NOVARTIS

Clinical Development

ICL670/deferasirox FCT/Exjade®

Study Number: CICL670F2429 / NCT03372083

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

Statistical Analysis Plan (SAP)

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Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
21-Aug-2017	Prior to FPFV	Creation of final version	N/A - First version	NA
14 July 2018	Amend 1	Visit schedule is modified in the protocol amendment 1 and thus the data analyses for ObsRO (mSICT, palatability and GI symptom questionnaires are impacted due to change in visit schedule.	• Spelled out how to analyze mSICT, palatability and GI symptom questionnaire for chelation naive and pre-treated chelation therapy patients.	Section 2.13
13-Dec-2019	Amend 2		• Allowed flagging for post-treatment data, if any	Section 2.1.2.7
			• Removed subgroup analysis as the patient population is too small	Section 2.3
			• Removed "Age will be calculated based on patient's first screening date" as age is collected on the CRF page directly	Section 2.5
			• Added prior medications/therapies to the listing and flagged them appropriately	Section 2.7
			• Removed proportion calculation based on the	Section 2.8.2

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			number of patients without event who will discontinue after the baseline visit prior to 2 week scheduled visis for primary endpoint. All patients will be considered for this analysis	
			• Changed the content in section 2.8.3 to Not applicable to align with protocol	Section 2.8.3
			• Corrected the equation to follow the standard	Section 2.8.4
			• Removed the disclosure related information as they will not be part of CSR	Section 2.11.1
			• Changed subgroup analysis to not applicable to maintain consistency with protocol	Section 2.11.2
			• Added clarification in analysis for ECG values	Section 2.11.7
			• Updated the notable range for vital signs to pediatric population requirements	Section 2.11.7.1
			• Clarified the 2 groups of patients in ObsRO as “Chelation naïve patients and patients treated with chelation therapy other than deferasirox who stopped chelation treatment more than 7 days prior to Screening visit” and “patients pre-treated with deferasirox”. Changed the box plots to scores instead of change from baseline.	Section 2.13

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List of abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase/serum glutamic pyruvic transaminase/SGPT
AST	Aspartate aminotransferase/serum glutamic oxaloacetic transaminase/SGOT
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CI	Confidence Interval
CrCl	Creatinine Clearance
CRF	Case report/record form
CTC	Common terminology criteria
CTCAE	Common Terminology Criteria for Adverse Events
CSR	Clinical study report
DAR	Dose administration record
DFX	Deferasirox
DRL	Drug reference listing
ECG	Electrocardiogram
eCRF	Electronic case report/record form
FAS	Full Analysis Set
FCT	Film coated tablet
GCP	Good Clinical Practice
GI	Gastrointestinal
ICL670	Deferasirox/Exjade®
ICT	Iron Chelation Therapy
MedDRA	Medical Dictionary for Regulatory Activities
mSICT	Modified Satisfaction with Iron Chelation Therapy
ObsROs	Observer-reported Outcomes
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCr	Serum Creatinine
SD	Standard deviation
SOC	System organ class
TBIL	Total Bilirubin
TLF	Tables, Listings and Figures

UPCR	Urine protein and creatinine ratio
SSD	Study Specification Document
WHO	World health organization

1 Introduction

The purpose of this Statistical Analysis Plan (SAP) is to describe the implementation of the statistical analysis specified in the protocol. Final Clinical Study Report (CSR) will be written based on this SAP. Current SAP is written following finalized protocol version 01 (Amended protocol), disease area standards and deferasirox (film coated tablet (FCT)) project specific standard TFLs. All decisions regarding final analysis, as defined in the SAP document, have been made prior to database lock of the study data.

1.1 Study design

This is an interventional, prospective, single arm, open label, global multi-center, non-randomized study to monitor and assess the safety profile of the crushed deferasirox FCT in pediatric patient's age between ≥ 2 to < 6 years with transfusional hemosiderosis over 24 weeks. The purpose of this study is to address a European Health Authorities (CHMP/PRAC) post-marketing requirement. CHMP/PRAC have requested Novartis for an additional post-authorization safety study to characterize the pediatric safety profile and to provide safety data on selected AEs (esophagitis, stomatitis, mouth ulceration, gastric ulcers, hemorrhage, abdominal pain, diarrhea, nausea, and vomiting).

This study will enroll at least 40 patients worldwide.

The study will include a screening period (from Day 0-14) with two visits at least 7 days apart to assess eligibility of patients that are chelation naïve or on a prior iron chelator treatment other than deferasirox (DFX). Only one screening visit (screening visit 1) will occur for prior DFX treated patients to determine eligibility. Any patients treated with prior chelation therapy except deferasirox will be discontinued to undergo a 5-day washout period before initiation of 24-week treatment period with crushed deferasirox FCT.

Safety assessments will be performed weekly after treatment initiation for the first 4 weeks and thereafter monthly during the study. Monthly serum ferritin values and trends will be used to adapt the treatment of the patients together with safety data. Patients will continue therapy for up to 24 weeks.

There is no interim analysis planned for this study.

1.2 Study objectives and endpoints

The study objectives and endpoints are described in the following table:

Table 1-1 Study objectives and endpoints

Objective	Endpoint
Primary	

To assess the safety of crushed deferasirox FCT with respect to selected gastrointestinal (GI) disorders in pediatric patients aged ≥2 to < 6 years with transfusional iron overload up to 24 weeks including 30 days safety follow up	Number and percentage of patients with selected gastrointestinal disorders (esophagitis, stomatitis, mouth ulceration, gastric ulcers, hemorrhage, abdominal pain, diarrhea, nausea, and vomiting) up to 24 weeks including 30 days safety follow-up
Secondary	
Evaluate AEs suspected to be related to the crushed deferasirox FCT	Number and percentage of patients who experienced AEs suspected to be related to study treatment up to 24 weeks including a 30 day follow up overall and by SOC.
To assess the overall safety of crushed FCT of deferasirox	Overall safety up to 24 weeks including 30 days safety follow-up as measured by frequency and severity of adverse events, serious adverse events (SAEs) and AEs leading to discontinuation and absolute change from baseline over time (shift tables will also be provided) for serum creatinine, creatinine clearance, UPCR, total bilirubin, ALP, ALT, AST). Other safety data (e.g., ECGs, vital signs, ocular, auditory examinations) will also be summarized.
To assess the efficacy of deferasirox FCT treatment	Change from baseline over time in SF up to 24 weeks of treatment
To evaluate patient treatment satisfaction, palatability, and GI symptoms with Observer-reported Outcomes (ObsROs)	Domain scores with ObsROs (Modified Satisfaction with Iron Chelation Therapy [mSICT], palatability, and GI symptom) questionnaires

2 Statistical methods

This section contains information that will be used to draft CSR Section 9.7 on statistical analysis.

2.1 Data analysis general information

Data will be analyzed by Novartis Oncology Biostatistics and Statistical programming personnel according to the data analysis described in Section 10 of the ICL670F2429 protocol, which will be available in Appendix 16.1.1 of the Clinical Study Report (CSR). Important information is given in the following sections and details are provided. For the final analysis, SAS version 9.4 or later (upon availability) will be used. As specified in the protocol, the study will continue until last patient received last dose plus 30-days follow-up. This date will be considered as the cut-off date.

Data from all patients who signed the main study informed consent for study participation in centers that participate in this study will be used in the analysis; due to expected small size of enrollment at individual centers, no center effect will be assessed. Each analysis will use all data in the database up to the analysis cutoff date, determined prior to database lock.

All available data from all patients up to the cutoff date will be reported. Data collected after patients' withdrawal of informed consent for further participation in the study will not be reported (except for death date which might be obtained from public records).

2.1.1 General presentation of descriptive summaries

Qualitative data (e.g., gender, race, etc.) will be summarized by frequency count and percentages. Percentages will be calculated using the number of patients in the relevant population as the denominator.

Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum, and maximum). For selected parameters 25th and 75th percentiles will also be presented in box plots.

2.1.2 General definitions

2.1.2.1 Investigational drug and study treatment

Investigational drug will refer to the crushed Deferasirox FCT only. In this document, the term investigational drug will be referred as ***study treatment*** and will be used throughout this document.

2.1.2.2 Date of first administration of study treatment

The date of first administration of study treatment will be derived as the first date when a nonzero dose of study treatment is administered as per the Dosage Administration CRF. For the sake of simplicity, the date of first administration of study treatment will also be referred as ***start of study treatment***.

2.1.2.3 Date of last administration of study treatment

The date of last administration of study treatment is defined as the last date when a nonzero dose of study treatment was administered as per Dose Administration (e)CRF.

2.1.2.4 Screening failure

Screening failures are patients who have been enrolled and failed screening criteria in a study. These patients will never receive investigational drug.

2.1.2.5 Study day

The study day ***for safety assessments*** (e.g. adverse event onset, laboratory abnormality occurrence, vital sign measurement, dose interruption etc.) and ***for efficacy assessment*** (e.g.

serum ferritin) and Observer-reported Outcomes will be calculated as the difference between the date of the event (onset date of an event, assessment date etc.) and the start of study treatment plus 1. The first day of study treatment is therefore study day 1 if event will start after start date of study treatment.

Study day=date of event – start date of study treatment+1

For any assessment or events such as baseline disease characteristics or medical history (e.g., time since diagnosis of disease) that is supposed to occur prior to treatment start date, study day will be negative and will be calculated as:

Study Day = Event date -treatment start date.

The study day will be displayed in the data listings.

2.1.2.6 Baseline

For the ***safety*** and the ***efficacy evaluations,*** the last available assessment on or before the date of start of study treatment will be defined as baseline. If patients have no value as defined above, the baseline result will be missing.

2.1.2.7 On-treatment assessment/event and observation periods

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

1. ***pre-treatment period***: from day of subject's first informed consent to the day before first administration of study treatment
2. ***on-treatment period***: from date of first administration of study treatment to 30 days after date of last actual administration of any study treatment (including start and stop date)
3. ***post-treatment period***: starting at day 30+1 after last administration of study treatment.

All safety data (including those from the pre-treatment period) will be listed and those collected during the pre-treatment period are to be flagged. If any safety data from the post-treatment period is collected, it will be flagged.

2.2 Analysis sets

The following analysis sets are defined in the study protocol.

2.2.1 Full Analysis Set

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

2.2.2 Safety Analysis Set

The Safety Set includes all patients who received at least one dose of deferasirox FCT during the study. Note that the Safety Set and the FAS will be the same for this single arm phase IV study.

2.2.3 Per-Protocol set

Not applicable

2.2.4 Dose-determining analysis set

Not applicable

2.2.5 Pharmacokinetic analysis set

Not applicable

2.2.6 Other analysis set

Not applicable

2.2.7 Efficacy/evaluable set

Not applicable

2.3 Subgroup of interest

Not Applicable

2.4 Protocol deviations

Frequency counts and percentages of patients with any CSR reportable protocol deviation (selection criteria not met, patient not withdrawn as per protocol, treatment deviation, prohibited concomitant medication, and other (Good Clinical Practice (GCP) deviation) will be tabulated by the deviation type category using FAS.

The full list of protocol deviations is documented in the Study Specification Document (SSD) Module 3. All protocol deviations will be listed.

2.5 Patient disposition, demographics and other baseline characteristics

Screen failures recorded in the end of screening phase disposition will comprise patients who have been enrolled i.e. signed the main ICF and were screened but were not treated. The screening failure disposition table will include:

- Number (%) of screen-failed patients
- Reasons for screening failure

The percentage for the screening phase disposition will be calculated based on the number of patients whose consents are obtained. All screen failure patients with reasons for screen failure will be listed.

Patient disposition will be summarized using the FAS. The disposition table will include:

- Number (%) of treated
- Number (%) discontinued before 24-week schedule visit
- Number (%) of patients who completed the end of treatment
- Primary reason for study treatment phase discontinuation (based on the 'End of Treatment Phase' page)

All demographic data and baseline disease characteristics will be summarized and listed based on the FAS. Categorical data (e.g. gender, age, race, and ethnicity) will be summarized by frequency counts and percentages; the number and percentage of patients with missing data will be provided. Continuous data (e.g. age, weight, height) will be summarized by descriptive statistics (n, mean, median, standard deviation, minimum and maximum).

Medical history

Medical history and ongoing conditions will be summarized and listed. The summaries will be presented by primary system organ class (SOC) and preferred term (PT). Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings. History of surgical and other medical procedures and any prior hepatic findings at baseline will be listed using FAS.

Other baseline characteristics

Clinically significant abnormality in ECG (yes or no) along with ECG parameters (heart rate, PR, QT, QTCF and QRS), overall interpretation in audiometric test (normal or clinically significant or insignificant abnormality as per CRF), and interpretation in ocular exam (normal or clinically significant or insignificant abnormality) at baseline will be summarized and listed using FAS.

The following variables will be summarized as a continuous and categorical data using FAS, except for urine protein/creatinine ratio which will be presented as categorical data as shown below:

- Creatinine will be categorized as: ≤ULN, >ULN - ≤1.5*ULN, >1.5*ULN
- Recalculated Creatinine Clearance (CrCl) will be categorized as: <90 and ≥90 mL/min
- ALT and AST will be categorized as: ≤ULN, >ULN-≤2.5*ULN, >2.5*ULN
- Urine protein/creatinine ratio: ≤0.5, >0.5
- Serum ferritin will be categorized as: ≥1000 to 2500, ≥2500 to 5000, >5000 ng/ mL

2.6 Treatments (study treatment and compliance)

2.6.1 Cumulative dose

The planned daily dose of a subject is collected on the CRF page as dose prescribed in mg/kg/day and the actual daily dose is calculated by dividing the total daily dose collected on the CRF page in mg by the current weight (kg) corresponding to that visit and based on the start and end dates. The current weight is equal to the weight on the same visit when dose was administered or the last available weight before the dosing visit if the same visit weight is missing. Cumulative dose (mg/kg) is defined as the sum over the daily doses of all days between first and last dose. For patients who did not take any drug, the cumulative dose is by definition equal to zero.
Cumulative dose = sum of (daily dose at a visit * (end date of dose –start date of dose +1))

The **planned cumulative dose (mg/kg)** for a study treatment component refers to the total planned dose as per the protocol up to the last date of investigational drug administration. The **actual cumulative dose (mg/kg)** refers to the total actual dose administered, over the duration for which the subject is on the study treatment as documented in the Dose Administration eCRF.

2.6.2 Duration of exposure

Duration of exposure to study treatment is considered by taking into account the duration of exposure to the investigational drug:
Duration of exposure (weeks) = [(last date of exposure to study treatment) - (date of first administration of study treatment) + 1]/7,

The last date of exposure to study treatment is the date when the last study drug will be administered (see section 2.1.2.3).

Summary of duration of exposure of study treatment in weeks will include categorical summaries and descriptive summaries (i.e. n, mean, standard deviation, median, max and min) in weeks. The time interval will be categorized as: <4 weeks, 4 to <12 weeks, 12-<20 weeks 20-<=24 weeks, >24 weeks. Frequency counts and percentages will be presented for the number of patients in each time interval using the Safety Set.

2.6.3 Planned and actual dose intensity

Planned dose intensity (PDI) and actual **dose intensity** (DI) for subjects with non-zero duration of exposure are defined as follows:

PDI (mg/kg/day) = [planned cumulative dose during the time of exposure (mg/kg)]/Duration of exposure (days)

DI (mg/kg/day) = [actual cumulative dose during the time of exposure (mg/kg)]/Duration of exposure (days)

Relative dose intensity (RDI) is defined as follows:

RDI (%) = (DI (mg/kg/day) / PDI (mg/kg/day)) *100

Planned dose intensity, actual dose intensity and relative dose intensity (<70%, 70%-90% and >90%) will be summarized by means of descriptive statistics using Safety Set.

2.6.4 Dose Change

'Dose interrupted', and 'Dose change' fields from the Dosage Administration CRF pages will be used to determine the dose reductions, dose interruptions. The corresponding fields 'Reason for dose changed/dose interrupted' will be used to summarize the reasons. Dose interruption and dose reduction are defined as follows:

- **Interruption** is defined as any period of zero actual daily dose prior to treatment end date.
- **Reduction** is a subset of the dose changes, defined as a decrease from the previous planned non-zero dose, even if this decrease has been directly preceded by an interruption. Patient has dose decrease or reduction at visit if the dose assignment at the visit will be nonzero and lower than the last available one before the visit and daily dose is nonzero at the visit. For example, in the sequence 14 mg/kg/day - 0 mg/kg/day - 7 mg/kg/day, the 7mg/kg/day dose will be counted as a reduction and in the sequence 14mg/kg/day - 7 mg/kg/day - 3.5 mg/kg/day, 3.5 mg/kg/day will be counted as two reductions.

The number and percentage of patients with dose interruption and/or dose reduction along with reasons for dose interruption/reduction will be summarized using the safety set. Dose increase will not be included in these summaries.

Listings of all doses of the study treatment along with dose reduction and dose interruption reasons will be produced using the Safety set.

2.7 Prior, concomitant and post therapies

Medications will be classified as prior or concomitant based on the following rules and will be coded using the WHO Drug Reference Listing (WHO DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (WHO ATC) classification system. Summaries will include:

- Prior medications will be defined to be drugs taken prior to the first dose of study medication.

- Concomitant medications will be medications taken during the on-treatment period. Medications which started prior to the first dose of study medication and continued thereafter will be counted in both summaries.

Concomitant medications and significant non-drug therapies prior to and after the start of study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system using Safety set. Prior medication/therapies that started before the first dose of study treatment, or those starting after 30 days from the last day of study medication will be flagged in the listing.

2.7.1.1 Prior chelation therapy

History of iron chelation therapy is collected in prior or concomitant medication CRF page. By the drug name, the prior chelation therapy will be identified.

Prior chelation therapy will be summarized by lowest ATC class and preferred term. Summaries will include time from last treatment to start of study treatment. Duration of iron chelation prior to start of study treatment will be categorized into time intervals (< 1, 1-<3, 3- <6 and >=6 months of cumulative therapy). Duration of prior chelation therapy will be calculated based on start and the end date of the therapy, i.e. duration (days) = end date – start date+1. Frequency counts and percentages will be presented for the number of patients in each interval.

Prior chelation therapy and chelation naïve patients will be listed using FAS.

2.7.1.2 Blood transfusion history

The number of patients with prior blood transfusions within the period of 3 months prior to Screening visit 1, and the average amount of RBC (in mL/kg/day) will be summarized using descriptive statistics and listed using the FAS.

2.7.2 Post therapies

The study will end after last dose of study treatment plus 30 days follow-up. Post therapies, if any will be flagged in the listings.

2.8 Analysis of the primary objective

The primary objective of the study is to assess the safety of crushed deferasirox FCT with respect to selected gastrointestinal (GI) disorders.

2.8.1 Primary endpoint

The primary endpoint is the proportion of patients with selected gastrointestinal disorders (esophagitis, stomatitis, mouth ulceration, gastric ulcers, hemorrhage, abdominal pain, diarrhea,

nausea, and vomiting) up to 24 weeks including 30 days safety follow-up. Selected gastrointestinal disorders will be captured from AE page of eCRFs and PT term will be used. Corresponding PT terms will be oesophagitis, Barrett's esophagitis, stomatitis, mouth ulceration, gastric ulcer, gastrointestinal haemorrhage, abdominal pain, diarrhoea, nausea and vomiting. If patients discontinue earlier than 24-week visit, the patients will be followed 30 days after discontinuation of study treatment.

2.8.2 Statistical hypothesis, model, and method of analysis

Proportion of patients with selected GI disorders will be provided together with the corresponding 95% confidence interval using the Clopper-Pearson exact method for this proportion (see section 5.3.1).

2.8.2.1 Statistical hypothesis test

No hypothesis will be tested for this primary endpoint.

2.8.3 Handling of missing values/censoring/discontinuations

Not applicable

2.8.4 Supportive analyses

Exposure-adjusted adverse event incidence will be presented by the severity and preferred term for the **primary** analysis. It is defined as:

$$\frac{\text{Number of patients with new or worsened AEs on selected gastrointestinal disorder during on} - \text{treatment period}}{\text{Patient} - \text{Year exposure}/365.25}$$

Patient-year exposure is counted in days up to the first qualifying adverse event (or end of time at risk for subjects without adverse event), divided by 365.25.

2.9 Analysis of the key secondary objective

Not applicable

2.10 Analysis of secondary efficacy objective(s)

The secondary efficacy objective for this study is to assess the efficacy of deferasirox FCT treatment.

2.10.1 Secondary endpoints

The secondary efficacy endpoint for this study will be the change from baseline over time in serum ferritin (SF) up-to 24 weeks of treatment.

2.10.2 Statistical hypothesis, model, and method of analysis

A summary table will be provided for the change in SF from baseline for each visit up-to 24 weeks of treatment using FAS. A listing will also be provided including current SF level, change from baseline by visit and by patient. A graphical representation of SF change from baseline by box-plot will be provided for each visit using FAS.

For the summary table, all scheduled and unscheduled visits will be considered. If a scheduled visit does not occur, then an unscheduled visit will be mapped to a scheduled visit by the below rule:

- The target date of a scheduled visit will be defined relative to Day 1 as (X-1)*7+1, where X is the number of weeks, such as X=1, 2, … For example, the target day for Week 12 visit will be (12-1)*7+1 = 78 days.
- Unscheduled visit then will be mapped to a scheduled visit by:
    - Weeks 2 and 3: -1 day / +1 day
    - Week 4 : -1 day/+7 days
    - Week 8,12,16, 20 and 24 (EOT): -7 days / +7 days

If a scheduled visit already exists, then no unscheduled visit will be mapped against a scheduled visit. If no scheduled visits exist, the unscheduled visit which is the closest to the target scheduled visit will be considered. If two unscheduled visits are equidistant from the targeted scheduled visit then prior to the targeted scheduled visit will be consider as scheduled visit. After mapping unscheduled visit to a scheduled visit, only scheduled visit will be considered for the summary level outputs.

2.10.3 Handling of missing values/censoring/discontinuations

Change from baseline will only be calculated for patients with both baseline and post baseline values as:

Change from baseline = post baseline value – baseline value.

In case of any post-baseline or baseline observation(s) is missing for any patient, the change of baseline value will be missing.

2.11 Safety analyses

As stated in the protocol (Section 10.5), the following secondary safety endpoints will be evaluated:

AEs suspected to be related to the crushed deferasirox FCT:

- Number and percentage of patients who experienced AEs suspected to be related to the study treatment up to 24 weeks including 30 day safety follow-up overall and by SOC, PT and severity (see section 2.11.1).

Overall safety of crushed deferasirox FCT:

- Number and percentage of patients with any AEs, SAEs, and AEs leading to discontinuation together with their severity up to 24 weeks including 30 days safety follow-up will be provided. Details regarding the analysis of AEs are described in section 2.11.1.
- Absolute change from baseline over time will be provided graphically by box plots for serum creatinine, creatinine clearance, UPCR, total bilirubin, ALP, ALT, AST for each visit. Furthermore, shift tables using low/normal/high classification will be provided. Details regarding laboratory abnormalities are described in Section 2.11.4. See section 2.10.2 for the mapping of an unscheduled visit to a scheduled visit and box plots and shift tables will be generated for each scheduled visit only after mapping an unscheduled visit.

2.11.1 Adverse events (AEs)

All AEs recorded during the study are coded using the latest version of the medical dictionary for regulatory activities (MedDRA). Adverse events will not be assessed according to the common terminology criteria for AEs (CTCAE); instead, AE severity (mild, moderate, severe) will be used to report treatment-emergent AEs starting on or after the date of first study medication (including AEs that start within 30 days after the discontinuation of the study medication).

Frequency tables for treatment-emergent AEs will be presented. The summary tables will include the number of patients, and the percentage of patients experiencing the AE. Multiple occurrences of the same event in the same patient will be counted only once in the frequency tables. However, all adverse events will be included in the AE listings.

Frequency tables will display at least the MedDRA system organ class or preferred term, AE severity (mild, moderate, severe) or both, and relationship to study treatment. The following tables will be generated based on the data up-to 24 weeks including 30 days follow-up:

- Adverse events, regardless of study treatment relationship
- Adverse events, suspected to be study treatment related
- Serious adverse events, regardless of study treatment relationship
- Serious adverse events, suspected to be study treatment relationship
- Adverse events leading to study drug discontinuation, regardless of study treatment relationship
- Adverse events leading to study drug discontinuation, suspected to be study treatment relationship
- Adverse events requiring dose adjustment or interruption, regardless of study treatment relationship
- Adverse events requiring additional therapy, regardless of study treatment relationship

- Adverse events which are not serious adverse events, regardless of study treatment relationship

2.11.1.1 Adverse events of special interest / grouping of AEs

Specific groupings of adverse events of special interest will be considered and the number of patients with at least one event in each grouping will be reported. Such groups consist of adverse events for which there is a specific clinical interest in connection with deferasirox treatment. Note that certain adverse events will be reported within multiple groupings/AESIs. AESIs are defined by MedDRA terms. Definition for retrieval (maintenance of terms considered AESI) is in case retrieval strategy (eCRS). To select the corresponding records from SAS dataset ECRS in Novartis computing environment, use

- Compound name = "ICL670",
- Compound indication = "ICL670 Chronic iron overload"
- and records without CRS Version End Date, means the latest version.

All safety topics flagged in the eCRS using the core safety flag will be considered for the analysis.
AESI will be summarized regardless of study drug relationship, by grouping, preferred term. Gastrointestinal AEs will also be summarized as a part of AESI.

2.11.2 Subgroup analysis

Not Applicable

2.11.3 Deaths

Summaries for on-treatment (treatment +30 days) deaths will be produced by system organ class, and preferred term using the Safety set.
All deaths will be listed for the safety set. If any data after end of treatment plus 30 days is collected, it will be flagged in the listing.

2.11.4 Laboratory data

All laboratory values will be converted into SI units and the severity grade calculated using the low/normal/high classifications based on local laboratory normal ranges and for selected parameters by notable/extended ranges.

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

- 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

Shift tables will be generated for each hematology and chemistry test, cross-tabulating low/normal/high/missing baseline laboratory values against low/normal/high/missing post-baseline values. In particular, the following shift tables will be produced:

- Shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value for the hematology parameters: hemoglobin, RBC counts, hematocrit and platelets
- Shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value for the chemistry parameters: ALT, AST, total bilirubin, direct bilirubin, serum creatinine, UPCR and alkaline phosphatase.

For selected lab assessments such as hematology parameters: hemoglobin, RBC counts, hematocrit and platelets; chemistry parameters: ALT, AST, total bilirubin, direct bilirubin, creatinine clearance, serum creatinine, UPCR and alkaline phosphatase observed values (and changes from baseline) will be summarized by descriptive statistics.

The number and percentage of patients with laboratory results (from scheduled and unscheduled visits) meeting the criteria for notable values (see table above) will be presented.

Table 2-1 Criteria for clinically notable and extended laboratory ranges

Parameter	Criteria
Absolute neutrophils	$<1.5\times10^9$/L (extended range $<0.5\times10^9$/L)
Platelets	$<100\times10^9$/L (extended range $<50\times10^9$/L)
ALT/AST	>5×ULN and >2×baseline value (extended range >10×ULN and >2×baseline value)
Alkaline phosphatase	<2×ULN
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)
Urinary total protein/creatinine ratio	>1.0 mg/mg at two consecutive measurements at least 7 days apart
Total bilirubin	>2×ULN
Direct bilirubin	>2×ULN

Summaries for the change from baseline will be provided for all parameters. Creatinine clearance will be estimated using the (modified) Schwartz formula (additional details in section 5.2). An unscheduled visit will be mapped to a scheduled visit per section 2.10.2.

Potential Hy's Law events are defined as patients with concurrent occurrence of AST or ALT > 3×ULN and TBIL > 2×ULN and ALP < 2×ULN in the same assessment sample during the on-treatment period. Potential Hy's law events will be tabulated using Safety set.

2.11.5 Other safety data

2.11.5.1 ECG and cardiac imaging data

2.11.5.1.1 Data handling

In case ECG measurements are replicated at any assessment, the average of the ECG parameters at that assessment will be used in the analyses.

2.11.5.1.2 Data analysis

12-lead ECGs including PR, QRS, QT, QTcF and HR intervals will be obtained for each subject during the study as clinically indicated. ECG data will be read and interpreted centrally.

- QT and QTcF
  - New value of > 450 and ≤ 480 ms
  - New value of > 480 and ≤ 500 ms
  - New value of > 500 ms
  - Increase from baseline of > 30 ms to ≤ 60 ms
  - Increase from baseline of > 60 ms
- HR
  - Increase from baseline >25% and to a value > 120 bpm
  - Decrease from baseline >25% and to a value < 65 bpm
- PR
  - Increase from baseline >25% and to a value > 160 ms
  - New value > 200 ms
- QRS
  - Increase from baseline >25% and to a value > 80 ms
  - New values of QRS > 120 ms

A listing of all ECG assessments will be produced using Safety set, notable values and post-treatment assessments (if any) will be flagged.

2.11.5.2 Vital signs

Vital sign assessments will be performed in order to characterize basic body function. The following parameters are collected: height (cm), weight (kg), body temperature (°C), supine systolic and diastolic blood pressure (mmHg) and supine pulse rate (bpm).
The change from baseline in systolic and diastolic blood pressures, pulse rate, temperature and weight will be summarized by scheduled visit with descriptive statistics. An unscheduled visit will be mapped to a scheduled visit per section 2.10.2.

A listing will be provided for all vital signs and BMI (Body Mass Index). Notable vital signs will be flagged. The criteria for notably abnormal vital signs are displayed in Table 2-2.

Table 2-2 Definition of notable ranges for vital signs

Vital sign (unit)	Notable high value	Notable low value
Weight (kg)	increase >= 10% from baseline	decrease >= 10% from baseline
Systolic blood pressure (mmHg)	>=110 and increase from baseline of >=20	<=85 and decrease from baseline of >=20
Diastolic blood pressure (mmHg)	>=72 and increase from baseline of >=15	<=50 and decrease from baseline of >=15
Pulse rate (bpm)	>=120 and increase from baseline of >15	<=50 and decrease from baseline of >15
Body temperature (°C)	>= 40	<=35

2.11.5.3 Auditory and ocular findings

Auditory and ocular exams will be performed at screening, EOT and as needed basis. Auditory data will be listed using the Safety set. The listing will include the date when the tests were performed, overall interpretation of the test and any clinical significant abnormality findings.

Ocular data will also be listed using the Safety set. The listing will include the date of assessment performed, overall interpretation and any clinical significant abnormality findings.

2.11.5.4 Hepatic dysfunction

Hepatic dysfunction will be captured through imaging, liver event pathology, liver event by autoimmune disorder, liver serology and liver function tests from the study eCRFs. Due to less number of patients enrolled in the study and considering hepatic cases observed are rare for this compound, no summary will be provided; instead, any findings of hepatic dysfunction will be listed using Safety set.

2.12 Pharmacokinetic endpoints

Not applicable.

2.13 Observer reported outcomes (ObsRO)

There are three set of PRO questionnaires designed to evaluate crushed deferasirox FCT:

- Modified Satisfaction with Iron Chelation Therapy (mSICT) questionnaire
- Palatability (taste and ability to consume medicine) questionnaire
- GI symptom questionnaire

All these questionnaires will be translated in caregivers' native language and will be answered electronically by the caregivers (legal guardian or the parent) at the time of protocol defined visits. The site study personnel will review and will ensure that all relevant observations with parent/ legal guardian are recorded before electronic submission.

2.13.1 mSICT

The mSICT questionnaire will be completed at screening visit 1, week 4, week 12 and EOT. The responses from screening visit 1 for mSICT questionnaire will be considered as baseline. The modified SICT consists of 20 items that represent 3 domains (see Figure 2-1):

- Adherence
- Preference
- Concerns

2.13.1.1 Adherence

Adherence domain will be captured from 2 perspectives:

- Child's perspective (a Domain score + a Checklist for reasons for non-adherence)
- Caregiver's perspective (a Domain score + a Checklist for reasons for non-adherence)

Even the adherence domain is divided into two perspective, all the items will be answered by the caregivers due to minors (2-6 years of age) enrolled in this study. First set of questionnaires will reflect about the child's devotion of taking the medicine and second set of questionnaires will reflect caregivers perspective of adherence for study medication. Out of 20 items of mSICT questionnaire, child's perspective domain scores consist of 6 items (Item: 3, 4, 5, 7, 8 and 9) while caregiver's perspective is captured by 6 items (Item: 13, 14, 15, 16, 18 and 19), i.e. overall 12 items will measure the adherence of the treatment.

Non-adherence items from the child perspective and caregiver's perspective domains consist of one item each (Item: 6) and (Item: 17) respectively.

Child's perspective of adherence:

Item 3 captures about the frequency of medicine intake and **item 5** discusses about how often child follows the doctor's instructions. **Items 3 and 5** will be measured using a 5-point response scale: "Always" =1 (best), "Most of the time" =2, "Sometimes" =3, "Rarely" =4 and "Never" =5(worst).

Item 4 discusses about how often the child express to stop the medication. The scale will be used to measure this as "Always" =5 (worst), "Most of the time" =4, "Sometimes" =3, "Rarely" =2, and "Never" =1 (best).

Two items (**Item 7 and 8**) use different response options. **Item 7** focuses on "How easy/hard did your child tell you it was to take his/her medicine" and uses the response scale "Very easy" =1 (best), "Easy" =2, "Neither easy or hard" =3, "Hard" =4, and "Very hard" =5 (worst). Similarly, **item 8** captures bother expressed by child for amount of time he/she had to wait to eat food after taking medication. The response scale for Item 8 will be "Very bothered" =5 (worst), "Quite Bothered" =4, "Moderately bothered" =3, "A little bothered" =2, and "Not bothered at all" =1 (best).

Item 9 reports "how happy your child appeared" and is scored on a scale from 1=Very happy (best) to 5=Very unhappy (worst).

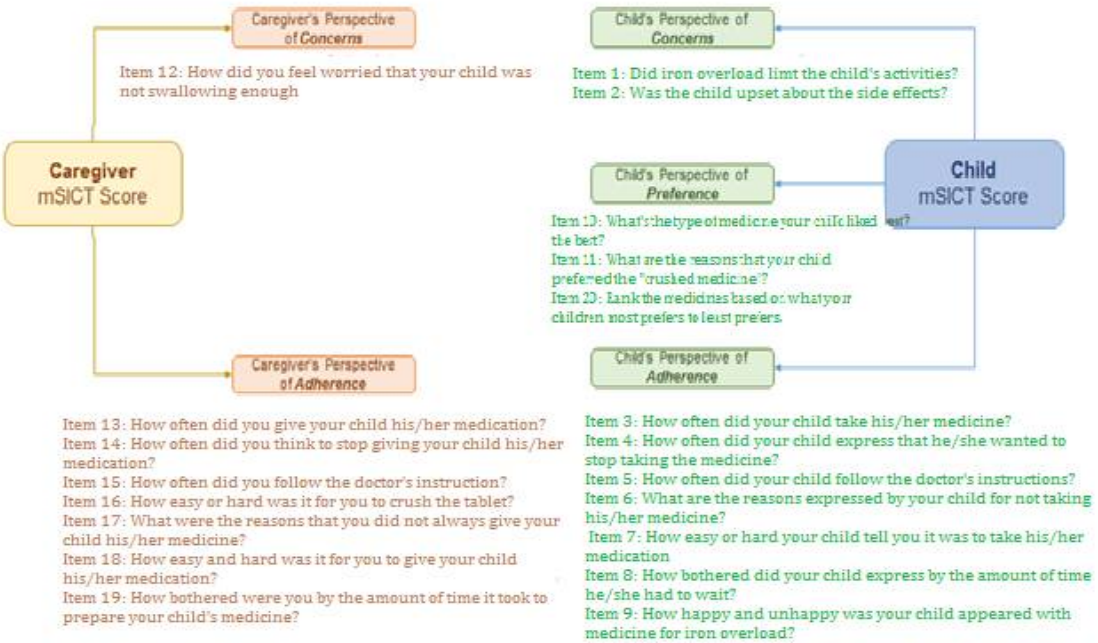
Caregiver's perspective of Adherence:

Item 13 asks the caregivers about how often medicine is given to the child and **item 15** asks about how often caregivers follow doctor's instruction for giving child his/her medicine. **Item 13** and **15** both are measured using a 5-point response scale: "Always" =1 (best), "Most of the time" =2, "Sometimes" =3, "Rarely" =4 and "Never" =5 (worst).

Conversely, **item 14** will capture the caregiver perspective about "how often he/she thought of stopping the medicine". **Item 14** will be scored as "Always" =5 (worst), "Most of the time" =4, "Sometimes" =3, "Rarely" =2, and "Never" =1 (best).

Item 16 and **18** focus on "how easy/hard was it to crush the medicine" and "How easy/hard was it to give your child his/her medicine" respectively and use the same response scale "Very easy" =1 (best), "Easy" =2, "Neither easy nor hard" =3, "Hard" =4, and "Very hard" =5 (worst). Similarly, **item 19** captures "bothered by the amount of time it took to prepare medication" and uses the response scale "Very bothered" =5 (worst), "Quite Bothered" =4, "Moderately bothered" =3, "A little bothered" =2, and "Not bothered at all" =1 (best).

Figure 2.1 Proposed Conceptual Models for the Modified Satisfaction with Iron Chelation Therapy Questionnaire



Adherence Domain Score Calculation

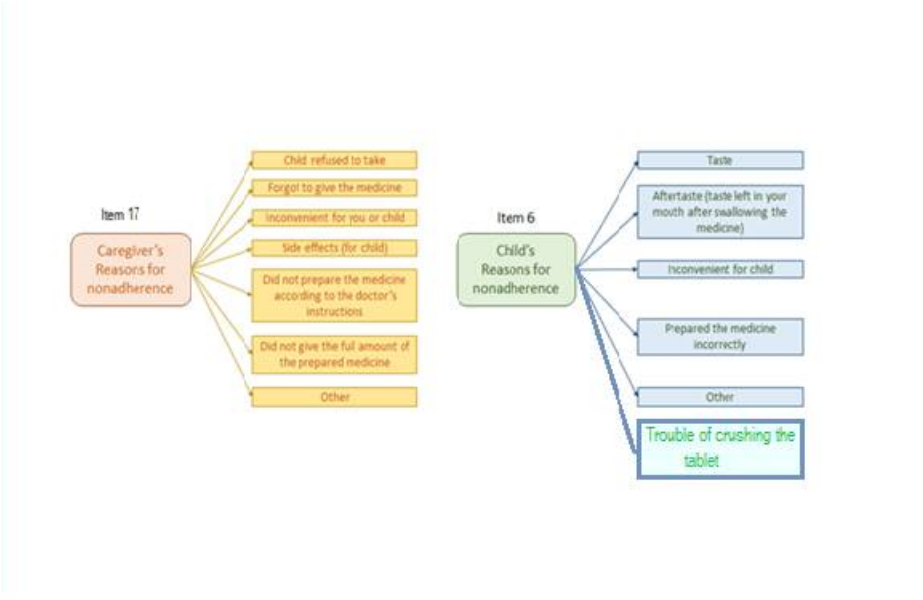
A separate adherence domain scores for the child's and caregiver's perspective will be calculated. A domain score will be calculated by summing item scores on respective domains. Overall, a lower domain score will indicate better adherence. Note that **Item 6 and 17** will be analyzed separately and thus will not be included while calculating caregiver's perspective for adherence, i.e. it will not be included in the summation.

Child's Perspective and Caregiver's Perspective Checklist for Non-adherence

Only respondents who, at **item 5** (for the child's perspective) and **item 15** (for the caregiver's perspective), indicate that they did not "Always" take their medication as instructed, are expected to give the reasons for non-adherence. For both the "child's perspective of adherence" and "caregiver's perspective of adherence," there is an item to capture the reasons for non-adherence, where the respondent can check all the reasons that apply.

From the child's perspective, **item 6** ("reason expressed by your child for not always taking the medicine as instructed by the doctor") and **item 17** from the caregiver perspective ("reason that you did not always give your child his/her medicine as instructed by the doctor") capture the reasons for non-adherence. These response options are treated as a standalone checklist, which captures the child's and caregiver's perspective on the reasons why the child did not always take their medication as instructed. See **Figure 2.2**

Figure 2.2 Conceptual models for item 6 and item 17 of the modified SICT



This item will be used as a standalone item to further understand the overall Adherence domain and the responses will be presented descriptively using frequency counts.

2.13.1.2 Preference

This domain consists of 3 items (**item 10, item 11 and item 20**). **Item 10** will assess "what type of medication did your child like the best". **Item 11** will assess "the reason of preference for crushed medicine". **Item 20** will capture the rank of the medicine based on whatever the children prefer. These item are to be considered a single items and the responses will be presented descriptively using frequency counts.

2.13.1.3 Concerns

Similar to adherence domain, concerns will be captured 2 ways:

1. based on the child's perspective (**Item 1** and **2**) and
2. also based on the caregiver's perspective (**Item 12**)

The concerns domain for the child's perspective has 2 items which focus on "limiting child's activity" (**Item 1**) and "getting upset about the side-effects" (**Item 2**). Both the items are measured using a 5-point response scale from "Always" =1 (worst), "Most of the time" =2, "Sometimes" =3, "Rarely" =4, and "Never" =5 (best); and a sum of scores for a Concerns domain for the child's perspective will be created if both items are non-missing. A higher score will indicate lesser concerns.

There is only a single item to capture concern in regards to caregiver's perspective. The **item 12** captures about "how worried whether the child is swallowing enough medication" and is scored on a 5-point response scale from "Always" =1 (worst), "Most of the time" =2, "Sometimes" =3, "Rarely" =4, and "Never" =5 (best). A higher score on the single item domain will indicate lesser caregiver concern.

For the mSICT questionnaire, the score for each domain (adherence and concerns) will be the mean of the score of items included in the corresponding domain. Note that for these domains, child's perspective and caregiver's perspective will be summarized separately. Standard descriptive analyses will be performed for each domain (adherence and concerns) score at screening visit 1 (baseline), week 4, week 12, and end of treatment visits, as well as their changes from baseline at week 4, week 12, and end of treatment for pre-treated chelation patients where baseline evaluation is available. For the Chelation naïve patients and patients treated with chelation therapy other than deferasirox who stopped chelation treatment more than 7 days prior to Screening visit, only descriptive statistics by visit will be provided. The standard descriptive analyses include: n, mean, standard deviation, minimum, median, and maximum. The 95% confidence intervals will be presented for the changes in mean from baseline for all domains at week 4 and week 12 and EOT for patients pre-treated with deferasirox only.

Box plot will be presented to summarize the scores graphically for each domain at week 4, week 12 and EOT.

All preference items will be analyzed descriptively by visit.

2.13.2 Palatability questionnaire

Like mSICT questionnaire, the palatability questionnaire will be completed at screening visit 1, week 4, week 12, and EOT. The responses at screening visit 1 for palatability questionnaire will be considered as baseline. The palatability questionnaire consists of 4 items. Two items measure the taste (**Item 1**) and aftertaste (**Item 2**) of the medication and are scored on a 5-point response scale with the response format "Very good" =1 (best), "Good" =2, "Neither good nor bad" =3, "Bad" =4, and "Very bad" =5 (worst).
The aftertaste item will be treated as an independent item (and will not be part of the scoring) and will be presented descriptively using frequency counts.

A summary of **items 1, 3 and 4** will be constructed using the following rules:

Recode **item 1**

"Very good", "Good" & "Not good or bad" =1
"Bad" & "Very bad" = 2

Recode **item 3**

"Swallowed ALL of the medicine" =1
"Spat out SOME of the medicine" & "Spat out ALL of the medicine" and "Swallowed none" =2
"Vomited within 30 minutes after swallowing the medicine" = 3

Recode **item 4**

"Not enough liquid" & "Too much liquid" = 1
"Just enough liquid" = 2

Table 2.2 Scoring Matrix for the Palatability Questionnaire

Score	Q1 – Taste	Q3 – What happened	Q4 – Amount	Definition
0	Bad & Very bad; 2	Vomited < 30 min; 3	Not enough & too much; 1	Worst palatability
1	Bad & Very bad; 2	Vomited < 30 min; 3	Just enough; 2	1
2	Bad & Very bad; 2	Spat some/ all out; 2	Not enough & too much; 1	2
3	Bad & Very bad; 2	Spat some/ all out; 2	Just enough; 2	3
4	Bad & Very bad; 2	Swallowed all: 1	Not enough & too much 1	4
5	Bad & Very bad; 2	Swallowed all: 1	Just enough 2	5
6	V. good, Good & Not good/bad; 1	Vomited < 30 min; 3	Not enough & too much; 1	6
7	V. good, Good & Not good/bad; 1	Vomited < 30 min; 3	Just enough; 2	7
8	V. good, Good & Not good/bad; 1	Spat some/ all out; 2	Not enough & too much; 1	8

9	V. good, Good & Not good/bad; 1	Spat some/ all out; 2	Just enough; 2	9
10	V. good, Good & Not good/bad; 1	Swallowed all: 1	Not enough & too much; 1	10
11	V. good, Good & Not good/bad; 1	Swallowed all: 1	Just enough; 2	Best palatability

For the palatability questionnaire, standard descriptive analyses based on the derived scores will be provided at screening visit 1 (baseline), week 4, week 12, and EOT, as well as their changes from baseline at week 4, week 12, and EOT for patients pre-treated with deferasirox. For the Chelation naïve patients and patients treated with chelation therapy other than deferasirox who stopped chelation treatment more than 7 days prior to Screening visit, only descriptive statistics by visit will be provided. The standard descriptive analyses include: n, mean, standard deviation, minimum, median, and maximum. The 95% confidence intervals will be presented for the mean changes from baseline at week 4 and week 12 and EOT for patients pre-treated with deferasirox.

Box plot will be presented to summarize the scores graphically at week 4, week 12 and EOT.

2.13.3 GI symptom questionnaire

The GI symptom questionnaire consists of 6 items, 5 of which are scored using a 1-5 rating scale with appropriate end anchors to rate the symptom. The items are “Pains in the belly”, “Nausea (feeling like throwing up)”, “Vomiting”, “Constipation” and “Diarrhea”. All are scored as “Always”=5 (worst), “Most of the time”=4, “Sometimes”=3, “Rarely”=2, “Never”=1 (best).

The **sixth item** assesses bowel movement frequency during the past week, using 7 response options 0 = 0 (“None”), 1 = 1, 2 = 2, 3 = 3, 4 = 4, 5 = “5 – 10” and 6 = “11 or more”.

The GI symptoms questionnaire will be completed at all visits starting at screening visit 1 (excluding screening visit 2) until end of treatment. Response from GI symptom questionnaire at screening visit 1 will be considered as baseline.

A GI symptom score will be created as a summary score of all items (5 items), where a lower score represents a less severe GI symptom and a higher score represents a more severe GI symptom. **Item 6** will be excluded from the calculation of the weekly GI Symptom score; it will be used as a standalone item and will be presented descriptively using frequency counts.

The weekly average will be calculated when there are at least 4 non-missing daily responses by a subject. No additional imputation will be carried out.

GI symptoms will be summarized over time by descriptive statistics for all visits and for all patients (i.e. either Chelation naïve patients and patients treated with chelation therapy other than deferasirox who stopped chelation treatment more than 7 days prior to Screening visit or patients pre-treated with deferasirox). Descriptive statistics and the 95% confidence intervals

for the absolute mean changes by visit will be provided for patients pre-treated with deferasirox. The standard descriptive analyses include: n, mean, standard deviation, minimum, median, and maximum.

GI symptom scores as well as item 6 (bowel movement) will be summarized using descriptive statistics with the change from baseline to week 2, week3, week4, week 8, week 12, week 16, week 20 and EOT for patients pre-treated with deferasirox.

Box plot will be presented to summarize the scores graphically at week 2, week3, week4, week 8, week 12, week 16, week 20 and EOT.

2.14 Biomarkers

Not applicable.

2.15 Other exploratory analyses

Not applicable

2.16 Interim analysis

Not applicable

3 Sample size calculation

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

Table 3-1 Clopper-Pearson 95% CI for different incidence of AEs and the corresponding probability to observe at least one AE

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

30%	(0.17, 0.47)	1.00

4 Change to protocol specified analyses

- According to statistical section 10.5.3.2 in the protocol, the number and frequency of overall AEs and gastrointestinal AEs will be summarized for naïve (no ICT prior to enrollment) and non-naïve patients. However, this will not be done. Further, only on-treatment deaths will be summarized instead of all deaths. All deaths will be presented in the listings with post-treatment deaths flagged.
- According to statistical section 10.5.3.4 in the protocol, Data on ECG, vital signs, height, weight, ocular and auditory findings will be listed, summarized and flagged as appropriate. However, ECG, auditory and ocular findings are only listed but not summarized due to the limited amount of data collected (only unscheduled assessments for ECG and mostly EOT visits for ocular and auditory at post baseline).

5 Appendix

This will be used later for drafting CSR Appendix 16.1.9.

5.1 Imputation rules

5.1.1 Study drug

The following rule will be used for the imputation of date of last administration for a given study treatment component.

Case 1: The date of last administration is completely missing, and the EOT visit date is complete, then this latter date should be used.

Case 2: Only Year (yyyy) of the dose end date is available and yyyy < the year of EOT date:

Impute date= Dec31yyyy

Case 3: Only Year (yyyy) of the dose end date is available and yyyy = the year of EOT date:

Impute date=EOT date

Case 4: Both Year (yyyy) and Month (mm) is available for the date of last administration, and yyyy = the year of EOT date and mm < the month of EOT visit:

Impute date= last day of the Month (mm).

After imputation, compare the imputed date with the start date of that specific record, if the imputed date is < start date of that record

Impute date= the start date of that record.

Subjects with missing start dates are to be considered missing and no imputation will be made. If the date of first administration is missing, then the date of last administration should not be imputed.

5.1.2 AE date imputation

Date imputation is the creation of a new, complete date from a partial one according to an agreed and acceptable algorithm. Missing date for AE will be handled according to STL standard.

A partial date is simply an incomplete date e.g., ddOCT2001 the days are missing from this DDMMMYYYY date.

Partial adverse event start dates, if left partial, would ultimately mean the following

- It would not be possible to place the adverse event in time.
- Therefore the treatment/dosage at the time of the event would be unknown.
- Therefore the event could not be reported/summarized appropriately - if at all.

There **will be no** attempt to impute the following

- **Missing** AE start dates
- AE start dates missing the year
- Partial/missing AE **end dates**

Table 5-1 AE/treatment date abbreviations

	Day	Month	Year
Partial AE start date	<not used>	AEM	AEY
Treatment start date (TRTSTD)	<not used>	TRTM	TRTY

The following matrix Table 5-2 describes the possible combinations and their associated imputations. In the boxes the upper text indicates the imputation and the lower text the relationship of the AE start date to the treatment start date (TRTSTD).

Table 5-2 AE partial date imputation algorithm

	AEM Missing	**AEM < TRTM**	**AEM = TRTM**	**AEM > TRTM**
AEY Missing	NC Uncertain	NC Uncertain	NC Uncertain	NC Uncertain
AEY < TRTY	(D) Before TRTSTD	(C) Before TRTSTD	(C) Before TRTSTD	(C) Before TRTSTD
AEY = TRTY	(B) Uncertain	(C) Before TRTSTD	(B) Uncertain	(A) After TRTSTD

AEY > TRTY	(E) After TRTSTD	(A) After TRTSTD	(A) After TRTSTD	(A) After TRTSTD

Table 5-3 AE/treatment date relationship and imputation

Relationship	
Before TRTSTD	Indicates AE start date prior to Treatment Start Date
After TRTSTD	Indicates AE start date after Treatment Start Date
Uncertain	Insufficient to determine the relationship of AE start date to Treatment Start Date
Imputation Calculation	
NC/Blank	No convention/imputation
(A)	01MONYYYY
(B)	TRTSTD+1
(C)	15MONYYYY
(D)	01JULYYYY
(E)	01JANYYYY

The following Table 5-4 gives a few examples.

Table 5-4 Example Scenarios

Partial AE start date	Treatment start date	Relationship	Imputation calculation	Imputed date
12mmyyyy	20OCT2001	Uncertain	NC	<blank>
ddmmm2000	20OCT2001	Before	(D)	01JUL2000
ddmmm2002	20OCT2001	After	(E)	01JAN2002
ddmmm2001	20OCT2001	Uncertain	(B)	21OCT2001
ddSEP2001	20OCT2001	Before	(C)	15SEP2001
ddOCT2001	20OCT2001	Uncertain	(B)	21OCT2001
ddNOV2001	20OCT2001	After	(A)	01NOV2001

5.1.3 Concomitant medication date imputation

The imputation of the start date of concomitant medication will follow the same convention for AE date. Partial concomitant medication end date will not be imputed.

5.1.3.1 Prior therapies date imputation

Start date:

The same rule which is applied to the imputation of AE/concomitant medication start date will be used with the exception that for scenario (B) will be replaced to be 'start date of study drug -1'.

End date:

Imputed date = min (start date of study drug, last day of the month), if day is missing; Imputed date = min (start date of study drug, 31DEC), if month and day are missing.

If the end date is not missing and the imputed start date is after the end date, use the end date as the imputed start date.

If both the start date and the end date are imputed and if the imputed start date is after the imputed end date, use the imputed end date as the imputation for the start date.

5.1.3.2 Other imputations

Incomplete date for death

All dates must be completed with day, month and year.

If the day or month is missing, death will be imputed to the maximum of the last contact date (excluding the date of death) and the following:

- Missing day: 15th of the month and year of death
- Missing day and month: July 1st of the year of death

5.2 Creatinine clearance recalculation

The recalculated creatinine clearance will be calculated using the Schwartz formula (pediatric population at baseline). The MDRD derivation will be provided in the derived datasets only for possible future requests.

In the formulae below, CrCl denotes Creatinine Clearance, SCr denotes Serum Creatinine in µmol/L; age in years is calculated from date of birth and date of the relevant blood sample. Weight and height are the last available measurements at the time of the relevant blood sample.

Schwartz formula (<18 years of age at beginning of the study),

CrCl (mL/min) = (k×height)/ (SCr×0.01131) with

k = 0.45 for children <1 year based on current age

k = 0.55 for children from 1 to 12 years based on current age

eGFR (mL/min/1.73m^2)=

$186.3\times (SCr\times 0.01131)^{-1.154}\times age^{-0.203}\times E\times S$ where,

E is ethnicity: E=1.212 if patient is black, else E=1

S is sex: S=0.742 if patient is female, else S=1

5.3 Statistical models

5.3.1 Primary analysis

Let X be the number of success observed in the sample and $Bin(n, \theta)$ is a binomial random variable with n trials and probability of success θ.

Because of the relationship between the binomial and the beta distribution, the Clopper-Pearson interval is sometimes presented as an alternative format that uses the beta distribution as:

$$B\left(\frac{\alpha}{2}; x, n-x+1\right) < \theta < B\left(1-\frac{\alpha}{2}; x+1, n-x\right)$$

Where x is the number of success n is the number of trials and $B(p, \alpha, \beta)$ is the p-th quantile from the beta distribution with shape parameters α, β.

When x = 0 the interval is $\left(0,\ 1-\left(\frac{\alpha}{2}\right)^{1/n}\right)$ and when x = n, it is $\left(\left(\frac{\alpha}{2}\right)^{1/n},\ 1\right)$ [1]

The beta distribution is, in turn, related to the F-distribution so another formulation of the Clopper-Pearson interval can be written using F-quantiles:

$$\left(1+\frac{n-x+1}{xF\left[\frac{\alpha}{2}; 2x, 2(n-x+1)\right]}\right)^{-1} < \theta < \left(1+\frac{n-x}{(x+1)F\left[1-\frac{\alpha}{2}; 2(x+1), 2(n-x)\right]}\right)^{-1} \quad [2]$$

Where x is the number of success, n is the number of trials and $F(c, d_1, d_2)$ is the c-th quantile from an F-distribution with d_1 and d_2 degrees of freedom.

Since Clopper-Pearson interval is the exact interval since it is based directly on the binomial distribution rather than any normal approximation to binomial distribution. Thus, Clopper-Pearson distribution will be used in calculating confidence interval.

5.3.2 Key secondary analysis

Not applicable

6 Reference

*Thulin, Måns (2014). "The cost of using exact confidence intervals for a binomial proportion". Electronic Journal of Statistics. **8** (1): 817–840. ISSN 1935-7524. doi:10.1214/14-EJS909.*

*Agresti, Alan; Coull, Brent A. (1998). "Approximate is better than 'exact' for interval estimation of binomial proportions". The American Statistician. **52**: 119–126. JSTOR 2685469. MR 1628435. doi:10.2307/2685469.*