An open label, multi-center, efficacy and safety study of deferasirox in iron overloaded patients with non-transfusion dependent thalassemia (THETIS)
Protocol Summary

Study title:
An open label, multi-center, efficacy and safety study of deferasirox in iron overloaded patients with non-transfusion dependent thalassemia

Study phase:
Phase IV

Study objectives:

Primary objective
To assess the efficacy of deferasirox in patients with non-transfusion dependent thalassemia based on change in liver iron concentration (LIC) from baseline after 52 weeks of treatment.

Secondary objectives
- Assess response rates in patients with baseline LIC values >15 mg Fe/g dw defined as the proportion of patients achieving an LIC<5 mg Fe/g dw and time to achieving LIC <5mg Fe/g dw
- Assess long-term efficacy and safety of treatment to target LIC of 3 mg Fe/g dw followed by one or more treatment holidays until the LIC is ≥5 mg Fe/g dw
- To evaluate the impact of deferasirox on adult Quality of Life (QoL) using the Medical Outcomes Study Short Form–36 (SF-36) (in patients >18 years of age)
- To evaluate the impact of deferasirox on pediatric QoL using the Pediatric Quality of Life questionnaire (in patients 13 thru 18 years of age)
- To evaluate the efficacy of deferasirox based on changes in LIC from baseline over time (approximately six month intervals)
- To assess the correlation of change in SF and LIC at baseline and end of study (EOS)
- To assess the efficacy of deferasirox based on change in LIC from baseline after 52 weeks of treatment by non-transfusion dependent thalassemia (NTDT) syndrome
- To assess the efficacy of deferasirox based on change in SF from baseline over time
- To evaluate the safety of deferasirox doses up to 30 mg/kg/day
- To assess the efficacy of deferasirox on endocrine function based on change from baseline over time for total and free testosterone (males), luteinizing hormone (LH) and follicle stimulating hormone (FSH) (females), thyroid stimulating hormone (TSH), total and free T4, total and free T3, insulin, insulin resistance, fasting plasma glucose (FPG) and cortisol
- To conduct pharmacokinetic (PK) analysis in a subset of patients

Study population:
Patients with non-transfusion-dependent congenital or chronic anemias inclusive of beta-thalassemia intermedia, HbE beta-thalassemia or alpha-thalassemia intermedia (HbH disease). Patients must be ≥ 10 years of age with a LIC ≥ 5 mg Fe/g dw and a serum ferritin ≥ 300 ng/mL.

Number of patients:
117

Overview of study design:
This will be an open label, single arm, multi-center study. A four week screening phase will determine patient eligibility. Deferasirox will be initiated at a dose of 10 mg/kg/day for 4 weeks. At week 4, dose escalation will then be dependent upon baseline LIC severity. At week 24, and approximately every 6 months thereafter (for up to five years), further dose adjustments may occur based on Week 24 LIC severity. The maximum dose of deferasirox throughout the study will be 30 mg/kg/day.
Statistical considerations:

The sample size was determined on the results observed in the ICL670E2209 trial, assuming a larger variance to reflect the broader patients population. 117 patients will have to be enrolled to obtain 90% power to detect a LIC absolute change of at least 2 mg Fe at Week 52 from the baseline value with a standard deviation of 6 mg Fe using a paired t-test at 5% two-sided significance level. Data from all centers participating in this study will be aggregated to have an adequate number of patients for the analyses. Standard descriptive analyses will include frequencies and percentages for categorical data, n, mean, standard deviation, minimum, median, 25th and 75th percentiles and maximum for continuous data.
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<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>ALT/SGPT</td>
<td>Alanine aminotransferase/serum glutamic pyruvic transaminase</td>
</tr>
<tr>
<td>AST/SGOT</td>
<td>Aspartate aminotransferase/serum glutamic oxaloacetic transaminase</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the curve</td>
</tr>
<tr>
<td>BUN</td>
<td>Blood Urea Nitrogen</td>
</tr>
<tr>
<td>Cmax</td>
<td>Maximum (peak) observed plasma concentration after single dose administration</td>
</tr>
<tr>
<td>CRO</td>
<td>Contract Research Organization</td>
</tr>
<tr>
<td>CS&amp;E</td>
<td>Clinical Safety and Epidemiology</td>
</tr>
<tr>
<td>CSR</td>
<td>Clinical study report</td>
</tr>
<tr>
<td>CTGF</td>
<td>Urinary connective tissue growth factor</td>
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<tr>
<td>DMC</td>
<td>Data Monitoring Committee</td>
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<tr>
<td>dw</td>
<td>Dry weight</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic Case Report/Record Form</td>
</tr>
<tr>
<td>EOS</td>
<td>End of study</td>
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<tr>
<td>FAS</td>
<td>Full analysis set</td>
</tr>
<tr>
<td>FE</td>
<td>Iron</td>
</tr>
<tr>
<td>FPFV</td>
<td>First patient first visit</td>
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<tr>
<td>FPG</td>
<td>Fasting plasma glucose</td>
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<tr>
<td>FSH</td>
<td>Follicle stimulating hormone</td>
</tr>
<tr>
<td>GGT</td>
<td>Gamma glutamyl transferase</td>
</tr>
<tr>
<td>GSTA</td>
<td>Glutathione transferase alpha</td>
</tr>
<tr>
<td>HbE</td>
<td>Hemoglobin E</td>
</tr>
<tr>
<td>HbH</td>
<td>Hemoglobin H</td>
</tr>
<tr>
<td>HBsAb</td>
<td>Hepatitis B surface antibody</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Hepatitis B surface antigen</td>
</tr>
<tr>
<td>HCV</td>
<td>Hepatitis C virus</td>
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<tr>
<td>HDPE</td>
<td>High density polyethylene</td>
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<tr>
<td>HRQOL</td>
<td>Health-related quality of life</td>
</tr>
<tr>
<td>i.v.</td>
<td>Intravenous(ly)</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
</tr>
<tr>
<td>IEC</td>
<td>Independent Ethics Committee</td>
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<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
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<tr>
<td>LDH</td>
<td>Lactate dehydrogenase</td>
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<tr>
<td>LH</td>
<td>Luteinizing hormone</td>
</tr>
<tr>
<td>LIC</td>
<td>Liver iron content</td>
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<tr>
<td>LOCF</td>
<td>Last observation carried forward</td>
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<tr>
<td>LPI</td>
<td>Labile plasma iron</td>
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<tr>
<td>LPLV</td>
<td>Last patient last visit</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>NTBI</td>
<td>Non-transferrin-bound iron</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<td>--------------</td>
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<tr>
<td>NTDT</td>
<td>Non-transfusion dependent thalassemia</td>
</tr>
<tr>
<td>o.d.</td>
<td>Omnia die/once a day</td>
</tr>
<tr>
<td>p.o.</td>
<td>Per os/by mouth/orally</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetic</td>
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<tr>
<td>PROs</td>
<td>Patient reported outcomes</td>
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<tr>
<td>QoL</td>
<td>Quality of Life</td>
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<td>REB</td>
<td>Research Ethics Board</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse event</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SF</td>
<td>Serum ferritin</td>
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<tr>
<td>SF-36</td>
<td>Medical Outcomes study short form-36</td>
</tr>
<tr>
<td>SJS</td>
<td>Stevens-Johnson syndrome</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
</tr>
<tr>
<td>SSC</td>
<td>Study steering committee</td>
</tr>
<tr>
<td>T 1/2</td>
<td>The elimination half-life associated with the terminal slope of a semi logarithmic concentration-time curve</td>
</tr>
<tr>
<td>THALASSA</td>
<td>Novartis Study CICL670E2209</td>
</tr>
<tr>
<td>Tmax</td>
<td>Time to reach maximum (peak) plasma concentration after single dose administration</td>
</tr>
<tr>
<td>TSH</td>
<td>Thyroid stimulating hormone</td>
</tr>
<tr>
<td>VEGF B</td>
<td>Vascular endothelial growth factor B</td>
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## Glossary of terms

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<tr>
<th>Term</th>
<th>Definition</th>
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<tr>
<td>Assessment</td>
<td>A procedure used to generate data required by the study</td>
</tr>
<tr>
<td>Control drug</td>
<td>A study treatment used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug</td>
</tr>
<tr>
<td>Enrollment</td>
<td>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)</td>
</tr>
<tr>
<td>Investigational drug</td>
<td>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 &quot;investigational new drug.&quot;</td>
</tr>
<tr>
<td>Investigational treatment</td>
<td>Drug whose properties are being testing 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</td>
</tr>
<tr>
<td>Medication number</td>
<td>A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study</td>
</tr>
<tr>
<td>Other study treatment</td>
<td>Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment</td>
</tr>
<tr>
<td>Subject Number (Subject No.)</td>
<td>A unique identifying number assigned to each patient/healthy volunteer who enrolls in the study</td>
</tr>
<tr>
<td>Period</td>
<td>A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.</td>
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<td>Premature patient withdrawal</td>
<td>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, unless the patient will be followed for progression and/or survival</td>
</tr>
<tr>
<td>Randomization number</td>
<td>A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment</td>
</tr>
<tr>
<td>Stage related to study timeline</td>
<td>A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.</td>
</tr>
<tr>
<td>Stage in cancer</td>
<td>The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body</td>
</tr>
<tr>
<td>Stop study participation</td>
<td>Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later</td>
</tr>
<tr>
<td>Study treatment</td>
<td>Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins.</td>
</tr>
<tr>
<td>Study treatment discontinuation</td>
<td>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</td>
</tr>
<tr>
<td>Variable</td>
<td>Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points</td>
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Amendment 2

Amendment rationale

At the time of this amendment, the study is closed for recruitment. One hundred thirty four (134) patients were enrolled in the study and 19 patients were discontinued.

The main purpose of this amendment is to provide guidance regarding dose modifications, concomitant medications, and contraception as detailed below. This amendment also clarifies the timing of the 2 analyses of this study: a one-year analysis and a final analysis.

The dose modification guidelines were updated to provide guidance on treating patients with moderate hepatic impairment (Child-Pugh Class B) and immediate discontinuation if Stevens-Johnson syndrome or severe hepatic impairment (Child-Pugh Class C) occurs, in alignment with the approved Exjade prescribing information.

Guidance on the use of contraception: “highly effective” (inadvertently introduced in Amendment 1) was changed to “effective” methods of contraception, in alignment with the approved Exjade prescribing information. Embryo-fetal development animal studies did not show evidence of teratogenicity and there were no developmental effects noted at doses that were not toxic to the maternal animals.

Additional guidance was added regarding treatment discontinuation of patients with creatinine clearance < 40 mL/min or serum creatinine > 2 times the age appropriate ULN and caution should be used in patients with creatinine clearance between 40 and less than 60 mL/min, particularly in cases where there are additional risk factors that may impair renal function such as concomitant medications, dehydration, or severe infections in alignment with the approved Exjade prescribing information.

Guidance was added regarding the concomitant administration of deferasirox with CYP1A2 substrates that have a narrow therapeutic index and the concomitant use of bile acid sequestrants in alignment with the approved Exjade prescribing information. Vitamin C was moved from the prohibited concomitant medication category to drugs that should be administered with caution in combination with deferasirox.

Criteria on when patients must be withdrawn from the study were clarified.

Clarification was added for visit schedules, liver function tests (serum transaminases, bilirubin, and alkaline phosphatase) and pregnancy testing.

In Amendment 1, the duration of the study was extended from one year to up to five years in order to evaluate long-term efficacy and safety of deferasirox in patients with NTDT and iron overload. The one-year analysis and the one-year clinical study report will be generated in alignment with the study’s primary objective to assess the efficacy of deferasirox in patients with NTDT based on an absolute change in LIC from baseline after 52 weeks of treatment and will include all assessments and events within treatment Year 1. The one-year study report will be issued at the end of the one-year treatment period. The final analysis and the final clinical study report will be prepared at the end of the study.

This amendment also clarifies the definition of the end of study. The maximum recommended restart dose is clarified when there is a change of serum ferritin.
Typographic errors were corrected, including the planned study visits every 4-weeks period between the visits described in the protocol and the deferasirox dosing table. Deferasirox background and reference sections were updated to include the recently approved indication in NTDT patients and the most recent available clinical information.

Changes to the protocol

Changes to Section “List of abbreviations”

- “LPI”: A typographic error in the definition of “LPI” abbreviation was corrected.

Change to Section 1 Background: Updated with the latest approved indication in NTDT patients and the most recent available clinical information.

Changes to Section 4 Study design:

- Section 4.3 Definition of end of the study: was updated to specify the time-point of final analysis

Changes to Section 5 Population:

- Section 5.3 Exclusion criteria: “Highly effective” birth control methods changed to “effective”
- Subheading ‘Women of child-bearing potential’: Definition of child bearing potential was updated and pregnancy prevention guidance was modified to describe “effective” methods of contraception

Changes to Section 6 Treatment:

- Table 6-1 Deferasirox dosing table for 5 mg/kg/day: Corrected a typographic error in the weight range requiring a dose of 375mg (the correct range is 62.6 - 87.5 kg).
- Table 6-6 Deferasirox dosing table for 30 mg/kg/day: Corrected a typographic error in the number of 500mg tablets required to achieve recommended dose (1250mg) when a patient’s weight is between 39.7 - 43.8kg.
- Section 6.3 Concomitant medications: Guidance was added regarding the concomitant administration of deferasirox with CYP1A2 substrates that have a narrow therapeutic index (to be administered with caution) and with bile acid sequestrants (prohibited).
- Section 6.4.2 Change in serum ferritin: the maximum dose at which study treatment should be restarted was clarified
- Section 6.4.4 Serum creatinine and Creatinine clearance: Caution added for creatinine clearance between 40 and less than 60 mL/min, especially in patients with additional risk factors. Added dose adjustment guidance regarding treatment discontinuation in case creatinine > 2xULN and/or creatinine clearance < 40 mL/min
- Section 6.4.6 Stevens-Johnson syndrome (SJS): New section added for patients with SJS
- Section 6.4.7 Skin rash (other than SJS): Dose adjustment guidance updated
- Section 6.4.9 Hepatic impairment: New section added, providing guidance to treatment dose modifications for patients with moderate or severe hepatic impairment (Child-Pugh class B or C).
- Section 6.5.2 Premature patient withdrawal / End of treatment: Criteria on when patients must be withdrawn from the study were clarified.
Changes to Section 7 Visit schedule and assessments:

- **Table 7-1** Visit evaluation schedule: screening evaluations which could be performed at visit 1 or visit 2 were clarified to reflect the screening assessments planned in the protocol.

- **Table 7-1** Visit evaluation schedule and **Table 7-2** Laboratory assessment schedule: Corrected to include the visits W108-124 and W160-176 missing from these tables but planned and described in the protocol as part of the 4-weeks between visits schedule during the 5 years study duration.

- **Table 7-2** Laboratory assessment schedule: in the “Category” column: The category was updated from “S” (Source document) to “D” (database) for the evaluation “Serum/Urine Pregnancy test” as this assessment is recorded in the database and not only in source document as indicated in the protocol.

- **Table 7-2** Laboratory assessment schedule: Liver function tests (serum transaminases, bilirubin, and alkaline phosphatase) are part of the monthly biochemistry panel; additional LFTs are required only at visits 5, 9, 17, 27, 36, 46, 55, 65, 74, 84, and 93 (2 weeks after dose initiation and after each dose escalation); all other visits overlapping with biochemistry tests were deleted in the LFT row, to avoid duplication.

- **Table 7-2** Laboratory assessment schedule was amended to separate serum pregnancy from urinary pregnancy testing and to indicate that serum testing is required shortly before treatment initiation and urinary testing at the End of Treatment visit. A corresponding footnote was added in the table legend.

- **Section 7.2.2.3** Height and weight: clarified that weight assessment can be done at screening either at visit 1 or at visit 2.

- **Section 7.2.2.5.2** Clinical chemistry: clarified that estimated Creatinine clearance is obtained monthly and at EoT (Serum creatinine is obtained more often, per Table 7-2)

- **Section 7.2.2.5.4** Pregnancy and assessment of fertility: Clarified that urinary pregnancy testing is required during the study in case of delayed menses and at the end of treatment visit. Added instruction to discontinue study in case of pregnancy. Deleted text on reporting and recording pregnancy events during the study, to avoid redundancy with **Section 8.4** (already referenced).

Change to Section 9 Data collection and management

- **Section 9.4** Database management and quality control was updated to include information concerning the final data lock.

Change to Section 10 Statistical methods and data analysis

- Analyses to be performed at one-year and at end of study (final analysis) were defined.

- **Section 10.4.5** One-year and final analysis were added to define both analyses.

- **Section 10.5.1** Response analysis in patients with baseline LIC greater than 15 mg Fe/g dw: a formatting error was corrected in the 97% quantile of the standard normal distribution described in the Agresti and Coull 1998 formula.

Change to Section 11.5 Publication of study protocol and results

- Information on two study reports to reflect the one-year analysis and the final study reports was added.
Change to References: Updated to reflect the references introduced to the background section. Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through font for deletions and underlined font for insertions.

**IRB/IEC/HA**

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.
Summary of previous amendment(s)

Amendment 1

Amendment rationale

The purpose of this amendment is to modify the duration of the study and to generate long-term efficacy and safety data of deferasirox in patients with NTDT and iron overload. The pivotal trial in NTDT (THALASSA) consisted of a one year core and a one year extension with a total study duration of only two years. To generate longer term data beyond two years, amendment 1 will extend the study duration to up to five years follow-up.

Secondary objectives have been added to assess the efficacy of treatment in patients with very high LIC (>15 mg Fe/g dw) at baseline and those who need re-treatment after having reached the target LIC <3 mg Fe/g dw during the study. The THALASSA study duration did not allow for the subgroup of patients with LIC 15 mg Fe/g dw to reach the therapeutic target LIC and for the subgroup of patients who reach the LIC <3mg Fe/g dw to re-accumulate enough iron overload that would necessitate re-treatment with deferasirox. Analyses of the secondary objectives have been modified to add these endpoints and reflect the change in study duration to include up to five year follow-up.

The interruption of treatment based on serum ferritin value <300 ng/mL was changed based on safety data from the THALASSA study and in accordance with the label recommendation of deferasirox treatment interruption in patients with NTDT and iron overload.

Dose adjustments based on LIC have been modified for clarification and extended duration of study.

The schedule of assessments has added the analysis of serum transaminases, bilirubin, and alkaline phosphatase at two weeks following the initiation of study drug, as per recommended safety monitoring. The schedule of assessments has also been modified to extend the visits to five years.

Clarifications regarding sample handling, ocular and auditory examination details, and new pregnancy language are also included in this amendment.

At the time of this amendment, 35 patients have started treatment in Thailand, Italy, Turkey, and Lebanon. Eight sites in five countries are actively screening patients. All 117 patients are expected to be enrolled by December 2013. Upon approval of amendment, patients who have already been enrolled in the study will sign a new consent form for the extended study duration and continue the appropriate visit schedule.
Changes to the protocol

Changes to Protocol Summary:
• Added two secondary objectives and changed wording to account for extended study duration. Replaced “genotype” with NTDT syndrome
• Overview of study design: Changed to account for extended study duration

Change to Section 2.1 Study rationale and purpose:
• Added “long-term”
• Replaced “escalations” with “adjustments”

Change to Section 2.2 Rationale for the study design:
• Replaced “52 week” with “five year”
• Added text with reason for extension of study duration

Change to Section 2.3 Rationale for dose regimen selection: Replaced “week 24” with “adjustments” and changed wording to account for extended study duration

Changes to Section 3 Objectives and endpoints:
• Added two secondary objectives and changed wording to account for extended study duration.
• Replaced “genotype” with “NTDT syndrome”

Changes to Table 3-1 Objectives and related endpoints: Added two secondary objectives with corresponding endpoints and changed wording for endpoints related to Quality of Life

Changes to Section 4.1 Description of study design:
• Dose adjustment guidance was clarified and language reflects change in study duration.
• Added guidance on study drug interruption and change to visit frequency.

Change to Figure 4-1 Study design: Replaced figure to reflect dose adjustment clarification.

Changes to Section 5.3 Exclusion criteria: New pregnancy language was included in criterion for patients of child-bearing potential and in the definition under the “Women of child-bearing potential” subheading. Both include details regarding the use of highly effective methods of contraception.

Changes to Section 6 Treatment:
• Section was updated to include extended study duration and clarification of dose adjustments.
• Added assessments of serum transaminases, bilirubin, and alkaline phosphatase 2 weeks after the initiation of treatment.

Change to Figure 6-1: Removed as it is a duplicate of Figure 4-1.
Change to Section 6.3 Concomitant medications: Added hormonal contraceptives to treatments NOT allowed

Change to Section 6.5 Treatment duration: Added five years.

Changes Section 7 Visit schedule and assessments:
- Table 7-1 Visit evaluation schedule: Table reflects the increase in number of visits due to five year study duration.
- Replaced “S” with “D” in category column for ocular and audiometry exams.
- Added assessments of serum transaminases, bilirubin, and alkaline phosphatase 2 weeks after the initiation of treatment.

Changes to Section 7.1.2 Screening: Added pregnancy test assessment and guidance on additional laboratory assessments in the event that 4-week screening period is exceeded.

Changes to Section 7.1.4 Treatment period: Added five year study duration and assessments of serum transaminases, bilirubin, and alkaline phosphatase 2 weeks after initiation of treatment.

Change to Section 7.2.1.3 Endocrine function laboratory parameters: Added assessment of endocrine function to be every three months following the first year of treatment.

Changes to Section 7.2.2.3 Height and Weight: Added visit dates

Added Section 7.2.2.4 Auditory and ocular examination: Added assessments included in exams

Changes to Section 7.2.2.5.2 Clinical chemistry:
- Added assessments of serum transaminases, bilirubin, and alkaline phosphatase 2 weeks after initiation of treatment.
- Added weekly serum creatinine assessment following dose escalation during study.

Change to Section 7.2.2.6.1 Electrocardiogram (ECG): Added annual ECG assessment

Change to Section 7.2.3 Pharmacokinetics: Added pediatric patients will not participate in PK subgroup.

Clarification of sample handling and shipment to central lab.

Change to Section 7.2.5.1 Health-related Quality of Life: Added additional assessments for extended study duration.

Change to Section 10.4 Primary Objective: Replaced “one year” with “52 weeks”

Change to Section 10.4.4 Supportive analyses: Added descriptive statistics for the proportion of patients with LIC decrease by at least 30% from baseline at week 52.

Change to Section 10.5 Secondary Objectives
- Added Section 10.5.1 Response analysis in patients with baseline LIC >15 mg Fe/g dw
- Added Section 10.5.2 Long term efficacy of treatment to target LIC of <3 mg Fe/g dw followed by one or more treatment holidays until the LIC is ≥5 mg Fe/g dw
Change to Section 10.5.3 Absolute change in LIC measured by MRI from baseline: Added analyses of additional measurements for five year study duration

Change to Section 10.5.4 Absolute change in LIC measured by MRI from baseline by underlying disease:
- Replaced “underlying disease” with NTDT syndrome in header
- Added analyses of additional measurement for five year study duration

Change to Section 10.5.5 Absolute change in serum ferritin from baseline:
- Replaced “52” with “260”
- Clarified definition of quarter for ferritin analyses

Change to Section 10.5.6 Correlation between serum ferritin and LIC at baseline and EOS”:
Added analysis

Change to Section 10.5.7 Medical Outcomes Study Short Form-36 (SF-36): Added additional visits

Change to Section 10.5.8 Pediatric Quality of Life Questionnaire: Added additional visits

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.

**IRB/IEC/HA**

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

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

1.1 Overview of disease pathogenesis, epidemiology and current treatments

The thalassemias comprise a heterogeneous group of inherited disorders in which normal hemoglobin production is partly or completely suppressed due to the defective synthesis of one or more of the components of the globin chains. Depending upon the genes involved, the defect is classified as α-thalassemia or β-thalassemia. β-thalassemia and α-thalassemia are the most common types of thalassemia (Thalassaemia International Federation 2008). β-thalassemia is prevalent in Mediterranean countries, 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 (Galanello and Origa 2010). Alpha-thalassemia, including Hemoglobin H (Hb H) disease, is particularly common in China and Southeast Asia (Vichinsky 2010). In addition, there are a significant number of thalassemia variants that are characterized not only by impaired synthesis of β- or α-globin, but also by the presence of abnormal hemoglobins that are produced as a result of point mutations within the globin genes. Hemoglobin E (HbE) β-thalassemia is the most common variant of β-thalassemia in Asia (Vichinsky 2007). Due to immigration patterns, patients with alpha and beta thalassemia may be found in many countries outside of the endemic regions.

The clinical picture of thalassemia may be mild (e.g. β-thalassemia minor), moderate (non-transfusion dependent thalassemia [NTDT]) or severe (e.g. β-thalassemia major). Patients with thalassemia minor are asymptomatic, while patients with thalassemia major present with severe anemia early in life requiring regular blood transfusions and chelation therapy to prevent or reverse transfusional iron overload. Patients with NTDT, e.g. β-thalassemia intermedia, HbE β-thalassemia, and HbH disease (α-thalassemia), have milder anemia compared to thalassemia major and therefore, they require no or only occasional blood transfusions. Nonetheless, NTDT patients develop clinically relevant iron overload, mainly due to increased intestinal absorption of iron driven by anemia due to ineffective erythropoiesis (Pippard 1979, Pootrakul 1988).

Excess iron deposition, especially in the liver, heart and endocrine organs, results in progressive tissue damage and organ failure, and is linked to iron-related promotion of free hydroxyl radical formation. Iron overload in NTDT may lead to the various clinical complications some of which are also seen in transfusional iron overload, namely liver cirrhosis and endocrine dysfunction. Studies show that NTDT patients have a risk of iron overload-related complications, such as abnormal liver function, metabolic (diabetes mellitus) and endocrine disorders, above certain thresholds of LIC and serum ferritin (Musallam 2013). In addition, the risk of some complications increases with age (Taher 2010).

Serum ferritin (SF) has been traditionally used to assess transfusional iron overload with a well-established correlation to liver iron concentration (LIC), a more direct measurement of liver tissue iron. However, serum ferritin levels have been reported to underestimate LIC in patients with NTDT as compared to regularly transfused patients (Origa 2007, Pakbaz 2007, Taher 2008, Musallam 2011, Taher-TIF NTDT Guidelines 2013). Magnetic resonance
imaging (MRI) is a sensitive and specific tool for non-invasively assessing hepatic iron overload (It has recently been approved by device regulatory authorities in USA, Europe and Australia. Results from the Exjade registration study, Study No. ICL670A0107, confirm that this method accurately measures LIC (Nick 2003).

NTDT patients with iron overload cannot be phlebotomized due to anemia and therefore, treatment with iron chelators is the only possibility to decrease or maintain body iron load in these patients. The use of iron chelators, such as deferoxamine and deferiprone, has been reported in thalassemia intermedia patients (Olivieri 1992, Rombos 2000, Pootrakul 2003) and in patients with Hb H disease (Chan 2006). Apart from reduced SF and LIC, these studies showed improvement in hematological and iron metabolism parameters, such as hemoglobin, erythropoietin (Pootrakul 2003) and labile plasma iron (LPI) (Pootrakul 2003); the latter is a component of non-transferrin bound iron (NTBI) which reflects the presence of potentially toxic free iron in the plasma. However, neither deferoxamine nor deferiprone have been systematically investigated, as those studies were either case reports or small non-randomized trials.

Published small, uncontrolled trials showed that NTDT patients with chronic iron overload could be treated with deferasirox (starting doses of 10-20 mg/kg/day with further escalation). The safety profile of deferasirox remained unchanged in this population (Ladis 2009, Voskaridou 2009). Study [ICL670E2209] (THALASSA), the first randomized, placebo-controlled study of iron chelation therapy in NTDT, confirmed that these patients may have substantial iron burden as demonstrated by high baseline LIC with moderately elevated levels of SF. The THALASSA study demonstrated that deferasirox at starting doses of 5 and 10 mg/kg/day, escalated to 10 and 20 mg/kg/day, compared to placebo, significantly reduced LIC and SF. Both doses had a similar frequency of overall adverse events (AEs) (Taheer 2012).

Notably, the reduction in LIC was dose-dependent and consistent across patient subgroups, including baseline iron overload and underlying NTDT syndromes (Taheer 2013). The 2 additional 1-year extensions demonstrated that continued treatment with deferasirox at appropriate doses resulted in a progressive reduction in iron overload, highlighting the value of long-term chelation therapy (Taheer 2013). Furthermore, there were no unexpected safety findings and the deferasirox safety profile remained consistent as patients approached near-normal body iron levels at the chelation interruption target LIC <3 mg Fe/g dw (Taheer 2014).

The continuously accumulating data on the risk of morbidities associated with iron overload, as well as the safety and efficacy of deferasirox, will further confirm the favorable benefit-risk profile of deferasirox in patients with transfusional iron overload and in those with NTDT.

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

To date, deferasirox has been approved in over 100 countries worldwide, including the 28 Member States of the European Union (EU), and the US.

Deferasirox is registered in the following indications:

- For the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in adult and pediatric patients (aged 2 years and over) at doses up to 40 mg/kg/day.
• For the treatment of chronic iron overload in patients with NTDT syndromes aged 10 years and older with LIC ≥5 mg Fe/g d and SF >300 ng/mL at doses of up to 20 mg/kg/day.

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

Deferasirox is formulated as a dispersible tablet for oral suspension which facilitates administration of the appropriate quantity of drug substance to both pediatric and adult patients. Deferasirox is supplied as 125 mg, 250 mg and 500 mg tablets which must be dispersed in water, orange juice or apple juice. A bioavailability study indicates that absorption is highly variable when deferasirox is taken together with food. Therefore, it is recommended that deferasirox is taken once daily, on an empty stomach, at least 30 minutes prior to a meal and no less than 2 hours after the last food intake, consistently at the same time of the day.

1.2.1 Overview of deferasirox

Deferasirox (ICL670, Exjade®) is an N-substituted bis-hydroxyphenyl-triazole, a representative of a new class of tridentate iron chelators (Lattmann 2001, Nick 2003), indicated for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in adult and pediatric patients (aged two years and over) at doses up to 40 mg/kg/day. It is also indicated for the treatment of chronic iron overload in patients with NTDT syndromes aged 10 years and older at doses up to 20 mg/kg/day. Exjade is available as a dispersible tablet containing 125, 250, or 500 mg of deferasirox as active substance.

1.2.1.1 Non-clinical experience

Two molecules of deferasirox form a complete complex with Fe³⁺. The high potency of deferasirox in mobilizing tissue iron and promoting iron excretion was demonstrated both in vitro and in vivo model systems (Nick 2003). Preclinical studies also revealed that deferasirox did not affect fertility and it is neither teratogenic nor carcinogenic.

1.2.1.2 Clinical experience

As of 31st of October 2013, the estimated cumulative exposure from post-marketing experience was 201,562 patient-treatment years. From 1 November 2012 to 31 October 2013, estimated exposure from marketing experience was 40,548 patient-treatment years. In addition, over 7098 subjects received deferasirox in clinical trials up to 31 October 2013.

The efficacy and safety of deferasirox has been evaluated in a large prospective clinical trials program that has generated long-term data in patients with transfusional iron overload with a variety of transfusion-dependent anemias; this information has recently expanded to also include patients with NTDT. Moreover, the data accumulated have characterized the safety profile of deferasirox across all age groups and for a wide range of transfusion-dependent and independent anemias, including β-thalassemia, sickle cell disease, MDS and NTDT indicating that the vast majority of adverse events are mild-to-moderate in severity and manageable with dose adjustments or interruptions.
Clinical studies have shown deferasirox to effectively chelate iron in patients with transfusional iron overload due to a variety of transfusion-dependent anemias, as demonstrated by decreases in LIC, SF and cardiac iron (MRI T2*) (Nick 2003, Cappellini 2006, Vichinsky 2007, Porter 2008, Cappellini 2010, Pennell 2012, Pennell 2014). Long-term studies (up to 5 years) in patients aged ≥ 2 have demonstrated that deferasirox administered at doses of 10-40 mg/kg/day effectively reduces or maintains total body iron, as assessed by SF or LIC (Cappellini 2011). Deferasirox also has been shown to be associated with improvement in liver pathology, as evidenced by biopsy-assessed Ishtak fibrosis staging and necroinflammatory scores (Deugnier 2011) and improvement in hematopoietic parameters in MDS patients using the International Working Group 2006 criteria (Gattermann 2012, List 2012, Angelucci 2014). Improvements in hematopoietic parameters were also seen in patients with Aplastic Anemia (Lee et al 2013). The efficiency of deferasirox in chelating iron appears to be constant at all doses ranging from 5 to 40 mg/kg/day and is not affected by age, gender, baseline LIC or underlying anemia (Porter 2005).

Deferasirox has demonstrated acceptable safety and tolerability in adult and pediatric patients with transfusional iron overload (Piga 2005, Cappellini 2006, Vichinsky 2007). The most frequent reactions reported during chronic treatment with deferasirox in adult and pediatric patients included gastrointestinal disturbances in about 26% of patients (mainly nausea, vomiting, diarrhea, or abdominal pain), and skin rash in approximately 7% of patients. These reactions were dose-dependent, mostly mild to moderate, generally transient and most resolved even if treatment was continued. In addition, there have been rare reports of upper gastrointestinal hemorrhages and ulcerations, primarily from clinical trials, in patients receiving deferasirox. There have been occasional post-marketing reports of leukocytoclastic vasculitis, urticaria, erythema multiforme, and hypersensitivity reactions (anaphylaxis and angioedema). Detailed information on the safety evaluation of deferasirox is provided in the current [Investigator Brochure]. Mild, non-progressive increases in serum creatinine, mostly within the normal range, occurred in approximately 36% of patients. These were dose-dependent, often resolved spontaneously and some were alleviated by reducing the dose. Rare cases of acute renal failure, mostly serum creatinine increases ≥ 2 x ULN have been reported following the prescription use of deferasirox; these were usually reversible after treatment interruption.

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

Reports of cytopenias have mostly been in patients with pre-existing blood disorders which are frequently associated with failure of the bone marrow to produce sufficient amounts of blood cells.

As with other iron chelator therapies, high frequency hearing loss and lenticular opacities (early cataracts) have been uncommonly observed in patients treated with deferasirox.
The risk of toxicity of deferasirox may be increased when inappropriately high doses are prescribed to patients with a low iron burden or with SF levels that are only slightly elevated. Detailed information regarding the correlation of toxicities and PK parameters (drug concentrations, Cmax) is provided in the current [Investigators’ Brochure].

A study of deferasirox was conducted in NTDT patients. Study No ICL670E2209, the THALASSA study, was a prospective, randomized, double-blind, placebo controlled trial of deferasirox with starting doses of 5 and 10 mg/kg/day in patients with NTDT.

The primary objective of this trial was to compare the efficacy of the two treatment groups of deferasirox based on the change in LIC (R2 MRI) from baseline after one year of treatment compared to placebo treated patients. One hundred and sixty-six patients with thalassemia intermedia (n=95), α-thalassemia (n=22) or HbE/ β-thalassemia (n=49) were randomized to starting deferasirox doses of 5 mg/kg/day (n=55) or matching placebo (n=28) and 10 mg/kg/day (n=55) or matching placebo (n=28). The average actual deferasirox dose (mean ± SD) was 5.6 ± 1.4 and 11.5 ± 2.9 mg/kg/day, respectively. The primary objective of this trial was met. After one year of treatment with deferasirox, LIC significantly decreased by –1.95 mg Fe/g dw (95% CI: –2.94, –0.96; BL: 13.11) and –3.80 mg Fe/g dw (95% CI: –4.76, –2.85; BL: 14.56) in the deferasirox 5 and 10 mg/kg/day groups, respectively, compared with an increase of 0.38 mg Fe/g dw (95% CI: –0.59, 1.34; BL: 15.94) in the placebo; the difference between deferasirox 5 and 10 mg/kg/day groups vs placebo was significant (–2.33 mg Fe/g dw, P=0.001 and –4.18 mg Fe/g dw, P<0.001, respectively). After one year of treatment, the percentage of patients with LIC decrease ≥3 mg Fe/g dw from baseline was greater in the deferasirox 5 and 10 mg/kg/day cohorts (32.7% and 56.4%) compared to placebo (10.7%). In addition, more patients in deferasirox 5 and 10 mg/kg/day cohorts achieved LIC reduction ≥30% from baseline (25.5% and 49.1%) compared to placebo (1.8%). The significant difference in the change in LIC from baseline between the 5 and 10 mg/kg/day group, –1.95 vs –3.80, p=0.009, justifies the starting dose of 10 mg/kg/day in this trial.

Mean SF significantly decreased at one year: –121 ng/mL (95% CI: –203, –38) and –222 ng/mL (95% CI: –304, –140) for deferasirox 5 and 10 mg/kg/day groups while there was an increase in the placebo (115 ng/mL: 95% CI: 33, 196); difference vs placebo was significant (–235 ng/mL, P<0.001 and –337 ng/mL, P<0.001 for deferasirox 5 and 10 mg/kg/day, respectively).

Overall AE rates were 80.4, 76.4 and 78.2% in the placebo, deferasirox 5 and 10 mg/kg/day groups; respectively. The most common investigator-assessed drug-related AEs in the overall placebo (n=56), deferasirox 5 and 10 mg/kg/day groups, respectively, were nausea (7.1, 5.5 and 7.3%), rash (1.8, 3.6 and 9.1%), diarrhea (1.8, 0 and 9.1%), headache (3.6, 3.6 and 1.8%) and upper abdominal pain (0, 3.6 and 1.8%). Serious AEs were reported in 14.3, 12.7 and 16.4% of patients in the placebo, deferasirox 5 and 10 mg/kg/day groups, respectively. Three (5.5%) deferasirox-treated patients (deferasirox 10 mg/kg/day) had 2 consecutive serum creatinine level increases >33% above baseline and >upper limit of normal (ULN). One patient in the placebo group had an ALT increase >5 x ULN and >2 x baseline and 2 patients had an AST increase to >5 xULN and > 2 x baseline, 1 in the deferasirox 10 mg/kg/day and 1 in the placebo group (Taher 2012).
Therefore, in patients with NTDT and iron overload, deferasirox at starting doses of 5 and 10 mg/kg/day with dose escalation up to 20 mg/kg/day reduced iron overload, as evidenced by significant decreases in LIC and SF and with an overall safety profile comparable to placebo (Taher 2012). The reduction in LIC was shown to be dose-dependent since the reduction in LIC by average actual dose showed that patients who received deferasirox >12.5–≤17.5 mg/kg/day achieved the greatest LIC decrease, followed by the ≥7.5–≤12.5 mg/kg/day subgroup and the >0–<7.5 mg/kg/day subgroup. Patients who had their dose doubled to 20 mg/kg/day achieved greater reductions in LIC compared with patients who remained on the 10 mg/kg/day starting dose (Taher et al. 2013). Continued treatment with deferasirox at appropriate doses for up to 2 years resulted in a progressive reduction in iron overload; mean change −7.14 mg Fe/g dry weight (dw) (mean dose 9.8±3.6 mg/kg/day; Taher 2013).

For patients receiving deferasirox for up to 2 years, approximately 40% and 16% reached LIC <5 and <3 mg Fe/g dw, respectively, with more patients reaching these targets during the second year. The safety profile remained consistent as patients achieved near-normal body iron burdens with no clinically relevant differences in renal and hepatic laboratory parameters measured close to the time of LIC <3 compared with measurements near the previous LIC assessment (Taher 2014).

Therefore, the continuously accumulating and available data to date confirm the favorable benefit-risk profile of deferasirox in patients with transfusional iron overload and in those with NTDT.

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

2 Rationale

2.1 Study rationale and purpose

The purpose of this study is to provide further assessment of the long-term efficacy and safety of deferasirox in NTDT patients with iron overload (LIC ≥ 5 mg Fe/g liver dw and SF ≥ 300 ng/mL) after the closure of the THALASSA trial. In addition, pharmacokinetic (PK), endocrine function, quality of life and resource utilization assessments will be included in the patient evaluations, as these were not conducted in THALASSA. Also, the patient population will be slightly broadened to include patients treated with hydroxyurea, erythropoietin and butyrate.

Liver iron content (LIC) will be estimated throughout the study by the use of a magnetic resonance imaging technique called R2 MRI, which is currently the most reliable non-invasive method for this purpose. This method was also utilized in the THALASSA trial. Dose adjustments throughout the trial will be based upon LIC assessments. The correlation between LIC and SF will be further studied to better understand the situations where the management of iron overload in NTDT can be performed using solely SF levels.

At the time the THALASSA protocol was written, iron chelation in this population was not well understood. The results from THALASSA have demonstrated that more aggressive chelation should be initiated earlier in the course of treatment (see Section 2.3).
2.2 Rationale for the study design

An open-label, single-arm study design and five year treatment period will be implemented in this trial, as the results from the double-blind, randomized THALASSA Study have already demonstrated the efficacy of deferasirox in this patient population when compared to placebo. After 52 weeks of treatment with deferasirox, LIC significantly decreased by –1.95 mg Fe/g dw (95% CI: –2.94, –0.96; BL: 13.11) and –3.80 mg Fe/g dw (95% CI: –4.76, –2.85; BL: 14.56) in the deferasirox 5 and 10 mg/kg/day groups, respectively, compared with an increase of 0.38 mg Fe/g dw (95% CI: –0.59, 1.34; BL: 15.94) in the placebo; the difference between deferasirox 5 and 10 mg/kg/day groups vs placebo was significant (–2.33 mg Fe/g dw, \( P=0.001 \) and –4.18 mg Fe/g dw, \( P<0.001 \), respectively).

The four week duration of the Screening Period will be implemented to adequately assess trial eligibility. The extended duration of the study is to provide follow-up for all patients up to five years and generate long-term efficacy and safety data.

2.3 Rationale for dose and regimen selection

The treatment regimens of deferasirox (starting dose of 10 mg/kg/day with dose escalation at week 4 and adjustments according to LIC response up to 30 mg/kg/day) have been chosen based on the results of the THALASSA study. The starting dose regimen of 10 mg/kg/day demonstrated significantly better efficacy in reducing LIC over one year when compared to the starting dose regimen of 5 mg/kg/day (mean absolute change: -3.80 vs -1.95 mg/g dw, \( p=0.009 \)) along with similar safety parameters. Furthermore, 47.3% of patients in the 5 mg/kg/day arm, and 45.5% of patients in the 10 mg/kg/day arm required dose increases; some of which were up to 20 mg/kg/day. Nevertheless, at week 52, LIC levels were reduced from 13.11 to 11.56 and from 14.56 to 10.58 mg/g dw in the 5 and 10 mg/kg/day arms; respectively. Thus, indicating a need to determine if a faster dose escalation of deferasirox will achieve a quick reduction of the iron burden in these patients with high baseline iron burden.

All patients will receive an initial treatment of 10 mg/kg/day for 4 weeks. After 4 weeks, dose escalations in increments of 5 or 10 mg/kg/day will be considered, according to the patient’s severity of baseline liver iron concentration. After 24 weeks of treatment, and approximately every six months thereafter (for up to five years), additional dosage adjustments will be considered in accordance with the patient’s response provided there are no safety or tolerability issues while patients are on their individualized dosage regimens. Response will be determined via the change in LIC (see Section 6.1.1) and the maximum dose of deferasirox will be 30 mg/kg/day. Results from THALASSA also demonstrated 38% of the patients assigned to the 10 mg/kg/day group who had baseline LICs >15 mg/g dw showed a rate of LIC decrease of 3.8 mg/g dw per year; thus, demonstrating a need for more aggressive chelation treatment in this population to 20 and 30 mg/kg/day, as these patients are at risk of liver fibrosis and cirrhosis.

2.4 Rationale for choice of combination drugs

Not applicable.
2.5  Rationale for choice of comparators drugs

Not applicable

3  Objectives and endpoints

Primary objective

To assess the efficacy of deferasirox in patients with NTDT based on change in LIC from baseline after 52 weeks of treatment.
Secondary objectives

- Assess response rates in patients with baseline LIC values >15 mg Fe/g dw defined as proportion of patients achieving an LIC <5 mg Fe/g dw and time to achieving LIC <5 mg Fe/g/dw
- Assess long-term efficacy and safety of treatment to target LIC of 3 mg Fe/g dw followed by one or more treatment holidays until the LIC is ≥5 mg Fe/g dw
- To evaluate the impact of deferasirox on adult Quality of Life (QoL) using the Medical Outcomes Study Short Form–36 (SF-36) (in patients >18 years of age)
- To evaluate the impact of deferasirox on pediatric QoL using the Pediatric Quality of Life questionnaire (in patients ≤18 years of age)
- To evaluate the efficacy of deferasirox based on change in LIC from baseline over time (approximately six month intervals) To assess the correlation of change in SF and LIC at baseline and end of study (EOS)
- To assess the efficacy of deferasirox based on change in LIC from baseline after 52 weeks of treatment by NTDT syndrome
- To assess the efficacy of deferasirox based on change in SF from baseline over time
- To evaluate the safety of deferasirox doses up to 30 mg/kg/day
- To assess the efficacy of deferasirox on endocrine function based on change from baseline over time of the following parameters:
  - Gonad: total and free testosterone (males), luteinizing hormone (LH) and follicle stimulating hormone (FSH) (females)
  - Thyroid: thyroid stimulating hormone (TSH), total and free T4, total and free T3
  - Pancreas: insulin, insulin resistance, fasting plasma glucose (FPG)
  - Adrenal gland: cortisol
- To conduct pharmacokinetic analysis in a subset of patients

Objectives and related endpoints are described in Table 3-1 below.
<table>
<thead>
<tr>
<th>Objective</th>
<th>Endpoint</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assess the efficacy of deferasirox in liver iron removal after 52 weeks of treatment</td>
<td>Change in LIC from baseline after 52 weeks of treatment</td>
<td>Refer to Section 10.4</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assess response rates in subset of patients with baseline LIC &gt;15 mg Fe/g dw</td>
<td>Proportion of patients with baseline LIC &gt;15 achieving LIC &lt;5 mg Fe/g dw and time to achieving LIC &lt;5 mg Fe/g dw</td>
<td>Refer to Section 10.5.1</td>
</tr>
<tr>
<td>Assess long-term efficacy of treatment to a target LIC of 3 mg Fe/g dw</td>
<td>Time from target LIC 3 mg Fe/g dw to the first LIC ≥5 mg Fe/g dw in the follow up period</td>
<td>Refer to Section 10.5.2</td>
</tr>
<tr>
<td>Evaluate the impact of deferasirox on adult QoL</td>
<td>Change in health-related outcomes using Medical Outcomes Study Form 36 (SF 36)</td>
<td>Refer to Section 10.5.7</td>
</tr>
<tr>
<td>Evaluate the impact of deferasirox on pediatric QoL</td>
<td>Change in health-related outcomes using the Pediatric Quality of Life questionnaire</td>
<td>Refer to Section 10.5.8</td>
</tr>
<tr>
<td>Evaluate the efficacy of deferasirox in liver iron removal</td>
<td>Change in LIC from baseline</td>
<td>Refer to Section 10.5.3</td>
</tr>
<tr>
<td>Assess the correlation of change in SF and LIC</td>
<td>SF vs LIC at baseline and EOS</td>
<td>Refer to Section 10.5.6</td>
</tr>
<tr>
<td>Confirm the efficacy of deferasirox in liver iron removal in NTDT syndrome</td>
<td>Change in LIC from baseline after 52 weeks of treatment by underlying NTDT syndrome</td>
<td>Refer to Section 10.5.4</td>
</tr>
<tr>
<td>Assess the efficacy of deferasirox in decreasing SF after 52 weeks of treatment</td>
<td>Change in SF from baseline after 52 weeks of treatment</td>
<td>Refer to Section 10.5.5</td>
</tr>
<tr>
<td>Evaluate the safety of deferasirox doses up to 30 mg/kg/day dose</td>
<td>Safety parameters, labs, adverse events (AEs)</td>
<td>Refer to Section 10.5.10</td>
</tr>
<tr>
<td>Assess the efficacy of deferasirox in endocrine function</td>
<td>Change from baseline during treatment period in total and free testosterone (males), LH and FSH (females), TSH, total and free T4, total and free T3, fasting plasma glucose, insulin, insulin resistance, and cortisol.</td>
<td>Refer to Section 10.5.9</td>
</tr>
<tr>
<td>Conduct PK analysis in a subgroup of patients</td>
<td>PK parameters (AUC, Cmax, tmax and trough levels) during the study period</td>
<td>Refer to Section 10.5.11</td>
</tr>
</tbody>
</table>
4 Study design

4.1 Description of study design

This open label, single-arm, multi-center study to evaluate the efficacy and safety of deferasirox in NTDT patients with iron overload will include the following phases:

Screening (4 weeks) to determine patient eligibility

Open label treatment with deferasirox:

- Starting dose 10 mg/kg/day for 4 weeks;
- At Week 4, dose adjustments according to baseline LIC:
  - 20 mg/kg/day for patients with baseline LIC > 15 mg Fe/g dw
  - 15 mg/kg/day for patients with baseline LIC > 7 but ≤ 15 mg Fe/g dw
  - Dose will remain at 10 mg/kg/day for patients with baseline LIC ≥ 5 but ≤ 7 mg Fe/g dw
- Approximately every 6 months, starting at Week 24, dose adjustments according to LIC:
  - Increase dose by 5-10 mg/kg/day, if LIC > 15 mg Fe/g dw, maximum of 30 mg/kg/day
  - May increase dose by 5 mg/kg/day if LIC > 7 but ≤ 15 mg Fe/g dw, maximum of 20 mg/kg/day
  - Same dose if LIC is ≥3 but ≤ 7 mg Fe/g dw, maximum of 10 mg/kg/day

The maximum dose of deferasirox throughout the study will be 30 mg/kg/day.

If LIC measurement is <3 mg Fe/g dw or SF is <300 ng/mL, treatment will be interrupted. Patients who have interrupted study treatment during the first year of the study due to LIC <3 mg Fe/g dw or SF <300 ng/mL will continue the monthly visit schedule. Patients who have treatment interruption due to LIC <3 mg Fe/g dw or SF <300 ng/mL after 52 weeks, will complete scheduled visit one month post-interruption and then be followed every three months.

Study treatment will restart at the previous effective dose when LIC ≥5 mg Fe/g dw and SF ≥ 300 ng/mL (maximum of 10 mg/kg/day). Once on treatment, patients will be followed monthly.

See Figure 4-1, for study design schematic.
Figure 4-1  Study Design

- Screening Phase (28 days)
- Open label, all patients treated with 10 mg/kg/day deferasirox (4 weeks)

Dose adjustments after 4 weeks of treatment according to baseline LIC

- Baseline LIC > 15 mg Fe/g dw: 20 mg/kg/day
- 7 < Baseline LIC ≤ 15 mg Fe/g dw: 15 mg/kg/day
- 5 ≤ Baseline LIC ≤ 7 mg Fe/g dw: 10 mg/kg/day

Dose adjustments at Week 24 and approximately every 6 months thereafter according to LIC

- Increase dose by 5-10 mg/kg/day, if LIC > 15 mg/g dw (maximum of 30mg/kg/day)
- May increase dose by 5 mg/kg/day if LIC > 7 and ≤ 15 mg Fe/g dw (maximum of 20mg/kg/day)
- Same dose if LIC is ≥ 3 and < 7 mg Fe/g dw (maximum of 10 mg/kg/day)
- Treatment will be stopped if LIC < 3 mg Fe/g dw or SF is < 300 ng/mL

The maximum dose of deferasirox throughout the study will be 30 mg/kg/day

Approximately 117 patients will be enrolled. Treatment duration will be five years.
Pharmacokinetic analysis will be conducted in a subset of 20 patients from selected participating centers.

4.2  Timing of interim analyses and design adaptations

No formal interim analysis based on primary endpoint will be performed.
Some basic safety annual analyses will be performed for PSUR (Periodic Safety Update Report).

4.3  Definition of end of the study

Patients will be followed up to five years. Completion of this study as a whole will occur after the last visit of the last patient of the study and upon the availability and accuracy verification of the last data point required for final statistical analysis.

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. The site will contact the patient, schedule a final visit and provide instruction to discontinue study drug administration. The same assessments must be performed as described in Section 7 for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient’s interests. The
investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

5 Population

5.1 Patient population

Approximately 117 patients will be enrolled in this trial.

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 must meet all of the following criteria:

- Male or female aged $\geq 10$ years with non-transfusion-dependent congenital or chronic anemias inclusive of beta-thalassemia intermedia, HbE beta-thalassemia or alpha-thalassemia intermedia (HbH disease)
- LIC $\geq 5$ mg Fe/g dw measured by R2 MRI at screening
- Serum ferritin $\geq 300$ ng/mL at screening (two consecutive values at least 14 days apart from each other)
- Written informed consent obtained prior to any screening procedures

5.3 Exclusion criteria

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

- Patients diagnosed with HbS-beta Thalassemia
- Anticipated regular transfusion program during the study. Patients having a sporadic transfusion (e.g. in case of infection) during the course of the study will not be excluded
- Any blood transfusion 6 months prior to study start
- Patients unable to undergo study assessments including MRI, e.g. who are claustrophobic to MRI, have a cardiac pacemaker, ferromagnetic metal implants other than those approved as safe for use in MR scanners (Example: some types of aneurysm clips, shrapnel), and patients who are obese (exceeding the equipment limits)
- Significant proteinuria as indicated by a urine protein/urine creatinine ratio $> 1.0$ mg/mg in a non-first void urine sample at visit 1 or visit 2 (or alternatively in two of three samples obtained for screening)
- Creatinine clearance $\leq 40$ ml/min on two measurements during visit 1 and visit 2
- Serum creatinine $> ULN$ on two measurements during visit 1 and visit 2
- ALT $> 5 \times ULN$ at visit 1 and visit 2
- Clinical evidence of active hepatitis B (positive HBsAg with negative HBsAb) or hepatitis C (positive HCV antibody and detectable HCV RNA with ALT above the normal range) (Note: Hepatitis B carriers will be allowed to enter the trial.)
- Known diagnosis of cirrhosis (confirmed by biopsy if available)
- A history of clinically relevant ocular and/or auditory toxicity related to iron chelation therapy
- History of positive HIV serology (ELISA or Western blot)
- Presence of a surgical or medical condition that might significantly alter the absorption, distribution, metabolism or excretion of the study drug
- Patients with active inflammatory diseases that interferes with the accurate measurement of serum ferritin
- Pregnant or breast feeding patients, or patients of child-bearing potential not employing an effective method of birth control. (See Women of child-bearing potential, below, for further details regarding effective methods of birth control.)
- Patients participating in another clinical trial or receiving a systemic investigational drug within the past 4 weeks or topical investigational drug within the past 7 days of screening
- History of non-compliance with medical regimens or patients who are considered potentially unreliable and/or not cooperative, unwilling or unable to comply with the protocol
- History of hypersensitivity to any of the study drug or excipients
- 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.)
- History of drug or alcohol abuse within the 12 months prior to enrollment

**Women of child-bearing potential**

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, including female adolescents who are menarchal or who become menarchal during the study, unless they are using effective methods of contraception during dosing of study treatment.

Effective contraception methods include:

1. Total abstinence: When this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
2. Female sterilization: have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to study. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
3. Male partner sterilization (at least 6 months prior to screening). For female study subjects, the vasectomized male partner must be the sole partner for that patient.
4. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository.
5. Placement of an intrauterine device (IUD) or intrauterine system (IUS).

Women are considered to be not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate,
history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the patient has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

The use of hormonal contraceptives (oral or injected) is prohibited in this study due to a decrease in efficacy when used in combination with deferasirox.

### 5.4 Exclusion criteria for pediatric patients

- A patient’s weight of at least 20 kg is required to allow dosing of 5 mg/kg with one tablet of 125 mg

### 6 Treatment

#### 6.1 Investigational treatment, other study treatment, supportive treatment

The investigational study drug used in this trial is deferasirox [ICL670, Exjade®]. Deferasirox will be initially administered by oral daily dosing of 10 mg/kg/day. After four weeks, the dose of deferasirox may be adjusted according to baseline LIC assessment; further dose adjustments may occur approximately every 6 months (starting at Week 24), up to five years, based upon LIC measurement (see Section 6.1.1).

Deferasirox [ICL670, Exjade®] will be provided as 125 mg, 250 mg, and 500 mg dispersible tablets packaged, labeled and supplied to the local Country Pharma Organizations, which will further distribute them to the study centers. Study medication will be open label.

Immediately before dispensing the package to the patient, investigator staff will detach the tear-off part of the label from the packaging and affix it to the source document (Drug Label Form) containing patient’s unique number.

**Definition of terms:**

- **Study drug:** deferasirox (ICL670, Exjade®) 125mg, 250mg and 500mg tablets for oral use
- **Study treatment:** Starting dose: 10 mg/kg/day p.o. deferasirox

#### 6.1.1 Dosing regimen

The starting dose of deferasirox for all patients will be 10 mg/kg/day for 4 weeks.

- After 4 weeks, the dose of deferasirox will be adjusted according to baseline LIC measurements:
  - 20 mg/kg/day for patients with baseline LIC > 15 mg Fe/g dw
  - 15 mg/kg/day for patients with baseline LIC > 7 but ≤ 15 mg Fe/g dw
  - Dose will remain at 10 mg/kg/day for patients with baseline LIC ≥ 5 but ≤ 7 mg Fe/g dw
• Approximately every 6 months (starting at Week 24), the dose of deferasirox will be further adjusted, according to the following LIC measurements:
  • Increase dose by 5-10 mg/kg/day if LIC is > 15 mg Fe/g dw, maximum of 30 mg/kg/day
  • May increase dose by 5 mg/kg/day if LIC is > 7 but ≤ 15 mg Fe/g dw, maximum of 20 mg/kg/day. Same dose if LIC is ≥3 but ≤7 mg Fe/g dw, maximum of 10 mg/kg/day

Patients who have been dose escalated will be monitored every week for four weeks after the escalation, to assess serum creatinine. Serum transaminases, bilirubin, and alkaline phosphatase will be assessed two weeks following dose escalation. This may be conducted at the local lab. After these periods (if they are applicable), the patient will visit the study center according to the monthly visit schedule.

If LIC measurement is < 3 mg Fe/g dw or SF is < 300 ng/mL, treatment will be interrupted. Patients will continue with visits during the period of treatment interruption and study treatment will restart at the previous effective dose when LIC ≥5 mg Fe/g dw and SF is ≥300 ng/mL (maximum of 10 mg/kg/day).

Dose adjustments based on safety issues are allowed in the study at any time. Investigator can reduce or interrupt study treatment and recommendations for such dose adjustments are described in Section 6.4.

The maximum dose of deferasirox throughout the study will be 30 mg/kg/day.

**Study Drug Administration**

The patient will be instructed how to prepare his/her daily dose from the three tablet strengths of deferasirox [ICL670, Exjade®] available (125 mg, 250 mg, 500 mg). The dose will be assigned based on the patient’s weight (see Table 6-1 through to Table 6-6). Given the available strengths of deferasirox tablets, the patient’s daily dose will be rounded to the nearest whole tablet size (relative to a 125 mg tablet).

Each time study medication is dispensed to the patient and/or the legal guardian, the investigator will provide detailed instructions on how to prepare and administer deferasirox.

At regular site visits the investigator or pharmacist will dispense to the patient and/or the legal guardian, an appropriate number of deferasirox bottles (see Table 6-1 through to Table 6-6) from a choice of 125 mg, 250 mg, 500 mg strengths, based on the patient’s calculated daily dose. Date and visit number must be recorded onto the trial drug label when dispensing the drug. The number of tablets of each strength dispensed will be recorded in the study drug dosing log. All deferasirox bottles (opened and unopened) returned by the patient will be counted and the sum entered into the study drug dosing log by the investigator or pharmacist at the study site.

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 subject 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 and the expiration date for study drug will be described on the medication label.
Patient Information

The investigator must instruct the patient to take the study drug exactly as prescribed. All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record electronic case report form (eCRF).

Deferasirox must be taken orally, once daily, on an empty stomach, at least 30 minutes before food and no less than 2 hours after the last food intake, preferable at the same time each day. The tablets are dispersed by stirring in a glass of water or orange or apple juice (100 ml to 200 ml) until a fine suspension is obtained. For daily doses less than 1 g, the tablets should be dispersed in at least 100 ml, and for daily doses from 1 g to 3 g, the tablets should be dispersed in at least 200 ml. Following full disintegration of the tablets, the liquid should be consumed promptly. Any residue in the glass and/or on the stirrer must be dispersed in additional liquid and swallowed.

The individual daily dose of deferasirox will be determined by the investigator and the amount of tablets corresponding to this dose will be calculated based on the patient’s body weight (see Table 6-1 through to Table 6-6).

Patient Numbering

Each patient in the study is uniquely identified by a 9 digit patient number which is a combination of his/her 4-digit center number and 5-digit subject number. The center number is assigned by Novartis to the investigative site.

When the patient has signed the informed consent form, the patient is assigned a patient number by the investigator. At each site, the first patient is assigned patient number 1, and subsequent patients are assigned consecutive numbers (e.g., the second patient is assigned patient number 2, the third patient is assigned patient number 3). The assigned patient number should be entered in the field labeled “Subject ID” on the electronic data capture (EDC) data entry screen.

Once assigned to a patient, the patient number will not be reused. If the patient fails to be enrolled, the patient is deemed a screen failure. In addition, the Screening Log will be completed for these patients.

Re-screened patients will be provided a new patient number.

Deferasirox dosing tables and guidance

<table>
<thead>
<tr>
<th>Table 6-1</th>
<th>Deferasirox dosing table for 5 mg/kg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt Weight in kg</td>
<td>Closest Dose</td>
</tr>
<tr>
<td>20 - 37.5</td>
<td>125</td>
</tr>
<tr>
<td>37.6 - 62.5</td>
<td>250</td>
</tr>
<tr>
<td>62.6 - 87.5</td>
<td>375</td>
</tr>
<tr>
<td>87.6 - 112.5</td>
<td>500</td>
</tr>
<tr>
<td>112.6 - 137.5</td>
<td>625</td>
</tr>
</tbody>
</table>
Table 6-2  Deferasirox dosing table for 10 mg/kg/day

<table>
<thead>
<tr>
<th>Pt Weight in kg</th>
<th>Closest Dose</th>
<th>125 mg</th>
<th>250 mg</th>
<th>500 mg</th>
</tr>
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<tr>
<td>20 - 31.3</td>
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<td>31.4 - 43.8</td>
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<td>43.9 - 56.3</td>
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<td>93.9 - 106.3</td>
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<td>106.4 - 118.8</td>
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<td>1</td>
<td></td>
<td>2</td>
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Table 6-3  Deferasirox dosing table for 15 mg/kg/day

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<th>Closest Dose</th>
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<th>500 mg</th>
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<tr>
<td>20 - 20.8</td>
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<tr>
<td>20.9 - 29.2</td>
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<td>29.3 - 37.5</td>
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</table>

Table 6-4  Deferasirox dosing table for 20 mg/kg/day

<table>
<thead>
<tr>
<th>Pt Weight in Kg</th>
<th>Closest dose</th>
<th>125 mg</th>
<th>250 mg</th>
<th>500 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>20.0 - 21.9</td>
<td>375</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22.0 - 28.1</td>
<td>500</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>28.2 - 34.4</td>
<td>625</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>34.5 - 40.6</td>
<td>750</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>40.7 - 46.9</td>
<td>875</td>
<td>3</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>47.0 - 53.1</td>
<td>1000</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>53.2 - 59.4</td>
<td>1125</td>
<td>1</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>59.5 - 65.6</td>
<td>1250</td>
<td>1</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>65.7 - 71.9</td>
<td>1375</td>
<td>3</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>72.0 - 78.1</td>
<td>1500</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>78.2 - 84.4</td>
<td>1625</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>84.5 - 90.6</td>
<td>1750</td>
<td>3</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>90.7 - 96.9</td>
<td>1875</td>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>97.0 - 103.1</td>
<td>2000</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>103.2 - 109.4</td>
<td>2125</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>109.5 - 115.6</td>
<td>2250</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>115.7 - 121.9</td>
<td>2375</td>
<td>4</td>
<td></td>
<td></td>
</tr>
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</table>
### Table 6-5  Deferasirox dosing table for 25 mg/kg/day

<table>
<thead>
<tr>
<th>Pt Weight in Kg</th>
<th>Closest dose</th>
<th>125 mg</th>
<th>250 mg</th>
<th>500 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>20.0 - 22.5</td>
<td>500</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>22.6 - 27.5</td>
<td>625</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>27.6 - 32.5</td>
<td>750</td>
<td></td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>32.6 - 37.5</td>
<td>875</td>
<td>3</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>37.6 - 42.5</td>
<td>1000</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>42.6 - 47.5</td>
<td>1125</td>
<td>1</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>47.6 - 52.5</td>
<td>1250</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>52.6 - 57.5</td>
<td>1375</td>
<td>3</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>57.6 - 62.5</td>
<td>1500</td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>62.6 - 67.5</td>
<td>1625</td>
<td>1</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>67.6 - 72.5</td>
<td>1750</td>
<td></td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>72.6 - 77.5</td>
<td>1875</td>
<td>3</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>77.6 - 82.5</td>
<td>2000</td>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>82.6 - 87.5</td>
<td>2125</td>
<td>1</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>87.6 - 92.5</td>
<td>2250</td>
<td></td>
<td>1</td>
<td>4</td>
</tr>
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<td>92.6 - 97.5</td>
<td>2375</td>
<td>3</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>97.6 - 102.5</td>
<td>2500</td>
<td></td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>102.6 - 107.5</td>
<td>2625</td>
<td>1</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>107.6 - 112.5</td>
<td>2750</td>
<td></td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>112.6 - 117.5</td>
<td>2875</td>
<td>3</td>
<td></td>
<td>5</td>
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<tr>
<td>117.6 - 122.5</td>
<td>3000</td>
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<td>6</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Pt Weight in Kg</th>
<th>Closest Dose</th>
<th>125mg</th>
<th>250 mg</th>
<th>500 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>20.0 - 22.9</td>
<td>625</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>23.0 - 27.1</td>
<td>750</td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>27.2 - 31.3</td>
<td>875</td>
<td>3</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>31.4 - 35.4</td>
<td>1000</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>35.5 - 39.6</td>
<td>1125</td>
<td>1</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>39.7 - 43.8</td>
<td>1250</td>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>43.9 - 47.9</td>
<td>1375</td>
<td>3</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>48.0 - 52.1</td>
<td>1500</td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>52.2 - 56.3</td>
<td>1625</td>
<td>1</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>56.4 - 60.4</td>
<td>1750</td>
<td></td>
<td>1</td>
<td>3</td>
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<td>60.5 - 64.6</td>
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<td>64.7 - 68.8</td>
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<td>4</td>
</tr>
<tr>
<td>68.9 - 72.9</td>
<td>2125</td>
<td>1</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>73.0 - 77.1</td>
<td>2250</td>
<td></td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>77.2 - 81.3</td>
<td>2375</td>
<td>3</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>81.4 - 85.4</td>
<td>2500</td>
<td></td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>85.5 - 89.6</td>
<td>2625</td>
<td>1</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>89.7 - 93.8</td>
<td>2750</td>
<td></td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>93.9 - 97.9</td>
<td>2875</td>
<td>3</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>98.0 - 102.1</td>
<td>3000</td>
<td></td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>102.2 - 106.3</td>
<td>3125</td>
<td>1</td>
<td></td>
<td>6</td>
</tr>
</tbody>
</table>
### 6.2 Ancillary treatments

Any additional therapy used to treat NTDT during this trial (e.g. therapy with hydroxyurea, erythropoietin, butyrate) will be permitted. Except for the study medication, no other iron chelation therapy will be administered while the patient is enrolled in the trial.

### 6.3 Concomitant medications

Use of the following treatments is NOT allowed after the start of study drug:

- Other investigational drugs
- Aluminum containing antacid therapies should be avoided because they may bind to deferasirox
- The concomitant use of deferasirox with potent UGT inducers (e.g. rifampicin, phenytoin, phenobarbital, ritonavir) may result in a decrease in deferasirox efficacy.
- The concomitant use of deferasirox with bile acid sequestrants (e.g., cholestyramine, colesvelam, colestipol) may result in a decrease in deferasirox efficacy.
- The use of hormonal contraceptives (oral or injected) is prohibited in this study due to a decrease in efficacy when used in combination with deferasirox.
- Any iron chelation therapy other than the study drug

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

- The concomitant administration of deferasirox and vitamin C has not been formally studied. Doses of vitamin C up to 200 mg/days have not been associated with adverse consequences.
- 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 metabolised through CYP3A4 (e.g. cyclosporin, simvastatin, hormonal contraceptive agents)
- Deferasirox is a moderate inhibitor of CYP2C8 and therefore it may increase serum concentrations of substances metabolised through CYP2C8 (e.g. repaglinide, paclitaxel)
- Concomitant administration of deferasirox with CYP1A2 substrates that have a narrow therapeutic index (e.g. theophylline, clozapine, tizanidine), is not recommended. When deferasirox and theophylline are used concomitantly, monitoring of theophylline concentration and theophylline dose reduction should be considered.

A sporadic transfusion depending on the patient’s condition (e.g. in case of infection) during the course of the study is allowed and will be recorded in the Transfusions eCRF.
The investigator must instruct the patient to notify the study site about any new medications (including over-the-counter products) 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 blood transfusions) administered after the patient starts treatment with study drug must be listed on the Concomitant medications/Significant non-drug therapies after start of study drug eCRF.

6.4 Guidelines for continuation of treatment

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

The majority of dose adjustments are covered in Section 6.4.1 to Section 6.4.11, below. For all cases where a dose adjustment is considered necessary but is not covered in the following sections, the investigator will send a written request to Novartis. The request must justify the dose change and provide all the supportive clinical and laboratory information for complete evaluation by Novartis. Any dose adjustment for reasons not included in this section needs to be authorized by Novartis. A written reply will be promptly sent back to the investigator by Novartis.

6.4.1 Change in patient weight

The dose of study drug will be adapted using Table 6-1 through to Table 6-6 according to the patient’s body weight throughout the course of the study.

6.4.2 Change in serum ferritin

If the serum ferritin level decreases to < 300 ng/mL at any visit, study drug will be held and the LIC will be assessed by R2 MRI. If repeat serum ferritin is < 300 ng/mL, treatment with the study drug will be interrupted. Repeat serum ferritin may be done locally, within two weeks of scheduled visit. If LIC is ≥ 5 mg Fe/g dw and repeat serum ferritin is ≥ 300 ng/mL, study drug treatment will be restarted at the same dose. Study drug will be held until LIC is ≥ 5 mg Fe/g dw and serum ferritin is ≥ 300 ng/mL. Study drug treatment will be restarted at the same dose (maximum restart dose of 10 mg/kg/day). The investigator will record this change on the dosage administration record eCRF and will notify Novartis at the time such a dose interruption is made, in order to facilitate optimal safety monitoring.

6.4.3 Change in liver iron content (LIC) as determined by liver MRI

See Section 6.1.1 Dosing regimen.

6.4.4 Serum creatinine and Creatinine clearance

Serum creatinine and creatinine clearance will be assessed at Weeks -4 and -2 before initiating therapy and should be monitored during the study as indicated in Table 7-2.

During the treatment period, patients who develop an increase in serum creatinine ≥ 33% above their baseline value (average of visit 1 and 2) resulting in a serum creatinine above the
upper limit of normal, on two consecutive occasions, the dose of the study drug will be reduced to:

- 15 mg/kg if the patient takes 30 mg/kg/day,
- 10 mg/kg if the patient takes 15-20 mg/kg/day,
- 5 mg/kg if patient takes 10 mg/kg/day,
- study drug held if patient takes 5 mg/kg/day of deferasirox until serum creatinine returns to below the ULN.

In case of a single increase in serum creatinine, the assessment will be repeated in 2 weeks. If after a dose reduction, a progressive increase in serum creatinine beyond the ULN is observed, a treatment interruption is recommended.

After an interruption, if serum creatinine falls below the age appropriate upper limit of normal range on two consecutive visits, it is recommended to resume therapy at 5 mg/kg/day, and after 1 month, if the serum creatinine increase does not recur, study medication can be doubled at one month intervals in order to return to the initial dose.

Caution should especially be used in patients with creatinine clearance between 40 and less than 60 mL/min, particularly in cases where there are additional risk factors that may impair renal function such as concomitant medications, dehydration, or severe infections.

Deferasirox therapy should be discontinued in case serum creatinine increases > 2 times the age-appropriate ULN or if creatinine clearance decreases < 40 mL/min.

6.4.5 Increased urinary proteinuria/creatinine ratio

Deferasirox must be temporarily discontinued if the urinary protein/creatinine ratio increases to > 1.0 (mg/mg) in two consecutive second-void urine samples separated by a period of at least 48 hours. Deferasirox can be resumed at the same dose once the urinary protein/creatinine ratio is ≤ 0.5 (mg/mg) in two consecutive urine samples, separated by a period of at least 48 hours. If proteinuria of this same magnitude recurs, deferasirox must be discontinued again and then resumed at 50% of the dose once the urinary protein/creatinine ratio is ≤ 0.5 (mg/mg) in two consecutive urine samples separated by a period of at least 48 hours. Dose adjustment will be based on central laboratory results.

In case of a single increase of the urinary protein/creatinine ratio, the assessment must be repeated in two weeks.

6.4.6 Stevens-Johnson syndrome

Severe skin reactions, including Stevens-Johnson syndrome (SJS), have been reported during Exjade therapy. If SJS is suspected, study treatment must be immediately discontinued and not be reintroduced.

6.4.7 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 worsens, treatment with study drug will be interrupted. After the rash resolves, study drug should be restarted. Resume deferasirox at 50% of the patient’s dose. If the rash does not recur, increase back to 100% of the patient’s dose after 2 weeks. If the rash recurs, contact Novartis.

For severe cases (defined as those causing distressing symptoms, particularly those which require the administration of systemic steroids for symptom relief) treatment with study drug must be stopped until resolution of the rash. If necessary, a brief course of oral steroids may be given. After the rash resolves, study drug should be restarted. Resume deferasirox at 50% of the patient’s dose. If the rash does not recur, increase dose by 5 mg/kg increments every 2 weeks until 100% of the patient’s last dose is achieved. If the rash recurs, study treatment may be discontinued if the investigator believes that it is in the best interest of the patient.

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

6.4.8 Gastrointestinal disturbances

Patients with gastrointestinal symptoms or patients who are unable to tolerate deferasirox may (in this order):

- In the first instance try changing the timing of administration from morning to evening (30 minutes before taking food), and in addition, try using an anti-diarrheal agent for 2 days in case of diarrhea.
- If the symptoms still continue, try administering the daily dose as a split dose b.i.d. after first contacting Novartis. Once the symptoms resolve, b.i.d should be switched to o.d.

6.4.9 Hepatic impairment

In patients who develop moderate hepatic impairment (Child-Pugh Class B) during the study, the study medication will be interrupted and patient monitored. If liver disease prognosis improves, study medication can be reintroduced at 10 mg/kg/day or 50% of previous dose, whichever is less. While monitoring continues, dose may be increased by 5 mg/kg/day increments 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.

6.4.10 Elevated liver function tests

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

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

6.4.12 Hypersensitivity reactions

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

6.4.13 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 must 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, once the cause of the cytopenia has been identified.

6.4.14 Follow-up for study drug modifications

Patients, whose treatment is modified, interrupted or permanently discontinued 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.

6.5 Treatment duration

The duration of treatment will be five years.

6.5.1 Study drug discontinuation

Patients who discontinue study drug entirely before completing the study must be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. The End of Treatment eCRF must be completed, documenting the date and reason for stopping the study drug. Any safety finding that leads to discontinuation of study drug must be captured on the Adverse Event eCRF.

All patients who discontinue study drug, including those who refuse to return for a final visit, will be contacted by the investigational site for safety evaluations during the 30 days following the last dose of study drug.

If patients refuse to return for these visits or are unable to do so, the investigator or a delegated person must make every effort to contact them or a knowledgeable informant by
telephone. However, patients are considered to be withdrawn from the study if it is clear that the patient will not return for these assessments.

6.5.2 Premature patient withdrawal / End of treatment

Patients may voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time. Patients who are pregnant, withdraw consent, died, fail to meet eligibility criteria, or are unwilling to comply with procedures as outlined in the study protocol must be withdrawn from the study.

If such withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient’s premature withdrawal from the study and record this information on the End of Treatment eCRF. Patients may be withdrawn from the study prematurely for one of the following reasons:

- Adverse event(s)
- Abnormal laboratory value(s)
- Abnormal test procedure result(s)
- Protocol violation
- Lost to follow-up
- Administrative problems

All unused/remaining study drugs must be returned by the patient withdrawn from study and must be accounted for.

If the patient fails to return, every effort should be made to contact the patient or a knowledgeable informant to determine the patient’s current health status. Attempts to contact the patient should be documented in the source documents.

6.6 Dose escalation guidelines (Phase 1 studies only)

Not applicable.

6.6.1 Study drug compliance and accountability

6.6.1.1 Study drug compliance

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

6.6.1.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability ledger. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.
At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability ledger to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.6.2 Disposal and destruction

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

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Written informed consent must be obtained before any study specific medical procedures are performed.

Patients will attend the study site at all visits to perform the scheduled assessments on the designated day, or as close as possible.

Table 7-1 and Table 7-2 list all of the assessments conducted during the Screening Period and Treatment Period, and indicate the visits when the assessments are to be performed with an “X”. All data obtained from these assessments must be supported in the patient’s source documentation. The tables also indicate which assessments produce data to be entered into the database (D) or remain in source documents (S) (“Category” column). The Reference column in the table indicates the section in this document where further information may be obtained regarding the assessment.
## Table 7-1  Visit evaluation schedule

<table>
<thead>
<tr>
<th>Week</th>
<th>Visit no.</th>
<th>Category</th>
<th>Reference</th>
<th>Screening</th>
<th>260 weeks study period</th>
<th>1-week periods</th>
<th>4-week periods between visits</th>
<th>EoT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td>-4 - 2</td>
<td>Day 1</td>
<td>1-2 3 4 5 6 7 8 12 16 20</td>
<td>24, 52, 76, 104, 128, 156, 180, 208, 232</td>
<td>28-48, 56-72, 80-100, 108-124, 152-156, 160-176, 204-232, 236-256</td>
</tr>
<tr>
<td></td>
<td>2</td>
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<td>15, 25, 34, 44, 53, 63, 72, 82, 91</td>
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<td>19-24, 29-33, 38-43, 48-52, 57-62, 777</td>
</tr>
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Demography/ Informed Consent

Inclusion / exclusion

Relevant medical history / current medical conditions

Transfusion history

Iron chelation therapy history

Diagnosis of NTDT
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Visit numbers highlighted in gray in the table above indicate visits conducted for assessments that may be performed locally (after dose initiation and dose escalations).

* Vital signs, height, weight and LIC assessment during screening should be performed at Visit 1 or at Visit 2
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**Laboratory assessment schedule**

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<td>Urinary protein/creatinine ratio</td>
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<td>Serum pregnancy test *</td>
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<td>Insulin</td>
<td>D 7.2.1.3</td>
<td>X</td>
<td>X X X</td>
<td>X (W36, 64, 88, 116, 140, 168, 192, 220, 244)</td>
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<td>D 7.1.2.3</td>
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<td>260 weeks study period</td>
<td>1-week periods</td>
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<td>24, 52, 76, 104, 128, 156, 180, 208, 232</td>
<td>28-48, 56-72, 80-100, 108-124; 132-152, 160-176, 184-204, 212-228, 236-256</td>
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<td>15, 25, 34, 44, 53, 63, 72, 82, 91</td>
<td>19-24, 29-33, 38-43, 48-52, 57-62, 67-71, 76-81, 86-90, 95-100</td>
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<td>Males: Total &amp; free testosterone</td>
<td>D</td>
<td>7.2.1.3</td>
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<td>Females: LH &amp; FSH</td>
<td>D</td>
<td>7.2.1.3</td>
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<td>Cortisol</td>
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<td>PK (subgroup)</td>
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<td>7.2.5.1</td>
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Visit numbers highlighted in gray in the table above indicate visits conducted for assessments that may be performed locally. After dose initiation and escalation occurs, the patient will have weekly assessments of serum creatinine. Assessments for serum transaminases, bilirubin, and alkaline phosphatase will be completed 2 weeks following dose initiation and escalation.

Blood samples for deferasirox pharmacokinetic assessment will be collected at pre-dose (0 hour), and at 2, and 4 hours at Week 4 (Visit 7). Trough blood samples will be taken at Week 12 (Visit 12) and Week 24 (Visit 15).

* For female patients capable of becoming pregnant serum pregnancy testing should be done within 72 hours prior to treatment start and urine testing at the end of treatment visit (see Section 7.2.2.5.4)
7.1.1 Pre-screening assessments

Not applicable.

7.1.2 Screening

Prior to commencement of the screening examination, the patient must have given full informed consent and have completed the study Informed Consent form. Once this has been signed and dated by the patient, the Investigator should perform the assessments to ensure full eligibility for trial participation. The Screening Period will be 4 weeks and will consist of two visits, visit 1 and visit 2. Laboratory assessments (hematology, blood biochemistry, serum ferritin, and urinalysis) collected at visit 1 and visit 2, must be at least 14 days apart from each other. LIC will be conducted at visit 1 or 2. The full list of assessments to be performed during the screening period (week -4 to week -1) is detailed in Table 7-1 and Table 7-2. Two screening visits are needed to perform key safety parameters prior to the first dose administration. All data obtained from these assessments must be supported in the patient’s source documentation. Women of child-bearing potential must have a negative serum pregnancy test ≤ 72 hours prior to initiating treatment. Please see Table 7-1 and Table 7-2 for the Screening Period assessments.

Should the 4-week screening period be exceeded due to delays in scheduling exams as outlined in the protocol (such as ocular exams, audiometry testing, MRI, etc) this delay will not be considered a protocol deviation and all laboratory assessments outlined in Visit 1 must be repeated.

Re-screening is permissible on a case-by-case basis. Please contact Novartis for guidance and refer to Section 7.1.2.2 for information on data to be collected on screening failures.

For patients being re-screened there is no need to re-assess LIC if the last assessment was performed within the last 3 months.

7.1.2.1 Eligibility screening

Patient eligibility will be confirmed by the site monitor during the monitoring visit.

7.1.2.2 Information to be collected on screening failures

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure. The reason for not being started on treatment will be entered on the Screening Log and each patient’s demographic information will be on the Demography CRF.

Patients who screen failed because one of the following criteria did not allow their inclusion in the study can be screened once again for re-eligibility 3 months later:

- If their LIC value was between 4.5 mg Fe/g dw and < 5 mg Fe/g dw
- If their serum ferritin was below 300 ng/mL at screening
- If their ALT was above 5 times ULN
7.1.2.3 Patient demographics and other baseline characteristics

At Visits 1 and/or 2, data will be collected on patient characteristics including demographic information (age, sex, ethnicity, etc.) and other background or relevant medical history/current medical condition, transfusion history, disease history and diagnosis, prior chelation therapy, presence of spleen, serum pregnancy test.

Other assessments conducted for the purpose of determining study eligibility include LIC by R2 MRI, serum ferritin, urine protein/creatinine ratio, creatinine clearance, serum creatinine, ALT, AST, hepatitis B, ECG, ocular exam, and audiometry.

7.1.3 Run-in period

Not applicable.

7.1.4 Treatment period

The Treatment Period will be five years. Visit frequency is every four weeks, while patient is receiving study drug. Following initiation of treatment and after dose escalation, patients will be monitored weekly for four weeks to assess serum creatinine. Serum transaminases, bilirubin, and alkaline phosphatase should be assessed 2 weeks following dose initiation or escalation. This is indicated as a shaded “X” in the Visit Schedule, Table 7-2. After these periods (if they are applicable), the patient will visit the study center according to the monthly visit schedule.

A patient whose treatment is modified, interrupted or permanently discontinued due to an adverse event or abnormal laboratory value, must be followed at least once a week for 4 weeks. In addition, patients who re-start treatment must perform weekly visits for 4 weeks including assessments of vital signs, physical examination, hematology parameters, blood chemistry and urinalysis.

Patients will attend the study site at all visits to perform the scheduled assessments on the designated day, or as close as possible.

PK samples will be collected from 20 patients during the visits indicated in Table 7-2.

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

7.1.5 End of treatment visit, including premature withdrawal and study discontinuation visit

Patients who discontinue study treatment before completing the study must be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. An End of Treatment eCRF page must be completed, giving the date and reason for stopping the study treatment. At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 30 days following the last dose of study treatment.

If a patient discontinues study treatment, but continues study assessments, the patient remains on study until such time as he/she completes protocol criteria for ending study assessments. At that time, the reason for study completion must be recorded on the Study Completion eCRF.
For criteria for premature withdrawal refer to Section 7.1.5.1.

End of treatment/Premature withdrawal visit is not considered as the end of the study.

7.1.5.1 Criteria for premature patient withdrawal

Patients may voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time. Patients must be withdrawn from the study if any of the following occur:

- Pregnancy
- Discovery of patient ineligibility
- Study compliance problems.

7.1.6 Follow up period

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

Patients lost to follow up must be recorded as such on the CRF. For patients who are lost to follow-up, the investigator must 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 Efficacy assessments

7.2.1.1 Liver iron content (LIC) assessment by MRI

Change in LIC from baseline after 52 weeks of treatment with study drug will be used as primary efficacy parameter. And, change in LIC from baseline after approximately six month intervals of treatment with study drug will be used as a secondary efficacy parameter.

LIC will be measured at Screening Visits 1 or 2, Visit 15 (week 24), Visit 25 (week 52), and approximately every six months thereafter (weeks 76, 104, 128, 156, 180, 208, 232, and 260) using a validated R2 MRI technique. All patients enrolled in the study will have MRI scans using a specific sequence. Raw image data will be analyzed centrally to determine the patient’s LIC value. The result of the measurement will be provided to the sites by the central laboratory.

7.2.1.2 Serum ferritin assessment

The assessment of the change in serum ferritin from baseline over five years of treatment with study drug will be used as a secondary efficacy parameter.

Serum ferritin levels will be measured at Screening Visits 1 and 2, Visit 3 and every 4 weeks thereafter by a central laboratory. Results will be provided to the sites within 24 hours after receiving samples by the central laboratory. Baseline serum ferritin will be calculated from the mean of the two values measured at Visit 1 and Visit 2, but with a minimum time lag of 14 days between these two assessments.
7.2.1.3 **Endocrine function laboratory parameters**

The assessment of endocrine function during the treatment period will be used as a secondary efficacy parameter. Blood samples collected at Visit 3 (baseline), Visit 12 (week 12), Visit 15 (week 24), Visit 21 (week 36), Visit 25 (week 52), and approximately every three months thereafter (weeks 64, 76, 88, 104, 116, 128, 140, 156, 168, 180, 192, 208, 220, 232, 244 and 260) for analysis of insulin, TSH, total and free T3, total and free T4, total and free testosterone (males), LH and FSH (females), and cortisol. Insulin resistance will be calculated using the Homeostatic Model Assessment (HOMA).

7.2.2 **Safety and tolerability assessments**

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

7.2.2.1 **Physical examination**

A physical examination will be performed at Screening Visit 1, Baseline Visit 3, Visit 15 (week 24), Visit 25 (week 52), and approximately every six months thereafter (weeks 76, 104, 128, 156, 180, 208, 232, and 260). 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.

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

Significant findings that are present prior to the start of study drug must be included in the Relevant Medical History/Current Medical Conditions page on the patient’s CRF. Significant findings made after the start of study drug which meet the definition of an Adverse Event must be recorded on the Adverse Event page of the patient’s CRF.

7.2.2.2 **Vital signs**

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

7.2.2.3 **Height and weight**

All subjects will have standing height measured at Screening Visit 1 or Visit 2. Pediatric patients will also have their height measured at Visits 15, 25, 34, 44, 53, 63, 72, 82, 91, and End of Treatment. Adult patients will have height measured yearly (Visits 25, 44, 63, 82 and
End of Treatment). Height will be measured in centimeters. This height measurement must be captured in the eCRF.

Body weight will be recorded for all patients at screening (Visit 1 or Visit 2), then at 4 week intervals and captured on the eCRF. Body weight will be measured to the nearest 0.1 kilogram. Weight must be measured while the patient is wearing ordinary clothing without shoes.

7.2.2.4 Auditory and ocular examination

Patients will undergo auditory and ocular examinations at screening and weeks 52, 104, 156, 208, 260 and at unscheduled visits (if needed).

The auditory examination includes the following assessments:
- Comprehensive audiometry threshold examination
- Speech recognition

The ophthalmologic examination includes the following assessments:
- Visual acuity test
- Tonometry
- Slit lamp exam of anterior segment
- Slit lamp exam of the lens
- Fundoscopic and retinal examination

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

7.2.2.5 Laboratory evaluations

A central 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].

7.2.2.5.1 Hematology

Hematology samples will be collected at Screening Visits 1 and 2, Visit 3 and then at 4 week intervals, thereafter, as described in the [Laboratory Manual]. Safety laboratory parameters monitored during the study will include hemoglobin, hematocrit, white blood cell (WBC) count with differential, platelet count, red blood cell (RBC) count, mean corpuscular volume (MCV), ANC and reticulocyte count. All hematology samples must be taken before blood transfusion and then be sent to the central laboratory.

7.2.2.5.2 Clinical chemistry

Clinical chemistry samples will be collected at Screening Visits 1 and 2, Visit 3 and then at 4 week intervals, thereafter, as described in the [Laboratory Manual]. Parameters to be measured will include: albumin, alkaline phosphatase, total/fractionated bilirubin, calcium, chloride, creatinine, gamma-glutamyl transpeptidase (GGT), fasting glucose, inorganic
phosphorus, potassium, total protein, ALT/SGPT, AST/SGOT, sodium, C-reactive protein, uric acid, lactase dehydrogenase (LDH), urea (BUN).

In accordance with the deferasirox label, serum creatinine, creatinine clearance, and ALT/SGPT must be assessed in duplicate before the initiation of therapy to establish a reliable pretreatment baseline.

In addition, serum creatinine will be measured weekly for the first four weeks of study drug administration at Visits 4, 5, 6, and weekly after any dose escalations for a duration of four weeks. Serum transaminases, bilirubin, and alkaline phosphatase will be measured two weeks after initiation of treatment or any dose escalations. See Section 6.1.1 These assessments after initiation of treatment and dose escalations may be conducted at a local lab.

Creatinine clearance will be estimated in adults using the Cockcroft-Gault equation and in pediatric patients using the Schwartz formula. This estimate will be provided at each monthly visit and at EOT.

7.2.2.5.3 Urinalysis

Urinalysis samples will be collected at Screening Visits 1 and 2, Visit 3 and every week during the first four weeks and then every four weeks thereafter. A midstream, second voided morning urine sample will be obtained. Specific gravity, pH, blood, glucose, protein, bilirubin, ketones, and leukocyte esterase will be assessed. Microscopic analysis will be performed only in case of positive dipstick. Dipsticks will be supplied by the central lab.

At Screening Visits 1 and 2, a urine sample (at least 15 ml) will be collected and sent to the central laboratory for urinary protein/creatinine ratio to assess the eligibility of the patient. In addition, urine samples for urinary protein/creatinine ratios will be collected at Visit 3 and then at 4 week intervals, thereafter, as described in the [Laboratory Manual]. First morning void samples must not be used for this analysis. Significant proteinuria is indicated by a urinary protein/creatinine ratio > 0.1 mg/mg.

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

7.2.2.5.4 Pregnancy and assessments of fertility

All female patients capable of becoming pregnant will have a pregnancy test (serum β-HCG) at Screening Visit 2. The results of the test must be available prior to initiating treatment with any study medication. Women of child-bearing potential must have a negative serum pregnancy test ≤ 72 hours prior to initiating treatment. Positive pregnancy tests will exclude a patient from participating in this trial.

During the treatment period, urine pregnancy testing will be performed locally if menses are delayed for more than 7 days in a female patient capable of becoming pregnant. A urinary pregnancy test will also be performed at the end of treatment visit.

Study drug must be discontinued in patients who become pregnant during the trial. See Section 8.4 for procedures to report pregnancy.
7.2.2.5.5 Hepatitis Viral tests

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

7.2.2.6 Cardiac assessments

7.2.2.6.1 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed at Screening and annually throughout the study (weeks 52, 104, 156, 208, and 260). Interpretation of the tracing must be made by a qualified physician and documented on the ECG CRF page. Each ECG tracing must be labeled with the study number, patient initials (where regulations permit), patient number, date, and kept in the source documents at the study site. Clinically significant abnormalities present when the patient signed the Informed Consent form must be reported on the Medical History CRF page. Clinically significant findings must be discussed with the Novartis Medical Monitor prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events CRF page.

7.2.3 Pharmacokinetics

Pharmacokinetic (PK) blood sampling will be performed in 20 study patients at specified time points (as shown in Table 7-2) at Visits 7, 12 and 15 (weeks 4, 12, and 24). These visits will be scheduled in the morning in order to allow the patient to withhold the dose until the pre-dose/trough PK sample is collected just prior to administration of the dose (approximately 24 hours after the previous dose). The patient must be on treatment without dose adjustment or treatment interruption (for any reason) for at least 4 consecutive days prior to scheduled PK sampling visit. If there has been a dosage change or interruption within 4 days of the visit, no PK blood samples should be collected, and an appropriate comment has to be made on the PK CRF page.

Thirty (30) minutes after the pre-dose/trough PK sampling is performed and the dose is administered, the patient may consume a standard breakfast. The patient may alternatively consume a light breakfast 2 hours prior to the pre-dose/trough PK sampling.

PK blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein or antecubital vein to determine plasma concentrations of deferasirox and its iron complex. Plasma concentrations of deferasirox and its iron complex will be presented in tabular format. AUCtau, Cmax, and tmax may be derived from plasma concentration-time profiles (week 4 only) using WinNonlin® (Pharsight, Mountain View, CA).

Multi-center participation in the PK sub-group will be optional. A total of 20 patients will participate in the PK analysis. Pediatric patients will not participate in the PK subgroup.
7.2.3.1 Pharmacokinetic blood collection and sample processing

Three (3) mL blood samples will be collected at each sampling time into a Vacutainer™ tube containing lithium heparin. Immediately after each tube of blood is drawn, it must 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 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, the upper plasma sample will be transferred into two separate 2 mL, tapered, polypropylene screw-cap tubes (Sarstedt #72.693 or equivalent without a skirted base) labeled as A and B. Each tube must have at least 0.5 mL of plasma and these 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 7-3. The exact clock time of dosing, as well as actual sample collection date and time must be captured on the PK CRF pages. Issues with obtaining samples will be noted in the comments field of the documents.

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<th>Visit</th>
<th>Week</th>
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<th>PK collection No.</th>
<th>PK sample No.</th>
<th>Sample volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>4</td>
<td>Pre-dose/0 h</td>
<td>1</td>
<td>1</td>
<td>3 mL</td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td>2 h post-dose</td>
<td>1</td>
<td>2</td>
<td>3 mL</td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td>4 h post-dose</td>
<td>1</td>
<td>3</td>
<td>3 mL</td>
</tr>
<tr>
<td>12</td>
<td>12</td>
<td>Pre-dose/0 h</td>
<td>2</td>
<td>4</td>
<td>3 mL</td>
</tr>
<tr>
<td>15</td>
<td>24</td>
<td>Pre-dose/0 h</td>
<td>3</td>
<td>5</td>
<td>3 mL</td>
</tr>
</tbody>
</table>

7.2.3.2 PK sample handling and shipping

All deferasirox samples must be labeled and frozen upon collection at -70°C +/- 15°C and kept frozen thereafter. All samples must be carefully packed in suitable packing material containing sufficient dry ice to keep them frozen during shipment. Include a list of all samples, including the study number, date, subject number and time of sampling. Clearly indicate if there are any missing samples. Samples will be sent to [China] for analysis.

7.2.3.3 PK analytical method

Deferasirox and its iron complex in plasma will be measured by [China]. Plasma concentrations of deferasirox and its iron complex will be determined by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay with a lower limit of quantitation of 0.670 µmol/L for deferasirox and 0.314 for its iron complex using 100 µL of plasma.
7.2.5 Other assessments

7.2.5.1 Health-related Quality of Life

Health-related Quality of Life will be assessed at Visits 3, 25, 44 and 63 (Day 1 and weeks 52, 104 and 156). The objective of the health economic component of the study is to evaluate the change in patient reported outcomes (PROs) using the SF-36 in adult patients and the PedsQL in pediatric patients.

SF-36

The Medical Outcomes Study Short Form 36 (SF-36) is a self-administered questionnaire for adults (greater than 18 years of age) and contains 36 items which measure eight dimensions: Physical functioning (10 items), Role limitation due to physical health problems (4 items), Bodily pain (2 items), General health perceptions (5 items), Vitality (4 items), Social functioning (2 items), Role limitations due to emotional problems (3 items) and General mental health (5 items). There is an additional single item giving information on health change over the past year. Item scores for each dimension are coded, summed and transformed to a scale from 0 (worst possible health state measured by the questionnaire) to 100 (best possible health state). The higher values indicate a better evaluation of health. Two summary scores of physical and mental health can also be calculated and scoring is norm-based, with normative values at 50 and no floor or ceilings. The SF-36 is well-documented in terms of reliability and validity in all available language versions (Ware and Sherbourne 1992). The SF-36 has a 4 week recall period. The questionnaire will be scored as per the instructions of the developers of the SF-36. In addition, the SF-6D, a utility measure of health states, can be derived from the SF-36 and the scoring for the SF-6D utility values will also be assessed using the scoring methods from the developers.
The PedsQL™ is a modular approach to measuring health-related quality of life (HRQOL) in children and adolescents. This will be administered to children between the ages of 13 to 18 years. The approach includes both a child self-report and parent proxy-report. The 23-item PedsQL™ Generic Core Scales encompass the essential core domains for pediatric HRQOL measurement: 1) Physical Functioning (8 items), 2) Emotional Functioning (5 items), 3) Social Functioning (5 items), and 4) School Functioning (5 items). The Generic Core Scales are designed to enable comparisons across patient and healthy populations.

Internal consistency reliability of the PedsQL™ was excellent, with alphas for the generic core scales in both self- and proxy-report greater than the 0.70 standard, and alphas for the full 23-item scale approaching 0.90 for self- and proxy-report. Missing data were minimal. Item response distributions were across the full scale range, with no floor effects, and minimal ceiling effects.

The validity of the PedsQL™ Generic Core Scales was demonstrated through known groups comparisons, and correlations with other measures of disease burden. The PedsQL™ self- and proxy-report distinguished between children with and without a chronic health condition, and within the group of children with a chronic condition, between those who did or did not have an overnight hospital visit in the last 12 months. Further, both child self-report and parent proxy-report correlated significantly with the number of days the child was too ill to pursue normal activities, needed someone to care for him or her, missed school in the last month, the number of days the parent missed from work in the last month, and parent-report of problems pursuing their normal work routine and concentrating at work. The PedsQL™ Generic Core Scales are also responsive to clinical change, as demonstrated in field trials.

7.2.5.2 Transfusion requirements
Transfusions (i.e. number and volume (ml) of PBRC and platelets administered during the course of the study) will be recorded in the appropriate transfusion eCRF.

8 Safety monitoring and reporting
8.1 Adverse events
8.1.1 Definitions and reporting
An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient’s signed informed consent has been obtained. Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Adverse events that begin or worsen after informed consent must be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent must be recorded in the Medical History CRF. Adverse event monitoring must 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 must be reported as a separate Adverse Event.

Severity of adverse events will be assessed as mild, moderate, or severe. Information about deaths will be collected through a Death form.

The occurrence of adverse events must 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 must be evaluated to determine:

1. The severity grade (mild, moderate, or severe)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study or investigational treatment for the adverse event (none, study treatment dose adjusted, study treatment temporarily interrupted, study treatment permanently discontinued, unknown, not applicable)
5. Whether concomitant medication or non-drug therapy was taken for the adverse event (No, Yes)
6. Outcome of the adverse event (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae (an after effect of the adverse event), fatal, unknown)
7. Whether it is serious (No, Yes) (a serious adverse event is defined as in Section 8.2.1)

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

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

### 8.1.2 Laboratory test abnormalities

#### 8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), must be recorded on the Adverse Events CRF. 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 must be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.
Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A severe event does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator’s discretion. A dose hold of study medication for the lab abnormality may be required by the protocol and is still, by definition, an adverse event.

8.1.3 **Adverse events of special interest**
See Section 6.4.1 through to Section 6.4.13.

8.2 **Serious adverse events**

8.2.1 **Definitions**
Serious adverse event (SAE) is defined as one of the following:
- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
  - 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
  - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - Social reasons and respite care in the absence of any deterioration in the patient’s general condition

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 must be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. 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 must be reported as a follow-up to that event regardless of when it occurs. The follow-up information must describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

8.3 Emergency unblinding of treatment assignment

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

8.4 Pregnancies

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

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

8.5 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided [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

The steering committee (SC) will be established comprising investigators participating in the trial, i.e. not being Novartis representatives from the Clinical Trial Team.
The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the Steering Committee will be defined in a Steering Committee charter.

9 Data collection and management

9.1 Data confidentiality

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

- What protected health information (PHI) will be collected from subjects in this study
- 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 at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

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

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

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator’s meeting, Novartis personnel (or designated CRO) will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.
The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on CRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

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

9.3 Data collection

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

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

9.4 Database management and quality control

For studies using eCRFs, Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments 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.

Samples and/or data will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

At the conclusion of the study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies 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.
For EDC studies, after final database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

10 Statistical methods and data analysis

This is an open label, single arm, multi-center, efficacy and safety study of deferasirox in iron overloaded patients with non-transfusion dependent thalassemia.

Data from all centers participating in this study will be aggregated to have an adequate number of patients for the analyses.

Standard descriptive analyses will include:

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

In order to optimize consistency within project, statistical methods considered are similar to companion study CICL670E2209 (NTDT patients).

Two analyses will be performed as follows:

- A one-year-analysis which will include assessments and events within treatment Year-1.
- A final analysis when the study is completed and the last patient enrolled has completed last study visit or discontinued.

Additional information for analysis methods will be available in RAP documentation. In addition to the overall population analysis, it is anticipated that statistical analysis will be performed according to subgroup Chinese/non-Chinese patients.

10.1 Analysis sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) consists of all patients who were assigned at least one dose of study drug. The FAS will be used for all efficacy analyses.

10.1.2 Safety Set

The Safety Set consists of all patients who received at least one dose of study drug.

10.1.3 Pharmacokinetic analysis set

The pharmacokinetic analysis set (PAS) consists of all patients from FAS set who have evaluable pharmacokinetic (PK) data.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data (including disease characteristics) will be summarized descriptively for the FAS.
10.3 **Treatments (study treatment, concomitant therapies, compliance)**

Duration of study drug exposure as well as average and cumulative planned (mg/kg/day) and prescribed treatment regimens (mg/kg/day) will be summarized. Frequency tables for dose adjustments and related reason will be provided as well as number and duration of dose interruptions. Any dose adjustments and reasons will be listed.

Compliance based on prescribed amount of study medication versus amount of medication taken based on dispensed and returned amount of study medication will be summarized.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will also be provided.

Results will be summarized for the safety set.

10.4 **Primary objective**

To assess the efficacy of deferasirox in patients with non-transfusion-dependent thalassemia based on absolute change in LIC from baseline after 52 weeks of treatment. As in previous studies within patients with transfusional iron overload, a normal distribution will be assumed for LIC absolute change. Handling of missing values is described in Section 10.4.3.

10.4.1 **Variable**

The primary efficacy variable is the absolute change in LIC measured by MRI from baseline after 52 weeks of treatment.

10.4.2 **Statistical hypothesis, model, and method of analysis**

Absolute change in LIC from baseline after 52 weeks of treatment will be analyzed using the FAS set. Null hypothesis (change from baseline at week 52 equal to 0) will be tested against alternative hypothesis using 2-sided one sample t-test with 5% type I error rate.

LIC values for baseline, week 24, week 52 and absolute changes from baseline will be provided.

10.4.3 **Handling of missing values/censoring/discontinuations**

In case of missing week 52 LIC the last available post-baseline LIC value before week 52 will be used instead in the calculation of the primary endpoint (Last-observation carried forward principle). Patients without any post-baseline LIC will have a missing value and will not be included in the analysis.

10.4.4 **Supportive analyses**

To further assess the absolute change and relative change in LIC from baseline at week 52, the descriptive statistics will be provided for:

- The proportion of patients with an LIC decrease by at least 3 mg Fe/g dw from baseline at week 52;
- The proportion of patients with an LIC decrease by at least 30% from baseline at week 52
10.4.5 One-year and Final analysis

At Week 52, the time defined for the primary objective, the one-year analysis will be performed. The primary objective and additional objectives performed in the one-year analysis are listed in Table 10-1.

The analyses supporting objectives not included in the one-year analysis and the objectives with assessments beyond treatment Year-1 will be performed at the completion of this study (details in Table 10-1).

The primary objective and the PK data will only be analyzed in the one-year analysis.

Table 10-1 One-year analysis and Final analysis

<table>
<thead>
<tr>
<th>Objective</th>
<th>Endpoint</th>
<th>Performed in the One-year Analysis?</th>
<th>Performed in the Final Analysis?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assess the efficacy of deferasirox in liver iron removal after 52 weeks of treatment</td>
<td>Change in LIC from baseline after 52 weeks of treatment</td>
<td>Yes¹</td>
<td>No²</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assess response rates in subset of patients with baseline LIC≥15 mg Fe/g dw</td>
<td>Proportion of patients with baseline LIC&gt;15 achieving LIC &lt;5 mg Fe/g dw and time to achieving LIC &lt;5 mg Fe/g dw</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Assess long-term efficacy of treatment to a target LIC of 3 mg Fe/g dw</td>
<td>Time from target LIC 3 mg Fe/g dw to the first LIC ≥5 mg Fe/g dw in the follow up period</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Evaluate the impact of deferasirox on adult QoL</td>
<td>Change in health-related outcomes using Medical Outcomes Study Form 36 (SF 36)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Evaluate the impact of deferasirox on pediatric QoL</td>
<td>Change in health-related outcomes using the Pediatric Quality of Life questionnaire</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Evaluate the efficacy of deferasirox in liver iron removal</td>
<td>Change in LIC from baseline</td>
<td>Yes¹</td>
<td>Yes</td>
</tr>
<tr>
<td>Assess the correlation of change in SF and LIC</td>
<td>SF vs LIC at baseline and EOS</td>
<td>Yes¹</td>
<td>Yes</td>
</tr>
<tr>
<td>Confirm the efficacy of deferasirox in liver iron removal in NTDT syndrome</td>
<td>Change in LIC from baseline after 52 weeks of treatment by underlying NTDT syndrome</td>
<td>Yes¹</td>
<td>No²</td>
</tr>
<tr>
<td>Assess the efficacy of deferasirox in decreasing SF after 52 weeks of treatment</td>
<td>Change in SF from baseline after 52 weeks of treatment</td>
<td>Yes¹</td>
<td>No²</td>
</tr>
<tr>
<td>Evaluate the safety of deferasirox doses up to 30 mg/kg/day dose</td>
<td>Safety parameters, labs, adverse events (AEs)</td>
<td>Yes¹</td>
<td>Yes</td>
</tr>
<tr>
<td>Assess the efficacy of deferasirox in endocrine function</td>
<td>Change from baseline during treatment period in total and free testosterone (males), LH and FSH (females), TSH, total and free T4, total and free T3, fasting plasma glucose, insulin, insulin resistance, and cortisol.</td>
<td>Yes¹</td>
<td>Yes</td>
</tr>
</tbody>
</table>
### 10.5 Secondary objectives

#### 10.5.1 Response analysis in patients with baseline LIC greater than 15 mg Fe/g dw

The proportion of patients with baseline LIC>15 mg Fe/g dw achieving an LIC <5 mg Fe/g dw during the study will be presented with a 95% confidence interval. The normal approximation will be used for the distribution, i.e. the confidence interval will be calculated as follows (Agresti and Coull 1998, formula (2)):

\[
100*(p + z_{0.975}^2/2n +/- z_{0.975}^*sqrt((p(1-p) + z_{0.975}^2/4n)/n) / (1 + z_{0.975}^2/n)
\]

Where p denotes the proportion, n the corresponding number of values, $z_{0.975}$ the 97.5% quantile of the standard normal distribution, and sqrt the square root function (see also Brown, Cai, DasGupta, 2001).

Time to the first LIC <5 mg Fe/g dw among patients with baseline LIC >15 mg Fe/g dw will be analyzed based on the Kaplan-Meier method. Kaplan-Meier curves for time to first LIC<5 mg Fe/ g dw and the medians along with 95% confidence intervals will be presented.

#### 10.5.2 Long-term efficacy of treatment to target LIC of 3 mg Fe/g dw followed by one or more treatment holidays until the LIC is greater or equal 5 mg Fe/g dw

Time from the target LIC <3 mg Fe/g dw to the first LIC ≥5 mg Fe/g dw in the follow-up period will be analyzed by using the Kaplan-Meier method. Kaplan-Meier curves for time to first LIC ≥5 mg Fe/g dw and the medians along with 95% confidence intervals will be presented.

#### 10.5.3 Absolute change in LIC measured by MRI from baseline over time

Absolute changes from baseline LIC at all scheduled LIC evaluation weeks will be analyzed in an analogous way as described in Section 10.4.2. Patients without any LIC post-baseline value at or prior to the scheduled LIC evaluation week will have missing values and will not be included in the analyses for the scheduled weeks.
Descriptive statistics and box plots will be provided for:

- LIC at baseline, at all scheduled LIC evaluation weeks (24, 52, 76, 104, 128, 156, 180, 208, 232, 260) and for last available LIC measurement;
- Absolute change from baseline LIC at all scheduled LIC evaluation weeks (24, 52, 76, 104, 128, 156, 180, 208, 232, 260) and for last available LIC measurement

10.5.4 Absolute change in LIC measured by MRI from baseline by NTDT syndrome

Absolute change from baseline LIC at all scheduled LIC evaluation weeks (24, 52, 76, 104, 128, 156, 180, 208, 232, and 260) by NTDT syndrome (beta-thalassemia intermedia, HbE beta-thalassemia or alpha-thalassemia intermedia (HbH disease)) will be analyzed in an analogous way as described in Section 10.4.2.

Very small subgroups are expected and therefore no inferential statistics will be provided.

10.5.5 Absolute change in serum ferritin from baseline over time

Descriptive statistics will be provided for serum ferritin (including absolute change from baseline) by visit up to week 260.

In order to reduce variability of serum ferritin values, patient-wise average will be defined per quarter:

- baseline serum ferritin as average of all available ferritin values from screening to last sample prior to first intake of study medication
- end of quarter is defined as average of available ferritin values from visit corresponding to end of quarter, visit prior, and visit after (e.g. end of first quarter includes average ferritin values from Visits 11, 12, and 13).

Similarly to analysis by visit, descriptive statistics will be provided for serum ferritin (including absolute change from baseline) by quarter up to week 260.

Absolute change from baseline at week 52 will be tested using a 2-sided one sample t-test. P-values will be considered as exploratory with no multiplicity considerations.

10.5.6 Correlation between serum ferritin and LIC at baseline and EOS

The following regression analyses will be performed without imputing any missing data:

- baseline serum ferritin versus baseline LIC, serum ferritin at 2nd quarter versus LIC at week 24, serum ferritin at 4th quarter versus LIC at week 52
- serum ferritin change from baseline at 2nd quarter versus change from baseline in LIC at week 24
- serum ferritin change from baseline at 4th quarter versus change from baseline in LIC at week 52
- serum ferritin change from baseline at week 260 versus change from baseline in LIC at week 260
10.5.7 Medical Outcomes Study Short Form-36 (SF-36)

See Section 7.2.5.1 for details on PROs.

Descriptive statistics will be provided for all items and PCS/MCS summary scores (including absolute change from baseline) by visit (baseline, week 52, 104, and 156).

Absolute change from baseline at week 52, 104, and 156 will be tested as exploratory using a 2-sided one sample t-test.

Additional information for PRO analysis methods will be available in RAP documentation. P-values will be considered as exploratory with no multiplicity considerations.

10.5.8 Pediatric Quality of Life Questionnaire

See Section 7.2.5.1 for details on PROs.

Descriptive statistics will be provided for all domains scores (including absolute change from baseline) by visit (baseline, week 52, 104, and 156).

Absolute change from baseline at week 52, 104, and 156 will be tested as exploratory using a 2-sided one sample t-test.

Additional information for PRO analysis methods will be available in RAP documentation. P-values will be considered as exploratory with no multiplicity considerations.

10.5.9 Endocrine function

Endocrine function parameters are: total and free testosterone (males), LH and FSH (females), TSH, total and free T4, total and free T3, fasting plasma glucose, insulin, insulin resistance, and cortisol).

Descriptive statistics will be provided for all parameters (including absolute change from baseline) by visit up to week 260.

10.5.10 Safety objectives

10.5.10.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used.

10.5.10.2 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. Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event.
Additionally, AEs with suspected relationship to study drug, requiring dose adjustment, leading to drug interruption/discontinuation will be specifically tabulated and listed.

### 10.5.10.3 Laboratory abnormalities

All laboratory values will be converted into SI units and the severity grade calculated using the low/normal/high classifications based on laboratory normal ranges, and for selected parameters (see Table 10-2 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 10-2 below).

For each hematology/iron metabolism parameter, observed values (and changes from baseline) averaged at baseline, after first intake of study medication to day 30, day 31 to day 90, and per subsequent quarter will be summarized by descriptive (n, mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum).

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 RAP.

**Table 10-2 Definition of notable/extended ranges for laboratory tests**

<table>
<thead>
<tr>
<th>Laboratory test</th>
<th>Criteria for notable ranges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count</td>
<td>&lt; 100 x 10^9/L (extended range &lt;50×10^9/L)</td>
</tr>
<tr>
<td>Absolute neutrophils</td>
<td>&lt; 1.5 x 10^9/L (extended range &lt;0.5×10^9/L)</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>&gt; 33% increase from baseline and &gt; ULN at two consecutive measurements at least 7 days apart</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>&lt;60 mL/min at two consecutive measurements at least 7 days apart (extended range &lt;40 mL/min at two consecutive measurements at least 7 days apart)</td>
</tr>
<tr>
<td>Urinary protein/urinary creatinine ratio</td>
<td>&gt;= 1.0 (mg/mg) at two consecutive measurements at least 7 days apart</td>
</tr>
<tr>
<td>SGOT/ALT and SGPT/AST</td>
<td>&gt;5 x ULN and 2 x baseline (extended range &gt;10×ULN and &gt;2×baseline value)</td>
</tr>
</tbody>
</table>

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

### 10.5.10.4 Other safety data

Data from electrocardiogram, vital signs, ocular and auditory examination will be listed and summarized (e.g., by investigator’s overall interpretation) as appropriate.

Any significant findings after start of study will be documented as adverse events and reported as such.
10.5.10.5 Tolerability

Incidence of grouped gastro-intestinal adverse events (defined by MedDRA terms to be specified in the more detailed RAP document) will be presented as well as Kaplan-Meier curves for time to first occurrence of such AEs.

10.5.11 Pharmacokinetics

PAS will be used in all pharmacokinetic data analysis and PK summary statistics. The pharmacokinetic parameters, AUCtau, Cmax and Tmax (week 4 data only) may be determined using non-compartmental method(s) for deferasirox and its iron complex.

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.

Descriptive statistics of all pharmacokinetic data and parameters will include arithmetic and geometric mean, median, SD, and CV, geometric CV, minimum and maximum. Zero concentrations will not be included in the geometric mean calculation. Since tmax is generally evaluated by a nonparametric method, median values and ranges will be given for this parameter.

10.5.11.1 Data handling principles

Missing concentration values will be reported as is in data listings. Concentration values below Lower Limit of Quantitation (LLOQ, BLLOQ) will be handled as zero, excluded in summary statistics, and reported as is in data listings.

10.5.13 Resource utilization

Not applicable.

10.5.14 Patient-reported outcomes

Not applicable.
10.7 Interim analysis

No formal interim analysis based on primary endpoint will be performed. Some basic safety annual analyses will be performed for PSUR (Periodic Safety Update Report).

10.8 Sample size calculation

Sample size is based on results from [ICL670A2209] (THALASSA) study, which was a prospective, double-blind, placebo controlled trial of deferasirox in starting doses of 5 and 10 mg/kg/day in patients with NTDT.

166 patients with randomized to starting doses of 5 mg (n=55) or matching placebo (n=28) and 10 mg (n=55) or matching placebo (n=28).

See in table below results for absolute change in LIC for this study:

<table>
<thead>
<tr>
<th>Time point Value</th>
<th>ICL670 5.mg/kg (N=55)</th>
<th>ICL670 10.mg/kg (N=55)</th>
<th>Placebo (N=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Value</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>55</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>Mean</td>
<td>13.11</td>
<td>14.56</td>
<td>15.94</td>
</tr>
<tr>
<td>SD</td>
<td>7.290</td>
<td>7.921</td>
<td>10.845</td>
</tr>
<tr>
<td><strong>Week.52.Value</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>51</td>
<td>54</td>
<td>54</td>
</tr>
<tr>
<td>Mean</td>
<td>11.56</td>
<td>10.58</td>
<td>16.38</td>
</tr>
<tr>
<td>SD</td>
<td>7.928</td>
<td>7.667</td>
<td>10.606</td>
</tr>
<tr>
<td><strong>Absolute.change.from.baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>51</td>
<td>54</td>
<td>54</td>
</tr>
<tr>
<td>Mean</td>
<td>-1.85</td>
<td>-3.78</td>
<td>0.26</td>
</tr>
<tr>
<td>SD</td>
<td>3.078</td>
<td>4.150</td>
<td>3.501</td>
</tr>
</tbody>
</table>

Note: Absolute change from baseline: value at timepoint – baseline value. Summary only includes patients with a value both at baseline and at considered timepoint. Source: [Table 14.2-1.9 from the ICL670A2209 trial] (29-Sep-2011 CSR).

The population of patients planned to be enrolled in this study will cover a broader type of patients (e.g. including patients treated with hydroxyurea, erythropoietin and butyrate) and
from multiple countries. This is likely to lead to more heterogeneity and thus to an increased variability compared to the one observed in the [ICL670A2209] study.

Assuming a true SD as high as 6 mg Fe and a drop-out rate of 20%, a sample size of 117 patients is required to obtain 90% power to detect a LIC absolute change of at least 2 mg Fe at Week 52 from the baseline value and using a paired t-test at 0.05 two-sided significance level.

Table below provides number of patients required according to different scenarios that ensure 80% power in case of lower true SD than expected (the others hypotheses remaining same):

<table>
<thead>
<tr>
<th>SD (mg Fe/g dw)</th>
<th>4.5</th>
<th>5.0</th>
<th>5.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Power (%)</td>
<td>80</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>n patients</td>
<td>51</td>
<td>63</td>
<td>75</td>
</tr>
</tbody>
</table>

Sample size has been computed using PASS 2008.

10.9 Power for analysis of key secondary variables

Not applicable.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

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

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Novartis before study initiation. 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 must 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 must be informed about the study to the extent possible given his/her understanding. If the patient is capable of
doing so, he/she must 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 must be documented in the patient source documents. The date when a subject’s Informed Consent was actually obtained will be captured in their CRFs.

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

11.4 Discontinuation of the study

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

11.5 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov.

Two study reports will be prepared, reporting on the one-year and the final analysis, respectively.

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

The investigator/institution must 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 must take measures to prevent accidental or premature destruction of these documents.

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

11.7 Confidentiality of study documents and patient records

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

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

11.9 Financial disclosures

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

12 Protocol adherence

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

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis must be notified of this action and the IRB/IEC/REB at the study site must be informed within 10 working days.
13 References (available upon request)


Galanello R and Origa R (2010). Beta-thalassemia. Orphanet J Rare Dis; 5:11


Musallam KM et al. (2011) Elevated liver iron concentration is a marker of increased morbidity in patients with β thalassemia intermedia. Haematologica. 96:1605–1612


