NOVARTIS

Clinical Development

ICL670, DEFERASIROX

Oncology Clinical Protocol CICL670FIC05 / NCT02993224

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

Statistical Analysis Plan (SAP)

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List of abbreviations

AE	Adverse event
ATC	Anatomical Therapeutic Classification
CSR	Clinical Study report
CTCAE	Common Terminology Criteria for Adverse Events
DT	Dispersible tablet
FAS	Full Analysis Set
FCT	Film-coated tablet
eCRF	Electronic Case Report Form
MedDRA	Medical Dictionary for Drug Regulatory Affairs
NCI	National Cancer Institute
NTDT	Non-transfusion- dependent thalassemia
PFS	Progression-Free Survival
PK	Pharmacokinetics
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
RAP	Report and Analysis Process
SAP	Statistical Analysis Plan
SOC	System Organ Class
TDT	Transfusion-dependent thalassemia
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

This analysis plan module describes the statistical methods which will be used in the Phase II clinical study CICL670FIC05.

The main purpose of this document is to provide a summary of the statistical methodology that will be used for this clinical study; this includes a detailed description of data summaries. Analyses plan in this document refers to the related statistical analysis sections in the clinical study report.

The analysis described here will be conducted by Novartis using statistical software SAS® Version 9.4 according to the Statistical methods and data analysis Section 10 of the study protocol which will be available in Appendix 16.1.1 of the CSR. Important information will be given in the following sections and further details are provided, as applicable, in the Appendix 16.1.9 of the CSR.

Unless otherwise specified, the statistical methodologies including the analysis sets, analysis models, algorithms and conventions are following the Oncology study protocol CICL670FIC05 final version.

1.1 Study design

This is an open-label, multicenter, single arm study of deferasirox. This study aims to assess treatment patient preference for new deferasirox formulation (film-coated tablet) compared to reference deferasirox dispersible tablet formulation in transfusion-dependent thalassemia (TDT) and non-transfusion-dependent thalassemia (NTDT) patients throughout a 48 week treatment period.

Patients will undergo up to 4 weeks of screening period and if deemed eligible, will receive deferasirox dispersible tablet (DT) formulation for 24 weeks. After completion of 24 weeks patients will be transitioned on Week 25 to an equivalent dose of the deferasirox film coated tablet (FCT) formulation and continue treatment till Week 48. Completion of Week 48 indicates “End of Trial” of the Core Phase.

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

Planned number of patients

It is intended that a total of 145 patients of age ≥ 2 years will be recruited in the study. Patients may have been previously treated with iron chelators (other than deferasirox DT) or be chelation-naïve.

The overall study design is as follows:

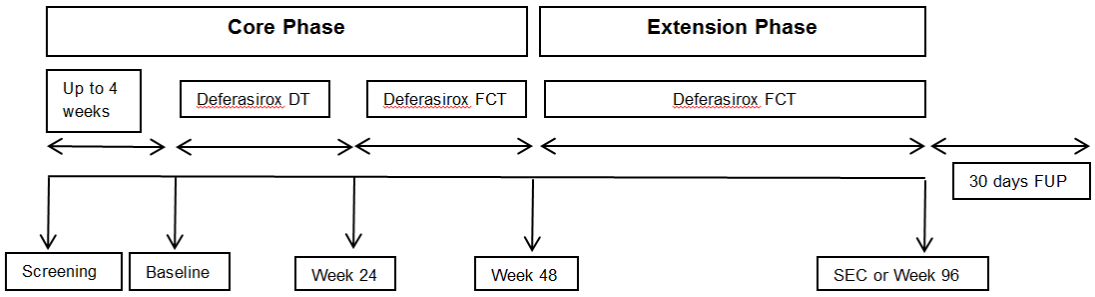
- **Core phase**:
    - Screening phase which lasts for maximum 4 weeks to determine whether the patient is eligible or not and is followed by
    - Baseline visit (Day 1)

- Period 1: deferasirox DT as 10-40 mg/kg/day dose regimen of dispersible tablet formulation for 24 weeks followed by
- Period 2: deferasirox FCT as 7-28 mg/ kg/ day dose regimen of film coated tablet for 24 weeks.

- **Extension Phase:**
  - Deferasirox FCT as 7-28 mg/kg/ day dose regimen of film-coated tablet.

The overall study design is given in the following figure:

Figure 1-1 Study Design



Patients who discontinue study treatment before completing the study should be scheduled for a visit as soon as possible, at which time all of the assessments listed for SEC must be performed.

Primary analysis time point

The primary analysis will be performed at Week 48 to evaluate patient preference of deferasirox DT vs. deferasirox FCT formulations.

Interim analysis

The interim analysis will be performed at Week 48 to assess the patient preference after 6 months with deferasirox FCT treatment in comparison to deferasirox DT.

1.2 Study objectives and endpoints

The objective of the study is to assess patient preference of deferasirox DT or deferasirox FCT in thalassemia patient.

Table 1.2.1: Study objectives and related endpoints

Objective	Endpoint
Primary	
To evaluate patient preference between deferasirox FCT and deferasirox DT	Proportion of patients claimed preference of deferasirox FCT over deferasirox DT as measured by preference questionnaire at Week 48

Objective	Endpoint
Secondary	
To evaluate patient preference of deferasirox FCT or deferasirox DT or previous iron chelation	Proportion of patients claimed preference of deferasirox FCT, deferasirox DT, and previous iron chelation as measured by preference questionnaire at Week 28
To evaluate patient preference of deferasirox DT or previous iron chelation	Proportion of patients claimed preference of deferasirox DT, over previous iron chelation as measured by preference questionnaire at Week 4 and Week 24
To evaluate the reason behind preference for deferasirox FCT or deferasirox DT	Proportion of preference reasons for deferasirox FCT over deferasirox DT as measured by preference questionnaire at Week 28 and Week 48
To evaluate the effect of deferasirox FCT compared with deferasirox DT on patient compliance using pill count	Relative consumed pill count during deferasirox FCT (Week 25 to 48) compared with deferasirox DT (Baseline day 1 to Week 24)
To evaluate the effect of deferasirox FCT compared with deferasirox DT or previous iron chelation on patient palatability using PRO	Absolute and relative change in domain scores of palatability questionnaire over time during deferasirox FCT (Week 28 to 48) compared with deferasirox DT (Week 4 to 24) or previous iron chelation (Screening)
To evaluate the effect of deferasirox FCT compared with deferasirox DT or previous iron chelation on patient satisfaction using PRO	Absolute and relative change in domain scores of SICT questionnaire over time during deferasirox FCT (Week 28 to 48) compared with deferasirox DT (Week 4 to 24) or previous iron chelation (Screening)
To evaluate the effect of deferasirox FCT compared with deferasirox DT or previous iron chelation on patient GI symptom using PRO	Absolute and relative change in domain scores of SICT questionnaire over time during deferasirox FCT (Week 28 to 48) compared with deferasirox DT (Week 4 to 24) or previous iron chelation (Screening)
To evaluate the overall safety of deferasirox FCT compared with deferasirox DT	Overall safety, as measured by frequency and severity of adverse events and changes in laboratory values of interest during deferasirox FCT (Week 25 to 48) compared with deferasirox DT (Baseline day 1 to Week 24)
To evaluate efficacy of deferasirox (both DT and FCT) in decreasing serum ferritin levels	Absolute and relative change from baseline (Day 1) in serum ferritin on monthly basis

2 Statistical methods

2.1 Data analysis general information

All analysis will be performed by NBS CONEXTS, Novartis.

It is planned that the data from all centers that participate in this study will be used for analysis. Analysis datasets and statistical outputs will be produced using the most recent SAS® Version 9.4 (SAS Institute Inc., Cary, NC, USA), and stored in Novartis global programming & statistical environment (GPS).

As the primary endpoint analysis will be performed at Week 48, there will be a database lock after all patients have completed Week 48 assessments. The proposed statistical analysis for interim analysis is described in Section 2.14. A final database lock will occur when all patients have completed the study.

All summary statistics for continuous variables will include n (number), mean, standard deviation (SD), median, lower and upper quartiles (Q1, Q3), minimum, maximum, and, where applicable, the estimate and the 95% confidence intervals (CI) of mean. For categorical variables, descriptive statistics will include the number (frequencies) and percentage of patients in each category. Summary statistics will also be presented graphically wherever applicable.

If not otherwise specified, p-values and CI will be presented as two-sided. Unless otherwise stated, the default level of significance will be set to 5% (two-sided, family-wise type-I-error).

All data analysis will be presented by treatment group, i.e. DFX DT and DFX FCT, iron chelation status (naïve or pre-treated) and by thalassemia transfusion status (TDT or NTDT), wherever applicable. Efficacy and safety data for the core and extension phases will also be presented by the above groups. Since this study also includes pediatric patients, all key safety and efficacy endpoints will also be summarized by the age groups as defined in the protocol and Section 2.2.1.

The analysis will be conducted on all patients' data at the specific time-points (Week 4, 24, 28, and 48), wherever applicable and at the time the study (both core and extension phases) ends.

Unless otherwise specified, if there are additional data available for any assessment (for example data on unscheduled visit) then the average of the available values will be presented under the dedicated visit.

2.1.1 General definitions

Study treatment

In this and subsequent analysis plan module (TFL and PDS), the terms "investigational drug", "study drug" and "study treatment" refers to deferasirox FCT as well as deferasirox DT.

Study treatment start and end date

Study treatment start date is defined as the first date when a non-zero dose of study drug is administered and recorded on the Drug Administration Record (DAR) CRF page. Similarly, study drug end date is defined as the last date when a non-zero dose of study drug is administered and recorded on the DAR CRF page of the study.

End of study

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

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

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

Patient completed

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

Study day

Study day will be calculated as (event date – study drug start date + 1 day) for events that occurred on or after study drug start date (e.g. visit, lab samples, AEs). For events prior to study drug start date (e.g. time of diagnosis), study day will be negative and calculated as (event date – study drug start date). Note that study drug start date is study day 1 and the day before study drug start date is study day -1 (i.e. no study day 0).

Due to the study drug dosing schedule, one month will be considered as 28 days. However, for "time since event" data (e.g. medical history), one month will be considered as 365.25/12 days for events that occurred prior to study Day 1. Time from events prior to the start of study drug, e.g., time since diagnosis, is calculated as the difference between the start date of study drug and the date of prior event.

Note that, the first dose day is Day 1, and the day before the first dose day is counted as Day -1 (not Day 0).

Baseline assessment:

Baseline assessment in general will be defined as the last assessment prior to the start of the study treatment which is the assessment taken at Day 1 of study. A baseline value refers to the last measurement made prior to administration of first dose of study treatment.

Post baseline assessment:

A post-baseline value refers to a measurement taken after the first dose of study treatment.

Treatment period

The planned treatment duration of the core phase is 48 weeks (24 weeks of DT followed by 24 weeks of FCT) and the planned treatment period for the extension phase is another 48 weeks of FCT.

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

Patients will be followed up for safety purposes for 30 days after the last dose of study drug (regardless if that situation occurs during core or extension phase).

Lost to follow up

The patients whose study completion status is unclear because they fail to appear for study visits without stating an intention to withdraw.

Visit window

Visit wise following window period will be used:

Visit 3 Date of visit should be 14 days from Visit 2 also consider buffer +/-2 days (e.g. Timeframe to do the visit is 12 days to 16 days)

Visit 4 Date of visit should be 28 days from Visit 2 also consider buffer +/-2 days (e.g. Timeframe to do the visit is 26 days to 30 days)

Visit 5 Date of visit should be 56 days from Visit 2 also consider buffer +/-2 days (e.g. Timeframe to do the visit is 54 days to 58 days)

Visit 6 Date of visit should be 84 days from Visit 2 also consider buffer +/-2 days (e.g. Timeframe to do the visit is 82 days to 86 days)

Visit 7 Date of visit should be 112 days from Visit 2 also consider buffer +/-2 days (e.g. Timeframe to do the visit is 110 days to 114 days)

Visit 8 Date of visit should be 140 days from Visit 2 also consider buffer +/-7 days (e.g. Timeframe to do the visit is 133 days to 147 days)

Visit 9 Date of visit should be 168 days from Visit 2 also consider buffer +/-7 days (e.g. Timeframe to do the visit is 161 days to 175 days)

Visit 10 Date of visit should be 196 days from Visit 2 also consider buffer +/-7 days (e.g. Timeframe to do the visit is 189 days to 203 days)

Visit 11 Date of visit should be 224 days from Visit 2 also consider buffer +/-7 days (e.g. Timeframe to do the visit is 217 days to 231 days)

Visit 12 Date of visit should be 252 days from Visit 2 also consider buffer +/-7 days (e.g. Timeframe to do the visit is 245 days to 259 days)

Visit 13 Date of visit should be 280 days from Visit 2 also consider buffer +/-7 days (e.g. Timeframe to do the visit is 273 days to 287 days)

Visit 14 Date of visit should be 308 days from Visit 2 also consider buffer +/-7 days (e.g. Timeframe to do the visit is 301 days to 315 days)

Visit 15 Date of visit should be 336 days from Visit 2 also consider buffer +/-7 days (e.g. Timeframe to do the visit is 329 days to 343 days)

Visit 16 Date of visit should be 364 days from Visit 2 also consider buffer +/-7 days (e.g. Timeframe to do the visit is 357 days to 371 days)

Visit 17 Date of visit should be 392 days from Visit 2 also consider buffer +/-7 days (e.g. Timeframe to do the visit is 385 days to 399 days)

Visit 18 Date of visit should be 420 days from Visit 2 also consider buffer +/-7 days (e.g. Timeframe to do the visit is 413 days to 427 days)

Visit 19 Date of visit should be 448 days from Visit 2 also consider buffer +/-7 days (e.g. Timeframe to do the visit is 441 days to 455 days)

Visit 20 Date of visit should be 476 days from Visit 2 also consider buffer +/-7 days (e.g. Timeframe to do the visit is 469 days to 483 days)

Visit 21 Date of visit should be 504 days from Visit 2 also consider buffer +/-7 days (e.g. Timeframe to do the visit is 497 days to 511 days)

Visit 22 Date of visit should be 532 days from Visit 2 also consider buffer +/-7 days (e.g. Timeframe to do the visit is 525 days to 539 days)

Visit 23 Date of visit should be 560 days from Visit 2 also consider buffer +/-7 days (e.g. Timeframe to do the visit is 553 days to 567 days)

Visit 24 Date of visit should be 588 days from Visit 2 also consider buffer +/-7 days (e.g. Timeframe to do the visit is 581 days to 595 days)

Visit 25 Date of visit should be 616 days from Visit 2 also consider buffer +/-7 days (e.g. Timeframe to do the visit is 609 days to 623 days)

Visit 26 Date of visit should be 644 days from Visit 2 also consider buffer +/-7 days (e.g. Timeframe to do the visit is 637 days to 651 days)

Visit 777 Date of visit should be 672 days from Visit 2 also consider buffer +/-7 days (e.g. Timeframe to do the visit is 665 days to 679 days)

2.2 Analysis sets

The following analysis sets will be used in this study.

Enrolled Set: The Enrolled Set comprises all patients enrolled in this study. Patients who discontinued from the study due to ineligibility immediately after Visit 2 are not considered as enrolled.

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

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

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

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

Any major protocol deviation will lead to exclusion of patients from PPS. The list of PDs is defined in Section 5.5.

2.2.1 Subgroup of interest

Since this study also includes pediatric patients, all key safety and efficacy analyses will be performed separately by age groups: 2-6 years (infant), 7-11 years (child), 12-17 years (adolescent), < 18 years (overall of infant, child and adolescent), and ≥ 18 years (adult). In addition, these summaries will be performed on prior intake of iron chelation status (naïve or pre-treated) and thalassemia transfusion status (TDT or NTDT).

2.3 Patient disposition, demographics and other baseline characteristics

Descriptive statistics will be provided for patient disposition, demographics and all baseline characteristics including baseline values of main efficacy endpoints.

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

Patients with missing data will not be included in the calculation of the percentages.

2.3.1 Patient disposition

The Enrolled Set will be used for the summary and listing of patient disposition. The overall number and percentage of patients who were screened, completed (core phase, extension phase) and discontinued the study (core phase or extension phase) along with reasons for discontinuation will be summarized.

2.3.2 Patient demographics

Summary statistics will be presented for continuous demographic variables by the subgroup of interest and for all patients in the Enrolled Set. For categorical variables, number and percentage of patients in each category will be presented for subgroup of interest and all patients.

The following demographic variables will be summarized:

Continuous variables:

- Age (years)
- Height (meter)
- Weight (kg)
- Body mass index (BMI) = (body weight in kilograms) / (height in meters)^2

  For BMI, height and body weight used is the last value prior to randomization. If there is no weight recorded prior to taking of study drug, BMI will be missing.

Categorical variables

- Age group (2 years ≤ age < 7 years, 7 years ≤ age < 12years, 12 years ≤ age < 18 years, < 18 years (overall of infant, child and adolescent), and age ≥ 18 years)
- Gender (male, female)
- Ethnicity (Hispanic/Latino, Chinese, Indian (Indian subcontinent), Japanese, Other)

2.3.3 Patient baseline characteristics

Summary statistics will be presented for continuous baseline variables by subgroup of interest and for all patients in the Enrolled set. For categorical variables, number and percentage of patients in each category will be presented for subgroup of interest and all patients. Baseline characteristics will be summarized depending on the following histories and tests:

- Disease history
- Prior chelation therapy
- Transfusion history

Baseline disease characteristics will be summarized for the following variables:

- Disease history continuous variables
  - Time since diagnosis (months)
- Disease history categorical variables
  - Disease type (Transfusion-dependent thalassemia, Non-transfusion-dependent thalassemia)
  - Patients who are hematologically stable since the examination (Yes/ No)
- Prior chelation therapy continuous variables
  - Time since last iron chelation therapy (from end date)
  - Duration of last iron therapy (days)
  - Average daily dose (DFO) (mg/kg)
  - Average daily dose (DFP) (mg/kg)
  - Average daily dose of DFO or DFP (mg/ kg)
  - Average daily dose 1 (Other) (mg/kg)
  - Average daily dose 2 (Other) (mg/kg)
- Prior chelation therapy categorical variables
  - Patients who have received a chelation therapy in at least last 6 months prior to start of study drug (Yes/ No), where 'Yes' means prior chelation treated and 'No' means prior chelation naïve.
  - Medication name (DFO, DFP, DFO and DFP, Other)
- Transfusion history continuous variable
  - Total number of transfusion(s) received in last 12 months (units)
  - Time since last transfusion received (days)
  - Number of units last transfused
    - Platelets
    - PRBC
    - White blood
- Transfusion history categorical variable
  - The subject received blood transfusion prior to study (Yes/ No)

Medical history

Relevant medical history and current medical conditions will be summarized by system organ class and preferred term of the MedDRA dictionary. Other relevant baseline information will be listed and summarized using descriptive statistics, as appropriate.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Study treatment

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

- The number of medications (pills) received for each dosing regimen
- The duration of exposure (in weeks) and in categories (< 4 weeks, 4-< 12 weeks, 12-< 24 weeks, ≥ 24 weeks)
- Average planned (mg/kg/day) and average actual daily dose (mg/kg/day)
- Cumulative planned (mg/kg) and cumulative total actual dose (mg/kg)
- Percentage of planned dose taken
- Dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure)
- Relative dose intensity (computed as the ratio of dose intensity and planned dose intensity)

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

The number of patients with 'switching'(this is a switch outside the normal switch at the end of Week 24) from one treatment to another at any treatment period along with the reasons of switching will also be summarized. In case of switching within each treatment period, duration of exposure will be calculated accordingly as described below.

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

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

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

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.

Patient compliance with study treatment will be evaluated using the pill count. The details of summary of compliance are explained in Section 2.7.2.

2.4.2 Prior, concomitant and post therapies

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

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

Medications will be presented in alphabetical order, by Anatomical Therapeutic Classification (ATC) codes and grouped by anatomical main group. Tables will show the overall number and percentage of patients receiving at least one treatment of a particular ATC code and at least one treatment in a particular anatomical main group.

Significant prior and concomitant surgeries and procedures will be summarized by primary system organ class and MedDRA preferred term.

The number and percentage of patients receiving prior and concomitant medication or therapy will be provided by system organ class and preferred term.

Prior or concomitant medication will be identified by comparing recorded or imputed start and end dates of medication taken to the reference start date.

2.5 Analysis of the primary objective

The primary objective of the study is to evaluate patient preference of deferasirox FCT or deferasirox DT at Week 48.

2.5.1 Primary endpoint

The primary endpoint is the proportion (and percentage, %) of patients who claim preference of deferasirox FCT over deferasirox DT as measured by preference questionnaire at Week 48.

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

2.5.2 Statistical hypothesis, model, and method of analysis

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

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

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

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

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

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

In other words,

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

versus

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

The primary analyses of testing patient preference of FCT over DT will be conducted via Mc Nemar's test. Both exact and asymptotic p-values will be presented for Mc Nemar's test for the matched pairs. Along with p-values, the estimates of proportions and percentages (%) of patient preferences and non-preferences for each study treatment will also be presented along with 95% CI (if required) using Clopper-Pearson method. The Type I error will be set to 2-sided α=5% or 1-sided α=2.5%. The testing will be done on the patients who have completed question 2 in the preference questionnaire.

2.5.3 Handling of missing values/censoring/discontinuations

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

Patients should be seen for all visits to perform the scheduled assessments on the designated day, or as close to it as possible, i.e., not exceeding ± 2 days for all assessments scheduled in Visits 1 to 7 and ± 7 days for all other visits till Visit 777. In this clinical study, a week is 7 calendar days.

2.5.4 Supportive analyses

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

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

The primary and above supportive analyses will also be performed for each subgroup of the baseline factor, i.e. on patients with TDT or NTDT and also on prior treatment status of iron chelation (naïve or pre-treated). Additionally, the primary analysis will be performed by age groups: 2-6 years (infant), 7-11 years (child), 12-17 years (adolescent), < 18 years (overall of infant, child and adolescent), and ≥ 18 years (adult). No p-values will be presented for subgroup analyses.

To identify the impact of preference on switching, the primary analyses will be performed separately for patients with or without switching before Week 48.

As a supportive analysis, the primary analysis will also be provided for PPS.

2.6 Analysis of the key secondary objective

Not applicable.

2.7 Analysis of secondary efficacy objective(s)

Refer to Table 1.2.1 of Section 1 for the list of secondary objectives.

2.7.1 Secondary endpoints

All the secondary efficacy evaluation will be performed on FAS population.

Refer to Table 1.2.1 of Section 1 for the list of secondary endpoints.

2.7.2 Statistical hypothesis, model, and method of analysis

No formal hypothesis testing will be conducted for secondary endpoints.

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

The proportion and percentage (%) of patients including 95% CI will be reported separately for preference and non-preference of FCT over DT, FCT over prior iron chelation, and DT over prior iron chelation at Week 28.

Homogeneity tests (including Cochran's Q test) will also be performed to check the homogeneity of the above three preferences. Exact and asymptotic p-values of Mc Nemar's test will also be presented as analogous to primary analysis, for pairwise treatment comparisons.

The OR of patient preference (i.e. $OR=p_{12}/p_{21}$), 95% CI and p-values will also be presented for pairwise comparisons. For comparisons with iron-chelation, only patients who were pre-treated with iron chelation will be selected for pairwise comparisons.

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

The proportion and percentage (%) of patients including 95% CI will be reported separately for preference and non-preference of DT over iron chelation at Week 4 and Week 24. Exact and asymptotic p-values of Mc Nemar's test will also be presented as analogous to primary analysis, described in Section 2.5.2. The OR of patient preference (i.e. $OR=p_{12}/p_{21}$), 95% CI and p-values will also be presented. Only patients who are pre-treated with iron-chelation will be considered.

Reasons of patient preference

The reasons or factors influencing behind patient preference of FCT over DT will be summarized at Week 28 and 48. The number and percentage (%) of patients for selecting each reason will be presented for preference of each study treatment. In addition to that, the summary of reasons behind non-preference of each study treatment will also be presented.

Similar summaries will also be provided for different preference comparisons at Week 4 and 24.

Compliance using pill count

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

The prescribed count corresponds to the count prescribed by the investigator for a period that the patient should have taken during this period. For each strength (125 mg, 250 mg and 500 mg tablets for Deferasirox DT; 90 mg, 180 mg and 360 mg tablets for Deferasirox FCT), the prescribed count for a period is calculated from the daily prescribed count at the beginning of this period multiplied by the duration (days) of this period. The daily prescribed count is the sum of counts prescribed per strength. The duration of a period will be calculated as (end date of the period) – (start date of the period) + 1. The following period duration calculation will exclude the start day. The total count prescribed is the sum of counts prescribed over all periods.

If a patient does not return the study drug, the compliance will not be calculated.

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

Summary statistics of number of pills (and percentages) will also be presented overall and by treatment and subgroups.

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

Summary statistics of change from baseline (absolute and difference, and 95% CI) will be presented by visit, treatment and subgroups (i.e. by age group, and status of previous iron chelators) and difference between treatments. Graphical presentation including mean (and SD) change from baseline plots will also be reported for all visits.

Palatability

Refer to PRO section (Section 2.11) for summary details.

mSICT

Refer to PRO section (Section 2.11) for summary details.

GI symptoms

Refer to PRO section (Section 2.11) for summary details.

2.7.3 Handling of missing values/censoring/discontinuations

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

Last observation carried forward can only be applied for serum ferritin levels.

2.8 Safety analyses

For all safety analyses, the Safety Set (SAF) will be used. All listings and summaries will be presented by treatment group (wherever applicable) and by TDT and NTDT. In addition, all key safety summaries will be reported separately for all age groups (defined earlier in Section 2.2.1). The safety analysis will also be presented separately for core and extension phases of the study.

The overall observation period will be divided into three mutually exclusive segments:

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

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

All data, regardless of observation period, will be listed. Safety assessments starting during the pre-treatment or post-treatment period will be flagged in the listings. Safety assessments starting prior to study day 1 will appear with negative study day in the listings.

2.8.1 Adverse events (AEs)

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

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

Severity is captured in CRF as per CTCAE V 4.03 grades. The mapping from CTCAE to severity grade is given below:

- Grade 1=Mild
- Grade 2= Moderate

- Grade 3= Severe
- Grade 4 = Life- threatening
- Grade 5= Death related to AE

In this study the grade ≥ 3 will be considered as severe.

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

The following adverse event summaries will be produced by treatment for Safety Set:

- Adverse events (overall and severe), regardless of study drug relationship by primary system organ class and preferred term
- Adverse events, regardless of study drug relationship by primary system organ class and preferred term and severity
- Adverse events (overall and severe), with suspected study drug relationship by primary system organ class and by preferred term
- Serious adverse events (overall and severe), regardless of study drug relationship, by primary system organ class and preferred term
- Adverse events leading to study drug discontinuation (overall and severe), regardless of study drug relationship, by primary system organ class and preferred term
- Adverse events requiring dose adjustment or study-drug interruption (overall and severe), regardless of study drug relationship, by primary system organ class and preferred term
- Adverse events requiring additional therapy (overall and severe), regardless of study drug relationship, by primary system organ class and preferred term

The incidences listed above will additionally be summarized by preferred term.

- Deaths by primary system organ class and preferred term.
- Non-serious adverse events, regardless of study drug relationship, by primary system organ class and preferred term (for clinicaltrials.gov purpose)

An overall summary of type of AEs (e.g. serious, leading to study drug discontinuation, requiring dose adjustment and/or interruption) will be presented by treatment (overall and severe). This summary as well as the incidence of AEs (overall and severe), regardless of study drug relationship, will additionally be provided separately for pediatric and adult patients. AEs will be summarized by presenting the number and percentage of patients having at least one AE, and having at least one AE by system organ class and/or preferred term, severity, and relation to study drug by treatment. A patient with multiple occurrences of an AE will be counted only once in the AE category.

All AEs, deaths and SAEs (including those from the pre and post-treatment periods) will be summarized and listed and those collected during the pre-treatment and post-treatment period will be flagged. Severity of AEs will be assessed as mild, moderate, or severe.

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

A graphical display of relative frequencies within system organ classes and risks difference =risk in FCT-risk in DT (because if in DT, patient count for some SOC becomes 0, then relative risk will be undefined), as appropriate, may be presented by forest plot.

The following formula will be used:

Table 2-1 Contingency Table for Risk*

	Treatment	
	DFX FCT	DFX DT
No of patient with AE	FCTE	DTE
No of Patient without AE	FCTN	DTN

*separate calculation will be done for each SOC

Risk difference (RD) $=\frac{FCTE}{FCTE+FCTN}-\frac{DTE}{DTE+DTN}=p_1-p_2$,

where $p_1=\frac{FCTE}{FCTE+FCTN}$ and $p_2=\frac{DTE}{DTE+DTN}$

The sampling distribution of RD is approximately normal.

Hence, Standard Error for RD = SE(RD)$=\sqrt{\frac{FCTE\cdot FCTN}{(FCTE+FCTN)^3}+\frac{DTE\cdot DTN}{(DTE+DTN)^3}}$

$=\sqrt{\frac{p_1(1-p_1)}{N_1}+\frac{p_2(1-p_2)}{N_2}}$,

where $N_1= FCTE + FCTN$ and $N_2= DTE + DTN$

95% CI of SE(RD)= $RD \pm 1.96 \times SE(RD)$

In plot all results will be presented in percentages (%).

2.8.1.1 Adverse events of special interest / grouping of AEs

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

All AESI groupings are defined through the use of Preferred Terms (PT), High Level Terms (HLT), System Organ Classes (SOC), Standardized MedDRA Queries (SMQ), Novartis MedDRA Queries (NMQ), or through a combination of these components.

The AESI search table will be used to map reported AEs to the notable AE groupings. The list of AESIs may be updated during the course of the study based on accumulating safety data. Therefore, the clinical study report will list the AE groupings used and provide a listing of the corresponding AESI search table.

Note that certain AEs may be reported within multiple groupings.

For AESIs, time-to-event analysis will be performed as appropriate. Results will be tabulated and the Kaplan-Meier estimates for the cumulative rate will be plotted.

2.8.2 Deaths

Separate summaries and listings will be provided for deaths for each treatment period (core and extension).

2.8.3 Laboratory data

The summary of laboratory evaluations will be presented for different groups of laboratory tests (hematology, serum chemistry, serum ferritin, serum creatinine, and urinalysis) for different treatment periods (core and extension). Descriptive summary statistics for the change from baseline to each study visit will be presented. These descriptive summaries will be presented by test group, laboratory test and treatment group. Change from baseline will be summarized only for the patients who have both baseline and post-baseline assessment. For each parameter, maximum change from baseline within each study period will be evaluated analogously.

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

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

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

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

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

- Reporting of all laboratory data with values flagged to show the corresponding CTCAE grades if applicable and the classifications relative to the laboratory normal ranges (Table 5.3.1)

For laboratory tests where grades are defined by CTCAE

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each patient will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE v4.3 grades to compare baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE

- Shift tables using the low/normal/high/ (low and high)
- Classification to compare baseline to the worst on-treatment value. Apart from the above laboratories summaries, summaries of Hepatitis Viral tests will also be performed.

In addition, a summary of serum ferritin will be presented by TDT and NTDT patients, by age group, and ICT-naive vs. ICT patients by visit.

For all lab assessments, the baseline of each period will be considered based on the actual baseline or start of that particular period, as applicable. Also the baseline data for FCT phase will be provided for only the number of patients available in the analysis set at the start of the period.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

Abnormalities of ECG parameters will be summarized together with an overall interpretation of the findings at screening and end of core phase, i.e. at Week 48. The following quantitative variables will be summarized: QTcB interval, QTcF interval, heart rate, PR interval, QT interval, QRS duration.

Number and percentage will be provided for the patients who have clinically significant abnormalities present.

Summary statistics will be presented for ECG variables at baseline and at end of core phase i.e. at Week 48. In addition, shift tables comparing baseline ECG interpretation (normal, abnormal, not available, total) with the Week 48 interpretation (normal, abnormal, not available, total) will be provided. A listing of all newly occurring or worsening abnormalities will be provided, as well as a by subject listing of all quantitative ECG parameters.

2.8.4.2 Vital signs

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

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

A listing will be provided for all vital signs and weight. Notable vital signs and weight values are flagged.

2.8.4.3 Auditory, ocular, and chest X-ray interpretation

Auditory, ocular, and chest X-ray overall interpretation will be summarized by normal, clinically insignificant abnormality, and clinically significant abnormality, with number and percentages.

2.9 Pharmacokinetic endpoints

Not applicable.

2.10 PD and PK/PD analyses

Not applicable.

2.11 Patient-reported outcomes

The following PROs will be summarized using FAS.

Preference questionnaire

The preference questionnaire is a three item questionnaire. There are three separate versions depending on the week(s) that the questionnaire is administered. Week 4 and 24 contains preference questions on DT and iron chelators, Week 28 contain questions on all three medications and Week 48 on DT and FCT only.

Summaries of the preference questionnaires will be performed at Visits 4, 24, 28 and 48, if data is available, in Core phase of the study and additionally from the data collected at the time of immediate next visit based on patients who had treatment switching. No total score is calculated on the preference questionnaire. Each item will be scored as the proportion of patients who select each response option.

The analysis of preference data has been explained in Section 2.5 and Section 2.7.

Palatability using PRO/ ObsRO questionnaire

The palatability questionnaire consists of 4 items. Two items measure the taste and aftertaste of the medication and are scored on a 5 point response scale. The remaining palatability items refer to whether the medication was taken (i.e. swallowed or vomited) and how the patient perceived the amount of medication to be taken.

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

The standard descriptive analyses include: n, mean, standard deviation, minimum, median and maximum. The 95% CI for the absolute and relative (or difference) change from baseline of the overall score will also be presented for the treatments.

mSICT using PRO / ObsRO questionnaire

The Modified SICT (mSICT) questionnaire consists of 15 items for the PRO version and 22 items for the ObsRO version that represent 3 domains; Adherence, Preference and Concerns.

For the mSICT questionnaire, the score for each domain based on the 15 questions common to both the PRO and ObsRO versions, will be the mean of the score of items included in the corresponding domain. The additional 7 questions that are included in the ObsRO version will be scored as standalone items. Standard descriptive analyses will be performed for both formulations (DT/FCT) for each domain score at Week 4, Week 24, Week 28 and Week 48, and at Screening for iron chelators. The baseline data for treatment period 1 and 2 will be Week 4 and Week 24 data respectively, only one assessment is observed at Screening period. The summary will be provided separately for PRO and ObsRO patient groups.

Weighted mean of both groups will also be reported to highlight the combined result. Separately weighted mean of both the groups for 15 common questions will also be reported. Pooled SD will be provided only if the data from both the groups follow the same distribution.

The standard descriptive analyses include: n, mean, SD, minimum, median and maximum. The 95% CI for the absolute and relative (or difference) changes from baseline in all domains will be presented for the treatments.

GI symptoms using PRO / ObsRO questionnaire

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

For GI symptom ObsRO, the following rules (as applicable in this study) are used for coding:

Over the last 2 weeks how often have you been troubled by abdominal pain or abdominal cramps?

0. Never
1. Rarely
2. Sometimes
3. Often
4. All the time

Over the last 2 weeks, how much of a problem have you had with bloating?

0. No problem
1. A minor problem
2. Some problem
3. A significant problem
4. A major problem

In the last 2 weeks, how much of a problem have you had with excessive wind?

0. No problem
1. A minor problem
2. Some problem
3. A significant problem
4. A major problem

Over the last 2 weeks, on average how often do your bowels move per day?

0. Less than once daily
1. 1-2 times per day
2. 3-4 times per day
3. 5-6 times a day
4. More than 6 times per day

In the last 2 weeks, how much of a problem have you had with loose stools?

0. No problem
1. A minor problem
2. Some problem
3. A significant problem
4. A major problem

How often during the last 2 weeks have you had an urgent need for your bowels to open or a sudden need for a toilet?

0. Never
1. Rarely
2. Sometimes
3. Often
4. All the time

How often during the last 2 weeks have you been woken from your sleep to open your bowels?

0. Never
1. Rarely
2. Sometimes
3. Often
4. All the time

Over the last 2 weeks, how often do your bowel motions float and require more than one flush?

0. Never
1. Rarely
2. Sometimes
3. Often
4. All the time

Over the last 2 weeks, how often have your bowel motions been oily or greasy?

0. Never
1. Rarely
2. Sometimes
3. Often
4. All the time

Over the last 2 weeks, how much of a problem have you had with foul smelling stools?

0. No problem
1. A minor problem
2. Some problem
3. A significant problem
4. A major problem

Over the last 2 weeks, how much of a problem have you had maintaining or getting to the weight you would like to be?

0. No problem
1. A minor problem
2. Some problem
3. A significant problem
4. A major problem

How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks?

0. Never
1. Rarely
2. Sometimes
3. Often
4. All the time

The GI symptoms will be summarized and listed.

Suitable graphs (domain scores plot and waterfall plot) will be presented related to PROs. For this purpose, 95% CI may be reported if appropriate.

2.12 Biomarkers

Not applicable.

2.13 Other Exploratory analyses

Not applicable.

2.14 Interim analysis

One interim analysis is planned in this study.

The interim analysis will be performed at end of Core phase (Week 48) that is after all patients complete Week 48, to assess the patient preference after 6 months with deferasirox FCT treatment in comparison to deferasirox DT. The primary analysis to evaluate the patient preference of FCT over DT will be performed at this interim. Along with primary analysis, all baseline, key efficacy and safety analyses will also be performed till Core phase.

3 Sample size calculation

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

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

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

EAST 6.0 is used to calculate the sample size.

4 Change to protocol specified analyses

Not applicable.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

Not applicable.

5.1.2 AE date imputation

AE date imputation is based only on a comparison of the partial AE start date to the treatment start date as mentioned in the Table 5.1-2 below.

1. If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.
2. If the AE start date year value is less than the treatment start date year value, the AE started before treatment. Therefore:
    a. If the AE year is less than the treatment year and the AE month is missing, the imputed AE start date is set to the mid-year point (01JulYYYY).
    b. Else if the AE year is less than the treatment year and the AE month is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).
3. If the AE start date year value is greater than the treatment start date year value, the AE started after treatment. Therefore:

a. If the AE year is greater than the treatment year and the AE month is missing, the imputed AE start date is set to the year start point (01JanYYYY).

b. Else if the AE year is greater than the treatment year and the AE month is not missing, the imputed AE start date is set to the month start point (01MONYYYY).

4. If the AE start date year value is equal to the treatment start date year value:

a. And the AE month is missing or the AE month is equal to the treatment start month, the imputed AE start date is set to one day after treatment start.

b. Else if the AE month is less than the treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).

c. Else if the AE month is greater than the treatment start month, the imputed AE start date is set to the start month point (01MONYYYY).

Table 5.1-2: AE date imputation

	MON **MISSING**	**MON < CFM**	**MON = CFM**	**MON > CFM**
YYYY MISSING	NULL	NULL	NULL	NULL
	Uncertain	Uncertain	Uncertain	Uncertain
YYYY < CFY	(D) = 01JULYYYY	(C)= 15MONYYYY	(C)= 15MONYYYY	(C)= 15MONYYYY
	Before Treatment Start	Before Treatment Start	Before Treatment Start	Before Treatment Start
YYYY = CFY	(B)= TRTSTD+1	(C)= 15MONYYYY	(A)= TRTSTD+1	(A)= 01MONYYYY
	Uncertain	Before Treatment Start	Uncertain	After Treatment Start
YYYY > CFY	(E)= 01JANYYYY	(A)= 01MONYYYY	(A)= 01MONYYYY	(A)= 01MONYYYY
	After Treatment Start	After Treatment Start	After Treatment Start	After Treatment Start
Before Treatment Start		Partial indicates date prior to Treatment Start Date		
After Treatment Start		Partial indicates date after Treatment Start Date		
Uncertain		Partial insufficient to determine relationship to Treatment Start Date		
LEGEND:				
(A)		MAX(01MONYYYY,TRTSTD+1)		
(B)		TRTSTD+1		
(C)		15MONYYYY		
(D)		01JULYYYY		
(E)		01JANYYYY		

5.1.3 Concomitant medication date imputation

Concomitant medication (CMD) date imputation uses both a comparison of the partial CMD start date to the treatment start date, and the value of the CMDTYP1C flag (1, 2, or 3). Event date comparisons to treatment start date are made based on the year and month values only (any day values are ignored) in Table 5.1-3 below.

1. If the CMD start date year value is missing, the date will be imputed based on the CMDTYP1C flag value. If the flag value is 1 or 3, the imputed CMD start date is set to one day before the treatment start date. Else, if the flag value is missing or 2, the imputed CMD start date is set to one day after the treatment start date. (Note that for some legacy data, the CMDTYP1C variable may not exist in the data. When this happens and the CMD start date year value is missing, the imputed date value will be NULL.)
2. If the CMD start date year value is less than the treatment start date year value, the CMD started before treatment. Therefore:
    a. if the CMD year is less than the treatment year and the CMD month is missing, the imputed CMD start date is set to the mid-year point (01JulYYYY).
    b. Else if the CMD year is less than the treatment year and the CMD month is not missing, the imputed CMD start date is set to the mid-month point (15MONYYYY).

If the CMD start date year value is greater than the treatment start date year value, the CMD started after treatment. Therefore:

    a. If the CMD year is greater than the treatment year and the CMD month is missing, the imputed CMD start date is set to the year start point (01JanYYYY).
    b. Else if the CMD year is greater than the treatment year and the CMD month is not missing, the imputed CMD start date is set to the month start point (01MONYYYY).

3. If the CMD start date year value is equal to the treatment start date year value:
    a. and the CMD month is missing or the CMD month is equal to the treatment start month,
        i. If the flag value is 1 or 3, the imputed CMD start date is set to one day before the treatment start date.
        ii. Else, if the flag value is missing or 2, the imputed CMD start date is set to one day after the treatment start date.
    a. Else if the CMD month is less than the treatment start month, the imputed CMD start date is set to the mid-month point (15MONYYYY).
    b. Else if the CMD month is greater than the treatment start month, the imputed CMD start date is set to the start month point (01MONYYYY).

Table 5.1-3: CMD date imputation

	MON MISSING	**MON < CFM**	**MON = CFM**	**MON > CFM**
YYYY MISSING	**(F)**	**(F)**	**(F)**	**(F)**
	Uncertain	Uncertain	Uncertain	Uncertain
YYYY < CFY	**(D)=01JULYYYY**	**(C)=15MONYY**	**(C)=15MONYY**	**(C)=15MONYY**
	Before Treatment Start	Before Treatment Start	Before Treatment Start	Before Treatment Start

YYYY = CFY	**(B)**	**(C)=15MONYY**	**(B)**	**(A)=01MONYYYY**
	Uncertain	Before Treatment Start	Uncertain	After Treatment Start
YYYY > CFY	**(E)= 01JANYYYY**	**(A)=01MONYYYY**	**(A)=01MONYYYY**	**(A)=01MONYYYY**
	After Treatment Start	After Treatment Start	After Treatment Start	After Treatment Start

Before Treatment Start	Partial indicates date prior to Treatment Start Date
After Treatment Start	Partial indicates date after Treatment Start Date
Uncertain	Partial insufficient to determine relationship to Treatment Start Date
LEGEND:	
(A)	MAX(01MONYYYY,TRTSTD+1)
(B)	IF CMDTYP1C IN (1,3) THEN TRTSTD-1 ELSE IF CMDTYP1C in(. , 2) THEN TRTSTD+1
(C)	15MONYYYY
(D)	01JULYYYY
(E)	01JANYYYY
(F)	IF CMDTYP1C IN (1,3) THEN TRTSTD-1 ELSE IF CMDTYP1C in (. , 2) THEN TRTSTD+1

5.1.3.1 Prior therapies date imputation

Not applicable.

5.1.3.2 Post therapies date imputation

Not applicable.

5.1.3.3 Other imputations

Not applicable.

5.2 AEs coding/grading

The verbatim term recorded on CRF will be identified as adverse event and will be coded by primary system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA) version 18.1 and above.

5.3 Laboratory parameters derivations

Table 5.3.1 Definition of notable/extended ranges for laboratory test

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

Table 5.3.2 Definition of notable ranges for vital signs and weight

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

5.4 Statistical models

5.4.1 Primary analysis

SAS code for Mc Nemar's test

```
proc freq data=;
        table p12*p21;
        exact mcnem;
        weight patients;
run;
```

p12 and p21 respectively denote the proportion of patients with preference of FCT over DT and vice versa.

5.4.2 Secondary analysis

SAS code for Homogeneity test:

proc freq data=;

tables Drug_A Drug_B Drug_C / nocum;

tables Drug_A*Drug_B*Drug_C / agree noprint;

format Drug_A Drug_B Drug_C $ResponseFmt.;

weight Count;

title ‘xxxxxxxx';

run; Drug_A=FCT, Drug_B= DT and Drug_C= iron chelation

SAS code for ANCOVA

proc glm data = ;

class treatmentgroups;

model compliance = treatmentgroups agegroup thalassemiatransdep;

run;

quit;

Example SAS Code for Forest plot

```
%let gpath='C:\';
%let dpi=200;

data ae;
  input Pref $1-30 NA NB SNA SNB;
datalines;
ABDOMINAL PAIN                 20    61    216    431
ANOREXIA                        2    15    216    431
ARTHRALGIA                      1    15    216    431
BACK PAIN                      10    23    216    431
BRONCHITIS                      8    11    216    431
CHEST PAIN                      9    12    216    431
CHRONIC OBSTRUCTIVE AIRWAY     76    95    216    431
COUGHING                       13    26    216    431
DIARRHEA                       23    90    216    431
DIZZINESS                       9    29    216    431
DYSPEPSIA                       8    42    216    431
DYSPNEA                        15     9    216    431
FATIGUE                         4    16    216    431
FLATULENCE                      6    20    216    431
GASTROESOPHAGEAL REFLUX         5    12    216    431
HEADACHE                       14    36    216    431
HEMATURIA                       2    14    216    431
HYPERKALEMIA                    4     9    216    431
INFECTION VIRAL                12    26    216    431
INJURY                         12    30    216    431
```

```
INSOMNIA                      4    26    216    431
MELENA                        7    12    216    431
MYALGIA                       6    12    216    431
NAUSEA                       10    82    216    431
PAIN                          4    17    216    431
RASH                          4     9    216    431
RESPIRATORY DISORDER          4    11    216    431
RHINITIS                     11    17    216    431
SINUSITIS                    13    28    216    431
UPPER RESP TRACT INFECTION   33    68    216    431
URINARY TRACT INFECTION       6    12    216    431
VOMITING                      6    37    216    431
WEIGHT DECREASE               2     9    216
run;

/*--Compute Proportions for treatment A & B, Mean and Risk--*/
data ae_risk;
  set ae;
  keep pref a b mean lcl ucl;
  a=na/sna;
  b=nb/snb;
  factor=1.96*sqrt(a*(1-a)/sna + b*(1-b)/snb);
  lcl=a-b+factor;
  ucl=a-b-factor;
  mean=0.5*(lcl+ucl);
run;

/*--Sort by mean value--*/
proc sort data=ae_risk out=ae_sort;
  by mean;
run;

/*--Add alternate reference lines--*/
data ae_ref;
  set ae_sort;
  if mod(_n_, 2) eq 0 then ref=pref;
run;
proc print;run;

/*--Create template for AE graph--*/
proc template;
  define statgraph AEbyRelativeRisk;
    dynamic _thk _grid;
    begingraph;
      entrytitle 'Most Frequent On-Therapy Adverse Events Sorted by Risk
Difference';
      layout lattice / columns=2 rowdatarange=union columngutter=5;

        /*--Row block to get common external row axes--*/
        rowaxes;
          rowaxis / griddisplay=_grid display=(tickvalues)
tickvalueattrs=(size=5);
        endrowaxes;

        /*--Column headers with filled background--*/
        column2headers;
```

```
          layout overlay / border=true backgroundcolor=cxdfdfdf opaque=true;
            entry "Proportion";
          endlayout;
          layout overlay / border=true backgroundcolor=cxdfdfdf opaque=true;
            entry "Risk Difference with 0.95 CI";
          endlayout;
        endcolumn2headers;

        /*--Left side cell with proportional values--*/
        layout overlay / xaxisopts=(display=(ticks tickvalues)
tickvalueattrs=(size=7));
             referenceline y=ref / lineattrs=(thickness=_thk)
datatransparency=0.9;
          scatterplot y=pref x=a /
markerattrs=graphdata2(symbol=circlefilled)
                      name='a' legendlabel="Treatment (N=&NA)";
          scatterplot y=pref x=b /
markerattrs=graphdata1(symbol=trianglefilled)
                      name='b' legendlabel="Control (N=&NB)";
        endlayout;

        /*--Right side cell with Relative Risk values--*/
        layout overlay / xaxisopts=(label='Less Risk                    More
Risk'
                         labelattrs=(size=8)  tickvalueattrs=(size=7));
          referenceline y=ref / lineattrs=(thickness=_thk)
datatransparency=0.9;
          scatterplot y=pref x=mean / xerrorlower=lcl xerrorupper=ucl
                     markerattrs=(symbol=circlefilled size=5);
          referenceline x=0 / lineattrs=graphdatadefault(pattern=shortdash);
        endlayout;

        /*--Centered side bar for legend--*/
        sidebar / spacefill=false;
          discretelegend 'a' 'b' / border=false;
        endsidebar;
      endlayout;
    endgraph;
  end;
run;


ods html close;
ods listing gpath=&gpath image_dpi=&dpi style=listing;

/*--Render the graph with grid lines without horizontal bands--*/
ods graphics / reset width=6in height=4in imagename='AEbyRelativeRisk';
proc sgrender data=ae_ref template=AEbyRelativeRisk;
  dynamic _thk='0' _grid='on';
run;

/*--Render the graph without grid lines and with horizontal bands--*/
ods graphics / reset width=6in height=4in imagename='AEbyRelativeRiskRef';
proc sgrender data=ae_ref template=AEbyRelativeRisk;
  dynamic _thk='9' _grid='off';
run;
```

```
# Here you have to creat a dataset for SOC with counts for DT and FCT and
then proceed.
```

Example code for Kaplan-Meier and Logrank test

```
proc lifetest data=BMT
plots=survival(atrisk(outside(0.15)));
time T * Status(0);
strata Group / order=internal;
format group bmtfmt.;
 run;

ods graphics on;

proc lifetest data=Exposed plots=(survival(atrisk) logsurv);

time Days*Status(0);

strata Treatment;

run;

ods graphics off;
```

5.5 Rule of exclusion criteria of analysis sets

Table 1 Protocol deviations that cause subjects to be excluded

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
D02	Patient enrolled correctly but did not receive any study treatment and not withdrawn.	EXCLUDE FROM FAS AND SAF	3
D03	Pregnancy occurred while pt actively participating in study. Study drug was administered after notice of pregnancy and the pt was NOT discontinued from the study.	EXCLUDE FROM PPS	4
D04	Patients not discontinued from study despite is fulfilling the discontinuation criteria as per protocol section 7.1.3.1 and 7.1.3.2.	EXCLUDE FROM PPS	4
E01	Creatinine clearance below the contraindication limit in the locally approved prescribing information. Creatinine clearance will be estimated from serum creatinine at screening visit.	EXCLUDED FROM PPS	4
E02	Serum creatinine > 1.5 x ULN at screening measured at screening visit.	EXCLUDED FROM PPS	4
E03a	ALT (SGPT) > 5 x ULN unless LIC >10mg Fe/dw within 6 months prior to screening visit	EXCLUDED FROM PPS	4

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
E03b	AST (SGOT) > 5 x ULN unless LIC >10mg Fe/dw within 6 months prior to screening visit	EXCLUDED FROM PPS	4
E04	Urinary protein / creatinine ratio >0.5 mg/mg in a non-first void urine sample at screening visit.	EXCLUDED FROM PPS	4
E05	Patients with significant impaired gastrointestinal function that may significantly alter the absorption of oral deferasirox at screening visit.	EXCLUDE FROM PPS	4
E06	Serum pregnancy test not done at visit 1 in females of child bearing potential.	INCLUDE IN EVERYTHING	0
E06a	Hepatitis B or Hepatitis C tests were not performed at visit 1.	INCLUDE IN EVERYTHING	0
E07	Clinical or laboratory evidence of active Hepatitis B or C at visit 1.	EXCLUDED FROM PPS	4
E08	Known history of HIV seropositivity (Elisa or Western blot).	EXCLUDED FROM PPS	4
E9	History of malignancy of any organ system, treated or untreated, within the past 5 years (protocol section 5.3)	EXCLUDED FROM PPS	4
E10	Patients participating in another clinical trial or receiving an investigational drug.	EXCLUDE FROM FAS	1
E11	History of hypersensitivity to any of the study drugs or their excipients	EXCLUDED FROM PPS	4
E12	Significant medical condition interfering with the ability to take part in this study	EXCLUDE FROM PPS	4
E13	Female of child bearing potential unwilling to use contraception as requested by the protocol	INCLUDE IN EVERYTHING	0
E14	Female not meeting post-menopausal criteria stated in the protocol and not using the contraception methods requested in the protocol	INCLUDE IN EVERYTHING	0
E15	Female of child bearing potential with a positive serum pregnancy in the screening visit however subject is enrolled into the study	EXCLUDE FROM PPS	4
E16	Sexually active males not using condom during intercourse while taking drug and for 28 days after stopping study medication	INCLUDE IN EVERYTHING	0
E17	Patients with psychiatric or addictive disorders preventing from giving informed consent or undergoing any of the treatment options or unable or unwilling to comply with the protocol	EXCLUDE FROM FAS AND SAF	3

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
G01	Patients not completed the safety follow up evaluation	INCLUDE IN EVERYTHING	0
G02a	Patient did not complete the preference questionnaire in each period (W28 and W48)	INCLUDE IN EVERYTHING	0
G02b	Patient did not complete/partially complete the preference questionnaire at the required visits as per protocol (for W4, W24, W28 and W48)	INCLUDE IN EVERYTHING	0
G02c	Patient did not complete/partially complete the preference questionnaire at immediate next visit after unplanned treatment switch protocol.	INCLUDE IN EVERYTHING	0
G03	Do not have the pill counting information for deferasirox FCT	INCLUDE IN EVERYTHING	0
G04	Do not have the pill counting information for deferasirox DT	INCLUDE IN EVERYTHING	0
G05	Non-Compliance with safety/serious adverse event (SAE) reporting as per protocol.	INCLUDE IN EVERYTHING	0
G06	Patient did not completed/partially completed the SICT, Palatability, GI symptoms questionnaire (for W1, W4, W24, W28 and W48)	INCLUDE IN EVERYTHING	0
G07	Any protocol deviation identified non GCP compliant as per protocol.	INCLUDE IN EVERYTHING	0
G08	Missing Lab Parameters for Lab Biochemistry at 2 consecutive Visits	INCLUDE IN EVERYTHING	0
G09	Missing Lab Parameters for Lab Bio chemistry at Visit 9 or Visit 15	INCLUDE IN EVERYTHING	0
G10	Missing Lab Parameters for Lab Hematology at 2 consecutive Visits	INCLUDE IN EVERYTHING	0
G11	Missing Lab Parameters for Lab Hematology at Visit 9 or Visit 15	INCLUDE IN EVERYTHING	0
G12	Missing Lab Parameters for Lab Urinalysis at 2 consecutive Visits.	INCLUDE IN EVERYTHING	0
G13	Missing Lab Parameters for Lab urinalysis at Visit 9 or Visit 15	INCLUDE IN EVERYTHING	0
G14	Serum pregnancy test not done at Visit 15 in females of child bearing potential	INCLUDE IN EVERYTHING	0
G15	Urine pregnancy test not done at Visit 2 in females of child bearing potential	INCLUDE IN EVERYTHING	0
G16	Full visit is missing.	EXCLUDE FROM PPS	4
G17	The visit has been performed out of protocol window.	INCLUDE IN EVERYTHING	0

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
G18	Patient did not complete/partially complete the preference questionnaire at the immediate next visit after treatment switch.	INCLUDE IN EVERYTHING	0
G19	Hepatitis B or Hepatitis C tests were not performed at visit 15	INCLUDE IN EVERYTHING	0
G20	Treatment start date is outside the window period without an official medical interruption.	EXCLUDE FROM PPS	4
G21	Ocular Examination was not performed	INCLUDE IN EVERYTHING	0
G22	Audiometric Examination was not performed	INCLUDE IN EVERYTHING	0
I01a	ICF is not obtained from Subject.	EXCLUDE FROM FAS AND SAF	3
I01b	ICF is not obtained from Parent(s) or Legal patient(s) representative.	EXCLUDE FROM FAS AND SAF	3
I01c	Missing informed consent date for Subject.	INCLUDE IN EVERYTHING	0
I01d	Missing informed consent date from parent(s) or legal patient's representative.	INCLUDE IN EVERYTHING	0
I02	Subject is < 2 years or age missing	EXCLUDE FROM PPS	4
I03a	Subjects being treated with Deferasirox during the 6 months within study participation.	EXCLUDE FROM PPS	4
I03b	Subjects being treated with other chelators during the 6 months within study participation.	EXCLUDE FROM PPS	4
I03c	Subjects being treated with DFP or DFO or combination (DFP+DFO) at least 6 months continuously.	EXCLUDE FROM PPS	4
I04	Subject is not willing to discontinue current iron chelation therapy at least 5 days prior to the first day and for the duration of the study	EXCLUDE FROM PPS	4
I05	Patients with transfusion-dependent thalassemia (independent of underlying condition) with transfusional iron overload as shown by: a serum ferritin level of <=1000 ng/ml at screening and if available, LIC <= 3 mg Fe/g dw until 6 months prior to screening	INCLUDE IN EVERYTHING	0

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
I06	Patients with non-transfusion-dependent thalassemia with iron overload as shown by: a serum ferritin level of < 800 ng/ml at screening and if available, LIC < 5 mg Fe/g dw until 6 months prior to screening	INCLUDE IN EVERYTHING	0
I07a	Date informed consent obtained from subject after screening procedures	INCLUDE IN EVERYTHING	0
I07b	Date informed consent obtained from parent(s) or legal patient's representative obtained after screening procedures	INCLUDE IN EVERYTHING	0
M01	Use of Prohibited medication as per protocol section 6.3.2.	EXCLUDE FROM PPS	4
M02	Any investigational drug other than the study drug	EXCLUDE FROM PPS	4
S01	Starting dose of deferasirox DT is not compliant with Protocol table 6-2.	EXCLUDE FROM PPS	4
S02	Starting dose of deferasirox FCT is not compliant with Protocol table 7-3.	EXCLUDE FROM PPS	4
S03	Deferasirox DT and/or FCT is not compliant with Protocol table 6-3 based on serum ferritin levels.	EXCLUDE FROM PPS	4
S04	Study dose should be adjusted if there is a change in body weight (increase or decrease) of minimum 10% compare to visit 2 or last dose adjustment due to change in patient's body weight.	EXCLUDE FROM PPS	4
S05	Patient in period 1 of Core phase received Deferasirox FCT by error (except patients who switched from Deferasirox DT to Deferasirox FCT)	EXCLUDE FROM FAS	1
S06	Patient in period 2 of Core phase or extension phase took Deferasirox DT by error (except patients who switched from Deferasirox FCT to Deferasirox DT).	EXCLUDE FROM FAS	1
S07a	Patient re-switched treatment within the same period of the study (that is, patient switched from Deferasirox DT to Deferasirox FCT and the switch back to Deferasirox DT)	EXCLUDE FROM FAS	1
S07b	Patient re-switched treatment within the same period of the study (that is, patient switched from Deferasirox FCT to Deferasirox DT, and then back to Deferasirox FCT)	EXCLUDE FROM FAS	1

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
S08	Iron chelation pre-treated patient who is well-managed on treatment with deferoxamine DFO/deferiprone DFP or combination of DFO+DFP did not receive the equivalent deferasirox DT/FCT dose per app. 14.1	EXCLUDE FROM PPS	4
S09	Dose adjustment (based on Serum ferritin levels and investigator's judgement) in ICT naïve patients done before 4 weeks of study treatment and it was not performed for safety reasons	EXCLUDE FROM PPS	4
S10	Dose adjustment (based on Serum ferritin levels and investigator's judgement) ICT pre-treated patients done before 3 months of study treatment and it was not performed for safety reasons	EXCLUDE FROM PPS	4
S11	The dose adjustment in deferasirox DT not performed in increments of 5-10 mg/kg/day	INCLUDE IN EVERYTHING	0
S12	The dose adjustment in deferasirox FCT not performed in increments of 3.5-7 mg/kg/day	INCLUDE IN EVERYTHING	0
S13	Deferasirox dose was not temporarily interrupted despite urinary protein/creatinine ratio increases to > 1.0 (mg/mg) in two consecutive second-void urine samples (a minimum of 48h apart)	INCLUDE IN EVERYTHING	0
S14	Deferasirox dose was not temporarily interrupted even though the skin rash persists for > 1 week or becomes more severe	INCLUDE IN EVERYTHING	0
S15	Maximum dose of deferasirox DT is not compliant with Protocol table 6-2.	EXCLUDE FROM PPS	4
S16	Maximum dose of deferasirox FCT is not compliant with Protocol table 6-2.	EXCLUDE FROM PPS	4
S17	Dose adjustment of deferasirox DT is not compliant with Protocol table 6-2.	EXCLUDE FROM PPS	4
S18	Dose adjustment of deferasirox FCT is not compliant with Protocol table 6-2.	EXCLUDE FROM PPS	4
S19	Patient received incorrect dose due to dispensing error.	Include in Everything	0
S20	Cautious re-initiation of Deferasirox treatment at a lower dose was not done following Study medication interruption due to Increased liver enzyme levels (ALT/AST).	Include in Everything	0

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
S21	Deferasirox dose reduction by 10 mg/kg/day for the DT formulation and by 7 mg/kg/day for the FCT formulation was not performed following a rise in serum creatinine by 33% above baseline value resulting in a serum creatinine above the ULN on two consecutive visits (a minimum of 7 days apart)	Include in Everything	0
S22	Resuming study medication dose is not done according to protocol following treatment interruption for abnormal Serum Creatinine.	Include in Everything	0

Table 2 Analysis set exclusions based on population codes

Analysis set	Population codes that cause a subject to be excluded
RAN	NA
SAF	2, 3, 6
FAS	1, 3
PPS	4, 6

Table 3 Population code text

Population Code	Population code text
0	INCLUDE IN EVERYTHING
1	EXCLUDE FROM FULL ANALYSIS SET (FAS)
2	EXCLUDE FROM SAFETY SET (SAF)
3	EXCLUDE FROM FAS AND SAF
4	EXCLUDE FROM PER-PROTOCOL SET (PPS)
6	EXCLUDE FROM SAF AND PPS

Unless otherwise stated, summary tables, figures and listings will be on all subjects included in the analysis set under consideration.

6 Reference

1. Study protocol: Oncology study protocol CICL670FIC05.
2. Taher AT, Origa R, Perrotta S et al (2018) Patient-reported outcomes from a randomized phase II study of the deferasirox film-coated tablet in patients with transfusion-dependent anemias. Health Qual Life Out; 16:216.