, 13, 14, 15 &16**	**777**	**778**
Week:			**-3 Weeks**		**1**	**2**	**3**	**5**	**9**	**13**	**17**	**21**	**25**	**29, 33, 37, 41 & 45 (monthly)**	**Within 7 days of last dose for patients not participating in extension phase. (Week 49 if going into extension phase.)**	**30 days after last dose**
Prior medications and non-drug therapies	(D)	6.3	X	X												
Physical examination	(S)	7.2.4.1	X		X	X	X	X	X	X	X	X	X	X	X	
Vital signs	(D)	7.2.4.2	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height	(D)	7.2.4.3	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weight	(D)	7.2.4.3	X	X	X	X	X	X	X	X	X	X	X	X	X	
Audiometry	(D)	7.2.4.4	X													
Ocular Exam	(D)	7.2.4.5	X										X		X	
ECG	(D)	7.2.4.7.1	X												X	
Echocardiogram	(D)	7.2.4.7.2	X												X	
Growth and development	(D)	7.2.4.8	X												X	
Transfusion/RBC History	(D)	7.1.1.3	X													
Transfusions	(D)	7.1.1.3			X	X	X	X	X	X	X	X	X	X	X	

[redacted]

Study Procedure	Category	Protocol Section	Screening (2 visits at least 7days apart)		Core Treatment Phase										End of CoreTreatment (continue to Visit 17 in Table 7-2 if going into extension phase)	Study Evaluation Completion (Core phase) including Safety Follow up if not continuing to optional extension phase
Visit:			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12, 13, 14, 15 &16**	**777**	**778**
Week:			**-3 Weeks**		**1**	**2**	**3**	**5**	**9**	**13**	**17**	**21**	**25**	**29, 33, 37, 41 & 45 (monthly)**	**Within 7 days of last dose for patients not participating in extension phase. (Week 49 if going into extension phase.)**	**30 days after last dose**
PK sampling (Pre-dose)	(D)	7.2.5			X		X	X	X	X	X	X	X	X		
PK sampling (Post-dose)	(D)	7.2.5						X	X							

[redacted]

Study Procedure	Category	Protocol Section	Screening (2 visits at least 7days apart)		Core Treatment Phase										End of CoreTreatment (continue to Visit 17 in Table 7-2 if going into extension phase)	Study Evaluation Completion (Core phase) including Safety Follow up if not continuing to optional extension phase
Visit:			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12, 13, 14, 15 &16**	**777**	**778**
Week:			**-3 Weeks**		**1**	**2**	**3**	**5**	**9**	**13**	**17**	**21**	**25**	**29, 33, 37, 41 & 45 (monthly)**	**Within 7 days of last dose for patients not participating in extension phase. (Week 49 if going into extension phase.)**	**30 days after last dose**
Laboratory assessments - Blood		7.2.4.6														
Hematology	(D)	7.2.4.6.1	X	X	X		X	X	X	X	X	X	X	X	X	
Biochemistry	(D)	7.2.4.6.2	X	X	X		X	X	X	X	X	X	X	X	X	
Serum Ferritin	(D)	7.2.2	X	X				X	X	X	X	X	X	X	X	
Serum Creatinine	(D)	7.2.4.6.2	X	X	X	X	X	X	X	X	X	X	X	X	X	
Creatinine clearance	(D)	7.2.4.6.2	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hepatitis testing	(D)	7.2.4.6.5	X													
Serum Pregnancy test	(D)	7.2.4.6.4	X													
Laboratory assessments - Urine		7.2.4.6														
Urine dipstick	(D)	7.2.4.6.3	X	X	X	X	X	X	X	X	X	X	X	X	X	

[redacted]

Study Procedure	Category	Protocol Section	Screening (2 visits at least 7days apart)		Core Treatment Phase										End of CoreTreatment (continue to Visit 17 in Table 7-2 if going into extension phase)	Study Evaluation Completion (Core phase) including Safety Follow up if not continuing to optional extension phase
Visit:			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12, 13, 14, 15 &16**	**777**	**778**
Week:			**-3 Weeks**		**1**	**2**	**3**	**5**	**9**	**13**	**17**	**21**	**25**	**29, 33, 37, 41 & 45 (monthly)**	**Within 7 days of last dose for patients not participating in extension phase. (Week 49 if going into extension phase.)**	**30 days after last dose**
Microscopic urine (in case of positive urine dipstick)	(D)	7.2.4.6.3	X	X	X	X	X	X	X	X	X	X	X	X	X	
Proteinuria (Urine protein/creatinine ratio)	(D)	7.2.4.6.3	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine Pregnancy test	(D)	7.2.4.6.4			X										X	
Dispensed stick pack / tablet count	(D)	7.2.1			X			X	X	X	X	X	X	X		
Study Drug administration	(D)	6.1			Daily intake of study drug for 48 weeks											
Returned stick pack / tablet count	(D)	7.2.1						X	X	X	X	X	X	X	X	
PRO / ObsRO		7.2.3														
Compliance Questionnaire	(D)	7.2.3			Daily completion of questionnaire until last day of treatment in core phase											

[redacted]

Study Procedure	Category	Protocol Section	Screening (2 visits at least 7days apart)		Core Treatment Phase										End of CoreTreatment (continue to Visit 17 in Table 7-2 if going into extension phase)	Study Evaluation Completion (Core phase) including Safety Follow up if not continuing to optional extension phase
Visit:			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12, 13, 14, 15 &16**	**777**	**778**
Week:			**-3 Weeks**		**1**	**2**	**3**	**5**	**9**	**13**	**17**	**21**	**25**	**29, 33, 37, 41 & 45 (monthly)**	**Within 7 days of last dose for patients not participating in extension phase. (Week 49 if going into extension phase.)**	**30 days after last dose**
Modified SICT questionnaire	(D)	7.2.3				X	X						X		X	
Palatability questionnaire	(D)	7.2.3				X	X						X		X (day of last dose)	
Concomitant medications	(D)	6.3			Recorded on an ongoing basis											
Adverse events	(D)	8.1	Recorded on an ongoing basis													

[redacted]

Table 7-2 Visit evaluation schedule (for the optional extension phase)

Study Procedure	Category	Protocol section	Optional Extension Treatment Phase																Optional Extension Treatment Phase	End of Treatment of Optional Extension Phase	Optional Extension phase - Study Evaluation Completion (Optional extension phase) including Safety Follow up
Visit			**17**	***18**	***19**	***20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**From visit 34 till visit 84**	**779**	**780**
			***Prior DT arm only**																			
Week			**49**	**50**	**51**	**52**	**53**	**57**	**61**	**65**	**69**	**73**	**77**	**81**	**85**	**89**	**93**	**97**	**101**	**From week 105 till week 305**	**Within 7 days of last dose**	**30 days after last dose**
Physical examination	(S)	7.2.4.1					X	X	X	X	X	X	X	X	X	X	X	X	X	Monthly	X	
Vital signs	(D)	7.2.4.2					X	X	X	X	X	X	X	X	X	X	X	X	X	Monthly	X	
Height	(D)	7.2.4.3	X				X	X	X	X	X	X	X	X	X	X	X	X	X	Monthly	X	
Weight	(D)	7.2.4.3	X				X	X	X	X	X	X	X	X	X	X	X	X	X	Monthly	X	
Audiometry	(D)	7.2.4.4	X																X	Annually	X	
Ocular Exam	(D)	7.2.4.5																	X	Annually	X	
ECG	(D)	7.2.4.7.1																		When clinically indicated		

[redacted]

Study Procedure	Category	Protocol section	Optional Extension Treatment Phase																Optional Extension Treatment Phase	End of Treatment of Optional Extension Phase	Optional Extension phase - Study Evaluation Completion (Optional extension phase) including Safety Follow up
Visit			**17**	***18**	***19**	***20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**From visit 34 till visit 84**	**779**	**780**
			***Prior DT arm only**																			
Week			**49**	**50**	**51**	**52**	**53**	**57**	**61**	**65**	**69**	**73**	**77**	**81**	**85**	**89**	**93**	**97**	**101**	**From week 105 till week 305**	**Within 7 days of last dose**	**30 days after last dose**
Echocardiogram	(D)	7.2.4.7.2																		When clinically indicated		
Growth and development	(D)	7.2.4.8																	X	Annually	X	
Transfusions	(D)	7.1.1.3																		When clinically indicated	X	
Laboratory assessments - Blood		7.2.4.6																				
Hematology	(D)	7.2.4.6.1							X			X			X			X		Every 3 months	X	
Serum Ferritin	(D)	7.2.2					X	X	X	X	X	X	X	X	X	X	X	X	X	Monthly	X	
Serum Creatinine	(D)	7.2.4.6.2		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Monthly	X	

[redacted]

Study Procedure	Category	Protocol section	Optional Extension Treatment Phase																Optional Extension Treatment Phase	End of Treatment of Optional Extension Phase	Optional Extension phase - Study Evaluation Completion (Optional extension phase) including Safety Follow up
Visit			**17**	***18**	***19**	***20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**From visit 34 till visit 84**	**779**	**780**
			***Prior DT arm only**																			
Week			**49**	**50**	**51**	**52**	**53**	**57**	**61**	**65**	**69**	**73**	**77**	**81**	**85**	**89**	**93**	**97**	**101**	**From week 105 till week 305**	**Within 7 days of last dose**	**30 days after last dose**
Creatinine clearance	(D)	7.2.4.6.2		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Monthly	X	
Liver function testing (ALT, AST, TBIL, alk phosphatase)	(D)	7.2.4.6.2					X	X	X	X	X	X	X	X	X	X	X	X	X	Monthly	X	
Laboratory assessments - Urine		7.2.4.6																				
Urine dipstick	(D)	7.2.4.6.3					X	X	X	X	X	X	X	X	X	X	X	X	X	Monthly	X	
Microscopic urine (in case of positive urine dipstick)	(D)	7.2.4.6.3					X	X	X	X	X	X	X	X	X	X	X	X	X	As needed	X	
Proteinuria (Urine	(D)	7.2.4.6.3					X	X	X	X	X	X	X	X	X	X	X	X	X	Monthly	X	

[redacted]

Study Procedure	**Category**	**Protocol section**	**Optional Extension Treatment Phase**																**Optional Extension Treatment Phase**	**End of Treatment of Optional Extension Phase**	**Optional Extension phase - Study Evaluation Completion (Optional extension phase) including Safety Follow up**
Visit			**17**	***18**	***19**	***20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**From visit 34 till visit 84**	**779**	**780**
			***Prior DT arm only**																			
Week			**49**	**50**	**51**	**52**	**53**	**57**	**61**	**65**	**69**	**73**	**77**	**81**	**85**	**89**	**93**	**97**	**101**	**From week 105 till week 305**	**Within 7 days of last dose**	**30 days after last dose**
protein/creatinine ratio)																						
Urine Pregnancy test	(D)	7.2.4.6.4	At discretion of Investigator																		X	
Dispensed stick pack	(D)	7.2.1	X				X	X	X	X	X	X	X	X	X	X	X	X	X	Monthly		
Study Drug administration	(D)	6.1	Daily intake of study drug																			
Returned stick pack / tablet bottle	(D)	7.2.1	X				X	X	X	X	X	X	X	X	X	X	X	X	X	Monthly	X	
Concomitant medications	(D)	6.3	Record on an ongoing basis																			
Adverse events	(D)	8.1	Record on an ongoing basis																			

[redacted]

7.1.1 Screening

Prior to commencement of the screening examination, the patient / caregiver must have given full informed consent on the appropriate form. Investigators will also obtain consent/assent of patients according to local guidelines. Once this has been signed and dated by the patient and/or by the caregiver, the investigator can take the patient through the study inclusion and exclusion criteria to make sure that the patient is fully eligible to participate.

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

Specific safety examinations like ocular and audiometry examinations, ECG and echocardiography (currently indicated to be performed at screening visit 1) can be performed at either screening visit 1 or screening visit 2 to make it possible for the site to plan the examinations properly. These assessments must be performed at least once prior to patient starting study drug.

Ocular and Audiometry examinations must be performed at screening (also when entering in the optional extension phase at visit 17). 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 at Screening (Visits 1 and 2) and the value will be used for eligibility criteria. The serum ferritin samples should be obtained in the absence of known infection.

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

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

Re-screening is permissible on a case by case basis. All screening assessments at V1 and V2 have to be repeated in case of re-screening of a patient with the exception of the Ocular, Audiometry and Echocardiography assessments. Please contact Novartis for guidance and see Section 7.1.1.2 to get information on how to process screen failures.

To enter the optional extension phase, patient must have completed core phase per protocol. Patients may proceed with entering the optional extension treatment phase once all Visit 777 and 17 assessments are performed. Lab results from Visit 777 will be checked as soon as they become available and if any dose modifications are required will occur per Table 6-2.

7.1.1.1 Eligibility screening

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

7.1.1.2 Information to be collected on screening failures

Patients who sign an informed consent but fail to be randomized and 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.

[redacted]

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

If the patient fails to be started on treatment, the IRT must be notified within 2 days of the screen fail that the patient was not randomized.

7.1.1.3 Patient demographics and other baseline characteristics

In the core phase, data will be collected on patient characteristics including demographic information (age, sex, ethnicity, etc.) and other background or relevant medical history/ current medical conditions, transfusion/RBC history (within 6 months prior to study entry), disease history, prior chelation history at Visits 1 and/or 2.

To determine eligibility to be enrolled into the study, patients will also undergo assessments as per the inclusion and exclusion criteria which include vital signs, hematology and biochemistry evaluations, serum ferritin, serum creatinine and creatinine clearance (calculated by the central laboratory), **[Egypt: Local laboratory will be used for analysis of all specimens collected],** hepatitis viral testing, a known history of HIV positive test result (ELISA or Western blot) which is documented in the source documents, serum pregnancy test and urinalysis.

Other assessments include ocular, audiometry, ECG, echocardiogram, and growth and development exams.

7.1.2 Treatment period

The study treatment duration is 48 weeks. Patient visits will occur weekly for the first 3 weeks of treatment and then every 4 weeks starting from Week 5 until Visit 777 (EOT).

Having completed the screening period, patients who are eligible will be enrolled and randomized to receive either deferasirox DT or deferasirox granules. The target 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 either deferasirox DT 20 mg/kg once daily or deferasirox granules 14 mg/kg once daily. All ICT pre-treated patients will use a deferasirox DT or an equivalent strength-adjusted granules starting dose corresponding to their pre-washout dose, please refer to Appendix 14.1.

For details on study design and dose adjustments, see Section 4 and Section 6.2.

For details of assessments during the treatment periods, see Table 7-1 and Table 7-2.

After the core phase has ended, the patients who have participated and completed the 48 weeks core treatment phase as per protocol and do not have access to the new formulation will have the possibility to enter the optional extension treatment phase until there is local access to the new formulation (granules or FCT) or up to of 5 years, whichever occurs first. If the patient does not enter the optional extension phase they must complete the core EOT visit, 30 day safety follow up and EOS visit.

[redacted]

- Patients who discontinue prior to Visit 17 will complete Visit 777 within 7 days of last dose of study drug. End of study (Visit 778) and safety follow-up will be performed within 30 days last dose was given in the core phase.
- All patients who have completed the core treatment phase per protocol will have an EOT visit (Visit 777) at Week 49. Patients who opt to continue to the optional extension treatment phase will proceed to Table 7-2 to complete the Visit 17 assessments on the same day. At completion of the optional extension treatment phase, or should patients discontinue at any time after starting the extension treatment phase they will complete the End of Treatment of Optional Extension Phase (Visit 779) within 7 days of last dose of study drug. End of study (Visit 780) and safety follow-up will be performed within 30 days last dose was given in the optional extension phase.

Patients who were on the DT arm during core phase of study will switch to granules in the optional extension phase at Visit 17. They will need to return weekly for the first month (visit 18, 19 and 20) after beginning the optional extension phase (granules) for serum creatinine and creatinine clearance. Thereafter they will follow the same schedule as patients who were on the granules arm during the core phase.

7.1.3 Discontinuation of study treatment

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

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

Study treatment must be discontinued under the following circumstances:

- Emergence of the following adverse events, please refer to Section 6.2
- Any of the following laboratory abnormalities, please refer to Section 6.2
- Pregnancy
- Unwillingness to comply with the prescribed study treatment
- Use of prohibited treatment refer to Section 6.3.2.
- Any other protocol deviation that results in a significant risk to the patient's safety

Patients who discontinue study treatment should undergo an end of study visit within 7 days of the last dose of the study treatment, at which time all the assessment listed for the End of Treatment (EOT) visit will be performed. An EOT eCRF page should be completed for all patients (for core or optional extension), giving the date and the reason for stopping the study treatment and then be discontinued from the trial.

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

[redacted]

7.1.4 Withdrawal of consent

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

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

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

Study treatment must be discontinued and no further assessments conducted.

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

7.1.5 Follow up period

All patients must have safety evaluations for 30 days after the last dose of study treatment. If death occurs during this period, this will be collected in the Study Evaluation Completion 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.

7.2 Assessment types

7.2.1 Compliance with prescribed treatment

The stick pack/tablet count will be performed by investigator or study personnel every 4 weeks (week 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45 and at EOT(core)/777 visits) during the core phase. Assessment of compliance using stick pack/tablet counts will be based on the actual count at the different time points, taking into account the amount of medication dispensed, returned and reported as lost/wasted by the patient in the core phase. Treatment prescribed will be recorded at every visit, including any dose adjustments performed in-between visits. Detailed information related to drug dispensation and returns will be captured in source documents (drug accountability logs) by the investigator or study personnel at each visit during the core phase. During the optional extension phase sites will only collect whether or not the stick pack(s) have been returned from the previous visit.

7.2.2 Serum Ferritin

Serum ferritin test will be performed during the core phase at Screening Visits 1 and 2 (in the absence of infection) to assess the eligibility of the patient. The baseline serum ferritin value is defined as the average of the two measurements obtained during the screening period. Thereafter serum ferritin testing will be performed at weeks 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45 and EOT(core)/777 visits to evaluate the clinical benefit related to improved compliance of the new formulation. This will be done monthly as per Exjade prescribing information during

[redacted]

the extension phase. A central laboratory will be used for analysis of all specimens collected. **[Egypt: Local laboratory will be used for analysis of all specimens collected]**

Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the [Laboratory Manual]. **[Egypt: Details on the collections, shipment of samples and reporting of results by the local laboratory are provided to investigators in the local laboratory manual]**

7.2.3 Patient / Observer Reported Outcomes

Patient satisfaction, palatability and compliance will be measured for both formulations using Patient / Observer Reported Outcomes (PRO/ObsRO) questionnaires.

For patients aged between 10 years and less than 18 years at enrollment, the PRO questionnaires will be completed by the patients themselves. The questionnaires for patients aged between 2 years and less than 10 years have been designed as observations made by caregivers such as the parent or legal guardian (ObsRO). For these patients the caregivers will continue completing the ObsRO questionnaires even after the patient turns 10 years for consistency in responses.

Three questionnaires were developed to evaluate both formulations: the modified Satisfaction with Iron Chelation Therapy (SICT), a palatability questionnaire and a compliance diary. All questions will be translated into the patient's native language.

All Patients/caregivers will complete the PRO/ObsRO questions via a handheld electronic device and they will receive training on the operation of this device. The device will be programmed to ensure that all relevant observations are recorded before submission.

In case of malfunctioning devices (confirmed by vendor support helpdesk and only under this condition, the patients/caregivers will be authorized to use paper questionnaires until vendor fixes issue(s) of devices. The back-up paper entry process in case of technical issues must be followed before any reporting in the database.

The modified SICT questionnaire will be completed at Visits 4 (Week 2), 5 (Week 3), 11 (Week 25), and 777 (within 7 days of the last dose of treatment for those not continuing to the extension phase). The Visit 4 assessment will be considered as baseline since the questionnaire asks for patient's satisfaction with the iron chelation therapy received 'in the past week'. The rationale for having the modified SICT completed also at Visit 5 is based on the need to conduct a test-retest reliability within trial, meaning that patients need to complete the modified SICT questionnaire within 2-14 days after the baseline data collection to ensure the stability of the measure over a period of time where little change would be expected.

The palatability questionnaire will be completed at Visits 4 (Week 2), 5 (Week 3), 11 (Week 25), and 777 (day of the last dose of treatment), in order to co-administer this questionnaire together with the modified SICT questionnaires. The Visit 4 palatability assessment will be considered as baseline and the Visit 5 assessment will allow to check the test-retest reliability within trial.

The handheld devices will be enabled with alarms that will remind the patient / caregiver to complete the modified SICT and the palatability questionnaires at the time points specified above.

[redacted]

The compliance questionnaire will be completed daily, starting at Visit 3 until Visit 777 (day of the last dose of treatment). This questionnaire asks whether the study medication was taken by the patient / given by the caregiver and at what time it was ingested. Alarms and reminders will prompt patients to complete the compliance questionnaire every day.

Daily diary records will be used to calculate the rate of dosing instructions deviations in each study arm (doses missed completely or not taken at approximately the same time every day).

PRO/ObsRO questionnaires as well as the compliance diary will not be collected during optional extension phase.

7.2.4 Safety and tolerability assessments

Safety will be monitored by assessing physical examination, vital signs, laboratory evaluations, as well as collecting information on adverse events at every visit. For details on AE collection and reporting, refer to Section 8.

As per Section 4.5, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur (every 4 weeks or more frequently if needed) for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

7.2.4.1 Physical examination

A physical examination will be performed during the core phase at Screening visit 1, Visit 3 and all subsequent visits. The physical examination at Visit 3 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. During the optional extension phase, physical exam will be done monthly as per Exjade prescribing information.

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.

7.2.4.2 Vital signs

Vital signs include body temperature, respiratory rate, blood pressure and pulse measurements and will be measured at all study visits (including EOT) at the core phase. During the optional extension phase, vital signs will be taken monthly as per Exjade prescribing information. 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

[redacted]

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.

7.2.4.3 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 at each Visit). During the optional extension phase, assessments will be done monthly as per Exjade prescribing information.

7.2.4.4 Auditory examination.

Patients will undergo auditory examinations during the core phase at screening (core phase) and Visit 17, annually and at EOT visit (extension phase).

The auditory examination should include the following assessments:

- Comprehensive audiometry threshold examination

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

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

7.2.4.5 Ocular Examination and Central Imaging Assessment

Patients will undergo ophthalmologic examinations during the core phase at Visit 1, 11, 777 (EOT Core) and at unscheduled visits (if needed). During the optional extension phase, assessments will be done annually as per Exjade prescribing information and at EOT of Extension phase.

The ophthalmologic examination includes the following assessments:

- Distance visual acuity test: in patients who don't need correction with glasses or contact lenses, visual acuity test may be performed without correction. In patients who need correction (either wears prescription glasses/contact lenses or uncorrected visual acuity is not within normal limits), best corrected visual acuity should be tested. Information about visual acuity without correction, best corrected visual acuity and prescription/correction must be documented in the source records.
- Applanation tonometry
- Slit Lamp exam and lens photography
- Fundus exam and wide angle fundus photography of the retina and optic nerve

Interpretation of the ocular examinations must be made by a qualified physician and documented on the CRF page.

Information about the results of the ocular examinations, including the lens photographs and the wide angle fundus photographs of the retina and optic nerve, must be present in the source documentation at study site. Significant findings of the ocular examinations that meet the definition of an AE must be recorded in the adverse event summary page of the case report form.

[redacted]

All screening and on-study wide angle fundus photographs and lens photographs, including photography acquired prior to the release of Protocol Amendment 6, must be sent to an imaging Contract Research Organization (CRO) designated by Novartis for central assessment.

Table 7-3 Central Imaging Assessments Collection Plan

Procedure	Screening/Baseline	During Treatment (core and extension phase)
Wide Angle Fundus Photography	Required	**Core phase**: Visit 11 (Week 25),Visit 777 (EOT Core) **Optional Extension phase**: Visit 33 (Week 101), annually thereafter until EOT Any unscheduled fundus photography during treatment
Lens Photography	Required	**Core Phase**: Visit 11 (Week 25), Visit 777 (EOT Core) **Optional Extension phase**: Visit 33 (Week 101), annually thereafter until EOT Any unscheduled lens photography during treatment

Details on transferring the fundus and lens photographs for reading by the imaging CRO are provided to investigators in the imaging CRO Site Operations Manual. All details of the central review methodology will be described in the Central Imaging Review Charter.

7.2.4.6 Laboratory evaluations

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

[Egypt: Local laboratory will be used for analysis of all specimens collected]

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

[Egypt: Details on the collections, shipment of samples and reporting of results by the local laboratory are provided to investigators in the local laboratory manual]

As per Section 4.5, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, if subjects cannot visit the site for safety lab assessments conducted through central labs, a local lab may be used.

The results of the local laboratory will be recorded in the CRF if any of the following criteria are met:

- a treatment decision was made based on the local results , or
- there are no concomitant central lab results available, or

[redacted]

- an AE was documented based on local lab result.

Table 7-4 Central Clinical laboratory parameters collection plan, [Egypt: Local Laboratory]

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, MCH, MCHC, MCV, Platelets, Red blood cells, White blood cells(WBC) count with differential, RBC Morphology with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)
Biochemistry	Albumin, Alkaline phosphatase, ALT, AST, Bicarbonate, Calcium, Chloride, Creatinine, Creatine kinase, Direct (conjugated) 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): Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen
Hepatitis markers	HbsAg, HbsAb, HbcAb, HCV RNA, Anti-HCV
Additional tests	Serum ferritin, creatinine clearance, urine protein/creatinine ratio, serum pregnancy test

7.2.4.6.1 Hematology

Hematology samples will be collected during the core phase at Screening Visits 1 and 2, Visit 3, 5 - 16 and 777 (EOT) and will be sent to the central laboratory, **[Egypt: Local laboratory].** During the optional extension phase, hematology samples will be collected every 3 months as per Exjade prescribing information. Hematology parameters monitored during the study are listed in Table 7-4.

7.2.4.6.2 Clinical chemistry

Clinical chemistry samples will be collected during the core phase at Screening Visits 1 and 2, at Visit 3, 5-16, and 777 (EOT) and will be sent to the central laboratory, **[Egypt: Local laboratory]**. During the optional extension phase, monthly assessments will be done as per Exjade prescribing information as per Table 7-2. Patients who were on the DT arm during core phase of study and decided to switch to granules as part of the optional extension phase will need to return weekly for the first month of the optional extension phase at Visits 18, 19 and 20 for serum creatinine and creatinine clearance monitoring. Thereafter they will follow the same schedule as patients who were on granules arm during the core phase. Clinical chemistry parameters to be measured are listed in Table 7-4.

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

In addition, serum creatinine will be measured weekly during the first three weeks (after the first study drug administration and at Visits 4, 5) and monthly thereafter (starting with Visit 6) till Visit 777 (EOT). During the optional extension phase, monthly assessments will be done as per Exjade prescribing information for patients previously on the granules arm of the core phase. Patients on the DT arm for the core phase of the study who have decided to switch to granules as part of the optional extension phase will need to return weekly for the first month at Visits

[redacted]

18, 19 and 20. Creatinine clearance will be calculated by the central lab **[Egypt: Local laboratory]** using the Schwartz formula for patients 17 years and younger and the Cockcroft-Gault formula for patients who turn 18 years old during the study, each time serum creatinine is collected.

7.2.4.6.3 Urinalysis

Urinalysis samples will be collected during the core phase at every study visit, from Screening until Visit 777 (EOT). During the optional extension phase, monthly assessments will be done as per Exjade prescribing information. A midstream, second voided morning urine sample will be obtained as this will provide the best results. Urinalysis parameters assessed are listed in Table 7-4.

The microscopic urinalysis will be performed only in case of positive dipstick. Dipsticks will be supplied by the central lab, **[Egypt: Local laboratory]**.

At Screening Visits 1 and 2, a urine sample (at least 15 ml) will be collected and sent to the central lab **[Egypt: Local laboratory]** for urinary protein/creatinine (UPC) ratio to assess the eligibility of the patient. Thereafter UPC ratio will be assessed at every visit, till EOT, as described in the [Central Laboratory Manual], **[Egypt: Local Laboratory Manual]**. 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 Table 6-2.

7.2.4.6.4 Pregnancy and assessments of fertility

Females of child-bearing potential are defined as all females physiologically capable of becoming pregnant. This includes female pediatric patients who are menarchal or who become menarchal during the study.

All menarchal girls and their parents/caregivers should be informed about the potential risks of pregnancy and the need to prevent pregnancy during the study. It is important to be sensitive in introducing this issue, as understanding and comprehension of puberty, sexual activity, pregnancy and contraception is influenced by age, as well as factors such as precocity, socio (educational) economic and familial background. These discussions with the patient and her parents/caregivers are therefore best performed by investigators familiar with the pediatric subject and her family and should be guided by requirements of the local regulatory authorities. These discussions should take into account the socio-economic, cultural factors and religious beliefs of the adolescent participant and her family.

The investigator should also discuss the management of the pregnancy test results with the patient and her parents/caregivers. The privacy of the patient should be considered in accordance with the local law and ethics.

Serum and/or urine pregnancy tests will be performed for all females of child-bearing potential according to the schedule in Table 7-1 for the core phase. Urine pregnancy tests will be at the EOT visit (777) and then at Investigator's discretion during the optional extension phase treatment period as per schedule in Table 7-2. Urine pregnancy tests will also be performed at

[redacted]

the end of treatment in the extension phase as per Novartis guidelines for pregnancy testing in clinical trials when basic contraception is requested.

Additional pregnancy tests may be performed at the investigator's discretion during the study. Patients becoming pregnant or breastfeeding must be discontinued from study drug.

However, a patient may choose to remain in the study should she become pregnant, and be followed according to the protocol-defined study visits.

Female patients of child-bearing potential, who are or might become sexually active, must be informed of the need to prevent pregnancy during the study.

The basic contraception methods are:

- Barrier method: Condom or Occlusive cap (diaphragm or cervical/vault caps). [For UK: with spermicidal foam/gel/film/cream/vaginal suppository].
- Placement of an intrauterine device (IUD) or intrauterine system (IUS).

The decision on the contraceptive method should be reviewed at least every 3 months to evaluate the individual need and compatibility of the method chosen.

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

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

7.2.4.6.5 Hepatitis Viral tests

Hepatitis Viral testing consists of the following items: Hepatitis B Surface Antibody (Anti-HBs), Hepatitis B core Antibody (HbcAb), Hepatitis C Antibody (Anti-HCV), Hepatitis B surface Antigen (HBsAg), Qualitative w/confirmation, HCV PCR (Quantitative). Hepatitis Viral testing will be conducted at Screening Visit 1 (core phase) to assess trial eligibility.

7.2.4.7 Cardiac assessments

7.2.4.7.1 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed and interpreted by site personnel during the core phase at the following visits:

- at screening Visit 1
- at visit 777 (EOT)

During the optional extension phase, ECG will be performed when clinically indicated.

Interpretation of the tracing must be made by a qualified physician and documented on the ECG CRF page. Each ECG tracing should be labeled with the study number, patient's initials (where regulations permit), patient number, date and kept in the source documents at the study site. Clinically significant abnormalities present 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.

[redacted]

7.2.4.7.2 Echocardiography

A standard echocardiogram will be performed and interpreted by the site personnel during the core phase at the following visits:

- at screening Visit 1
- at visit 777 (EOT)

During the optional extension phase, echocardiography assessments will be done when clinically indicated.

Interpretation of the echocardiogram must be made by a qualified physician and documented on the CRF page. Each echocardiography should be labeled with the study number, patient's initials (where regulations permit), patient number, date and kept in the source documents at the study site. Clinically significant abnormalities present 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.

7.2.4.8 Growth and Development

7.2.4.8.1 Growth velocity assessment in pediatric patients

At the end of core phase, the growth velocity will be assessed from the difference between the end of-core phase and the baseline height measurements during the core phase.

During the optional extension phase, growth assessment will be performed annually as per Exjade prescribing information.

7.2.4.8.2 Pubertal stage

Pubertal stage will be scored at baseline and end of core phase according to Tanner staging system.

During the optional extension phase, pubertal stage assessment will be performed annually as per Exjade prescribing information.

7.2.5 Pharmacokinetics

Detailed instructions for the collection, handling, and shipment of PK samples will be presented in the [CICL670F2202 Pharmacokinetics Laboratory Manual]. PK sampling will only be performed during the core phase.

7.2.5.1 PK blood sample collection and handling

7.2.5.1.1 Blood collection plan

PK blood samples will be collected in all patients **[Egypt: no PK samples will be collected]** at weeks 1, 3, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41 and 45 visits to support the assessment of compliance (see Table 7-5). Patients / caregivers will be instructed that study drug should not be administered in the morning of these visits.

[redacted]

Table 7-5 PK blood collection log (all patients)

Visit	Week	Day	Scheduled time point	PK collection number		PK Sample No	Sample volume [mL]
3	1	1	Pre-dose	1		1	2
5	3	1	Pre-dose	2	102	6***	2
6	5	1	Pre-dose	3	103	7	2
6	5	1	Post-dose 3 hour (+/- 1 hour)	3		9	2
7	9	1	Pre-dose	4	104	12	2
7	9	1	Post-dose 3 hour (+/- 1 hour)*	4		13	2
8	13	1	Pre-dose	5	105	14	2
9	17	1	Pre-dose	6	106	15	2
10	21	1	Pre-dose	7	107	16	2
11	25	1	Pre-dose	8	108	17	2
12	29	1	Pre-dose	9	109	18	2
13	33	1	Pre-dose	10	110	19	2
14	37	1	Pre-dose	11	111	20	2
15	41	1	Pre-dose	12	112	21	2
16	45	1	Pre-dose	13	113	22	2
999	Unscheduled**		--	--		1001+	2
	Total						30

PK collection numbers 1 to 13 correspond to the dose taken on the day of the visit.

PK collection numbers 102 to 113 correspond to the dose taken the day before each study visit.

*One PK blood sample should be collected between 2 and 4 hours post-dose

** Each unscheduled PK blood sample will be uniquely numbered with sample number 100X (e.g., 1001, 1002, etc.) and will add 2 mL of blood to the total quantity collected

*** Certain PK samples have been removed as part of Protocol Amendment V.01 so PK sample numbers are no longer consecutive. Please follow numbering convention in Table 7-5.

On the days of visit 6 (Week 5) and visit 7 (Week 9) deferasirox should be administered at the study site under supervision of the investigator/site staff. This is to ensure appropriate draws of pre- and post-dose administration blood samples for PK assessments.

At Week 1, the pre-dose sample should be obtained before the first drug administration. At Week 5 and Week 9, the pre-dose PK sample should be obtained within 24 ± 2 hours from the previous dose, and one post-dose PK sample should be obtained between 2 and 4 hours post-dose administration.

The time of all blood draws will be recorded on the PK blood collection page in the eCRF. All samples will be taken by either direct venipuncture or indwelling cannula inserted in a forearm vein.

Blood samples (2 mL each sample) will be collected at each sampling time into a Vacutainer™ tube containing lithium heparin provided by central lab **[Egypt: No PK samples will be collected]**.Immediately after each tube of blood is drawn, it should be inverted gently several times to ensure the mixing of tube contents with the anticoagulant (avoiding prolonged contact with the rubber stopper). Samples must be cooled immediately by placing the tube upright in a test tube rack sitting in an ice-water bath or cryoblock until placed in the centrifuge. Within 30 minutes of sample draw, the samples are centrifuged at about 5°C for 15 minutes at 2000 g (to be adapted according to the radius of the centrifuge). Within 10 minutes after centrifugation,

[redacted]

the upper plasma sample will be transferred into two separate 2 mL, tapered, polypropylene screw-cap tubes labeled as primary sample and back-up sample. The tube A should have at least 0.5 mL of plasma and the tube B contains the remaining plasma. Both samples will be stored frozen at -70°C +/- 15°C within 60 min of collection.

Each sample will be given a unique sample number as indicated in Table 7-5. The exact clock time of dosing on each PK sampling day, as well as the actual sample collection date and time must be captured on the appropriate source documents for PK sample collection at Week 5 and Week 9. Issues with obtaining samples will be noted in the comments field of the documents.

7.2.5.1.2 PK sample labeling

The sample labels must be completed in water proof ink and attached to the tube. The labels should include the information indicated below (Table 7-6)

Table 7-6 PK sample labels

Study number	CICL670F2202
Subject ID	xxxx_xxxxx
Subject initials	ABC
Treatment Arm	Arm 1, Arm 2
Visit	W1, W3, W5, W9, W13, W17, W21, W25, W29, W33, W37, W41, W45
Study day	D1
PK time point	00:00 (taken pre-dose), 03:00 (taken post-dose)
PK sample number	1, 2, 3, etc.
Sample aliquot	Primary or Back-up

7.2.5.2 PK analytical method

Deferasirox concentration will be measured in plasma using a validated liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) method with an anticipated lower limit of quantification of 0.670 µmol/L by a Novartis Qualified external Service Provider.

Other assessments

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

7.2.6 Resource utilization

Not Applicable.

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.

[redacted]

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 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 in this trial as mild, moderate, severe and life-threatening, (corresponding to CTCAE Grades 1 – 4). CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected though an EOT form during treatment period. Deaths that occur within the 30 day safety follow up after last study drug dose will be collected on the Study Evaluation Completion eCRF (visit 778 in the core phase or visit 780 in the optional extension phase).

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

- The severity grade (mild, moderate, severe and life-threatening corresponding to CTCAE Grades 1 – 4)
- Its duration (Start and end dates or Ongoing at End of Study)
- Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
- Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
- Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
- 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) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

[redacted]

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events 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 (CTCAE Grade 3) 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
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- 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
- 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, and whether the patient continued or withdrew from study participation.

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

8.3 Emergency unblinding of treatment assignment

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

8.4 Pregnancies

Serum and urine pregnancy tests will be performed for all females of child-bearing potential according to the schedule in Table 7-1 for the core phase. Urine pregnancy tests will be at the Investigator's discretion during the optional extension phase treatment phase as per schedule in Table 7-2 and will also be performed at the end of treatment in the optional extension phase as per Novartis guidelines for pregnancy testing in clinical trials when basic contraception is requested.

To ensure patient safety, each pregnancy in a patient after signing the informed consent 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. The study drug must be discontinued, though the patient may choose to remain in the study, if she wishes to do so. If the patient chooses to remain in the study, all assessments that are considered as a risk during pregnancy must not be performed. The patient may continue all other protocol assessments.

Pregnancy must be recorded on a Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Chief Medical Office and Patient Safety (CMO&PS) Department.

Pregnancy follow-up should be recorded on the same form and should 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.

After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery.

8.5 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided [Investigator Brochure]. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.6 Data Monitoring Committee

Not applicable.

8.7 Steering Committee

Not applicable.

[redacted]

9 Data collection and management

9.1 Data confidentiality

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

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

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

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

9.2 Site monitoring

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

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

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/assent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan.

[redacted]

9.3 Data collection

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

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner. Samples for Central lab, PK and ocular examination photographs should be sent to the vendors on timely manner, **[Egypt: only safety samples will be sent to Local laboratory, no PK samples will be collected]**. Please refer to the corresponding section for more information.

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

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

Data for PK, Laboratories sampling and ocular examination photographs will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO). **[Egypt: For Egypt sites, data for laboratories sampling will be processed locally and the results will be sent electronically to Novartis (or a designated CRO) including normal ranges]**.

ObsRO/PRO questionnaires and diary data will be entered into an electronic questionnaire/paper questionnaire (only in case of ePRO malfunctioning) by the patient/caregiver. The system will be supplied by a vendor(s), who will also manage the database. The database will be sent electronically to Novartis personnel (or designated CRO).

Randomization codes and data about all study treatments dispensed to the patient and all IRT assigned dosage changes will be tracked using an Interactive Response Technology. The system will be supplied by a vendor(s), who will also manage the database. The data will be sent electronically to Novartis personnel (or designated CRO).

The occurrence of any protocol violations will be determined. After these actions have been completed and the data has been verified to be complete and accurate, the database will be declared locked. Authorization is required prior to making any database changes to locked data, by joint written agreement between the Global Head of Biostatistics and Data Management and the Global Head of Clinical Development.

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

[redacted]

10 Statistical methods and data analysis

This is a randomized, open-label, multicenter, two arm, phase II study to investigate the treatment compliance, efficacy and safety of an improved deferasirox granule formulation in pediatric patients with iron overload.

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

Standard descriptive analyses will include:

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

In PK analysis, geometric mean, CV%, CV% of geometric-mean will be included besides the analyses mentioned above. Additional information for analysis methods will be available in Statistical Analysis Plan. Statistical analysis will be performed according to treatment formulation groups: DT and deferasirox granule formulation.

The handling of any potential impact due to a Public Health emergency (e.g. pandemic, epidemic or natural disaster etc.) on the analyses will be detailed in the SAP.

10.1 Analysis sets

10.1.1 Full Analysis Set

The Full Analysis Set 1 (FAS-1) comprises all ICT naïve patients to whom study treatment has been assigned by randomization during the core phase.

The Full Analysis Set 2 (FAS-2) comprises all ICT pre-treated patients to whom study treatment has been assigned by randomization during the core phase.

The Full Analysis Set 3 (FAS-3) comprises all ICT pre-treated and naïve patients to whom study treatment has been assigned by randomization during the core phase.

According to the intent to treat principle, patients will be analyzed according to the treatment and stratification factors they have been assigned to during the randomization procedure.

10.1.2 Safety Set

The Safety Set 1 includes all ICT naïve patients who received at least one dose of study medication during the core phase.

The Safety Set 2 includes all ICT pre-treated patients who received at least one dose of study medication during the core phase.

The Safety Set 3 includes all ICT pre-treated and naïve patients who received at least one dose of study medication during core phase.

The Safety Set 4 will consist of all patients who received at least one dose of granule formulation during the core or extension phase.

[redacted]

Patients will be analyzed according to the study treatment they actually received. A precise definition of "actually received" and of the analysis set used for pre-dose PK data analyses will be added in the SAP.

10.1.3 Per protocol Set

The Per Protocol Set consists of all ICT naïve patients from the FAS-1 without any major protocol deviation.

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

10.1.4 Pharmacokinetic Analysis Set

The Pharmacokinetic Analysis Set (PAS) consists of all patients who have at least one evaluable pre- or post-dose PK concentration (deferasirox).

A PK concentration is considered evaluable if it fulfills all of the following criteria:

- The actual dose or leading dose prior to pre-dose sampling must be as planned by protocol. In addition, the patient should have received the same dose during the last 4 days prior to sampling (except for Week 1 Day 1).
- The elapsed time between dose administration and PK concentration is documented.
- The PK concentration must NOT be associated with any vomiting within 4 hours of dosing.

10.2 Patient demographics/other baseline characteristics

Demographic and other background data will be summarized descriptively by formulations and overall separately for the FAS-1, FAS-2 and the FAS-3.

Demographic data included age, age categories (2 to <10 years and 10 to <18 years), gender, race. Other background data included weight, weight group (<20 kg, 20-<35 kg, 35-<55 kg, 55-<75 kg, ≥75 kg), height, main underlying disease, history of splenectomy (Yes/No), prior iron chelation therapy (Yes/No), prior deferasirox (Yes/No), type of last chelation therapy prior to the study, hepatitis B and C status, medical history by MedDRA primary SOC and preferred term, abnormality in baseline ECG (Yes/No) and (clinically significant/non-significant), abnormality in baseline echocardiogram (Yes/No) and (clinically significant/non-significant), abnormality in baseline audiometric test (Yes/No) and (clinically significant/non-significant), abnormality in baseline ocular exam (Yes/No) and (clinically significant/non-significant, baseline creatinine, baseline creatinine group (≤upper limit of normal range (ULN), >ULN-≤1.5*ULN and >1.5*ULN), baseline creatinine clearance, baseline creatinine clearance group (<40, ≥40-<60, , ≥60-<90 and ≥90 mL/min), baseline ALT, baseline ALT group (≤ULN, >ULN-≤3*ULN, >3*ULN-≤5*ULN and >5*ULN), baseline AST, baseline AST group (≤ULN, >ULN-≤3*ULN, >3*ULN-≤5*ULN and >5*ULN), urine protein/creatinine ratio (≤0.2 mg/mg,>0.2-≤0.5, >0.5-≤1 mg/mg and >1 mg/mg), baseline serum ferritin and baseline serum ferritin group (<1000, ≥1000 to ≤2500, >2500 to ≤5000, >5000 ng/mL).

[redacted]

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

10.3 Treatments (duration of exposure, concomitant therapies, percentage of planned dose taken)

The following variables will be summarized with descriptive measures separately for the Safety Set-1, Safety Set-2, Safety Set-3 and Safety Set-4 by formulation: duration of exposure, in weeks and in categories (core phase: <4 weeks, 4-<12 weeks, 12-<20 weeks, 20-<28 weeks, 28-<36 weeks, 36-<44 weeks, ≥44 weeks and extension phase: <6 months, 6-<12 months, 12-<24 months, 24-<36 months, 36-<48 months, >48 months); average planned (mg/kg/day) and average actual daily dose; cumulative planned (mg/kg) and total actual dose (mg/kg); percentage of planned dose taken; frequency of interruptions, decreases and increases in planned dose, overall and by reason for change as recorded in the eCRF.

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

The duration of exposure, defined as the number of weeks (core phase) / months (extension phase) between the start and end of study medication, will be summarized by formulation and by phase. 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, excluding 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).

Prior and concomitant medications and significant non-drug therapies will be summarized through frequency tables according to their WHO ATC class and WHO generic term by phase. Prior medications are defined to be drugs taken prior to the first dose of study medication. Concomitant medications are medications taken between the first day of study medication and up to 30 days after the last day with study medication or medications starting prior to the first day of study medication and continuing after the start date of study medication.

10.4 Primary objective

The primary objective of this study is to evaluate patient compliance with study treatment, as measured by the count of deferasirox granules stick packs/dispersible tablets and to evaluate the change in serum ferritin over time for both formulations of deferasirox in pediatric ICT naive patients with iron overload during core phase, after 24 weeks of treatment.

10.4.1 Variables and analysis set

All analyses for the primary objective will be performed on the FAS-1 and presented by treatment group: deferasirox DT and deferasirox granule formulation.

[redacted]

The co-primary efficacy variables are:

- Compliance measured by stick pack /tablet count based on amount of medication dispensed, returned and reported as lost/wasted by the patient or caregiver, over 24 weeks of treatment (i.e. assessed at week 25 visit). Compliance will be calculated 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 over 24 weeks of treatment (i.e. assessed at week 25 visit);
  - total count prescribed is cumulative prescribed count over 24 weeks of treatment (i.e. assessed at week 25 visit).
- Change from baseline in serum ferritin after 24 weeks of treatment (i.e. assessed at the week 25 visit).

10.4.2 Statistical method of analysis

The primary efficacy analysis will be the comparison of means between the two treatment arms of change from baseline after 24 weeks of treatment in SF and mean relative consumed stick pack /tablet count over 24 weeks of treatment.

The trial will be claimed successful if the superiority of granule formulation relative to DT formulation could be demonstrated with regard to both endpoints. Therefore, no adjustment for multiplicity of the type I error (alpha) is required.

The primary inferential analysis described below will be based on the FAS-1.

Let $\mu_{SF,G}$ and $\mu_{SF,DT}$ denote the mean change from baseline in SF to week 25 visit for granule and DT formulations, respectively. Let $\mu_{C,G}$ and $\mu_{C,DT}$ be similarly defined for compliance measured by stick pack /tablet count.

The null and the alternative hypothesis are defined as follows:

$H_{0,SF}$: $\mu_{SF,G} = \mu_{SF,DT}$ no effect of granule formulation with regard to change in SF, and/or

$H_{0,C}$: $\mu_{C,G} = \mu_{C,DT}$ no effect of granule formulation with regard to compliance

versus

$H_{1,SF}$: $\mu_{SF,G} < \mu_{SF,DT}$ mean change in SF favorable for granule formulation compared to DT formulation, and

$H_{1,C:}$ $\mu_{C,G} > \mu_{C,DT}$ mean compliance favorable for granule formulation compared to DT formulation

Analysis of covariance (ANCOVA) will be performed for comparison between both treatment groups. The ANCOVA model for compliance endpoint will include treatment group and age group (2 to<10 years, 10 to <18 years) as factors. The model for serum ferritin endpoint will also include the serum ferritin value at baseline as covariate.

For each of the endpoint the following estimates from the ANCOVA will be provided:

- the least squares mean with 2-sided 95% confidence interval for each treatment arm
- the least squares means with 2-sided 95% confidence interval, p-value for the difference between treatment arms

[redacted]

10.4.3 Handling of missing values/discontinuations

In case of missing serum ferritin value after 24 weeks of treatment, the last available post-baseline serum ferritin value will be used in the calculation of the primary endpoint. Patients without post-baseline serum ferritin value will be excluded from the analysis.

10.4.4 Supportive analyses

The following supportive and supplementary analyses will be provided:

- The primary analysis will be repeated for the FAS-2 and FAS-3.
- The primary analysis will also be provided for the PPS;
- If more than 10% of patients have no serum ferritin value after 24 weeks of treatment, supplementary analyses will be performed for the primary analysis for serum ferritin using imputation techniques. Details will be provided in the study SAP.

Other supportive analyses may be detailed in the SAP.

10.5 Secondary objectives

10.5.1 To evaluate both formulations on change in serum ferritin and compliance measured by stick pack /tablet count after 48 weeks of treatment in ICT naïve patients

Descriptive analyses will be performed after 48 weeks of treatment for the FAS-1. Absolute and relative change from baseline in serum ferritin for core phase will be summarized after 48 weeks of treatment using standard descriptive statistics by treatment arm.

In addition at the time of primary analysis if more than 10% of patients have no serum ferritin value after 48 weeks of treatment or missing compliance measured by stick pack/tablet count over 48 weeks of treatment, a supplementary analysis will be performed using multiple imputation method. Details will be provided in the study SAP.

10.5.2 To evaluate both formulations on change in serum ferritin in ICT naïve and pre-treated patients

Absolute and relative change from baseline in serum ferritin for core phase will be summarized after 24 weeks (i.e. assessed at week 25 visit) and 48 weeks of treatment using standard descriptive statistics by treatment arm for the FAS-1 and FAS-2. The 95% confidence intervals for mean will additionally be provided.

A forest plots will be presented with change in SF after 24 weeks and 48 weeks of treatment and the corresponding exact 95%CI. Point estimates and 95% CI will be generated for the FAS-1, FAS-2 and FAS-3.

Furthermore, the mean and standard deviation values of serum ferritin will be plotted by treatment group and week.

10.5.3 To evaluate both formulations on patient satisfaction and palatability using PRO/ObsRO questionnaires

The FAS-1, FAS-2 and the FAS-3 will separately be used for the analysis of patient satisfaction and palatability using a PRO/ObsRO questionnaire for the core phase.

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 for each domain score at Week 2, Week 3, Week 25 and the EOT (core)/777 visits as well as their absolute changes at Week 25 and EOT (core)/777 visits from Week 2. The standard descriptive analyses include: n, mean, standard deviation, minimum, median and maximum. The 95% confidence intervals for the absolute changes in all domains at Week 25 and EOT (core)/777 visits from Week 2 will be presented for both formulations.

For the palatability questionnaire the overall score will be constructed using a scoring matrix from the score of items. Standard descriptive analyses will be performed for both formulations for the overall score at the Week 2, Week 3, Week 25 visits, and last day of study drug intake and the absolute changes of the overall score at the Week 25 visit and last day of study drug from Week 2. The standard descriptive analyses include: n, mean, standard deviation, minimum, median and maximum. The 95% confidence interval for the absolute change of the overall score at the Week 25 visit and last day of study drug from Week 2 will be presented for both formulations.

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

10.5.4 To evaluate both formulations on overall safety, measured by frequency and severity of adverse events and changes in laboratory values

The Safety Set 1, Safety Set 2 and the Safety Set-3 will separately be used. The overall observation period will be divided into three mutually exclusive segments:

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

10.5.4.1 Adverse events (AEs)

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

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

[redacted]

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

Specific groupings of adverse events of special interest will be considered and the number of patients with at least one event in each grouping will be reported. Such groups consist of adverse events for which there is a specific clinical interest in connection with Deferasirox treatment or adverse events which are similar in nature (although not identical). Note that certain adverse events may be reported within multiple groupings/AESIs.

AESIs are defined by MedDRA terms. All AESI definitions or AE groupings are specified in the Novartis electronic Case Retrieval Strategy (eCRS). The latest version of the eCRS available at the time of the analysis will be used.

Incidence of AESI will be summarized by grouping, preferred term and treatment arm.

Summary tables for adverse events (AEs) will be repeated for the optional extension phase on the Safety Set 4.

10.5.4.2 Laboratory abnormalities

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

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

- shift tables using normal/notable/extended ranges to compare baseline to the worst on-treatment value
- listing of all laboratory data with values flagged to show the corresponding normal/notable/extended ranges (see Table 10-1 below).

For laboratory parameters observed values (and changes from baseline), and per subsequent quarter will be summarized by descriptive statistics overtime (n, mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum).

Laboratory abnormalities will be described for the optional extension phase on the Safety Set 4.

In addition to the above mentioned tables and listings, other exploratory analyses, for example figures plotting time course of raw or change in laboratory tests over time or box plots might be specified in the SAP.

[redacted]

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

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)

10.5.5 To evaluate compliance using a daily PRO/ObsRO questionnaire

Patient adherence to medication regimen instructions will be assessed via daily diary records (PRO / ObsRO questionnaire) providing information on two dimensions: whether the study medication is consumed and the time of medication intake. These data will be summarized over time by descriptive statistics for both formulations. The rate of dosing instructions deviations (doses missed completely or not taken at approximately the same time every day) will be calculated for each study arm.

The FAS-1, FAS-2 and FAS-3 will separately be used for the analysis of compliance using a daily PRO/ObsRO questionnaire.

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

10.5.6 Pharmacokinetics

The PAS will be used to summarize (pre-dose) Cmin and (post-dose) Cmax concentrations and to assess patients' compliance and analysis of PK concentrations. PK/PD (PK/safety and PK/Efficacy) analyses will be based on the Safety Set or FAS accordingly. Other analyses and listings of PK concentration will use the FAS.

10.5.6.1 To evaluate pre-dose PK data to support the assessment of compliance

Pre-dose PK concentrations (Cmin) from the PAS will be analyzed to support the assessment of compliance. Predicted individual Cmin concentrations will be derived from a power model considering dose and potential other covariates, such as body weight. Predicted individual Cmin concentrations will be compared to respective observed pre-dose concentrations at steady-state of all patients. Distributions of the difference between predicted and observed Cmin values will be shown graphically by boxplots for both treatment groups and visit.

10.5.6.2 Description of individual PK concentrations and parameters

PK concentrations will be summarized by treatment, visit and time point. PK parameters will be summarized by treatment and visit.

[redacted]

Descriptive statistics of PK concentration and PK parameters will include arithmetic and geometric means, median, SD, CV%, CV% of the geometric mean, minimum and maximum. Zero concentrations will not be included in the geometric mean calculation.

All analyses will be based on the PAS.

10.5.6.3 To explore PK/PD relationship

Serum ferritin change from baseline will be fitted by a linear mixed effect model with log-transformed matching pre-dose concentrations as covariates and subject as random effect.

Serum creatinine change from baseline, serum creatinine clearance change from baseline and urine protein creatinine ratio change from baseline will be fitted by a linear mixed effect model with log-transformed matching pre-dose and post-dose concentrations respectively as covariates and subject as random effect.

Incidence of notable serum creatinine events as defined in Table 10-1 will be analyzed by a logistic regression fitted by GEE methods as appropriate including matching log-transformed pre- and post-dose concentrations, respectively.

Incidence of notable serum creatinine clearance events as defined in Table 10-1 will be analyzed by a logistic regression fitted by GEE as appropriate methods including matching log-transformed pre- and post-dose concentrations, respectively.

For all statistical models other covariates such as demographic characteristics may be included if appropriate.

Other non-linear mixed effect models, such as effect-compartment models, may be established if appropriate to further explore exposure efficacy or safety relationship and will be reported separately.

10.5.6.4 Data handling principles

Biofluid concentrations will be expressed in mass per volume units. All concentrations below the limit of quantitation or missing data will be reported as such in the concentration data listings. Concentrations below the limit of quantitation will be treated as zero in summary statistics.

10.6 Other analyses

10.6.1 Other safety data

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

10.6.1.1 Cardiac evaluation

ECG and Echocardiogram will be performed at baseline and EOT in the core phase. ECG will be performed when clinically indicated during the optional extension phase. Abnormalities will be reported together with an overall interpretation of the findings. Any abnormalities at baseline will be summarized. At post-baseline assessment, the investigator will flag all abnormalities

[redacted]s will be recorded

on the AE eCRF page. All findings of patients with new or worsened clinically significant abnormalities will be listed.

10.6.1.2 Vital signs and body weight

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 pulse rate and weight values are flagged. The criteria for notably abnormal pulse rate and weight are displayed in Table 10-2.

Table 10-2 Definition of notable ranges for pulse rate and weight

Parameter			
Weight	High	Increase from baseline ≥ 10%	
	Low	Decrease from baseline ≥ 10%	
Pulse rate (beats per minute)	High[1]	12-18 months	> 140
		18-24 months	> 135
		2-3 years	> 128
		3-4 years	> 123
		4-6 years	> 117
		6-8 years	> 111
		8-12 years	> 103
		12-15 years	> 96
		15-18 years	> 92
	Low[1]	12-18 months	< 103
		18-24 months	< 98
		2-3 years	< 92
		3-4 years	< 86
		4-6 years	< 81
		6-8 years	< 74
		8-12 years	< 67
		12-15 years	< 62
		15-18 years	< 58

[1]: Fleming et al 2011.

10.6.1.3 Auditory and ocular assessment evaluations

Auditory evaluations will be performed at baseline, visit 17 if entering the optional extension phase and annually during the optional extension phase and ocular evaluations at baseline, Week 25 visit (Visit 11) and at EOT(core) visit (Visit 777) during the core phase and annually

[redacted]

during the optional extension phase. 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.

10.6.1.4 Growth and Development

For pediatric patients, growth velocity and pubertal stage will be listed at baseline, at EOT visit 777 and annually during the optional extension phase and summarized using descriptive statistics as appropriate.

10.6.1.5 Serum ferritin during the optional extension phase

Change from baseline in serum ferritin at every year will be described for the Safety Set 4.

10.7 Interim analysis

One interim analysis has been added to allow for early analysis of the core phase data if requested by the health authority. All chelation-naïve patients randomized in the study and who have completed a minimum of 12 weeks of treatment exposure or discontinued from treatment core phase at the time of the cutoff date will be included in the interim analysis.

All the analyses included in the interim analysis will be descriptive. Testing of hypotheses will not be performed and no decisions regarding the future course of the trial is anticipated at the time of the IA and the trial will continue. Therefore adjustment for multiplicity is not performed.

Descriptive statistics will be provided by treatment arm on the primary endpoints (i.e. change from baseline in serum ferritin and compliance measured by stick pack /tablet count) and key safety data.

Details on the analyses will be described in the statistical analysis plan.

10.8 Sample size calculation

The primary objective of this study is to evaluate patient compliance (using stick packs or tablets counts) and change in serum ferritin (SF) over time for both formulations of deferasirox in pediatric ICT naïve patients with iron overload.

The sample size was estimated to demonstrate superiority and statistical significance for both co-primary endpoints.

The assumptions made for this study were:

- For serum ferritin:

  An expected improvement between both formulations in SF change from baseline after 24 weeks of treatment of −450ng/mL with a standard deviation (SD) of 900 ng/mL based on results from study CICL670A0107 in pediatric patients treated with Exjade on ≥25 mg/kg/day after 24 weeks of treatment.

[redacted]

- For compliance using stick packs or tablets counts:

  An expected improvement between both formulations in mean relative consumed tablet count of 10% with a SD equal to 17.625% based on the pooled analysis on pediatric patients (77) from Exjade studies [ICL670A2206] (39), [ICL670A2204] (24) and [ICL670A2214] (14).

The sample size, driven by the calculation of serum ferritin, has been determined to obtain 76% power at a one-sided 5% level of significance for showing superiority of granule formulation over DT formulation with respect to change from baseline after 24 weeks of treatment in serum ferritin.

A sample size of 45 in each group will have 76% power to detect a difference in means of 400.0 ng/mL assuming that the common SD is 800.0 ng/mL using a two group t-test with a 0.050 one-sided significance level. With 45 patients per arm, the power to detect a difference of 10% or more in mean compliance is about 84%.

Considering a potential of 5% dropout rate patients, the required sample size to achieve the primary objective is 48 chelation naïve patients for each treatment group (96 patients in total).

In addition, the clinical trial will enroll patients previously treated with iron chelation patients. Considering that a direct comparison of granule and DT formulations in terms of efficacy is not foreseen in previously chelated patients, the required sample size is not based on power calculations as usual. The selection of number of patients is based on the precision in the estimate of SF change after 48 weeks of treatment and on practical considerations.

A maximum of 120 (60 patients will be in each formulation group) previously chelated patients will be enrolled. Sixty patients will provide an estimate of SF change with precision (half-width of 95% confidence interval) equal to 303.6.

Table 10-3 below lists the precisions in the estimates of SF change for different numbers of patients using the estimated SD obtained from the [CICL670A0107] study results in pediatric patients treated with Exjade on ≥25 mg/kg/day at week 48 of treatment.

Table 10-3 Precision in the estimate of the serum ferritin change

Number of patients	Half-width of 95% confidence interval in the estimate of the SF change
40	371.8
45	350.6
50	332.6
55	317.1
60	303.6

The total required sample size for this clinical trial is up to 108 patients for each treatment group (up to 216 patients in total), including 48 iron chelation naive patients per group (96 patients in total).

[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.

As per Section 4.5, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain

a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local Heath Authority.

Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

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.

[redacted]

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/assent 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 prior to study start by study personnel who are directly involved in the treatment or evaluation of patients at the site.

12 Protocol adherence

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

12.1 Amendments to the protocol

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

[redacted]

13 References (available upon request)

Borgna-Pignatti C, Rugolotto S, De Stefano P et al (2004) Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. Haematologica; 89:1187-1193Cappellini MD, Cohen A, Piga A, et al. (2006) A Phase III study of deferasirox (ICL670), a once-daily oral iron chelator, in patients with ß-thalassemia. Blood; 107:3455-62

Cappellini MD (2008a) Long-term efficacy and safety of deferasirox. Blood Rev; Suppl 2:S35-41

Cappellini MD, Elalfy M, Kattamis J, et al. (2008b) Efficacy and safety of once-daily, oral iron chelator deferasirox (Exjade) in a large group of regularly transfused patients with β-thalassemia major. ASH, San Francisco, USA, 6-9 December 2008; Poster III-960

Fleming S, Thompson M, Stevens R, et al (2011) Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet; 377:1011-8.

Gabutti V, Piga A. (1996) Results of long-term iron-chelating therapy. Acta Haematol ; 95:26-36

Haghpanah S, Zarei T, Zahed Zi,et al. (2014) Compliance and satisfaction with deferasirox (Exjade®) compared with deferoxamine in patients with transfusion-dependent beta-thalassemia. Hematology; 19: 187-191

Inati A, Khoriaty E, Musallam KM (2011) Iron in Sickle-Cell Disease: What Have We Learned Over the Years? Pediatr Blood Cancer; 56:182-190

Kushner J, Porter J, and Olivieri N (2001) Secondary Iron Overload. Hematology; 47-61

Mednick LM, Braunstein J, Neufeld E (2010) Oral Chelation: Should It Be Used With Young Children? Pediatr Blood Cancer; 55:603-605

Osborne RH, De Abreu Lourenço R, Dalton A, et al (2007) Quality of life related to oral versus subcutaneous iron chelation: a time trade-off study. Value Health;10(6):451-6

Osterberg L, Blaschke T (2005) Adherence to Medication. N Engl J Med; 353:487-97

Partridge AH, Avorn J, Wang PS, Winer EP (2002) Adherence to Therapy With Oral Antineoplastic Agents. Journal of the National Cancer Institute; 94(9):652-661

Rudd P, Byyny RL, Zachary V et al (1989) The natural history of medication compliance in a drug trial: Limitations of pill counts. Clin Pharmacol Ther, Vol 46, No 2: 169-176Trachtenberg F, Vichinsky E, Haines, D, et al (2011) Iron chelation adherence to deferoxamine and deferasirox in thalassemia. Am J Hematol; 86(5): 433–436

Tuleu C (2011) Acceptability and Palatability – methods available for assessment.

Vichinsky E (2008) Oral Iron Chelators and the Treatment of Iron Overload in Pediatric Patients With Chronic Anemia.Pediatrics;121;1253-1256

Vichinsky et al (2012) Standards of Care Guidelines for Thalassemia (Internet) Available from: http://thalassemia.com/documents/SOCGuidelines2012.pdf (Accessed 29 Jan 2015).

Weatherall DJ (2010) The inherited diseases of hemoglobin are an emerging global health burden. Blood; 115: 4331-4336.

[redacted]

Workshop on Paediatric Formulations II for Assessors in National Regulatory Agencies, Nov 8, 2011, EMA/432389/2011, Human Medicines Development and Evaluation.

[redacted]

14 Appendices

14.1 Equivalent dose guidance

All iron chelation pre-treated patients well-managed on treatment with deferasirox will use the same starting DT dose or an equivalent granules dose (see Table 14-1).

For patients pre-treated with deferoxamine, a starting dose of DT or an equivalent granules 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 granules), see Table 14-2.

Dose equivalence between deferiprone and deferasirox is not established in clinical studies. For patients pre-treated with deferiprone (DFP), investigators should decide on the starting dose of DT or granules in the study, taking into consideration the iron overload status of the patients and their transfusional regimen.

Table 14-1 Patients pre-treated with deferasirox

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

Table 14-2 Patients pre-treated with deferoxamine

Previous dose of Deferoxamine (mg/kg/day)	Equivalent dose to be used	
	Deferasirox DT (mg/kg/day)	Deferasirox granules (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]

Table 14-3 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 hummuus or 2 oz. meat	27	1
apple	medium (2.75" across)	72	0
salsa, red, cooked	6 Tablespoons	26	0
carrots & celery sticks	4 carrot sticks (3" long) and small 5" stalk of celery	14	0
	Total:	**263-295**	**2**

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

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

[redacted]

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

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

[redacted]

14.2 Dosing tables (Deferasirox DT, Deferasirox granules)

For each patient the investigator and/or pharmacist will calculate a target daily dose taking into account patient's body weight at randomization. When the calculated dose cannot be reached with the deferasirox tablet / stick pack strengths available, the closest daily dose available will be prescribed. The following dosing tables provide an efficient combination of tablet / stick pack strengths reaching a certain daily dose for each body weight range.

Examples illustrating this approach are provided below:

- For a patient with a body weight of 46 kg and a deferasirox DT dose of 20 mg/kg/day, the calculated daily dose is 920 mg. Taking into account the available DT strengths of 125, 250 and 500 mg deferasirox, the closest daily dose the patient can receive is 875 mg, by taking 3 deferasirox tablets: 1 x 125 mg + 1 x 250 mg + 1 x 500 mg. This combination can be found in the 'Tablets' column, for patients receiving 20 mg/kg/day of deferasirox DT and with a body weight between 41-46 kg.
- For a patient with a body weight of 46 kg and a deferasirox granules dose of 14 mg/kg/day, the calculated daily dose is 644 mg. Taking into account the available stick pack strengths of 90, 180 and 360 mg deferasirox, the closest daily dose the patient can receive is 630 mg, by taking 3 stick packs: 1 x 90 mg + 1 x 180 mg + 1 x 360 mg. This combination can be found in the 'Stick packs' column, for patients receiving 14 mg/kg/day of deferasirox granules and with a body weight between 42-48 kg.

These dosing tables have been constructed for each dosing group using lower and upper body weight limits of 5 and 140 kg, respectively. This is taking into account that the study will enroll male or female children and adolescents, ≥ 2 and < 18 years. However, for some patients with a low body weight (e.g. below 19 kg in the 5 mg/kg/day dosing group) the dosing requirements given in Section 6.1.1 will not allow for the use of the smallest strength available (Eg: 125 mg for DT, or 90 mg for granules). In such cases a written request will be sent to Novartis, to advise on the individual patient enrolment / dose adjustments options.

[redacted]

Table 14-4 Dosing table for deferasirox DT

Body weight ranges per dosing group (kg)								Tablets		
5 mg/kg/day [kg]	10 mg/kg/day [kg]	15 mg/kg/day [kg]	20 mg/kg/day [kg]	25 mg/kg/day [kg]	30 mg/kg/day [kg]	35 mg/kg/day [kg]	40 mg/kg/day [kg]	125 mg	250 mg	500 mg
19 - 37	10 - 18	9 - 12	5 – 9	5 - 7	5 - 6	5		1		
38 - 62	19 - 31	13 - 20	10 - 15	8 - 12	7 - 10	6 - 8	5 - 7		1	
63 - 87	32 - 43	21 - 29	16 - 21	13 - 17	11 - 14	9 - 12	8 - 10	1	1	
88 - 112	44 - 56	30 - 37	22 - 28	18 - 22	15 - 18	13 - 16	11 - 14			1
113 - 137	57 - 68	38 - 45	29 - 34	23 - 27	19 - 22	17 - 19	15 - 17	1		1
138 - 140	69 - 81	46 - 54	35 - 40	28 - 32	23 - 27	20 - 23	18 - 20		1	1
	82 - 93	55 - 62	41 - 46	33 - 37	28 - 31	24 - 26	21 -23	1	1	1
	94 - 106	63 - 70	47 - 53	38 - 42	32 - 35	27 - 30	24 - 26			2
	107 - 118	71 - 79	54 - 59	43 - 47	36 - 39	31 - 33	27 - 29	1		2
	119 - 131	80 - 87	60 - 65	48 - 52	40 - 43	34 - 37	30 - 32		1	2
	132 - 140	88 - 95	66 - 71	53 - 57	44 - 47	38 - 41	33 - 35	1	1	2
		96 - 104	72 - 78	58 - 62	48 - 52	42 - 44	36 - 39			3
		105 - 112	79 - 84	63 - 67	53 - 56	45 - 48	40 - 42	1		3
		113 - 120	85 - 90	68 - 72	57 - 60	49 - 51	43 - 45		1	3
		121 - 129	91 - 96	73 - 77	61 - 64	52 - 55	46 - 48	1	1	3
		130 - 137	97 - 103	78 - 82	65 - 68	56 - 58	49 - 51			4
		138 - 140	104 - 109	83 - 87	69 - 72	59 - 62	52 - 54	1		4
			110 - 115	88 - 92	73 - 77	63 - 66	55 - 57		1	4
			116 - 121	93 - 97	78 - 81	67 - 69	58 - 60	1	1	4
			122 - 128	98 - 102	82 - 85	70 - 73	61 - 64			5
			129 - 134	103 - 107	86 - 89	74 - 76	65 - 67	1		5
			135 - 140	108 - 112	90 - 93	77 - 80	68 - 70		1	5
				113 - 117	94 - 97	81 - 83	71 - 73	1	1	5
				118 - 122	98 - 102	84 - 87	74 - 76			6
				123 - 127	103 -106	88 - 91	77 - 79	1		6

[redacted]

Body weight ranges per dosing group (kg)								Tablets		
5 mg/kg/day [kg]	10 mg/kg/day [kg]	15 mg/kg/day [kg]	20 mg/kg/day [kg]	25 mg/kg/day [kg]	30 mg/kg/day [kg]	35 mg/kg/day [kg]	40 mg/kg/day [kg]	125 mg	250 mg	500 mg
				128 - 132	107 - 110	92 - 94	80 - 82		1	6
				133 - 137	111 - 114	95 - 98	83 - 85	1	1	6
				138 - 140	115 - 118	99 - 101	86 - 89			7
					119 - 122	102 -105	90 - 92	1		7
					123 - 127	106 -108	93 - 95		1	7
					128 - 131	109 - 112	96 - 98	1	1	7
					132 - 135	113 - 116	99 - 101			8
					136 - 139	117 - 119	102 - 104	1		8
					140	120 - 123	105 - 107		1	8
						124 - 126	108 - 110	1	1	8
						127 - 130	111 - 114			9
						131 - 133	115 - 117	1		9
						134 - 137	118 - 120		1	9
						138 - 140	121 - 123	1	1	9
							124 - 126			10
							127 - 129	1		10
							130 - 132		1	10
							133 -135	1	1	10
							136 - 139			11
							140	1		11

[redacted]

Table 14-5 Dosing table for deferasirox granules

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

[redacted]

Body weight ranges per dosing group (kg)								Stick packs		
3.5 mg/kg/day [kg]	7 mg/kg/day [kg]	10.5 mg/kg/day [kg]	14 mg/kg/day [kg]	17.5 mg/kg/day [kg]	21 mg/kg/day [kg]	24.5 mg/kg/day [kg]	28 mg/kg/day [kg]	90 mg	180 mg	360 mg
				137 - 140	114 - 117	98 - 101	86 - 88	1	1	6
					118 - 122	102 - 104	89 - 91			7
					123 - 126	105 -108	92 - 94	1		7
					127 - 130	109 -112	95 - 98		1	7
					131 - 135	113 - 115	99 - 101	1	1	7
					136 - 139	116 - 119	102 - 104			8
					140	120 - 123	105 - 107	1		8
						124 - 126	108 - 110		1	8
						127 - 130	111 - 114	1	1	8
						131 - 134	115 - 117			9
						135 - 137	118 - 120	1		9
						138 - 140	121 - 123		1	9
							124 - 126	1	1	9
							127 - 130			10
							131 - 133	1		10
							134 - 136		1	10
							137 -139	1	1	10
							140			11

[redacted]