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Detailed Statistical Methodology

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Version	Date	Changes
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Version	Date	Changes
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		scoring rule to derive domain scores for the Palatability questionnaire (Section 2.9.1.2). To clarify the formula to compute the weekly average of dose violation rate (Section 2.9.1.3). Pharmacokinetics parameters (Section 2.9.2): To update the pharmacokinetic analyses to align with the protocol. To update the time-windows criterion for the pre-dose PK data analysis to align with the PAS-1 definition (Section 2.9.3.2). To clarify the dose-adjusted PK concentrations/ parameters calculation (Section 2.9.3.3). - Interim analysis (Section 2.12): To add details about the interim analysis. Section 3 – Change to protocol specified analyses - Removal of the changes to protocol specified analyses to align with the protocol. - ObsRO/PRO not analyzed at the time of the IA as per protocol amendment 4, rational provided. Section 4 – Additional details on implementation of statistical methodology - Time windows (Section 4.1): Addition of time windows for ocular data analysis. Clarification of EOT time window (Section 4.1.2). - Stratification (Section 4.5): Clarification on the stratification ID numbers for ICT naïve patients. - Removal of SAS codes (Sections 4.6.1 and 4.6.2) - Addition of method of calculation of probability of success (Section 4.6.3) - Efficacy evaluations (Section 4.6): - Handling of missing or partial dates (Section 4.8): To clarify that only the date of last dose of study drug can be imputed from DAR eCRF records (Section 4.8.5).
5.0	26 Mar 2017	Final version – Amendment 3 This amendment reflects changes based on the study protocol amendment 5. Section 1 – Introduction - Study objectives (Section 1.2): Update on primary and secondary objectives to align with the protocol. Section 2 – Statistical methods - Data analysis (Section 2.1): Clarification on cut-off definition for the primary analysis. - Analysis sets (Section 2.2): Correction of ID for major protocol deviations for PPS to reflect the last VAP. - Analysis sets (Section 2.3): Removal of Safety Set 1, 2, FAS-1 and FAS-2 populations for the laboratory parameters description' at baseline.

Version	Date	Changes
		- Treatments (Section 2.6): Clarification on dose reduction and increase flag derivation. - Baseline (Section 2.7): Clarification on baseline definition: the last available assessment i.e. non-missing assessment. - Analysis of the primary variable (Section 2.8): Modification of the primary analysis variables and analysis as well as supportive analysis to align with protocol (Sections 2.8.1 to 2.8.4). Addition of secondary analyses to align with the protocol (Section 2.8.5). - Analysis of the secondary variables (Section 2.9): Addition of FAS-1 and FAS-2 populations for ObsRO/PRO data analysis to align with protocol (Section 2.9.1). Addition of AESI descriptive summaries by severity, SAE, relationship, etc. (Section 2.9.2). Correction of the visit numbers for pharmacokinetics analyses under PAS-2 (Section 2.9.3). - Sample size (Section 2.11): Modification of sample size for the primary analysis to align with protocol. Section 3 – Change in protocol specified analyses Removal of changes to protocol specified analysis to align with the protocol. Section 4 – Additional details on implementation of statistical methodology - Time windows (Section 4.1) Clarification of time-windows derivation for drug exposure, laboratory data and ocular data analysis - Efficacy evaluations (Section 4.6) Clarification on SAS procedures for primary and sensitivity analysis. - Safety evaluations (Section 4.7) Removal of eGFR formula: NA - Handling of missing or partial dates (Section 4.8) Clarification of imputation rule for incomplete date of last dose of study drug.

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AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATC	Anatomical Therapeutic Classification
AUC	Area under concentration-time curve
BMI	Body mass index
BP	Blood Pressure
CA	Compartmental Analyses
CI	Confidence Interval
CrCl	Creatinine Clearance
CRF	Case Report/Record Form
CSR	Clinical Study Report
CV	Coefficient of Variation
DAR	Dosage Administration Record
DBP	Diastolic Blood Pressure
DRL	Drug Reference Listing
DT	Dispersible Tablet
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
PRO/ObsRO	Patient Reported Outcomes/Observer Reported Outcomes
EOT	End of Treatment
FAS	Full Analysis Set
FCT	Film Coated Tablet
FU	Follow Up
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
HLT	High Level Terms
IA	Interim Analysis
ICT	Iron Chelation Therapy
IRT	Interactive Response Technology
ITT	Intention To Treat
Kg	Kilogram
LLOQ	Lower Limit of Quantitation
MDRD	Modification of Diet in Renal Disease
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities

NA	Not Applicable
NCA	Non-Compartmental Analyses
NEU	Neutrophils
NMQ	Novartis MedDRA Queries
PAS	Pharmacokinetic Analysis Set
PDS	Programming Datasets Specifications
PK	Pharmacokinetic
PPS	Per-Protocol Set
PT	Preferred Terms
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SCIT	Satisfaction with Iron Chelation Therapy
SI	International System
SMQ	Standardized MedDRA Queries
SOC	System Organ Classes
SCr	Serum Creatinine
TBL	Total Bilirubin
TEAE	Treatment Emergent Adverse Event
TFL	Tables Figures Listings
ULN	Upper Limit of Normal
UNK	Unknown
WBC	White Blood Cell
WHO	World Health Organization

1 Introduction

This document details the planned statistical analysis for data collected in the study CICL670F2202.

Clinical Study Report (CSR) deliverables (tables, figures, listings - TFLs) and further programming specifications are described in separate documents namely TFL Shells and Programming Datasets Specifications (PDS), respectively. This analysis plan describes the primary analysis for the primary CSR planned at the end of the core phase and the analyses for the final CSR planned at the end of the extension phase. One interim analysis is planned to allow for early analysis of the core phase if requested by Health Authority. This document also details the statistical methods to be used for reporting results in the interim CSR.

1.1 Study design

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

Patients whose eligibility is confirmed will be enrolled prior to commencing a 48-week randomized treatment period in the core phase with either deferasirox DT (taken as per local label) or deferasirox granule formulation (taken with or without a light meal) beginning on Day 1.

Randomization will be stratified by age groups (2 to <10 years, 10 to <18 years) and by prior Iron Chelation Therapy (ICT) (Yes/No). Up to 240 naïve and pre-treated patients (120 ICT naïve and up to 120 pre-treated) will be randomized.

There will be two study phases which include a 1 year core phase where patients will be randomized to a 48 week treatment period to either Deferasirox DT or granules, and an optional extension phase where all patients will receive the granules up to 5 years. Patients who demonstrate benefit to granules or DT in the core phase, and/or wish to continue in the optional extension phase on granules, will be offered this possibility until there is local access to the new formulation (granules or FCT) or up to 5 years, whichever occurs first.

During the 48 week treatment period in the core phase, patients will return to the site for study assessments weekly for the first 3 weeks and then every 4 weeks starting from week 5 (weeks 9, 13, 17, 21, 25, 29, 33, 37, 41 and 45) until the core End Of Treatment (EOT) visit.

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

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

1.2 Objectives

The study objectives as outlined in the [protocol Section 3] are as follows (Table 1-1).

Table 1-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		
• To evaluate both formulations on patient compliance, using stick pack/tablet count over 24 weeks of treatment in ICT naïve patients during core phase	• Compliance measured by stick pack/tablet count over 24 weeks of treatment (i.e. assessed at week 25 visit)	Refer to Protocol Section 10.4 / SAP Section 2.8
• To evaluate the change from baseline in serum ferritin after 24 weeks of treatment for both formulations in ICT naïve patients	• Change from baseline in serum ferritin after 24 weeks of treatment (i.e. serum ferritin at week 25 visit)	
Secondary (Core phase)		
To evaluate both formulations on change in serum ferritin and compliance in ICT naive patients, after 48 weeks of treatment	● Compliance measured by stick pack/tablet count after 48 weeks of treatment ● Change from baseline in serum ferritin after 48 weeks of treatment	Refer to Protocol Section 10.5 / SAP Section 2.8.5
To evaluate both formulations on change in serum ferritin after 24 weeks and 48 weeks of treatment in ICT naïve and pre-treated patients	Change from baseline in serum ferritin after 24 weeks (i.e. assessed at week 25 visit) and 48 weeks of treatment	Refer to Protocol Section 10.5.1 / SAP Section 2.8.5
To evaluate both formulations on patient satisfaction and palatability using Patient / Observer Reported Outcomes (PRO/ObsRO) questionnaires	Domain scores of treatment satisfaction and palatability over time	Refer to Protocol Section 10.5.2 / SAP Section 2.9.1
To evaluate both formulations on overall safety	Overall safety, as measured by frequency and severity of adverse events (including active monitoring for renal toxicity; including renal failure, hepatic toxicity; including hepatic failure, and gastrointestinal hemorrhage), and changes in laboratory values from baseline (serum creatinine, creatinine clearance, ALT, AST, RBC and WBC). In addition, vital signs, physical, ophthalmological, audiometric, cardiac, and growth and development evaluations will be assessed.	Refer to Protocol Section 10.5.3 / SAP Section 2.9.2
To evaluate compliance using a daily PRO/ObsRO questionnaire	Rate of dosing instructions deviations (doses missed / not taken at the same time every day)	Refer to Protocol Section 10.5.4 / SAP Section 2.9.1
To evaluate pre-dose PK data to support the assessment of compliance	Pre-dose deferasirox concentrations in all patients [except Egypt] at weeks 1, 3, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41 and 45 (13 samples)	Refer to Protocol Section 10.5.5.1 / SAP Section 2.9.3
Post-dose data to be analyzed along with pre-dose PK data	Post-dose deferasirox concentrations between 2 and 4 hours post-dose at Weeks 5 and 9 (2 samples)	Refer to Protocol Section 10.5.5.2 / SAP Section 2.9.3
To explore exposure-response relationships for measures of safety and effectiveness	Serum creatinine change from baseline, notable serum creatinine events, serum creatinine clearance change from baseline and notable serum creatinine clearance events,	Refer to Protocol Section 10.5.5.3 / SAP Section 2.9.3

Objective	Endpoint	Analysis
	urine protein creatinine ratio change from baseline and serum ferritin change from baseline, in relationship to pre- and post-dose deferasirox concentrations.	
Secondary (Optional Extension phase)		
To assess additional safety data about new formulation (granules) in pediatric population	Overall safety, as measured by frequency and severity of adverse events (including active monitoring for renal toxicity; including renal failure, hepatic toxicity; including hepatic failure, and gastrointestinal hemorrhage), and changes in laboratory values from baseline (serum creatinine, creatinine clearance, ALT, AST, RBC and WBC). In addition, vital signs, physical, ophthalmological, audiometric, and growth and development evaluations will be assessed.	Protocol sections 10.5.3 and 10.6.1 / SAP Section 2.9.2

2 Statistical methods

This section will be imported to section 9.7 of the CSR after the analyses have been conducted and follows the CSR template structure as of the release date of the first final version of this document.

Section 4 Additional details on of the SAP provides statistical and programming conventions.

2.1 Data analysis

Data will be analyzed by Novartis Oncology Biostatistics and Statistical Programming personnel according to the data analysis section 10 of the study protocol as detailed in this analysis plan.

SAS® version 9.4 (or later version if available at time of database lock) will be used for all analyses.
Data from all patients who signed informed consent will be used in the analysis. The analysis cut-off date for the primary analysis of study data will be established 24 weeks after approximatively 96 ICT naïve patients have been randomized. For the interim analysis a cut-off date will be established. All randomized iron chelation naïve patients who have completed a minimum of 12 weeks of treatment exposure or discontinued from treatment core phase at the time of the cut-off date will be included in the interim analysis (see Section 2.12).

All statistical analyses will be performed using all data collected in the database up to the data cutoff date. All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations.

All events with a start date before or on the cut-off date and an end date after the cut-off date will be reported as ‘ongoing. The same rule will be applied to events starting before or on the cut-off date and not having documented end date. This approach applies, in particular, to

adverse event and concomitant medication reports. For these events, the end date will not be imputed and therefore will not appear in the listings.

Subsequent to the primary analysis, the study will remain open to collect efficacy and safety data from core phase and safety data from the extension phase until the end of the study has been declared (all patients have completed the safety follow-up period of the extension phase).

The primary and interim statistical analyses will be performed using the data from the core phase: the core phase is defined as the time period from start of the trial up to the stop date of the core phase as defined in Table 2-1.

Table 2-1 Definition of core and extension phases

Core phase			Extension phase		
Treatment	Start date	Stop date	Treatment	Start date	Stop date
Granules	Date of first IC signed	Minimum[Date of latest administration of Granules in core phase + 30 days, cut-off date, Visit 17 date – 1 day]	Granules	Visit 17 date	Date of the last administration of Granules in extension + 30 days
DT	Date of first IC signed	Minimum[Date of latest administration of DT + 30 days, cut-off date, Visit 17 date – 1 day]	Granules	Date of first administration of Granules	Date of the last administration of Granules in extension + 30 days

Only data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) in the core phase will be summarized in the interim and primary analysis.

Summaries will be based on:

- Core phase comparing data for Granules versus DT formulations (blue rectangle in Figure 2-1).
- Entire granule period of patients randomized to Granule combining core and extension phases (dark green rectangle in Figure 2-1) side-by-side with Granules for patients randomized to DT who switched to Granules in extension phase (light green rectangle in Figure 2-1).Cross-over treatment group corresponds to the patients randomized to DT who switched to Granules in the extension phase.

Figure 2-1 Core and extension phases

General analysis conventions

Pooling of centers: Unless specified otherwise, data from all study centers will be pooled for the analysis. Due to expected small number of patients enrolled at centers, no center effect will be assessed.

Qualitative/categorical data (e.g., sex, race) will be summarized by frequency counts and percentages. Percentages will be calculated using the number of patients in the relevant treatment arm or subgroup as the denominator.

Continuous data (e.g., age, body weight) will be summarized using appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum, and maximum) by treatment arm. Lower and upper quartiles will also be presented when applicable.

2.2 Analysis sets

All screened patients

A patient is considered to be screened into the study if they have signed the study informed consent/assent form. Only patients who have signed informed consent will be included in the All screened patients analysis set.

Screen failures

Screen failures analysis set includes all patients who have been screened and who failed to be randomized for any reason (i.e. failing to meet inclusion or exclusion criteria or any other screening procedure).

Safety Set

The Safety Set 1 will consist of all ICT naïve patients (as per eCRF) who received at least one dose of the study drug during the core phase.

The Safety Set 2 will consist of all ICT pre-treated patients (as per eCRF) who received at least one dose of study drug during the core phase.

The Safety Set 3 will consist of all patients who received at least one dose of study drug during the core phase.

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

Patients will be analyzed according to the treatment actually received and strata information recorded in the eCRF.

Treatment actually received is defined as the treatment the patient received at the first day of study medication in the core phase.

Full Analysis Set

Full Analysis Set (FAS) is defined according to the Intention to Treat (ITT) principle.

The Full Analysis Set 1 (FAS-1) consists of all ICT naïve (as per IRT, see Section 4.5) randomized patients.

The Full Analysis Set 2 (FAS-2) consists of all ICT pre-treated (as per IRT) randomized patients.

The Full Analysis Set 3 (FAS-3) consists of all randomized patients.

Following the intent-to-treat principle patients are analyzed according to the treatment and stratification factors they were assigned to at randomization during the core phase.

Per-protocol set

The Per-Protocol Set (PPS) will consist of all ICT naïve patients from the FAS-1 without any major protocol deviation.

The major protocol deviations that will lead to exclusion of patients from the PPS are listed below:

- No transfusion dependent anemia (ID=I05);
- Serum ferritin ≤ 1000 µg/L at Screening (ID=I07);
- First administered study medication different from medication assigned by randomization (ID=S02);
- Absence of serum ferritin assessment at baseline and at least 1 post-baseline assessment (ID=G28);
- Any safety-related exclusion criteria met (ID= E01A3, E02A3, E03A3, E05, E06, E07, E08, E09, E10, E11, E13, E14, E18A4 or E19);
- No dose-adjustment for efficacy due to change in serum ferritin at weeks 13 and 25 (ID=S11 at weeks 13 or 25);
- Intake of any prohibited concomitant medication (ID= M01, M03, M04 or M05).
- Strata assigned for randomization differs from strata reported by investigator on CRF (ID=G32).

Pharmacokinetic Analysis Set

The Pharmacokinetic Analysis Set 1 (PAS-1) consists of all patients who have at least one evaluable pre- or 3 hours post-dose PK concentration (deferasirox) regardless of whether the pre-dose was taken under the original or current protocol instructions.

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

- The actual dose or leading dose prior to pre-dose or post-dose sampling must be as planned by protocol and be documented. In addition, the patient should have received the same dose during the last 4 days prior to the PK sampling (except for Week 1 Day 1).
- The elapsed time between dose administration and PK concentration is documented.
- The pre-dose sample should be within 24 ± 4 hours from the previous dose. The 3h post-dose sample should be obtained between 2 and 4 hours post-dose administration.

- The PK concentration must NOT be associated with any vomiting within 4 hours of dosing.

For statistical analysis based on PAS-1, only evaluable PK samples from patients in PAS-1 will be considered.

The Pharmacokinetic Analysis Set 2 (PAS-2) consists of all patients enrolled under the original protocol who have an evaluable PK profile. PK parameters will be calculated by the clinical pharmacologist if a minimum of 12 patients with evaluable PK profile are available.

- An evaluable PK profile is assessed as such by the Clinical Pharmacologist.

For statistical analysis based on PAS-2, only evaluable PK samples from patients in PAS-2 will be considered

Reporting

Frequency counts and percentages (using FAS-3 or Safety Set 4 as denominator) of patients in each of the above defined analysis sets will be summarized. In addition, listings of patients excluded from each of the analysis sets will be provided.

2.3 Patient demographics and other baseline characteristics

The FAS-1, FAS-2, FAS-3 and Safety Set 4 will be used for all patient demographic and baseline characteristic summaries, unless otherwise specified. Summaries will be produced by treatment arm and overall. Listings will be produced by treatment arm for the FAS-3 and Safety Set 4.

Enrollment status

The number of patients screened and randomized will be summarized respectively by region, country, center and treatment arm on the FAS-3 and Safety Set 4. The number of patients randomized will also be summarized by stratification factor (age group: 2 to <10 years versus 10 to <18 years and prior ICT: Yes versus No) and treatment arm on the FAS-3. IRT versus eCRF stratification factors will be tabulated on the FAS-3.

Basic demographic and other baseline characteristics

Basic demographic data

Categorical data (sex, age groups, weight group, race, and ethnicity) will be summarized by frequency counts and percentages. Continuous data (age, weight and height) will be summarized by descriptive statistics.

The following variables will be summarized as a continuous and categorical data:

- Age (years) will be categorized as: 2 to <10 years and 10 to < 18
- Weight (kg) will be categorized as: <20, 20 to <35, 35 to <55, 55 to <75 and ≥75

The number of patients by sex and age categories and the number of patients by race will be tabulated on the Safety Set 3 and Safety Set 4.

History of disease

The main underlying disease as well as the time since the diagnosis date will be summarized by treatment arm.

Time since the diagnosis (years) = (Screening visit 1 date – date of diagnosis + 1) / 365.25.

Prior iron chelation therapy

Frequency counts and percentages will be tabulated by treatment arm, for prior Iron Chelation Therapy (ICT) prior to start of study drug (yes or no), prior Deferasirox (yes or no) and type of last ICT received. Time since last dose of prior ICT will be summarized by descriptive statistics.

Time since last dose of prior iron chelation therapy (days) = (Screening visit 1 date – stop date + 1).

History of blood transfusion

Descriptive statistics will be tabulated by treatment arm, for total number of blood transfusions received.

Other baseline characteristics

Descriptive statistics, frequency counts and percentages will be tabulated by treatment arm, as appropriate, for history of splenectomy (yes or no), for hepatic B and C status (see Table 4-4). In addition, clinically significant abnormality in ECG (yes or no), overall interpretation in echocardiogram (normal or clinically significant or insignificant abnormality), overall interpretation in audiometric test (normal or clinically significant or insignificant abnormality), overall interpretation in ocular exam (normal or clinically significant or insignificant abnormality) will be summarized on the Safety set 3 and 4.

The following continuous variables will be summarized categorically on the Safety Set 3 and 4, and on the FAS-3 and Safety Set 4 for serum ferritin:

- Creatinine will be categorized as: ≤ULN, >ULN - ≤1.5*ULN, >1.5*ULN
- Recalculated Creatinine Clearance (CrCl) will be categorized as: <40, 40 to <60, 60 to <90 and ≥90mL/min
- ALT and AST will be categorized as: ≤ULN, >ULN-≤3*ULN, >3*ULN-≤ 5*ULN and >5*ULN
- Urine protein/creatinine ratio: ≤0.2 mg/mg,>0.2- ≤0.5, >0.5-≤1 mg/mg, >1 mg/mg
- Serum ferritin will be categorized as: <1000, ≥1000 to 2500, >2500 to 5000, >5000 ng/mL.

Medical history

Medical history and ongoing conditions will be summarized and listed by treatment arm on the FAS-3 and Safety Set 4. Separate summaries will be presented for ongoing and historical medical conditions. The summaries will be presented by primary system organ class,

preferred term and treatment arm. Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Data presented for screen failure patients

The total number and the reasons for screen failure (based on reasons recorded in 'Screening log' page) will be summarized.

The following listings will be provided for screen failure patients:

- Patient demographics (age, sex, race and ethnicity)
- Patient disposition
- Serious Adverse Events (SAE)

2.4 Protocol deviations

Frequency counts and percentages of patients with any protocol deviation (selection criteria not met, patient not withdrawn as per protocol, treatment deviation, prohibited concomitant medication, other Good Clinical Practice (GCP) deviation) will be tabulated by the deviation type category and treatment arm on the FAS-3 for the core phase and on the Safety Set 4 for the entire granule period. Protocol deviations leading to exclusion of patients from the PPS will be tabulated separately by treatment arm on the FAS-1.

The full list of protocol deviations is documented in the Validation And Planning (VAP) Module 3 document.

All protocol deviations will be listed on the FAS-3 and Safety Set 4.

2.5 Patient disposition

Listings will be produced on the FAS-3 and Safety Set 4.

The summaries of patient disposition during the core phase by treatment arm on the FAS-1, FAS-2 and FAS-3 will show:

- Number (%) of randomized patients who were not treated;
- Number (%) of randomized patients who were treated;
- Number (%) of patients who completed the core phase;
- Number (%) of patients who discontinued the core phase;
- Number (%) for each reasons for core phase discontinuation;

The summaries of patient disposition during the entire granule period by treatment arm on the Safety Set 4 will show in addition:

- Number (%) of patients who entered in the optional extension phase;
- Number (%) of patients who were not treated during the optional extension phase;
- Number (%) of patients who were treated during the optional extension phase;
- Number (%) of patients who completed the optional extension phase;
- Number (%) of patients who discontinued the optional extension phase;
- Number (%) for each reasons for optional extension phase discontinuation;

2.6 Treatments (study drug exposure, concomitant therapies)

The Safety Set 1, Safety Set 2, Safety Set 3 and Safety Set 4 will separately be used for medication data summaries unless otherwise specified. Listings will be produced by treatment arm on the Safety Set 3 and Safety Set 4.

Study drug and study treatment

The terms study drug and study treatment are equivalent and will refer both to deferasirox DT or deferasirox granule.

Date of first/last administration of study drug

The date of first administration of study drug is derived as the first date when a non-zero actual dose of study drug was administered as recorded on Dosage Administration Record (DAR) Electronic Case Report Form (eCRF). The date of first administration of study drug will also be referred as 'start of study treatment'.

The date of last administration of study drug is defined as the last date when a non-zero actual dose of study drug was administered as recorded on DAR eCRF. This date will also be referred as 'last date of study treatment'.

Study day

The study day **for safety and pharmacokinetics assessments** (e.g. adverse event onset, laboratory abnormality occurrence, vital sign measurement, Electrocardiogram (ECG), PK concentration, etc.) will be calculated using the start date of study treatment as the reference. For assessments occurring

- **on or after the start date of study treatment**, the study day will be calculated as (date of safety assessment) – (start date of study treatment) + 1. Study day 1 will therefore be the first day of study treatment.
- **before the start date of study treatment**, the study day will be calculated as (date of safety assessment) – (start date of study treatment).

For example, if an adverse event starts 3 days before the start of study treatment the study day displayed on the listing will be negative, i.e. -3.

The study day **for efficacy assessments** (e.g. serum ferritin, PRO) will be calculated using the randomization date as the reference. For assessments occurring

- **on or after randomization date**, the study day will be calculated as (date of non-safety assessment) – (date of randomization) + 1. Then study day 1 will be the day of randomization.
- **before randomization date**, the study day will be calculated as (date of non-safety assessment) – (date of randomization).

The study day will be displayed in the data listings.

Study drug exposure

Definitions of duration of exposure, total patient-years exposure, average daily dose, cumulative total dose as well as percentage of planned dose taken are defined in Table 2-2:

Table 2-2 Deferasirox: Study drug exposure

Overall duration of exposure (day):	[(date of last study treatment) – (date of first study treatment) + 1]
Drug exposure on dose X (days)	[(date of last study treatment on dose X) – (date of first study treatment on dose X) + 1]
Average dose (planned and actual, in mg/kg/day):	Mean dose over all days between first and last dose, including interruptions: sum of all (X dose * corresponding duration of exposure on dose X) / overall duration of exposure
Cumulative dose (planned and actual, in mg/kg):	Sum over daily doses of all days between first and last dose
Total patient-years (years):	Overall duration of exposure (days) / 365.25
Percentage of planned dose taken:	100 × [Cumulative actual dose / Cumulative planned dose]

The actual dose in mg/kg/day will be obtained by dividing the actual total daily dose administered in the DAR eCRF page by the last available weight at the time of dose administration reported in the vital signs eCRF page.

Overall duration of exposure, average planned and actual daily dose, cumulative actual dose, total patient-years and percentage of planned dose taken will be summarized by treatment arm for the core phase and for the entire granule period.

The following variables will also be summarized by treatment arm and for each phase as appropriate as:

- Duration of exposure will be categorized in the core phase as: <4 weeks, 4 to <12 weeks, 12-<20 weeks 20-<28 weeks, 28-<36 weeks, 36-<44 weeks, ≥44 weeks; and in the entire granule period as: <6 months, 6-<12 months, 12-<24 months, 24-<36 months, 36-<48 months, ≥48 months).
- Deferasirox DT average dose will be categorized as: <15, 15 to <25, 25 to <35 and ≥35 mg/kg/day
- Deferasirox granule average dose will be categorized as: <10.5, 10.5 to <17.5, 17.5 to <24.5 and ≥24.5 mg/kg/day

In addition, the number of patients who have dose reduction, increase or dose interruption, with corresponding reasons and the average length of dose interruptions will be summarized.

Dose reduction will be considered if the actual dose is not equal to 0 (or not counted as interruption) and [the planned dose level is lower than the previous non-missing planned dose level Or the dose change is equal to 'yes' and the actual total daily dose administered (mg) is lower (> 15%) than the calculated dose amount based on the planned dose (mg)]. Any dose change to correct a dosing error will not be considered a dose reduction (patient goes back to the previous planned/actual dose after a dose change due to dosing error). Number of reductions will be derived programmatically.

Dose increase will be considered if the actual dose is not equal to 0 (or not counted as interruption) and [the planned dose level is higher than the previous non-missing planned dose level Or the dose change is equal to 'yes' and the actual total daily dose administered (mg) is higher (> 15%) than the calculated dose amount based on the planned dose (mg)]. Note that a dose rechallenge i.e when a patient goes back to the previous planned dose after an interruption or a dose reduction is not considered as an increase.

Dose interruption will be considered if an actual dose of zero in a unit of time between two non-zero actual dosing records. Any rest period as part of the schedule is not considered as an interruption. For the purpose of summarizing interruptions and reasons, in case multiple entries for interruption that are entered on consecutive days with different reasons will be counted as separate interruptions. However, if the reason is the same in this mentioned multiple entries on consecutive days, then it will be counted as one interruption.

Furthermore, box plot of average actual daily dose will be plotted by month and treatment (see Table 4-1 for month definition) on the core phase only.

For each patient, listings of each dose of the study drug administered along with dose change reasons will be produced.

Concomitant therapy

Prior and concomitant therapies are defined as any medication, and significant non-drug therapies administered to a subject preceding or coinciding with the study assessment period.

Medications will be coded using the World Health Organization (WHO) Drug Reference Listing (WHO DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (WHO ATC) classification system.

Concomitant therapies will include medications and significant non-drug therapies taken between the first and last day with study medication, excluding medications start on the last day of study medication. Prior therapies will include medications or significant non-drug therapies starting and ending prior to the start of study treatment.

Concomitant and prior therapies will be summarized by ATC class, preferred term and treatment arm for the Safety Set 3 and Safety Set 4. Medications starting prior to the start of study treatment and continuing after the start of study treatment will be counted in both summaries.

All prior and concomitant therapies will be listed.

2.7 Baseline

Baseline is considered as the result of an investigation describing the 'true' uninfluenced state of the patient.

For **efficacy evaluations**, (e.g. serum ferritin), the last available (i.e. non-missing) assessment before or on the date of randomization is taken as 'baseline' value or 'baseline' assessment.

For **safety evaluations** (e.g. laboratory, vital signs, etc.) the last available (i.e. non-missing) assessment before or on the date of start of study treatment is taken as 'baseline' value or 'baseline' assessment.

If patients have no value as defined above, the baseline result will be missing.

If an assessment is planned to be performed prior to the first dose of study drug in the protocol and the assessment is performed on the same day as the first administration of study drug, it will be assumed that it was performed prior to study drug administration, if assessment time point is not collected or is missing. Unscheduled assessments will be considered in the determination of baseline.

Patients who start treatment and discontinue from the study on the same day may have 2 different sets of data collected on study Day 1, one being reported to the week 1 visit, the other reported to the End Of Treatment (EOT) visit. Data reported at the EOT visit are not eligible for baseline selection.

For analyses of the extension phase (entire granule period) requiring comparison to baseline value (e.g. lab shift tables) the baseline is defined as follows. For patients randomized to DT formulation who switched to granule formulation in the extension phase, the last assessment prior or equal to the start date of granules in the extension phase will be defined as pre-granule value which will be reference value for changes in the extension time. For patients randomized to granules continuing in extension phase the initial baseline value at study start will be taken.

2.8 Analysis of the primary variables

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

2.8.1 Variable

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

The co-primary efficacy variables are:

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

  The prescribed count corresponds to the count prescribed by the investigator for the relevant visit 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 granule), the prescribed count for the relevant visit period is calculated from the daily prescribed count at the beginning of this period multiply by the duration (days) of this period. The duration of a period will be calculated as (end date of

the period) – (start date of the period) + 1. The total count prescribed is the sum of counts prescribed per strength.

- Change from baseline in serum ferritin after 24 weeks of treatment (i.e. assessed at week 25 visit).

2.8.2 Statistical hypothesis, model, and method of analysis

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

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

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

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

The null and the alternative hypothesis are defined as follows:

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

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

versus

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

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

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

2.8.3 Handling of missing values/discontinuations

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

No imputation will be performed for the compliance endpoint calculation. However, patient who discontinued before the week 25 visit will be included in the compliance endpoint calculation.

2.8.4 Supportive analyses

The following supportive analyses will be provided:

- The primary analysis as described in Section 2.8.2 & Section 2.8.3 will be also performed for the PPS, FAS-2 and FAS-3 as supportive efficacy analyses;
- In addition, descriptive summaries will be provided for the FAS-1 by treatment arm:

  • Summary of absolute and relative change from baseline values in serum ferritin assessed at week 25 visit and 95% confidence intervals for means (see Table 4-2 for time window definition);

  • Summary statistics of overall compliance measured by stick pack/tablet count assessed at week 25 visit and 95% confidence intervals for means. Patient who discontinued before the week 25 visit will be included in the compliance endpoint calculation.

  These descriptive analyses will be repeated by the age stratification factor, by average actual daily dose category, by baseline serum ferritin category, and underlying disease (see Table 2-6).

  • A forest plot of mean difference between treatments will be presented with absolute change in serum ferritin after 24 weeks of treatment and the corresponding exact 95%CI including these subgroups. Point estimates and 95% CI will be generated.
- If more than 10% of patients have no serum ferritin value after 24 weeks of treatment, sensitivity analysis will be performed for the primary analysis for serum ferritin using multiple imputation method. This analysis will be performed for the FAS-1.

2.8.5 Secondary and other analyses of the primary variables

Secondary analyses of the primary variables

Descriptive summaries as specified in Section 2.8.4 will be repeated:

- For the FAS-1 after 48 weeks of treatment. In addition, if more than 10% of patients have no serum ferritin value after 48 weeks of treatment or missing compliance measured by stick pack/tablet count over 48 weeks of treatment, a sensitivity analysis will be performed using multiple imputation method.
- For the FAS-2 and FAS-3, after 24 and 48 weeks of treatment (as for the FAS-1). Furthermore, a graphical presentation of mean and standard deviation of absolute value in serum ferritin will be plotted by treatment arm and time-window (see Table 4-2 for time-window definition) for FAS-1, FAS-2 and FAS-3.

Other analyses of the primary variable

Relative and absolute change from baseline in serum ferritin at every year visit during the entire granule period will be described for the Safety Set 4.

2.9 Analysis of secondary variables

Secondary variables include patient reported outcomes/observer reported outcomes, safety assessments (i.e. adverse events, laboratory parameters, vital signs, etc.) and

Pharmacokinetics (PKs) parameters. All secondary variables will be analyzed by treatment group.

2.9.1 Patient reported outcomes/Observer reported outcomes

Patient satisfaction, palatability and compliance with study drug will be evaluated for both treatment groups using Patient Reported Outcomes/Observer Reported Outcomes (PRO/ObsRO).

Three PRO/ObsRO questionnaires have been developed: the modified SICT questionnaire, a palatability questionnaire and a compliance diary. Patients/caregiver will complete all PRO/ObsRO questions via a handheld electronic device (exceptionally paper could be used in specific situation). The diaries will be completed daily at home and the palatability and modified SICT will be completed at pre-determined site visits.

The three questionnaires were developed using patient input in one on one interview. The PRO questionnaires were validated for their psychometric properties, and the ObsRO questionnaires will be validated in a within-trial data for validation that will be conducted by Adelphi Value. The statistical analysis plan, the data analysis as well as the results report for ObsRO psychometric validation will be done and provided by Adelphi Value.

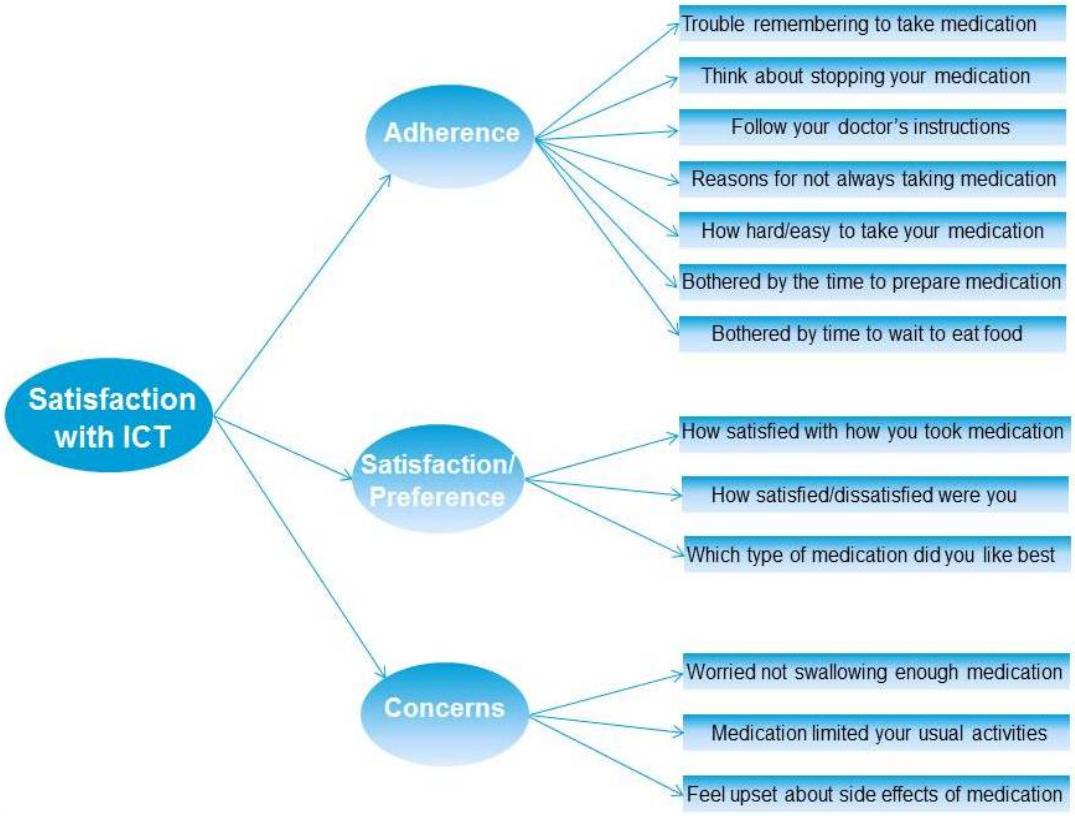
The FAS-1, FAS-2 and FAS-3 will be used for the three PRO/ObsRO questionnaires analysis for the core phase, unless otherwise specified.

2.9.1.1 Modified SICT questionnaire

Patient reported outcomes

The Modified SICT questionnaire consists of 13 items that represent 3 domains; Adherence, Preference and Concerns (see Figure 2-2).

Figure 2-2 Conceptual model for the Modified Satisfaction with Iron Chelation Therapy questionnaire



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

Items 4 and 5 use the response format 1 "Never"", 2 "Rarely" 3 "Sometimes" 4 " Most of the time" and 5 "Always"; item 6 uses the response format 1 "Always", 2 "Most of the time" 3 "Sometimes" 4 "Rarely" and 5 "Never;; Item 8 uses the response format 1 "Very easy", 2 "Easy", 3"Neither easy or hard", 4 "Hard" and 5 "Very hard"; Items 9 and 10 use the response format 5 "Very bothered", 4"Bothered" 3"Moderately bothered", 2 "A little bothered" and 1 "Not bothered at all". An Adherence domain score will be calculated by summing these 6 items and as a result a higher score will indicate worse adherence.

Item 7 captures the reasons that the patient did not always take their medication as instructed and is only asked of patients who, at Item 6, indicated that they did not "Always" take their medication as instructed. These patients are instructed to choose all reasons that apply (Figure 2-3). Each response category will be coded as binary item, for example taste will be an item with the response format 0 "Not endorsed" 1 "Endorsed".

Figure 2-3 Conceptual model for Item 7 of the modified SICT

Satisfaction/preference domain consists of 3 items, 2 (Items 11 and 12) assess the patients' satisfaction with the medication and are measured using a 5 point response scale with the response format 1 "Very satisfied", 2"Satisfied", 3 "Neither satisfied nor dissatisfied", 4"Dissatisfied" 5"Very dissatisfied". A Satisfaction domain score will be calculated by summing these two items. Higher scores will indicate worse satisfaction.

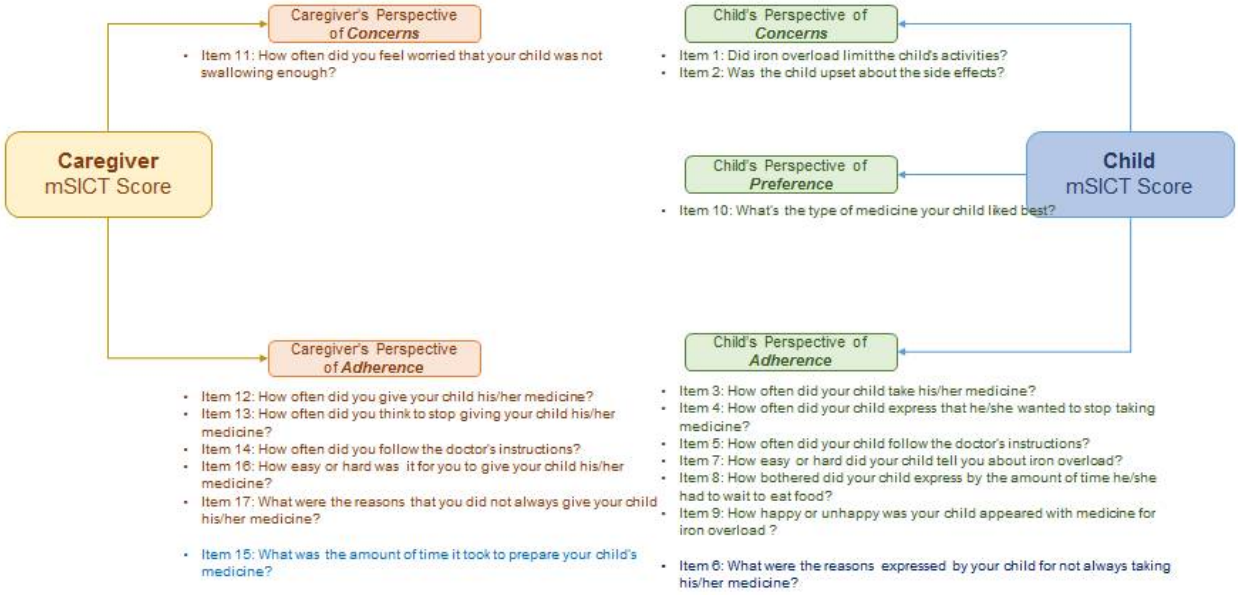
The third item (Item 13) asks the patient to assess which medication for iron overload they prefer.

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

Observer reported outcomes

The modified SICT consists of 17 items that represent 3 domains: Adherence, Preference, and Concerns (see Figure 2-4).

Figure 2-4 Conceptual Model for the Modified Satisfaction with Iron Chelation Therapy Questionnaire



The conceptual framework consists of 2 separate scales to capture the child's and caregiver's perspective; these are further broken into 3 domains for the child: Concerns, Preference, and Adherence and 2 domains for the caregiver: Concerns and 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)

There will be 2 separate domain scores for overall adherence, the caregiver's perspective of adherence domain consists of 6 items (Items 12, 13, 14, 16 and 17), while the child's perspective of adherence domain consists of 7 items (Items 3, 4, 5, 7, 8 and 9).

Child's perspective of Adherence: Items 3 and 5 are measured using a 5-point response scale: "Always" =1, "Most of the time" =2, "Sometimes" =3, "Rarely" =4, and "Never" =5. Item 4 is measured on a scale from "Always" =5, "Most of the time" =4, "Sometimes" =3, "Rarely" =2, and "Never" =1. 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, "Easy" =2, "Neither easy or hard" =3, "Hard" =4, and "Very hard" =5. 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 is "Very bothered" =5, "Bothered" =4, "Moderately bothered" =3, "A little bothered" =2, and "Not bothered at all" =1. Item 9 reports "how happy your child appeared" and is scored on a scale from 1=Very happy and 5=Very unhappy.

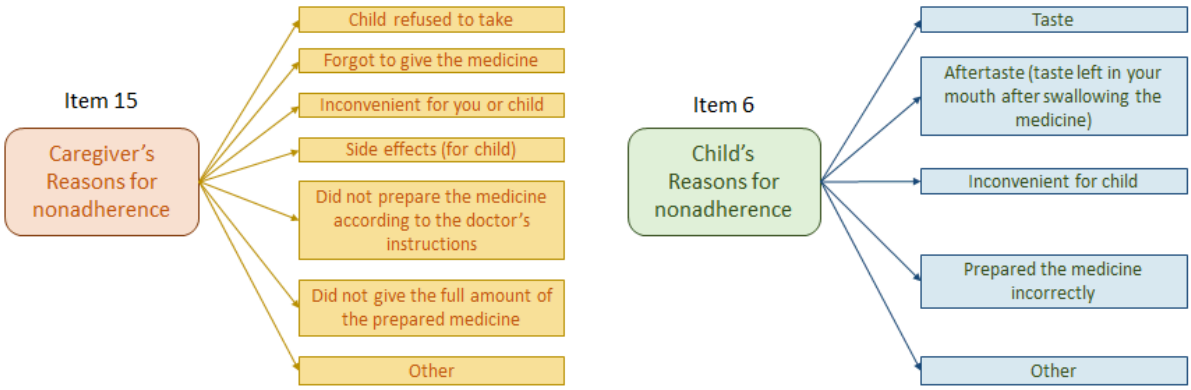
Caregiver's perspective of Adherence: Items 12 and 14 are measured using a 5-point response scale: "Always" =1, "Most of the time" =2, "Sometimes" =3, "Rarely" =4, and "Never" =5. Conversely, Item 13 is scored as "Always" =5, "Most of the time" =4, "Sometimes" =3, "Rarely" =2, and "Never" =1. Two items (Item 16 and 17) use different response options. Item 16 focuses on "How easy/hard was it to give your child his/her medicine" and uses the

response scale "Very easy" =1, "Easy" =2, "Neither easy or hard" =3, "Hard" =4, and "Very hard" =5. Similarly, Item 17 captures "bothered by the amount of time it took to prepare medication" and uses the response scale "Very bothered" =5, "Bothered" =4, "Moderately bothered" =3, "A little bothered" =2, and "Not bothered at all" =1.

Separate adherence domain score 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.

The checklist item from each perspective will evaluate the reason for non-adherence. Only respondents who, at Item 5 (for the child's perspective) and Item 14 (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 perspectives the respondent can check all the reasons that apply (Figure 2-5). For the child's perspective (item 6), each of the 5 response options (i.e. taste, aftertaste, inconvenience, prepared medicine incorrectly, and other) will be coded as binary item, for example taste will be an item with the response format 0 "Not endorsed" 1 "Endorsed". Similarly, for the caregiver perspective (item 15), each of the 7 response options (i.e. child refuse to take, forgot, inconvenient, side-effect, not prepare medication per doctor's instruction, did not give full amount, and others) will be coded as binary item (0/1).

Figure 2-5 Conceptual model for item 6 and item 15 of the modified SICT



Preference of the Child: This domain consists of 1 item (Item 10), to assess which medication they prefer (like). The item is to be considered a single item domain.

Concerns domain will be captured from 2 perspectives:

- Child's perspective (Item 1 and 2)
- Caregiver's perspective (Item 11)

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, "Most of the time" =2, "Sometimes" =3, "Rarely" =4, and "Never" =5. A sum score for a Concerns domain for the child's perspective will be created. A higher score will indicate lesser concerns.

There is only a single item to capture concern in regards to caregiver's perspective. The item 11 captures "worry if the child is swallowing enough medication" and is scored on a 5-point response scale from "Always" =1, "Most of the time" =2, "Sometimes" =3, "Rarely" =4, and "Never" =5. A higher score on the single item domain will indicate lesser caregiver concern.

Adherence, satisfaction/preference and concerns domain scores will be summarized using standard descriptive statistics by treatment arm, type of questionnaire (ObsRO questionnaire versus PRO questionnaire) and week (weeks 2, 3, 25 and core EOT). Additionally, absolute change from week 2 to week 25 and core EOT in the domain scores will be summarized including 95% confidence intervals for mean.

Graphical representation of PRO scores over weeks will be provided by domain by type of questionnaire and treatment. The y-axis will be the mean and SD for the domain score and the x-axis will be the week number.

In addition, all items from adherence, satisfaction/preference and concerns domains will be summarized by treatment arm by type of questionnaire and week using frequency counts and percentages for the FAS-3.

The number of patients completing the modified SICT questionnaire and the number of missing or incomplete assessments will be summarized by treatment arm, type of questionnaire and week for the FAS-3.

2.9.1.2 Palatability questionnaire

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 1 "Very good", 2 "Good", 3 "Not good or bad" for PRO/ 3 "Neither good nor bad" for ObsRO, 4 "Bad' and 5 "Very bad". The PRO aftertaste item offers an additional response option of "no aftertaste". This response option will be recoded such that all patients have a response, for example, patients who choose this option will be coded 0 and patients who rated the aftertaste will be coded 1. This will result in binary (yes/no) aftertaste item.

Note for ObsRO: Item 1 the response format for 3 refers to "Neither good nor bad" and for Item 3 the response format 1 refers to "Swallowed and retained ALL of the medicine". Same scoring rule will be used for both ObsRO and PRO.

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

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

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

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

The Table 2-3 presents the Items 1, 3 and 4 scoring matrix leading to the palatability summary score:

Table 2-3 Scoring Matrix

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

The palatability summary score will be summarized using descriptive statistics by treatment arm, type of questionnaire (ObsRO questionnaire versus PRO questionnaire) and week (weeks 2, 3, 25 and core EOT). Additionally, absolute change from week 2 to week 25 and core EOT will be summarized including 95% confidence intervals for mean.

Graphical representation of this 11 point response scale will be provided over weeks by treatment and type of questionnaire. The y-axis will be the mean and SD and the x-axis will be the week number.

In addition, all of the 4 Items from the palatability questionnaire will be summarized using descriptive statistics by treatment arm, type of questionnaire and week using frequency counts and percentages for the FAS-3.

The number of patient completing the palatability questionnaire and the number of missing assessments will be summarized by treatment arm, type of questionnaire and week for the FAS-3.

2.9.1.3 Compliance diary

The Compliance questionnaire consists of 2 items. Item 1 assessed whether the medication was taken (yes/no) and Item 2 is a record of the time when the medication was taken with a not applicable option for patients who did not take their ICT.

The daily compliance questionnaire diary records will also be used to calculate the rate of dose violations. For a given day, a dose violation is defined as a dose that is either missed completely or not taken in accordance with the timing instruction (no later than 12:00 pm). The dose violation rate is calculated as:

[Number of dose violations / Drug exposure (days)] *100

Weekly average of dose violation rate will be calculated and summarized using descriptive statistics by treatment arm, type of questionnaire (ObsRO questionnaire versus PRO questionnaire) and week (weeks 1, 13, 25, 37 and core EOT). Additionally, absolute change from week 1 will be tabulated including 95% confidence intervals for mean. A graphical representation will be provided over all week periods by treatment arm and type of questionnaire. The y-axis will be the mean and SD and the x-axis will be the corresponding week period (see Table 4-3 for week periods definition).

Due to the use of ePRO there will be no individual items missing. The weekly average rates will be calculated when there are at least four non missing daily responses. For a given week the denominator will be the number of non-missing days. No additional imputation will be carried out.

The number of patients completing the compliance diary and the number of expected and missing days will be summarized by each treatment arm and type of questionnaire for the FAS-3.

2.9.2 Safety evaluations

Unless otherwise specified, the following analyses will be performed separately for the Safety Set 1, Safety Set 2, Safety Set 3 for the core phase and the Safety Set-4 for the entire granule period. Listings will be provided for the Safety Set 3 and the Safety Set-4.

On-treatment period

For the core phase, the overall observation period will be divided into three mutually exclusive segments taking into account stop rules as per Table 2-1:

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

For the entire granule period, the following conventions will be taken into account while deriving the three observation periods:

- For patients enrolled in DT formulation in the core phase, the pre-treatment period will not be derived;
- For patients enrolled in Granule formulation in the core phase, the first dose of study drug will be the day of first dose in the core phase.

Unless otherwise specified, the safety summary tables will include only assessments from the on-treatment period.

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.

Adverse events

AEs will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) available prior to clinical database lock.

Any information collected (e.g. relatedness to study drug, action taken etc.) will be listed.

The following adverse event summaries will be produced by treatment arm:

- 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
- Serious adverse events (overall and severe), with suspected 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
- Deaths (all and on-treatment) by primary system organ class and preferred term (Safety Set 3 and 4 only).

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables will be produced for the Safety Set 3 on combined core and extension phases at the time of the final CSR:

- Non-serious adverse events with an incidence greater than 5%;

- Serious adverse events (SAE) and SAE suspected to be related to study treatment will be provided by system organ class and preferred term. The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective will also be provided.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

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, severity and relation to study drug by treatment arm. A patient with multiple occurrences of an AE will be counted only once in the AE category.

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

All AEs will be listed. Any information collected (e.g. regardless to study drug, action taken etc.) will be listed as well as the duration of the AE. The listings of all deaths, serious adverse events, adverse events leading to study drug discontinuation, and adverse events requiring dose adjustment or interruption will also be provided.

Adverse events of special interest

Specific groupings of AESI will be considered and the number of patients with at least one event in each grouping will be reported. Note that certain adverse events 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 MedDRA terms to be used are defined in an independent AESI search table which is located in the document management system in the “CREDI Projects/I/ICL670A/Integrated Medical Safety” folder. The latest AESI search table has to be used.

The AESI search table will be used to map reported adverse events to the AESI groupings. The list of adverse events of special interest may be updated during the course of the trial based on accumulating safety data. Therefore clinical study report will list the AE groupings used and provide a listing of the corresponding AESI search table. AESI will be summarized by grouping, preferred term and treatment arm (specifying severity, SAE, relationship, leading to treatment discontinuation, leading to dose adjustment/interruption and requiring additional therapy).

Laboratory data

Laboratory data from all sources (central and local laboratories) will be combined. All laboratory values will be converted into International System (SI) units.

Raw values as well as absolute and relative change from baseline values for hematology, biochemistry and urinalysis laboratory parameters will be summarized descriptively per time window and treatment arm on the Safety Set 3 and 4 (see Table 4-2 for time windows definition).

Shift tables based on normal ranges to compare baseline to the worst post-baseline value will be provided by parameter and treatment arm for hematology, biochemistry and urinary laboratory data. Same shift table will be provided based on notable/extended ranges for key safety laboratory parameters defined in Table 2-4.

Table 2-4 Definition of notable/extended ranges for key safety laboratory parameters

Laboratory parameters	Criteria for notable/extended 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
Recalculated 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/AST	>5 x ULN and 2 x baseline (extended range >10×ULN and >2×baseline value)

Recalculated creatinine clearance will be calculated using the Schwartz formula (for pediatric population at baseline) described in Section 3.6.3. The Modification of Diet in Renal Disease (MDRD) derivation will be provided in the derived datasets only for possible future requests.

A listing of all laboratory values with values flagged to show the corresponding range classifications relative to the laboratory reference ranges will be provided by laboratory data and treatment arm. Assessment day relative to first dose of study drug will be included and all laboratory assessments collected outside of the on-treatment period will be flagged.

A listing of patients with laboratory abnormalities based on normal ranges and notable/extended ranges will also be provided.

Normal ranges by laboratory parameter will also be provided in a separate listing.

In addition to the above mentioned tables and listings, box plots of absolute value and the absolute change from baseline value for key safety laboratory parameters per time window and treatment arm will be provided as appropriate.

Vital signs, weight and body mass index

The following criteria define clinically notable abnormalities for vital signs and weight values:

- Clinically notable elevated values
  - Systolic Blood Pressure (BP): ≥ 180 mmHg and an increase ≥ 20 mmHg from baseline
  - Diastolic BP: ≥ 105 mmHg and an increase ≥ 15 mmHg from baseline.
  - Pulse rate: ≥ 120 bpm with increase from baseline of ≥15 bpm
  - Weight: increase from baseline of ≥ 7%
- Clinically notable low values
  - Systolic BP: ≤ 90 mmHg with decrease from baseline of ≥ 20 mmHg
  - Diastolic BP: ≤ 50 mmHg with decrease from baseline of ≥ 15 mmHg
  - Pulse rate: ≤ 50 bpm with decrease from baseline of ≥ 15 bpm
  - Weight: ≥ 7% decrease from baseline

Descriptive statistics will be tabulated per time window and treatment arm using absolute change from baseline values for each vital sign measure, weight and BMI (see Table 4-2 for time windows definition) separately for Safety Set 3 and 4.

All vital sign assessments, weight and BMI will be listed by treatment arm, patient and parameter. In the listings, clinically notable values will also be flagged.

Cardiac evaluations

Cardiac evaluations include ECG and echocardiogram. Any abnormalities at baseline will be summarized as described in Section 2.3. All findings of patients with new or worsened abnormalities since baseline will be listed separately for Safety Set 3 and Safety Set 4.

Ocular evaluations

The number of patients with available assessment for each type of ocular evaluation and eye side will be provided by treatment group.

Visual acuity

Visual acuity will be measured using the Snellen visual acuity. This is determined by establishing the smallest optotypes that can be identified correctly by the patient at a given observation distance. Snellen visual acuity can be reported as a Snellen fraction (m/M) in which the numerator (m) indicates the test distance and the denominator (M) indicates the distance at which the gap of the equivalent Landolt ring subtends 1 minute of arc. For each timepoint, the LogMAR score will be calculated as $-\log(m/M)$.

Descriptive statistics of the LogMAR scores at baseline, at each post-baseline visit and changes from baseline at each post-baseline visit will be presented, for each eye by treatment group provided that for a given patient, the assessment was done in the same condition (with/without correction) as done at baseline.

The LogMAR value will be compared at baseline and worst post-baseline based on the identifying clinically meaningful deterioration in LogMAR of ≤0, >0 to <0.1, 0.1 to <0.2, 0.2 to <0.3 and ≥0.3, for each eye side by treatment group.

Number and percentage of patients with clinically relevant LogMAR change from baseline more or equal than 0.2 and more or equal than 0.3 will be summarized by treatment arm. For patients with such values, a listing will also be provided.

Slit lamp

For each considered evaluation type and eye, the number of patients with and without abnormality (normal, insignificant, significant and any) will be provided by treatment arm. In addition, a shift table will present any changes in interpretation compared to baseline. A listing of patients with any abnormality will be provided.

Tonometry

Descriptive statistics of the intraocular pressure at baseline, at each post-baseline visit and changes from baseline at each post-baseline visit will be presented, by eye and treatment group.

The number of patients with clinically relevant changes from baseline intraocular pressure above 5 mmHg and 10 mmHg will be summarized by treatment arm. For patients with such values, a listing will also be provided.

Intraocular pressure will also be summarized in shift table (baseline and worst post baseline value) for each eye side considering the following categories: <22, ≥ 22 and <30 and ≥ 30 mmHg.

Fundus occuli

For each eye, the number of patients with and without abnormality (normal, insignificant, significant and any) will be provided by treatment arm. In addition, shift table will be done to present any changes in interpretation compared to baseline. A listing of patients with any abnormality will be provided.

Growth and Development

Growth velocity will be listed at baseline and core EOT visit and summarized using descriptive statistics by sex and age group during the core phase for the Safety Set 3. Summaries and listing will be repeated for the entire granule period on the Safety Set 4.

The growth velocity in height which evaluates the rate of growth per year will be calculated on the difference with the previous measure of height (in cm) and the time period (in days) as:

Growth velocity (cm / year) =

$$\frac{(height\,V_x - height\,V_{x-1}) * F}{date\,V_x - date\,V_{x-1}}$$

(with Vx = actual visit ; Vx-1 = previous visit ; $F = 365.25$).

Pubertal stage assesses the stage of physical development of sex characteristics. The characteristics breast development, pubic hair, testes and penis size are evaluated based on the Tanner scale: for each characteristic there are 5 classes (Tanner stage 1 to 5) indicating the level of development of that specific characteristic.

The age will be summarized descriptively at baseline and core EOT visit for the core phase by sex, characteristic, Tanner stage and treatment arm. For the entire granule period, the same summary will be repeated at baseline and at each annual assessment.

A listing will be provided including the Tanner stage as well as the individual records for each sex characteristic by visit.

Other safety data

All data from auditory evaluation, hepatitis testing, and pregnancy test will be listed.

Patients with clinically significant abnormal interpretations or abnormal values will be flagged as well as positive pregnancy test results.

Data related to blood transfusion during treatment phase will be listed by treatment arm.

2.9.3 Pharmacokinetics parameters

2.9.3.1 General considerations

Pharmacokinetic (PK) analyses will be based on PK parameters derived by Non-Compartmental Analyses (NCA) and Compartmental Analyses (CA) (Table 2-5) and on PK concentrations. PK concentrations and Parameters are based on serum Exjade concentrations.

Table 2-5 Pharmacokinetic Parameters (NCA and CA)

NCA Parameters	
AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume^{-1})
AUCinf	The area under the plasma concentration-time curve extrapolated to infinity (mass x time x volume^{-1})
AUCtau	The AUC calculated to the end of a dosing interval (tau) at steady-state (mass x time x volume^{-1})
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration (mass x volume^{-1})
Tmax	The time to reach maximum (peak) plasma drug concentration after dose administration (time)
R	Accumulation index calculated as (AUC0-24h at steady state)/(AUC0-24h after the first dose)
CA Parameters	
ka	absorption rate constant (hr^{-1})
CL/F	apparent clearance for ICL670 and where F is the bioavailability (L/h)
V1/F	apparent volume of the central compartment for ICL670 (L)
Q/F	apparent distributional clearance for ICL670 (L/h)
V2/F	apparent peripheral volume for ICL670 (L)

Note: PK parameters are defined assuming a two compartment disposition model with first order absorption. In the unexpected case, the structure of the compartmental model require a change (e.g. for concentrations after granule application) PK parameter may change.

The daily dose categories defined in Table 2-6 will be used.

The PAS-1 will be used for the analysis of PK concentrations and characterization of Cmin and Cmax. The PAS-2 will be used to summarize PK parameters and visualize PK profiles. PK/safety analyses will be based on the Safety Set 3 and PK/efficacy analyses on the FAS-3 patients who also belonged to the PAS-1.

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

Coefficient of variation CV (%) is calculated as follows: 100*(SD/arithmetic mean). Geometric CV (%) is calculated as follows: CV(%)=100$\sqrt{}$(exp (σ^2)-1) where σ^2 denotes the variance of the log-transformed values.

Unscheduled samples will not be included in the descriptive analysis by time point but these samples will be flagged in the corresponding concentration listing.

Missing concentrations will not be imputed. Concentrations below the Lower Limit of Quantification (LLOQ) will be labeled as such in the concentration data listings.

Concentrations below the limit of quantitation will be treated as zero in summary statistics and excluded from geometric mean and geometric Coefficient of Variation (CV%) computation.

All individual data will be listed on the FAS-3 and those excluded from the analysis will be flagged.

2.9.3.2 Evaluation of pre-dose PK data to support the assessment of compliance

Pre-dose (Cmin) PK data from patients in the PAS-1 will be analyzed to assess variability of individual patient's compliance. The following approach will be used:

A linear mixed effect power model to pre-dose samples which fulfill compliance criteria in terms of steady state (4 consecutive same doses prior to the PK drawn), time-windows (PK sample drawn 20 to 28 hours after previous dose) and without any vomiting episodes within the 4 hours prior to the PK sample will be fitted. The model will consider dose, treatment group, stratification factors and potential other factors, such as body weight as covariates.

Predicted pre-dose concentrations will be compared with observed pre-dose concentrations considering all patients and pre-dose samples in PAS-1. Distributions of the difference between predicted and observed Cmin values will be shown graphically by boxplots for both treatment groups and visit.

2.9.3.3 Pharmacokinetics analyses

Dose-adjusted PK concentrations will be summarized by treatment, visit and time point based on PAS-1. The individual dose-adjusted pre-dose concentration will be plotted for Week 1, Week 3, Week 5, Week 9, Week 13, Week 17, Week 21, Week 25, Week 29, Week 33, Week, 37, Week 41 and Week 45 based on data from all patients. In addition arithmetic mean dose-adjusted pre-dose concentration will be plotted over time by treatment. These analyses will be based on the PAS-1.

Dose- adjusted PK parameters will be summarized by treatment for Week 1 and Week 5based on PAS-2. In addition, dose-adjusted PK concentrations will be summarized by treatment and time point for Week 1 and Week 5 on the PAS-2. Dose-adjusted individual concentration-time profiles will be plotted for Week 1 and Week 5. These analyses will be based on the PAS-2.

The dose-adjusted PK concentration and dose-adjusted PK parameter will be calculated as follows:

- For patients taking deferasirox DT:
  Dose-adjusted PK concentration or parameter = (PK concentration or parameter/actual dose)*20
- For patients taking deferasirox granules:
  Dose-adjusted PK concentration or parameter = (PK concentration or parameter/actual dose)*14

2.9.3.4 Exploration of PK/PD relationship

To characterize the exposure-efficacy relationship, serum ferritin change from baseline will be fitted by a linear mixed effect model with log- transformed matching pre-dose concentrations and post-dose concentrations as covariates and subject as random effect.

To characterize the exposure-safety relationship: Serum creatinine change from baseline, creatinine clearance change from baseline and urine protein creatinine ratio change from baseline will be fitted by a linear mixed effect model with log-transformed matching pre-dose and post-dose concentrations as covariates and subject as random effect. A model on post-baseline measurement and adjusted by corresponding baseline as covariate might be considered if improves the model fit.

Incidence of notable serum creatinine and incidence of notable serum creatinine clearance events will be analyzed by a logistic regression fitted by GEE methods as appropriate including log-transformed pre- and post-dose concentrations (see Table 2-4 for notable range definition). These analyses will be conducted if notable events were reported for a minimum of 20 patients. If notable events were reported for less than 20 patients a descriptive approach will be followed.

For all statistical models other covariates such as demographic characteristics may be included if appropriate (e.g. underlying disease).

PK/PD listing will be provided.

All PK/safety and PK/efficacy analyses will be based on the Safety Set 3 and on the FAS-3, respectively.

2.10 Subgroup analysis

Table 2-6 provides details on the subgroups definition and planned analyses.

Table 2-6 Subgroups definition and use

Subgroup	Categories	Definition/identification method	Use
Age categories	2 to <10 versus 10 to <18	Based on IRT	Supportive analysis
Average actual daily dose categories	- Deferasirox DT average dose will be categorized as: <15, 15 to <25, 25 to <35 and ≥35 mg/kg/day - Deferasirox granule average dose will be categorized as: <10.5, 10.5 to <17.5, 17.5 to <24.5 and ≥24.5 mg/kg/day	Based on DAR eCRF page	Supportive analysis
Baseline serum ferritin categories	≥1000 to 2500 versus >2500 to 5000 versus >5000 ng/mL	Based on laboratory datasets	Supportive analysis
Underlying disease	- Thalassemia: Beta-thalassemia major, Beta-thalassemia intermedia - Sickle cell disease - Other	Based on history of disease eCRF	Supportive analysis

2.11 Sample size

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

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

The assumptions made for this study were:

- For serum ferritin:

  An expected improvement between both formulations in serum ferritin change from baseline after 24 weeksof treatment of −450ng/mL with a standard deviation (SD) of 900 ng/mL based on results from study CICL670A0107 in pediatric patients treated with Exjade on ≥ 25 mg/kg/day after 24weeks of treatment
- For compliance using stick packs or tablets counts:

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

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

A sample size of 45 in each group will have 76% power to detect a difference in means of 450 ng/mL assuming that the common SD is 900 ng/mL using a two group t-test with a 0.050 one-sided significance level. With 45 patients per arm, the power to detect a difference of 10% or more in mean compliance is about 84%.

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

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

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

Table 2-7 below lists the precisions in the estimates of SF change for different numbers of patients using the estimated SD obtained from the [CICL670A0107] study results in pediatric patients treated with Exjade on ≥25 mg/kg/day at week 48 of treatment.

Table 2-7 Precision in the estimate of the serum ferritin change

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

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

2.12 Interim analysis

At the time of the Interim Analysis (IA) safety and efficacy data will be provided on all randomized iron chelation naïve patients (ICT naïve based on either in IRT or CHY eCRF page) who have completed a minimum of 12 weeks (≥84 days) of treatment exposure or discontinued from treatment core phase at the time of the cut-off date.

Unless otherwise specified, the FAS-1 will be used for the analysis of efficacy endpoints as well as for patient demographic and baseline characteristic, patient disposition and protocol deviations summaries. Similarly, the Safety Set 1 will be used for all safety data summaries. All analyses will be presented by treatment arm. Only descriptive analysis will be performed.

There is no intent to stop (neither for futility nor for efficacy) or to modify the design of the study as a consequence of this look. Therefore no alpha will be spent at this interim look. At the time of the IA data from approximately 74% of the patients expected to be enrolled will be available.

The primary endpoints, i.e. serum ferritin change from baseline and overall compliance measured by stick pack /tablet count, and key safety data will be summarized descriptively. The Interim CSR deliverables are specified in the TFL Shells document.

In addition, two supportive analyses will be performed:

- Descriptive summary of serum ferritin change from baseline will be provided after imputing missing values using multiple imputation method (see Section 4.6.1).
- Predictive probability of success of the primary analysis for serum ferritin change from baseline will be assessed using normal approximation based on observed interim analysis data.

3 Change to protocol specified analyses

Table 3-1 Changes to protocol specified analysis or descriptions and rationale

Protocol section	Protocol description	Change	Rationale
NA			

4 Additional details on implementation of statistical methodology

The sections below contain additional details on statistical methodology that will be included in Appendix 16.1.9 (Documentation of Statistical Methods) of the CSR as well as programing rules that will be followed to implement the analyses described in Section 2.

4.1 Time windows

4.1.1 Study drug exposure

Study drug will be dispensed at randomization (week 1), then every four weeks. Dose adjustments based on safety are allowed at any time point during the study.

Information on study drug strength will be collected on the Dose Administration Record (DAR) eCRF and includes the planned dose (mg/kg/day), actual total daily dose (mg) taken, reason for the dose change, start date and end date.

Table 4-1 shows the defined study periods for drug exposure.

All assessments within a time period will be used to calculate the drug exposure for the corresponding period.

Table 4-1 Study periods for drug exposure

Period	Visit Period Definition
Month 1	Study Day 1 – 28
Month 2	Study Days 29 – 56
Month y** (with y=3, 4, 5,…)	Study Days (y-1)*28+1 to (y)*28
Etc.	

*Study Day 1 = first day of study treatment
** For the core phase data analysis: y=1 to k=12

4.1.2 Laboratory data and vital signs

Laboratory data (biochemistry, hematology and urinary parameters as well as serum creatinine, creatinine clearance and proteinuria) and vital signs will be collected at screening visits, at each regularly patient visit and at end of treatment visit.
If two or more assessments are performed within a time window then the assessment closest to the planned visit is used in analyses by time window. When two values are equidistant from the planned assessment, the later one is used in analyses. When multiple values are reported on the same day then the average value is used in analyses. For parameters with categorical results, the one from central laboratory is used in analyses.

For worst post-baseline assessment, all on-treatment values are considered regardless of time windows.

Table 4-2 shows the defined time windows.

Table 4-2 Time windows for laboratory data, vital signs, weight and BMI

Time Window	Planned Visit Timing	Time Window Definition
On treatment		
Baseline	On or before Study Day 1*	≤ Study Day 1
Week 2**	Study Day* 8	Study Days 2 – 11 (excluded baseline assessment)
Week 3**	Study Day* 15	Study Days 12 – 18
Week 4**	Study Day* 22	Study Days 19 – 25
Week 5	Study Day* 29	Study Days 26 – 42
Every 4 weeks thereafter		
Week y=5+4*k (with k*** = 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11,…)	Study Day (5+4*k-1)*7+1	Study Days (5+4*k-1)*7+1-14 to (5+4*k-1)*7+1+13 Notes: - EOT data visit are included if obtained within 7* days of last non-0 dose intake or within 14* days for ocular assessments (*NA for patients continuing in extension phase).

*Study Day 1 = first day of study treatment
** where appropriate (e.g. week 2 time-window NA for serum ferritin)
*** For the core phase data analysis: k=1 to k=11 with EOT_Core corresponding to week 49 time-window

4.1.3 Compliance diary

Patients will be asked to fill-out the PRO compliance questionnaire daily from Week 1 Day 1 visit to end of treatment visit.

Table 4-3 shows the defined week periods for this two PRO questionnaire.

All daily assessments within a week period will be used in analysis by week.

Table 4-3 Week periods for compliance diaries

Week Period	Week Period Definition
Week 1 period	Study Day 1 – 7
Week 2 period	Study Days 8 – 14
Week 3 period	Study Days 15 – 21
Week y period (with y=4, 5, 6,…)	Study Days (y-1)*7+1 to y*7
Etc.	

Study Day 1 = first day of study treatment

4.1.4 Ocular data

Ocular data will be collected at screening visit, at patient visit 11 and at end of treatment visit during the core phase and annually during the extension phase.

Table 4-4 shows the defined time windows.

Table 4-4 Time windows for ocular data

Time Window	Planned Visit Timing	Time Window Definition
On treatment		
Baseline	On or before Study Day 1*	≤ Study Day 1
Week 25	Study Day 169	Study Days 140 – 197
EOT_Core	NA	Data collected at the EOT visit; if no data were collected at the EOT visit the last post-baseline available data obtained before EOT will be used

*Study Day 1 = first day of study treatment

4.2 Month/year derivation

For all derivations, a year will be defined as 365.25 days and a month will be calculated as (365.25 / 12) = 30.4375 days. If duration is to be reported in months, duration in days will be divided by 30.4375.

4.3 Body mass index

Body mass index, in $kg/m^{2,}$ is a measure of relative weight based on an individual's mass and height.

It is calculated using the following formula, where weight is in kilograms and height is in meter:

$BMI = Weight / Height^2$

Baseline BMI will be determined using the last available height and weight prior to start of study drug.

4.4 Other baseline characteristics

Table 4-4 Medical history terms for other baseline characteristics

Disease	Terms (PT)
Splenectomy	SPLENECTOMY
Hepatic B	HEPATITIS B
	HEPATITIS B CORE ANTIGEN POSITIVE
	HEPATITIS B SURFACE ANTIGEN POSITIVE
	HEPATITIS B VIRUS TEST POSITIVE
	HEPATITIS B E ANTIGEN POSITIVE
	HEPATITIS B ANTIGEN POSITIVE

Disease	Terms (PT)
Hepatic C	HEPATITIS C
	HEPATITIS C ANTIBODY POSITIVE
	HEPATITIS C RNA POSITIVE
	HEPATITIS C VIRUS TEST POSITIVE

4.5 Stratification

In this study, two randomization lists have been developed:

- Patients enrolled in the initial protocol will be randomized using a central stratified block randomization with the following stratification factor: age group (2 to <10 years versus 10 to <18 years).
- Patients enrolled after protocol amendment 1 will be randomized using a central stratified block randomization with the following stratification factors: age group (2 to <10 years versus 10 to <18 years) and prior ICT (Yes versus No).

Therefore, the FAS-1, considering only ICT naïve patients as per IRT, will include patients randomized in the following strata: 2 years to <10 years (stratification id=1), 2 to < 10 years + PICT No (stratification id=4) and 10 to < 18 years (stratification id=2) 10 to < 18 years + PICT No (stratification id=6).

4.6 Efficacy evaluations

4.6.1 Primary endpoint

An ANCOVA will be used for comparison between both treatment groups. PROC GLM procedure in SAS will be used for the primary analysis.

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

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

Multiple imputation technique will be used for sensitivity analysis for the primary analysis for serum ferritin if more than 10% of the patients have no serum ferritin value after 24 weeks of treatment. PROC MI procedure in SAS will be used for this analysis.

4.6.2 Pharmacokinetics endpoint

4.6.2.1 Elapsed time

For pre-dose the elapsed time is calculated as the difference between the PK sampling time and the dosing time on the day prior to the PK draw.

For post-dose, the elapsed time is calculated as the difference between the dosing time on the day of the PK draw and the PK sampling time.

4.6.2.2 Model-based analyses

A linear mixed model will be used to evaluate pre-dose PK data to support the assessment of compliance and to characterize exposure-efficacy and exposure-safety relationships as described in Section 2.9.3.4. PROC MIXED procedure in SAS will be used for this analysis. Further statistical details of those analyses will be described in Appendix 16.1.9.

A logistic regression model will evaluate the potential effect of PK pre and post-dose concentration on odds of having renal safety events as described in Section 2.9.3.4. PROC GENMOD procedure in SAS will be used for this analysis. Further statistical details of those analyses will be described in Appendix 16.1.9.

4.6.3 Calculation of predictive probability of success for serum ferritin change from baseline

The predictive probability of observing a significant treatment effect at the end of study will be calculated and provided as supportive information at the time of the interim analysis.

We will use the following notations:

- PoS is the probability of success
- μ denotes the true (unknown) mean difference between the treatment arms in serum ferritin change from baseline at week 25, respectively
- $Y_{Primary}$ is the mean difference between treatment arms in serum ferritin change from baseline at week 25 at the primary analysis,
- $\hat{Y}_{interim}$ is the observed mean difference between treatment arms in serum ferritin change from baseline at week 25 at the interim analysis,
- Y_c the critical value for the primary analysis
- σ is the "outcome standard deviation" of the observed mean difference
- Φ is the cumulative distribution function of the standard normal distribution
- n1, n2 and n are the number of patients at the interim analysis, between the interim and the primary analysis, and the total number of patients, respectively.

Assuming a normal likelihood, i.e.

$$Y_{Primary} \sim N\ (\mu, \frac{\sigma^2}{n})$$

and a non-informative (improper) prior for μ

$$\mu \propto 1$$

This implies:

$$\mu \mid \hat{Y}_{interim} \sim N\left(\hat{Y}_{interim}, \frac{\sigma^2}{\sqrt{n1}}\right)$$

$$Y_{Primary} \mid \hat{Y}_{interim} \sim N\left(\hat{Y}_{interim}, \sqrt{\frac{n2\sigma^2}{n1(n1+n2)}}\right)$$

$$\text{PoS} = P\left(Y_{Primary} > Y_c \mid \hat{Y}_{interim}\right)$$

$$= P\left(\sqrt{\frac{n1(n1+n2)}{n2\sigma^2}}\left(Y_{Primary} - \hat{Y}_{interim}\right) > \sqrt{\frac{n1(n1+n2)}{n2\sigma^2}}\left(Y_c - \hat{Y}_{interim}\right)\right)$$

$$= 1 - \Phi\left(\sqrt{\frac{n1(n1+n2)}{n2\sigma^2}}\left(Y_c - \hat{Y}_{interim}\right)\right)$$

For the actual calculation, $\hat{Y}_{interim}$ and σ will be obtained from an ANCOVA adjusted for the stratification factor age. Specifically, $\hat{Y}_{interim}$ is the corresponding point estimate from the ANCOVA and $\sigma = \sqrt{n1}se(\hat{Y}_{interim})$, where $se(\hat{Y}_{interim})$ is the standard error from the ANCOVA.

4.7 Safety evaluations

The text below gives more detailed instructions and rules needed for programming of the safety analyses described in Section 2.

4.7.1 Multiple assessments within post-baseline visits

For all analyses regarding abnormal assessments or analyses based on worst post-baseline value (e.g. laboratory, ECGs, vital signs), all post-baseline values will be included (scheduled, unscheduled, repeat). All unscheduled and repeat measurements will be included in listings.

4.7.2 Baseline

As defined in Section 2.7, for safety evaluations, the last available assessment before or on the date of start of study drug is defined as ‘baseline’ value or ‘baseline’ assessment. Recalculated creatinine clearance

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
k = 0.55 for girls ≥ 13 years based on current age
k = 0.70 for boys ≥ 13 years based on current age

4.8 Handling of missing or partial dates

A date is considered as missing when no information at all is available, i.e. the day, the month and the year are missing.

A partial (or incomplete) date is a date for which part of date information is missing, i.e. either the day or the day and month are not available. Partial dates, if left partial, would possibly mean an event cannot be placed in time, treatment/dosage at the time of the event is unknown and the event cannot be reported/summarized appropriately – if at all. Therefore it is important to perform date imputation for selected dates to ensure that as many data events are represented as correctly as possible.

Date imputation is the creation of a new, complete date from the partial information available according to an agreed and acceptable algorithm.

4.8.1 AE date imputation

Missing and partial date for AE will be handled according to rules specified below.

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

- Completely Missing AE start dates
- AE start dates missing the year.
- Partial/missing AE end dates

For partial AE start date, the date imputation will be based on the temporal relation between the partial date and start of treatment date.

Table 4-5 provides examples of the different considered imputations for AE start date.

The full description will be provided in the PDS.

Table 4-5 AE start date imputation example scenarios

Partial AE start date	Treatment start date	Temporal relationship compared to treatment start	Imputed Date
12mmyyyy	20OCT2001	Uncertain	<blank>
ddmmm2000	20OCT2001	Before	01JUL2000
ddmmm2002	20OCT2001	After	01JAN2002
ddmmm2001	20OCT2001	Uncertain	21OCT2001
ddSEP2001	20OCT2001	Before	15SEP2001
ddOCT2001	20OCT2001	Uncertain	21OCT2001
ddNOV2001	20OCT2001	After	01NOV2001

4.8.2 Concomitant medication date imputation

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

4.8.3 Incomplete date of diagnosis of main underlying disease

Incomplete dates for date of diagnosis of main underlying disease will be imputed with the earliest possible date, provided that at least the year of diagnosis is known and that imputed diagnosis date occurred before screening visit 1.

4.8.4 Incomplete date for last iron chelation therapy

Stop date:

Imputed date = min (randomization date-1, last day of the month), if day is missing;

Imputed date = min (randomization date-1, 31DEC), if month and day are missing.

4.8.5 Incomplete date of last dose of study drug

The following rule should be used for the imputation of date of last administration:

Scenario 1: If the date of last administration is completely missing and there is no EOT eCRF page, the patient is considered as on-going. The patient should be treated as on-going and the cut-off date should be used as the last dosing date.

Scenario 2: If the date of last administration is completely or partially missing and the EOT eCRF page is available (prior to any death date or withdrawal of consent date, if available):

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

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

Use Dec31yyyy

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

Use EOT date

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

- mm < the month of EOT visit:

  Use last day of the Month (mm)

- mm = the month of EOT visit:

  Use EOT day.

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

Use the start date of that record.

Patients with missing start dates are to be considered missing for all study treatment component related calculations and no imputation will be made. If the date of first administration is missing, then the date of last administration should not be imputed.

There will be no attempt to impute any other date from eCRF DAR page.

5 References

Food and Drug Administration. Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims Establishment and Operation of Clinical Trial Data Monitoring Committees. December 2009.

International Conference on Harmonization. E9: Statistical Principles for Clinical Trials.

Schwartz GJ, Brion LP, Spitzer A (1987) The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents. Pediatr Clin North Am; 34(3):571-90.

Tanner JM. Growth at adolescence. Oxford: Blackwell Scientific Publications, 1962.

NOVARTIS

Clinical Development

ICL670/deferasirox

Study Number: CICL670F2202 / NCT02435212

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

Statistical Analysis Plan (SAP) – End of Core Phase
Detailed Statistical Methodology

Authors:	[redacted] Statistician; [redacted] Statistician

Document type:	RAP Documentation
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Document History – Changes compared to previous version of SAP.

Version	Date	Changes
1.0	23 June 2021	Initial version (based on the SAP Amendment 3 (dated 26Mar2018))

Table of contents

List of tables

List of figures

List of abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATC	Anatomical Therapeutic Classification
AUC	Area under concentration-time curve
BMI	Body mass index
BP	Blood Pressure
CA	Compartmental Analyses
CI	Confidence Interval
CrCl	Creatinine Clearance
CRF	Case Report/Record Form
CSR	Clinical Study Report
CV	Coefficient of Variation
DAR	Dosage Administration Record
DBP	Diastolic Blood Pressure
DRL	Drug Reference Listing
DT	Dispersible Tablet
EoC	End of Core Phase
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
PRO/ObsRO	Patient Reported Outcomes/Observer Reported Outcomes
EOT	End of Treatment
FAS	Full Analysis Set
FCT	Film Coated Tablet
FU	Follow Up
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
HLT	High Level Terms
IA	Interim Analysis
ICT	Iron Chelation Therapy
IRT	Interactive Response Technology
ITT	Intention To Treat
Kg	Kilogram
LLOQ	Lower Limit of Quantitation
MDRD	Modification of Diet in Renal Disease
MDS	Myelodysplastic syndrome

MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable
NCA	Non-Compartmental Analyses
NEU	Neutrophils
NMQ	Novartis MedDRA Queries
PAS	Pharmacokinetic Analysis Set
PDS	Programming Datasets Specifications
PK	Pharmacokinetic
PPS	Per-Protocol Set
PT	Preferred Terms
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SCIT	Satisfaction with Iron Chelation Therapy
SI	International System
SMQ	Standardized MedDRA Queries
SOC	System Organ Classes
SCr	Serum Creatinine
TBL	Total Bilirubin
TEAE	Treatment Emergent Adverse Event
TFL	Tables Figures Listings
ULN	Upper Limit of Normal
UNK	Unknown
WBC	White Blood Cell
WHO	World Health Organization

1 Introduction

This document details the planned statistical analysis for data collected during the core and extension phases in the study CICL670F2202. The SAP from the primary analysis (CSR SAP Amendment 3, dated 26Mar2018) will be used as a reference for this SAP. The CSR SAP is located at the following CREDI location:

[redacted]

Clinical Study Report (CSR) deliverables (tables, figures, listings - TFLs) and further programming specifications are described in separate documents namely TFL Shells and Programming Datasets Specifications (PDS), respectively. An interim and the primary analysis were performed in the study. The data cut-off date for the interim analysis was 16-Nov-2017 and included all randomized ICT naïve patients who had completed a minimum of 12 weeks of treatment exposure or discontinued from the treatment core phase by the cut-off date. The primary analysis was performed when 96 randomized ICT naive patients had completed 24 weeks of treatment or discontinued early (data cut-off date: 31-May-2018). All data collected within the core phase of the study at the time of the primary data cut-off date were reported in the primary analysis CSR.
This analysis plan describes the analyses for an End of Core Phase (EoC) CSR requested by the CHMP that will include the cumulative data from the completed core phase and extension phase with a data cut-off date of 18-Jan-2021. This data cut-off date allows the inclusion of all patients who have completed a minimum of 3 years of treatment or discontinued from treatment in the core or extension phase. Only the analyses based on the core and extension phase described in this analysis plan will be performed for this EoC phase CSR. Analyses that were presented in the primary CSR and for which no additional data was collected after the primary analysis data cut-off date (e.g. baseline demographics) will not be repeated for the EoC phase analysis.

1.1 Study design

Refer to section 1.1 of CSR SAP Amendment 3.

1.2 Objectives

The study objectives as outlined in the protocol version 5, Section 3 are as follows (Table 1-1).

Table 1-1 Objectives and related endpoints

Objective	Endpoint	To be reported in EoC CSR
Primary		

Objective	**Endpoint**	**To be reported in EoC CSR**
• To evaluate both formulations on patient compliance, using stick pack/tablet count over 24 weeks of treatment in ICT naïve patients during core phase • To evaluate the change from baseline in serum ferritin after 24 weeks of treatment for both formulations in ICT naïve patients	• Compliance measured by stick pack/tablet count over 24 weeks of treatment (i.e. assessed at week 25 visit) • Change from baseline in serum ferritin after 24 weeks of treatment (i.e. serum ferritin at week 25 visit)	Primary analysis planned as per protocol was conducted in the primary analysis CSR and the study did not meet its primary objective. Analyses reported in the EoC CSR, will be descriptive and testing of hypothesis will not be performed
Secondary (Core phase)		
To evaluate both formulations on change in serum ferritin and compliance in ICT naive patients, after 48 weeks of treatment	● Compliance measured by stick pack/tablet count after 48 weeks of treatment ● Change from baseline in serum ferritin after 48 weeks of treatment	Yes
To evaluate both formulations on change in serum ferritin after 24 weeks and 48 weeks of treatment in ICT naïve and pre-treated patients	Change from baseline in serum ferritin after 24 weeks (i.e. assessed at week 25 visit) and 48 weeks of treatment	Yes
To evaluate both formulations on patient satisfaction and palatability using Patient / Observer Reported Outcomes (PRO/ObsRO) questionnaires	Domain scores of treatment satisfaction and palatability over time	Yes
To evaluate both formulations on overall safety	Overall safety, as measured by frequency and severity of adverse events (including active monitoring for renal toxicity; including renal failure, hepatic toxicity; including hepatic failure, and gastrointestinal hemorrhage), and changes in laboratory values from baseline (serum creatinine, creatinine clearance, ALT, AST, RBC and WBC). In addition, vital signs, physical, ophthalmological, audiometric, cardiac, and growth and development evaluations will be assessed.	Yes
To evaluate compliance using a daily PRO/ObsRO questionnaire	Rate of dosing instructions deviations (doses missed / not taken at the same time every day)	Yes
To evaluate pre-dose PK data to support the assessment of compliance	Pre-dose deferasirox concentrations in all patients [except Egypt] at weeks 1, 3, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41 and 45 (13 samples)	No
Post-dose data to be analyzed along with pre-dose PK data	Post-dose deferasirox concentrations between 2 and 4 hours post-dose at Weeks 5 and 9 (2 samples)	No
To explore exposure-response relationships for measures of safety and effectiveness	Serum creatinine change from baseline, notable serum creatinine events, serum creatinine clearance change from baseline and notable serum creatinine clearance	No

Objective	Endpoint	To be reported in EoC CSR
	events, urine protein creatinine ratio change from baseline and serum ferritin change from baseline, in relationship to pre- and post-dose deferasirox concentrations.	
Secondary (Optional Extension phase)		
To assess additional safety data about new formulation (granules) in pediatric population	Overall safety, as measured by frequency and severity of adverse events (including active monitoring for renal toxicity; including renal failure, hepatic toxicity; including hepatic failure, and gastrointestinal hemorrhage), and changes in laboratory values from baseline (serum creatinine, creatinine clearance, ALT, AST, RBC and WBC). In addition, vital signs, physical, ophthalmological, audiometric, and growth and development evaluations will be assessed.	Yes

2 Statistical methods

This section describes the analysis for the Core and extension phase data. Refer to the CSR SAP Amendment 3 for additional details.

Section 4 of the SAP provides statistical and programming conventions.

2.1 Data analysis

Data will be analyzed by Novartis Oncology Biostatistics and Statistical Programming personnel according to the data analysis section 10 of the study protocol as detailed in this analysis plan.

SAS® version 9.4 (or later version if available at time of database lock) will be used for all analyses. Data from all patients who signed informed consent will be used in the analysis. 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 per local laws).

All statistical analyses will be performed using all data collected in the database up to the data cutoff date. All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations.

All events with a start date before or on the cut-off date and an end date after the cut-off date will be reported as 'ongoing'. The same rule will be applied to events starting before or on the cut-off date and not having documented end date. This approach applies, in particular, to adverse event and concomitant medication reports. For these events, the end date will not be imputed and therefore will not appear in the listings.

The time periods defined in Table 2-1 will be used to define the core and extension phases for the analysis.

Table 2-1 Definition of core and extension phases

Core phase			Extension phase		
Treatment	Start date	Stop date	Treatment	Start date	Stop date
Granules	Date of first IC signed	Date of last treatment of granules + 30 days	No treatment	Nil	Nil
DT	Date of first IC signed	Date of last treatment of DT + 30 days	No treatment	Nil	Nil
Granules	Date of first IC signed	date of first administration of granules in extension phase*– 1 day	Granules	date of first administration of granules in extension phase*	Date of the last administration of Granules in extension + 30 days
DT	Date of first IC signed	Date of first administration of granules* – 1 day	Granules	Date of first administration of Granules*	Date of the last administration of Granules in extension + 30 days

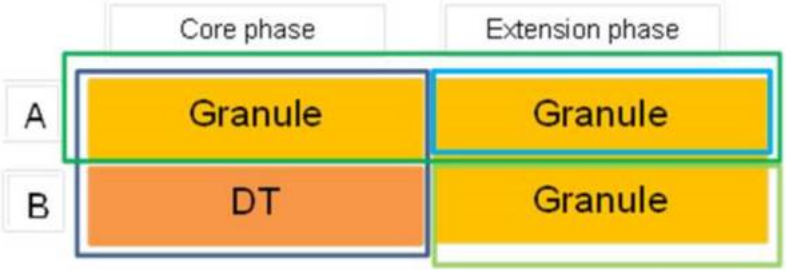
*including 0 doses for patients to identify the extension start date only

Summaries will be based on:

- **Core phase*** - comparing data for Granules versus DT formulations (blue rectangle in Figure 2-1).
- **Extension phase*:** summaries will only display extension phase data from patients randomized to Granules (light blue rectangle in Figure 2-1) side-by-side with patients randomized to DT who switched to Granules in extension phase (light green rectangle in Figure 2-1). Cross-over treatment group corresponds to the patients randomized to DT who switched to Granules in the extension phase.
- **Entire granule period** - patients randomized to Granules combining core and extension phases (dark green rectangle in Figure 2-1) side-by-side with Granules for patients randomized to DT who switched to Granules in extension phase (light green rectangle in Figure 2-1). Cross-over treatment group corresponds to the patients randomized to DT who switched to Granules in the extension phase.

*Note for exception to Table 2-1: For analyses by time point in patients who continue into extension phase, EOT-core assessments done at the beginning of extension phase will be displayed in core phase reports.

Figure 2-1 Core and extension phases



General analysis conventions

Pooling of centers: Unless specified otherwise, data from all study centers will be pooled for the analysis. Due to expected small number of patients enrolled at centers, no center effect will be assessed.

Qualitative/categorical data (e.g., sex, race) will be summarized by frequency counts and percentages. Percentages will be calculated using the number of patients in the relevant treatment arm as the denominator.

Continuous data (e.g., age, body weight) will be summarized using appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum, and maximum) by treatment arm. Lower and upper quartiles will also be presented when applicable.

2.2 Analysis sets

Safety Set

The Safety Set 1 will consist of all ICT naïve patients (as per eCRF) who received at least one dose of the study drug during the core phase.

The Safety Set 2 will consist of all ICT pre-treated patients (as per eCRF) who received at least one dose of study drug during the core phase.

The Safety Set 3 will consist of all patients who received at least one dose of study drug during the core phase.

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

Patients will be analyzed according to the treatment actually received and strata information recorded in the eCRF.

Treatment actually received is defined as the treatment the patient received at the first day of study medication in the core phase.

Full Analysis Set

Full Analysis Set (FAS) is defined according to the Intention to Treat (ITT) principle.

The Full Analysis Set 1 (FAS-1) consists of all ICT naïve (as per IRT, see Section 4.4) randomized patients.

The Full Analysis Set 2 (FAS-2) consists of all ICT pre-treated (as per IRT) randomized patients.

The Full Analysis Set 3 (FAS-3) consists of all randomized patients.

Following the intent-to-treat principle patients are analyzed according to the treatment and stratification factors they were assigned to at randomization during the core phase.

Reporting

Frequency counts and percentages (using FAS-3 or Safety Set 4 as denominator) of patients in each of the above defined analysis sets will be summarized. In addition, listings of patients excluded from each of the analysis sets will be provided.

2.3 Patient demographics and other baseline characteristics

All patient demographic and baseline characteristics summaries were presented by FAS-1, FAS-2 and FAS-3 in the primary analysis CSR and will not be repeated for the EoC CSR.

Enrollment status

The number of patients screened and randomized was summarized respectively by region, country, center and treatment arm on the FAS-3 in the primary CSR analysis and will not be repeated for the EoC CSR.

2.4 Protocol deviations

Frequency counts and percentages of patients with any protocol deviation (selection criteria not met, patient not withdrawn as per protocol, treatment deviation, prohibited concomitant medication, other Good Clinical Practice (GCP) deviation) will be tabulated by the deviation type category and treatment arm on the FAS-3 for the core phase and on the Safety Set 4 for the entire granule period. Patients with COVID-19 related protocol deviations will be presented separately in the table and listing for Safety Set 4 by category and relationship.

The full list of protocol deviations is documented in the Validation And Planning (VAP) Module 3 document. The COVID-related protocol deviations and relationship to pandemic will be identified and maintained in an independent tracker located in the document management system in the "CREDI Studies/ICL670F2202/TMF (Study Level)/Protocol Deviations" folder. The latest available tracker prior to database lock will be used.

All protocol deviations will be listed on the FAS-3 and COVID related protocol deviations on Safety Set 4.

2.5 Patient disposition

Listings will be produced on the FAS-3 with a flag for extension phase data.

The summaries of patient disposition during the core phase by treatment arm on the FAS-1, FAS-2 and FAS-3 will show:

- Number (%) of randomized patients who were not treated;
- Number (%) of randomized patients who were treated;
- Number (%) of patients who completed the core phase;
- Number (%) of patients who discontinued the core phase;
- Number (%) for each reasons for core phase discontinuation;

The summaries of patient disposition during the extension phase by treatment arm on the Safety Set 4 will show in addition:

- Number (%) of patients who entered in the optional extension phase;
- Number (%) of patients who were not treated during the optional extension phase;
- Number (%) of patients who were treated during the optional extension phase;
- Number (%) of patients who are ongoing in the optional extension phase;
- Number (%) of patients who completed the optional extension phase;
- Number (%) of patients who discontinued the optional extension phase;
- Number (%) for each reasons for optional extension phase discontinuation;

2.6 Treatments (study drug exposure, concomitant therapies)

The Safety Set 1, Safety Set 2, Safety Set 3 and Safety Set 4 will separately be used for medication data summaries unless otherwise specified. Listings will be produced by treatment arm on the Safety Set 3 and Safety Set 4.

Study drug and study treatment

The terms study drug and study treatment are equivalent and will refer both to deferasirox DT or deferasirox granule.

Date of first/last administration of study drug

The date of first administration of study drug is derived as the first date when a non-zero actual dose of study drug was administered as recorded on Dosage Administration Record (DAR) Electronic Case Report Form (eCRF). The date of first administration of study drug will also be referred as 'start of study treatment'.

The date of last administration of study drug is defined as the last date when a non-zero actual dose of study drug was administered as recorded on DAR eCRF. This date will also be referred as 'last date of study treatment'.

Study day

The study day **for safety and pharmacokinetics assessments** (e.g. adverse event onset, laboratory abnormality occurrence, vital sign measurement, Electrocardiogram (ECG), PK concentration, etc.) will be calculated using the start date of study treatment as the reference. For assessments occurring

- **on or after the start date of study treatment**, the study day will be calculated as (date of safety assessment) – (start date of study treatment) + 1. Study day 1 will therefore be the first day of study treatment.
- **before the start date of study treatment***,* the study day will be calculated as (date of safety assessment) – (start date of study treatment).

For example, if an adverse event starts 3 days before the start of study treatment the study day displayed on the listing will be negative, i.e. -3.

The study day **for efficacy assessments** (e.g. serum ferritin, PRO) will be calculated using the randomization date as the reference. For assessments occurring

- **on or after randomization date**, the study day will be calculated as (date of non-safety assessment) – (date of randomization) + 1. Then study day 1 will be the day of randomization.
- **before randomization date**, the study day will be calculated as (date of non-safety assessment) – (date of randomization).

The study day will be displayed in the data listings.

Study drug exposure

Definitions of duration of exposure, total patient-years exposure, average daily dose, cumulative total dose as well as percentage of planned dose taken are defined in Table 2-22:

Table 2-2 Deferasirox: Study drug exposure

Overall duration of exposure (day):	[(date of last exposure) – (date of first study treatment) + 1]
Drug exposure on dose X (days)	[(date of last exposure on dose X) – (date of first study treatment on dose X) + 1]
Average dose (planned and actual, in mg/kg/day):	Mean dose over all days between first and last dose, excluding interruptions: sum of all (X dose * corresponding duration of exposure on dose X) / overall number of dosing days
Cumulative dose (planned and actual, in mg/kg):	Sum over daily doses of all days between first and last dose
Total patient-years (years):	Overall duration of exposure (days) / 365.25
Percentage of planned dose taken:	100 × [Cumulative actual dose / Cumulative planned dose]

For the core phase only where patients do not enter the extension phase, date of the first administration and last exposure of study drug refer to the first and last dates respectively when a non-zero actual dose of study drug was administered during the study core phase as defined in Table 2-1.

For patients who switch from DT to granules in the extension phase, date of last exposure of study drug in core phase refers to the day prior to the date of the first administration of granules in extension phase (including a zero actual dose) as defined in Table 2-1.

For patients who switch from DT to granules, the date of the first administration of study drug (granules) refers to the first date of granules in the extension phase (including a zero actual dose) to account for treatment interruptions due to efficacy and safety reasons. The last exposure of the granules refers to the last date when a non-zero actual dose of granules was administered during the study extension phase as defined in Table 2-1.

For patients receiving granules throughout the study, the date of the first administration and last exposure of study drug refer to the first and last dates respectively when a non-zero actual dose of study drug (granules) was administered during the study.

The actual dose in mg/kg/day will be obtained by dividing the actual total daily dose administered in the DAR eCRF page by the last available weight at the time of dose administration reported in the vital signs eCRF page.

Overall duration of exposure, average planned and actual daily dose, cumulative actual dose, total patient-years and percentage of planned dose taken will be summarized by treatment arm for the core phase and for the entire granule period.

The following variables will also be summarized by treatment arm and for each phase as appropriate as:

- Duration of exposure will be categorized in the core phase as: <4 weeks, 4 to <12 weeks, 12-<20 weeks 20-<28 weeks, 28-<36 weeks, 36-<44 weeks, ≥44 weeks; and in the entire granule period as: <6 months, 6-<12 months, 12-<24 months, 24-<36 months, 36-<48 months, ≥48 months).
- Deferasirox DT average dose will be categorized as: <15, 15 to <25, 25 to <35 and ≥35 mg/kg/day
- Deferasirox granule average dose will be categorized as: <10.5, 10.5 to <17.5, 17.5 to <24.5 and ≥24.5 mg/kg/day

In addition, the number of patients who have dose reduction, increase or dose interruption, with corresponding reasons and the average length of dose interruptions will be summarized.

Dose reduction will be considered if the actual dose is not equal to 0 (or not counted as interruption) and [the planned dose level is lower than the previous non-missing planned dose level Or the dose change is equal to 'yes' and the actual total daily dose administered (mg) is lower (> 15%) than the calculated dose amount based on the planned dose (mg)]. Any dose change to correct a dosing error will not be considered a dose reduction (patient goes back to the previous planned/actual dose after a dose change due to dosing error). Number of reductions will be derived programmatically. The first dose in the extension phase for patient's switching from DT to granules will not be considered as reduction as per protocol section 14.1 (Equivalent dose guidance).

Dose increase will be considered if the actual dose is not equal to 0 (or not counted as interruption) and [the planned dose level is higher than the previous non-missing planned dose level Or the dose change is equal to 'yes' and the actual total daily dose administered (mg) is higher (> 15%) than the calculated dose amount based on the planned dose (mg)]. Note that a dose rechallenge i.e when a patient goes back to the previous planned dose after an interruption or a dose reduction is not considered as an increase.

Dose interruption will be considered if an actual dose of zero in a unit of time between two non-zero actual dosing records. For the purpose of summarizing interruptions and reasons, in case multiple entries for interruption that are entered on consecutive days with different reasons will be counted as separate interruptions. However, if the reason is the same in this mentioned multiple entries on consecutive days, then it will be counted as one interruption.

For each patient, listings of each dose of the study drug administered along with dose change reasons will be produced.

Concomitant therapy

Prior and concomitant therapies are defined as any medication, and significant non-drug therapies administered to a subject preceding or coinciding with the study assessment period.

Medications will be coded using the World Health Organization (WHO) Drug Reference Listing (WHO DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (WHO ATC) classification system.

Concomitant therapies will include medications and significant non-drug therapies taken between the first day of study medication and up to 30 days after the last day of study medication (see section 2.9.6 for the on-treatment period definitions).

Concomitant therapies will be summarized by ATC class, preferred term and treatment arm for the Safety Set 3 and Safety Set 4. Medications starting prior to the start of study treatment and continuing after the start of study treatment will be included in this summary for the core phase and entire granule period as defined in Table 2-1.

Prior therapies will include medications or significant non-drug therapies starting and ending prior to the start of study treatment. Prior therapies were summarized in the primary CSR analysis and will not be repeated for the EoC CSR.

All prior and concomitant therapies will be listed.

2.7 Baseline

Baseline is considered as the result of an investigation describing the 'true' uninfluenced state of the patient.

For **efficacy evaluations**, (e.g. serum ferritin), the last available (i.e. non-missing) assessment before or on the date of randomization is taken as 'baseline' value or 'baseline' assessment.

For **safety evaluations** (e.g. laboratory, vital signs, etc.) the last available (i.e. non-missing) assessment before or on the date of start of study treatment is taken as 'baseline' value or 'baseline' assessment.

If patients have no value as defined above, the baseline result will be missing. Unscheduled assessments will be considered in the determination of baseline for both safety and efficacy evaluations.

For safety assessments, if an assessment is planned to be performed prior to the first dose of study drug in the protocol and the assessment is performed on the same day as the first administration of study drug, it will be assumed that it was performed prior to study drug administration, if assessment time point is not collected or is missing.

Patients who start treatment and discontinue from the study on the same day may have 2 different sets of data collected on study Day 1, one being reported to the week 1 visit, the other reported to the End Of Treatment (EOT) visit. Data reported at the EOT visit are not eligible for baseline selection.

For analyses of the extension phase or entire granule period requiring comparison to baseline value (e.g. lab shift tables) the baseline is defined as follows. For patients randomized to DT formulation who switched to granule formulation in the extension phase, the date of the last assessment prior or equal to the start date of granules in the extension phase will be defined as pre-granule value which will be reference value for changes in the extension time. For patients randomized to granules continuing in extension phase the initial baseline value at study start will be taken.

2.8 Analysis of the primary variables

The primary objectives of this study are to evaluate patient compliance with study treatment, as measured by the count of deferasirox granule stick packs/dispersible tablets and to evaluate the change in serum ferritin after 24 weeks of treatment for both formulations of deferasirox in pediatric ICT naive patients with iron overload during core phase. Cumulative data up to week 24 from all ICT naive patients will be analyzed in the EoC CSR and reported descriptively.

2.8.1 Variable

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

The co-primary efficacy variables are:

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

  The prescribed count corresponds to the count prescribed by the investigator for the relevant visit 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 granule), the prescribed count for the relevant visit period is calculated from the daily prescribed count at the beginning of this period multiply by the duration (days) of this period. The duration of a period will be calculated as (end date of the period) – (start date of the period). The total count prescribed is the sum of counts prescribed per strength. The end date of the period is defined as the date of next assessment.
- Change from baseline in serum ferritin after 24 weeks of treatment (i.e. assessed at week 25 visit).

2.8.2 Statistical hypothesis, model, and method of analysis

For the EoC CSR, there will be no formal testing of hypotheses.

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

2.8.3 Handling of missing values/discontinuations

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

No imputation will be performed for the compliance endpoint calculation. However, patient who discontinued before the week 25 visit will be included in the compliance endpoint calculation.

2.8.4 Supportive analyses

The supportive analyses for the primary endpoint were presented in the primary CSR and will not be repeated for the EoC CSR.

2.9 Analysis of secondary variables

Secondary variables include compliance after 48 weeks of treatment, changes in SF from baseline after 24 weeks in ICT pre-treated patients and after 48 weeks of treatment in ICT-naive and pre-treated patients, patient reported outcomes/observer reported outcomes and safety assessments (i.e. adverse events, laboratory parameters, vital signs, etc.). All secondary variables will be analyzed by treatment group.

2.9.1 Compliance after 48 weeks of treatment during core phase

Summary statistics of overall compliance measured by stick pack/tablet count assessed at week 48 visit and 95% confidence intervals for means will be provided for FAS-1, FAS-2 and FAS-3. Patient who discontinued before the week 48 visit (end of core phase) will be included in the compliance endpoint calculation. End-of-core visit for patients who continue into extension phase will be calculated based on their last visit before the initiation of treatment of extension phase.

2.9.2 Changes from baseline in serum ferritin after 24 weeks of treatment during core phase

Summary of absolute and relative change from baseline values in serum ferritin assessed at week 24 (week 25 visit) and 95% confidence intervals for means (see Table 4-2 for time window definition) will be provided by FAS-2 and FAS-3.

2.9.3 Changes from baseline in serum ferritin after 48 weeks of treatment during core phase

Summary of absolute and relative change from baseline values in serum ferritin assessed at week 48 visit and 95% confidence intervals for means (see Table 4-2 for time window definition) will be provided for FAS-1, FAS-2 and FAS-3.

Furthermore, a graphical presentation of mean and standard deviation of absolute value in serum ferritin will be plotted by treatment arm and time-window (see Table 4-2 for time-window definition) for FAS-1, FAS-2 and FAS-3.

2.9.4 Other analyses of change from baseline in serum ferritin

Relative and absolute change from baseline in serum ferritin at every year visit during the entire granule period will be described for the Safety Set 4.

2.9.5 Patient reported outcomes/Observer reported outcomes

Patient satisfaction, palatability and compliance with study drug will be evaluated for both treatment groups using Patient Reported Outcomes/Observer Reported Outcomes (PRO/ObsRO). For patients aged between 10 years and less than 18 years at enrollment, the PRO questionnaires will be completed by the patients themselves. The questionnaires for patients aged between 2 years and less than 10 years have been designed as observations made by caregivers such as the parent or legal guardian (ObsRO). For these patients the caregivers will continue completing the ObsRO questionnaires even after the patient turns 10 years for consistency in responses.

Three PRO/ObsRO questionnaires have been developed: the modified SICT questionnaire, a palatability questionnaire and a compliance diary. Patients/caregiver will complete all PRO/ObsRO questions via a handheld electronic device (exceptionally paper could be used in specific situation). The diaries will be completed daily at home and the palatability and modified SICT will be completed at pre-determined site visits.

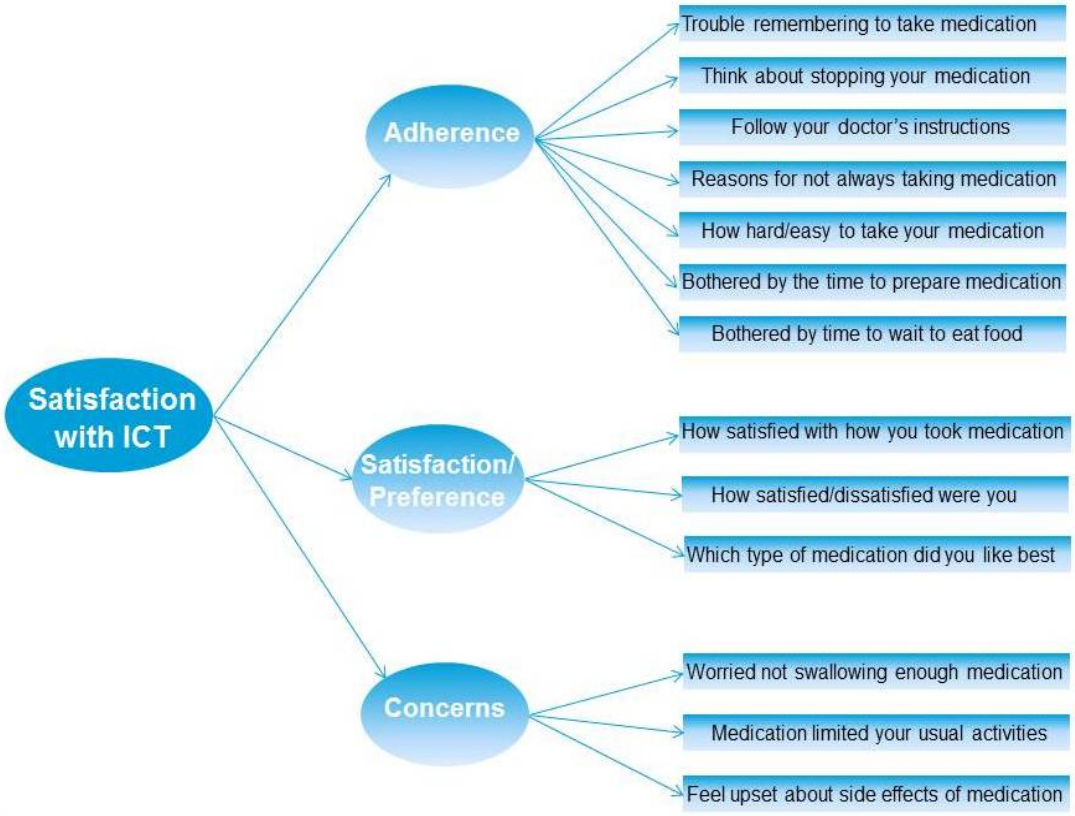
The three questionnaires were developed using patient input in one on one interview. The FAS-1, FAS-2 and FAS-3 will be used for the three PRO/ObsRO questionnaires analysis for the core phase, unless otherwise specified.

2.9.5.1 Modified SICT questionnaire

Patient reported outcomes

The Modified SICT questionnaire consists of 13 items that represent 3 domains; Adherence, Preference and Concerns (see Figure 2-2).

Figure 2-2 Conceptual model for the Modified Satisfaction with Iron Chelation Therapy questionnaire



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

Items 4 and 5 use the response format 1 "Never"", 2 "Rarely" 3 "Sometimes" 4 " Most of the time" and 5 "Always"; item 6 uses the response format 1 "Always", 2 "Most of the time" 3 "Sometimes" 4 "Rarely" and 5 "Never;; Item 8 uses the response format 1 "Very easy", 2 "Easy", 3"Neither easy or hard", 4 "Hard" and 5 "Very hard"; Items 9 and 10 use the response format 5 "Very bothered", 4"Bothered" 3"Moderately bothered", 2 "A little bothered" and 1 "Not bothered at all". An Adherence domain score will be calculated by summing these 6 items and as a result a higher score will indicate worse adherence.

Item 7 captures the reasons that the patient did not always take their medication as instructed and is only asked of patients who, at Item 6, indicated that they did not "Always" take their medication as instructed. These patients are instructed to choose all reasons that apply (Figure 2-3). Each response category will be coded as binary item, for example taste will be an item with the response format 0 "Not endorsed" 1 "Endorsed".

Figure 2-3 Conceptual model for Item 7 of the modified SICT

Satisfaction/preference domain consists of 3 items, 2 (Items 11 and 12) assess the patients' satisfaction with the medication and are measured using a 5 point response scale with the response format 1 "Very satisfied", 2"Satisfied", 3 "Neither satisfied nor dissatisfied", 4"Dissatisfied" 5"Very dissatisfied". A Satisfaction domain score will be calculated by summing these two items. Higher scores will indicate worse satisfaction.

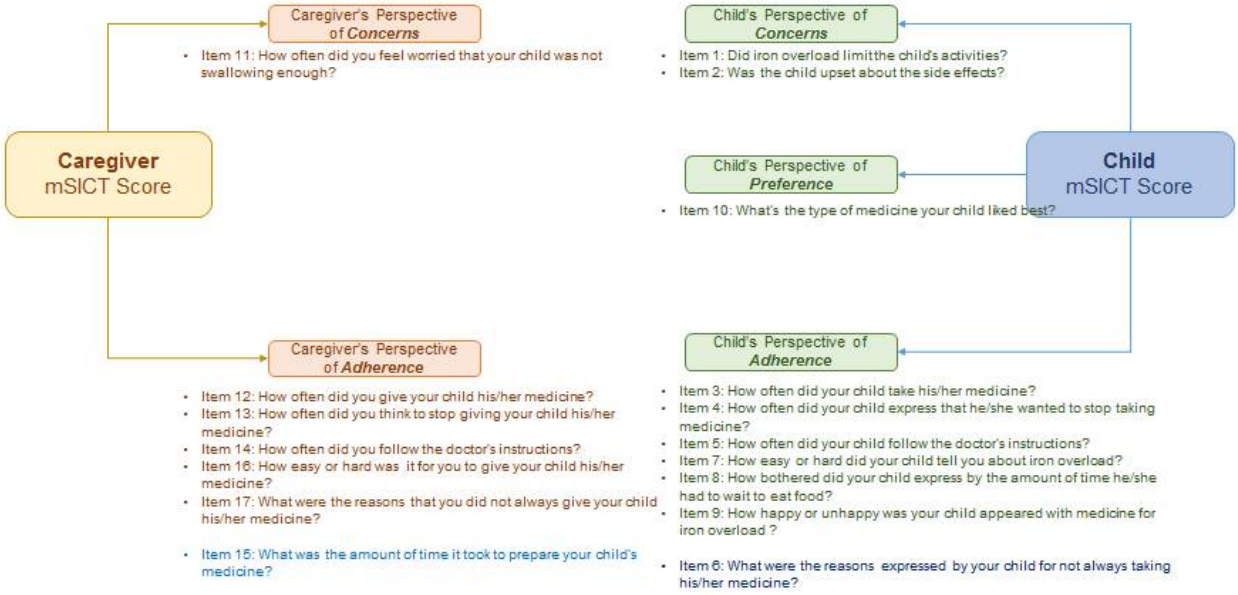
The third item (Item 13) asks the patient to assess which medication for iron overload they prefer.

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

Observer reported outcomes

The modified SICT consists of 17 items that represent 3 domains: Adherence, Preference, and Concerns (see Figure 2-4).

Figure 2-4 Conceptual Model for the Modified Satisfaction with Iron Chelation Therapy Questionnaire



The conceptual framework consists of 2 separate scales to capture the child's and caregiver's perspective; these are further broken into 3 domains for the child: Concerns, Preference, and Adherence and 2 domains for the caregiver: Concerns and 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)

There will be 2 separate domain scores for overall adherence, the caregiver's perspective of adherence domain consists of 6 items (Items 12, 13, 14, 16 and 17), while the child's perspective of adherence domain consists of 7 items (Items 3, 4, 5, 7, 8 and 9).

Child's perspective of Adherence: Items 3 and 5 are measured using a 5-point response scale: "Always" =1, "Most of the time" =2, "Sometimes" =3, "Rarely" =4, and "Never" =5. Item 4 is measured on a scale from "Always" =5, "Most of the time" =4, "Sometimes" =3, "Rarely" =2, and "Never" =1. 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, "Easy" =2, "Neither easy or hard" =3, "Hard" =4, and "Very hard" =5. 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 is "Very bothered" =5, "Bothered" =4, "Moderately bothered" =3, "A little bothered" =2, and "Not bothered at all" =1. Item 9 reports "how happy your child appeared" and is scored on a scale from 1=Very happy and 5=Very unhappy.

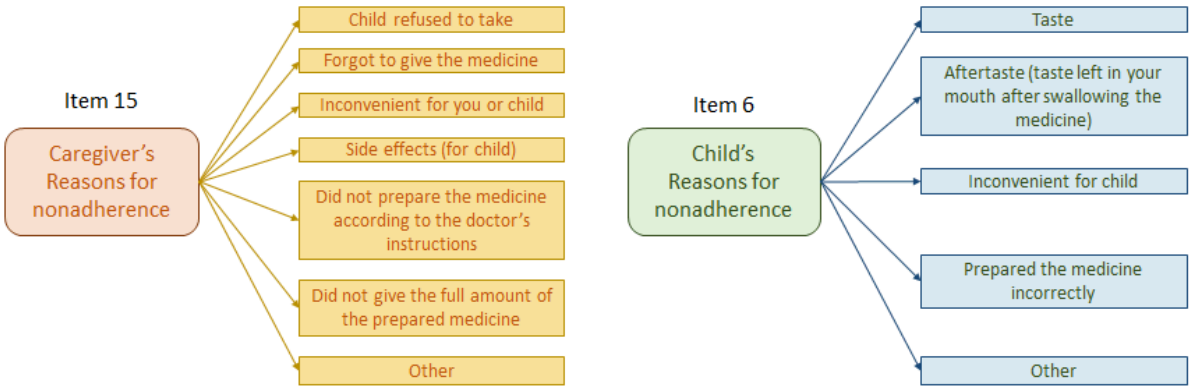
Caregiver's perspective of Adherence: Items 12 and 14 are measured using a 5-point response scale: "Always" =1, "Most of the time" =2, "Sometimes" =3, "Rarely" =4, and "Never" =5. Conversely, Item 13 is scored as "Always" =5, "Most of the time" =4, "Sometimes" =3, "Rarely" =2, and "Never" =1. Two items (Item 16 and 17) use different response options. Item 16 focuses on "How easy/hard was it to give your child his/her medicine" and uses the response scale

"Very easy" =1, "Easy" =2, "Neither easy or hard" =3, "Hard" =4, and "Very hard" =5. Similarly, Item 17 captures "bothered by the amount of time it took to prepare medication" and uses the response scale "Very bothered" =5, "Bothered" =4, "Moderately bothered" =3, "A little bothered" =2, and "Not bothered at all" =1.

Separate adherence domain score 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.

The checklist item from each perspective will evaluate the reason for non-adherence. Only respondents who, at Item 5 (for the child's perspective) and Item 14 (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 perspectives the respondent can check all the reasons that apply (Figure 2-5). For the child's perspective (item 6), each of the 5 response options (i.e. taste, aftertaste, inconvenience, prepared medicine incorrectly, and other) will be coded as binary item, for example taste will be an item with the response format 0 "Not endorsed" 1 "Endorsed". Similarly, for the caregiver perspective (item 15), each of the 7 response options (i.e. child refuse to take, forgot, inconvenient, side-effect, not prepare medication per doctor's instruction, did not give full amount, and others) will be coded as binary item (0/1).

Figure 2-5 Conceptual model for item 6 and item 15 of the modified SICT



Preference of the Child: This domain consists of 1 item (Item 10), to assess which medication they prefer (like). The item is to be considered a single item domain.

Concerns domain will be captured from 2 perspectives:

- Child's perspective (Item 1 and 2)
- Caregiver's perspective (Item 11)

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, "Most of the time" =2, "Sometimes" =3, "Rarely" =4, and "Never" =5. A sum score for a Concerns domain for the child's perspective will be created. A higher score will indicate lesser concerns.

There is only a single item to capture concern in regards to caregiver's perspective. The item 11 captures "worry if the child is swallowing enough medication" and is scored on a 5-point response scale from "Always" =1, "Most of the time" =2, "Sometimes" =3, "Rarely" =4, and "Never" =5. A higher score on the single item domain will indicate lesser caregiver concern.

Adherence, satisfaction/preference and concerns domain scores will be summarized using standard descriptive statistics by treatment arm, type of questionnaire (ObsRO questionnaire versus PRO questionnaire) and week (weeks 2, 3, 25 and core EOT). Additionally, absolute change from week 2 to week 25 and core EOT in the domain scores will be summarized including 95% confidence intervals for mean.

Graphical representation of PRO scores over weeks will be provided by domain by type of questionnaire and treatment. The y-axis will be the mean and SD for the domain score and the x-axis will be the week number.

In addition, all items from adherence, satisfaction/preference and concerns domains will be summarized by treatment arm by type of questionnaire and week using frequency counts and percentages for the FAS-3.

The number of patients completing the modified SICT questionnaire and the number of missing or incomplete assessments will be summarized by treatment arm, type of questionnaire and week for the FAS-3.

2.9.5.2 Palatability questionnaire

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 1 "Very good", 2 "Good", 3 "Not good or bad" for PRO/ 3 "Neither good nor bad" for ObsRO, 4 "Bad' and 5 "Very bad". The PRO aftertaste item offers an additional response option of "no aftertaste". This response option will be recoded such that all patients have a response, for example, patients who choose this option will be coded 0 and patients who rated the aftertaste will be coded 1. This will result in binary (yes/no) aftertaste item.

Note for ObsRO: Item 1 the response format for 3 refers to "Neither good nor bad" and for Item 3 the response format 1 refers to "Swallowed and retained ALL of the medicine". Same scoring rule will be used for both ObsRO and PRO.

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

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

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

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

The Table 2-3 presents the Items 1, 3 and 4 scoring matrix leading to the palatability summary score:

Table 2-3 Scoring Matrix

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

The palatability summary score will be summarized using descriptive statistics by treatment arm, type of questionnaire (ObsRO questionnaire versus PRO questionnaire) and week (weeks 2, 3, 25 and core EOT). Additionally, absolute change from week 2 to week 25 and core EOT will be summarized including 95% confidence intervals for mean.

Graphical representation of this 11 point response scale will be provided over weeks by treatment and type of questionnaire. The y-axis will be the mean and SD and the x-axis will be the week number.

In addition, all of the 4 Items from the palatability questionnaire will be summarized using descriptive statistics by treatment arm, type of questionnaire and week using frequency counts and percentages for the FAS-3.

The number of patient completing the palatability questionnaire and the number of missing assessments will be summarized by treatment arm, type of questionnaire and week for the FAS-3.

2.9.5.3 Compliance diary

The Compliance questionnaire consists of 2 items. Item 1 assessed whether the medication was taken (yes/no) and Item 2 is a record of the time when the medication was taken with a not applicable option for patients who did not take their ICT.

The daily compliance questionnaire diary records will also be used to calculate the rate of dose violations. For a given day, a dose violation is defined as a dose that is either missed completely or not taken in accordance with the timing instruction (no later than 12:00 pm). The dose violation rate is calculated as:

[Number of dose violations / Drug exposure (days)] *100

Weekly average of dose violation rate will be calculated and summarized using descriptive statistics by treatment arm, type of questionnaire (ObsRO questionnaire versus PRO questionnaire) and week (weeks 1, 13, 25, 37 and core EOT). Additionally, absolute change from week 1 will be tabulated including 95% confidence intervals for mean. A graphical representation will be provided over all week periods by treatment arm and type of questionnaire. The y-axis will be the mean and SD and the x-axis will be the corresponding week period (see Table 4-3 for week periods definition).

Due to the use of ePRO there will be no individual items missing. The weekly average rates will be calculated when there are at least four non missing daily responses. For a given week the denominator will be the number of non-missing days. No additional imputation will be carried out.

The number of patients completing the compliance diary and the number of expected and missing days will be summarized by each treatment arm and type of questionnaire for the FAS-3.

2.9.6 Safety evaluations

Unless otherwise specified, the following analyses will be performed separately for the Safety Set 1, Safety Set 2, Safety Set 3 for the core phase and the Safety Set-4 for the entire granule period. Listings will be provided for the Safety Set 3 and the Safety Set-4.

On-treatment period

For the core phase, the overall observation period will be divided into three mutually exclusive segments taking into account stop rules as per Table 2-1:

- Pre-treatment period: from day of patient's first informed consent to the day before first dose of study drug;
- On-treatment period: from day of first dose of study drug to 30 days after last dose of study drug *for patients who do not enter the extension phase*; from day of first dose of study drug in the core phase to one day prior to the start of the first dose of study drug in the extension phase *for patients who enter the extension phase*.

- Post-treatment period: starting at day 30+1 after last dose of study treatment.

For the entire granule period, the following conventions will be taken into account while deriving the three observation periods above:

- For patients enrolled in DT formulation in the core phase, the pre-treatment period will not be derived;
- For patients enrolled in Granule formulation in the core phase, the first dose of study drug will be the day of first dose in the core phase.

Unless otherwise specified, the safety summary tables will include only assessments from the on-treatment period.

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.

Any COVID-19 related safety events will be flagged in listings.

Adverse events

AEs will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) available prior to clinical database lock.

Any information collected (e.g. relatedness to study drug, action taken etc.) will be listed.

The following adverse event summaries will be produced by treatment arm:

- Adverse events (overall and severe), regardless of study drug relationship by primary system organ class and preferred term
- 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
- Serious adverse events (overall and severe), with suspected 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
- Deaths (all and on-treatment) by primary system organ class and preferred term (Safety Set 3 and 4 only).

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, severity and relation to study drug by treatment arm. A patient with multiple occurrences of an AE will be counted only once in the AE category.

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

All AEs will be listed. Any information collected (e.g. regardless to study drug, action taken etc.) will be listed as well as the duration of the AE. The listings of all deaths, serious adverse events, adverse events leading to study drug discontinuation, and adverse events requiring dose adjustment or interruption will also be provided.

Adverse events of special interest

Specific groupings of AESI will be considered and the number of patients with at least one event in each grouping will be reported. Note that certain adverse events 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. All AESI definitions or AE groupings are specified in the electronic Case Retrieval Strategy (eCRS). The latest version of the eCRS available at the time of the analysis will be used.

AESI will be summarized by grouping, preferred term and treatment arm (specifying severity, SAE, relationship, leading to treatment discontinuation, leading to dose adjustment/interruption and requiring additional therapy).

Laboratory data

Laboratory data from all sources (central and local laboratories) will be combined. All laboratory values will be converted into International System (SI) units.

Raw values as well as absolute and relative change from baseline values for hematology, biochemistry and urinalysis laboratory parameters will be summarized descriptively per time window and treatment arm on the Safety Set 3 and 4 (see Table 4-2 for time windows definition).

Shift tables based on normal ranges to compare baseline to the worst post-baseline value will be provided by parameter and treatment arm for hematology, biochemistry and urinary laboratory data. Same shift table will be provided based on notable/extended ranges for key safety laboratory parameters defined in Table 4-2.

Table 2-4 Definition of notable/extended ranges for key safety laboratory parameters

Laboratory parameters	Criteria for notable/extended 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
Recalculated 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/AST	>5 x ULN and 2 x baseline (extended range >10×ULN and >2×baseline value)

Recalculated creatinine clearance will be calculated using the Schwartz formula (for pediatric population at baseline) described in Section 4.6.3. The Modification of Diet in Renal Disease (MDRD) derivation will be provided in the derived datasets only for possible future requests.

A listing of all laboratory values with values flagged to show the corresponding range classifications relative to the laboratory reference ranges will be provided by laboratory data and treatment arm. Assessment day relative to first dose of study drug will be included and all laboratory assessments collected outside of the on-treatment period will be flagged.

A listing of patients with laboratory abnormalities based on normal ranges and notable/extended ranges will also be provided.

Normal ranges by laboratory parameter will also be provided in a separate listing.

Vital signs, weight and body mass index

The following criteria define clinically notable abnormalities for vital signs and weight values:

Table 2-5 Definition of clinically notable abnormalities for vital signs and weight values

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

[1]Systolic and diastolic blood pressure will be listed individually.

[2]Fleming S, Thompson M, Stevens R, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet 2011; published online March 15. DOI: 10.1016/S0140-6736(10)62226-X.

Descriptive statistics will be tabulated per time window and treatment arm using absolute change from baseline values for each vital sign measure, weight and BMI (see Table 4-2 for time windows definition) separately for Safety Set 3 and 4.

All vital sign assessments, weight and BMI will be listed by treatment arm, patient and parameter. In the listings, clinically notable values will also be flagged.

Cardiac evaluations

Cardiac evaluations include ECG and echocardiogram. Any abnormalities at baseline will be summarized as described in Section 2.3. All findings of patients with new or worsened abnormalities since baseline will be listed separately for Safety Set 3 and Safety Set 4.

Ocular evaluations

The number of patients with available assessment for each type of ocular evaluation and eye side will be provided by treatment group.

Visual acuity

Visual acuity will be measured using the Snellen visual acuity. This is determined by establishing the smallest optotypes that can be identified correctly by the patient at a given observation distance. Snellen visual acuity can be reported as a Snellen fraction (m/M) in which the numerator (m) indicates the test distance and the denominator (M) indicates the distance at which the gap of the equivalent Landolt ring subtends 1 minute of arc. The following formula for conversion from Snellen acuity results to the logMAR score (Holladay 1997) will be applied and the LogMAR score will be calculated for each timepoint.

$$\text{logMAR score} = -\log_{10}(m/M).$$

LogMAR scores will be categorized as follows: <0.1, ≥0.1 to <0.2, ≥0.2 to <0.3, ≥0.3 to <0.6, ≥0.6. Shift tables using these categories to compare baseline to increases and decreases from baseline of logMAR score will be presented at each visit, for each eye side by treatment group in the core phase. Number and percentage of patients with worst change from baseline for each logMAR category will be summarized by treatment arm. Changes from baseline at each visit will be calculated for assessments done in the same condition (with/without correction) as at baseline. The shift tables and summaries will be repeated for the safety set 4.

A listing with the Snellen fraction and logMAR score will be provided for all patients with a flag for patients who have 0.2 or more increase in the post-baseline logMAR score.

Slit lamp

For each considered evaluation type and eye, the number of patients with and without abnormality (normal, insignificant, significant and any) will be provided by treatment arm. In addition, a shift table will present any changes in interpretation compared to baseline. A listing of patients with any abnormality will be provided.

Tonometry

The number of patients with clinically relevant post-baseline value of less than or equal to 5 mmHg and changes from baseline intraocular pressure above 5 mmHg and 10 mmHg will be summarized by treatment arm. For patients with such values, a listing will also be provided.

Intraocular pressure will also be summarized in shift tables (baseline and post baseline value at each time point) for each eye side considering the following categories: ≤5, >5 to ≤21, >21 to ≤30 and > 30 mmHg.

Fundus oculi

For each eye, the number of patients with and without abnormality (normal, insignificant, significant and any) will be provided by treatment arm. In addition, shift table will be done to present any changes in interpretation compared to baseline. A listing of patients with any abnormality will be provided.

Growth and Development

Growth velocity will be listed at baseline and core EOT visit and summarized using descriptive statistics by sex and age group during the core phase for the Safety Set 3. Summaries and listing will be repeated for the entire granule period on the Safety Set 4.

The growth velocity in height which evaluates the rate of growth per year will be calculated on the difference with the previous measure of height (in cm) and the time period (in days) as:

Growth velocity (cm / year) =

$$\frac{(height\,V_x - height\,V_{x-1}) * F}{date\,V_x - date\,V_{x-1}}$$

(with Vx = actual visit ; Vx-1 = previous visit ; *F = 365.25).*

Pubertal stage assesses the stage of physical development of sex characteristics. The characteristics breast development, pubic hair, testes and penis size are evaluated based on the Tanner scale: for each characteristic there are 5 classes (Tanner stage 1 to 5) indicating the level of development of that specific characteristic.

The age will be summarized descriptively at baseline and core EOT visit for the core phase by sex, characteristic, Tanner stage and treatment arm. For the entire granule period, the same summary will be repeated at baseline and at each annual assessment (core phase and extension phase displayed separately).

A listing will be provided including the Tanner stage as well as the individual records for each sex characteristic by visit. Patients with delayed puberty will be flagged in the listing. Delayed puberty in boys is defined as failure to attain Tanner Stage 2 (for both testis and pubic hair) by age 14 (Crowley and Pitteloud 2012) and in girls is defined as the failure to attain Tanner Stage 2 (for both breast development and pubic hair) by age 13, or absence of menarche by age 15 or absence of menarche within 5 years of attainment of Tanner Stage 2 (Fenichel 2012).

Other safety data

All data from auditory evaluation, hepatitis testing, and pregnancy test will be listed.

Patients with clinically significant abnormal interpretations or abnormal values will be flagged as well as positive pregnancy test results.

Data related to blood transfusion during treatment phase will be listed by treatment arm.

2.9.7 Pharmacokinetics parameters

2.9.7.1 Pharmacokinetics analyses

The assessment of pharmacokinetic parameters was characterized in the primary CSR and will not be repeated for the EoC CSR. For details on this analysis, refer to the primary analysis SAP.

In the EoC CSR, all individual PK concentration data will be listed on the FAS-3.

2.9.7.2 Exploration of PK/PD relationship

The exposure-efficacy relationship was characterized in the primary CSR and will not be repeated for the EoC CSR since no additional data was collected for these endpoints after the primary CSR data cut-off. For details on this analysis, refer to the primary analysis SAP.

2.10 Sample size

Refer to Section 2.11 of the primary analysis SAP for details.

2.11 Interim analysis

Refer to Section 2.12 of the primary analysis SAP for details.

3 Change to protocol specified analyses

Table 3-1 Changes to protocol specified analysis or descriptions and rationale

Protocol section	Protocol description	Change	Rationale
10.3	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).	Average daily dose should be calculated excluding dose interruptions. (Table 2-2 in this SAP)	Incorrectly defined in the study protocol and primary CSR.
10.3	Concomitant medications are medications taken between the first and last day with study medication, excluding medications start on the	All concomitant medications taken between the first dose and up to 30 days after the last dose will be summarized.	Concomitant medications are collected up to 30 days after treatment discontinuation as per protocol.

Protocol section	Protocol description	Change	Rationale
	last day of study medication.	(Section 2.6 of this SAP)	
10.6.1.2	Table 10-2 Definition of notable ranges for vital signs and weight	Table 2-5 in this SAP	The thresholds for clinically notable vital signs were incorrectly provided for adults in the study protocol.

4 Additional details on implementation of statistical methodology

The sections below contain additional details on statistical methodology that will be included in Appendix 16.1.9 (Documentation of Statistical Methods) of the CSR as well as programing rules that will be followed to implement the analyses described in Section 2.

The time windows are used for tables and figures where analysis is performed by timepoint. In case of listings, the visit name will be presented as collected in the database.

4.1 Time windows

Only core phase analysis windows will be defined for subjects discontinuing from the core phase except for exposure.

4.1.1 Study drug exposure

Study drug will be dispensed at randomization (week 1), then every four weeks. Dose adjustments based on safety are allowed at any time point during the study.

Information on study drug strength will be collected on the Dose Administration Record (DAR) eCRF and includes the planned dose (mg/kg/day), actual total daily dose (mg) taken, reason for the dose change, start date and end date.

Table 4-1 shows the defined study periods for drug exposure.

All assessments within a time period will be used to calculate the drug exposure for the corresponding period.

Table 4-1 Study periods for drug exposure

Period	Visit Period Definition
Month 1	Study Day 1 – 28
Month 2	Study Days 29 – 56
Month y** (with y=3, 4, 5,…)	Study Days (y-1)*28+1 to (y)*28
Etc.	

*Study Day 1 = first day of study treatment
** For the core phase data analysis: y=1 to k=12

4.1.2 Laboratory data and vital signs

Laboratory data (biochemistry, hematology and urinary parameters as well as serum creatinine, creatinine clearance and proteinuria) and vital signs will be collected at screening visits, at each regularly patient visit and at end of treatment visit.
If two or more assessments are performed within a time window then the assessment closest to the planned visit is used in analyses by time window. When two values are equidistant from the planned assessment, the later one is used in analyses. When multiple values are reported on the same day then the average value is used in analyses. For parameters with categorical results, the one from central laboratory is used in analyses.

For worst post-baseline assessment, all on-treatment values are considered regardless of time windows.

Table 4-2 shows the defined time windows.

Table 4-2 Time windows for laboratory data, vital signs, weight and BMI

Time Window	Planned Visit Timing	Time Window Definition
On treatment		
Baseline	On or before Study Day 1*	≤ Study Day 1
Week 2**	Study Day* 8	Study Days 2 – 11 (excluded baseline assessment)
Week 3**	Study Day* 15	Study Days 12 – 18
Week 4**	Study Day* 22	Study Days 19 – 25
Week 5	Study Day* 29	Study Days 26 – 42
Every 4 weeks thereafter		
Week y=5+4*k (with k*** = 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12…)	Study Day (5+4*k-1)*7+1	Study Days (5+4*k-1)*7+1-14 to (5+4*k-1)*7+1+13 Notes: - EOT data visit are included if obtained within the next 7* days of last non-0 dose intake (*NA for patients continuing in extension phase).

*Study Day 1 = first day of study treatment
** where appropriate (e.g. week 2 time-window NA for serum ferritin)
*** For the core phase data analysis: k=1 to k=11 with EOT_Core corresponding to week 49 time-window for subjects who continue into the extension phase.

4.1.3 Compliance diary

Patients will be asked to fill-out the PRO compliance questionnaire daily from Week 1 Day 1 visit to end of treatment visit.

Table 4-3 shows the defined week periods for this two PRO questionnaire.

All daily assessments within a week period will be used in analysis by week.

Table 4-3 Week periods for compliance diaries

Week Period	Week Period Definition
Week 1 period	Study Day 1 – 7
Week 2 period	Study Days 8 – 14
Week 3 period	Study Days 15 – 21
Week y period (with y=4, 5, 6,…)	Study Days (y-1)*7+1 to y*7
Etc.	

Study Day 1 = first day of study treatment

4.1.4 Ocular data

Ocular data will be collected at screening visit, at patient visit 11 and at end of treatment visit during the core phase and annually during the extension phase. If two or more assessments are

performed within a time window then the assessment closest to the planned visit is used in analyses by time window. When two values are equidistant from the planned assessment, the later one is used in analyses.

For worst post-baseline assessment, all on-treatment values are considered regardless of time windows.

Table 4-4 and Table 4-5 shows the defined time windows.

Table 4-4 Time windows for ocular data in core phase

Time Window	Planned Visit Timing	Time Window Definition
On treatment		
Baseline	On or before Study Day 1*	≤ Study Day 1
Week 25	Study Day 169	Study Days 140 – 197
EOT_Core	NA	- EOT-core visit are included if obtained within the next 14^ days of last non-0 dose intake (^NA if patients continuing in extension phase). - Week 49 visit for patients continuing into extension - For the post-baseline assessments, if no data were collected at the EOT visit the last available post-baseline data will be used for EOT - Core.
*Study Day 1 = first day of study treatment		

Table 4-5 Time windows for ocular data in extension phase

Time Window	Planned Visit Timing	Time Window Definition
On treatment		
Baseline	On or before Study Day 1*	≤ Study Day 1
Week# y=5+4*k with (k = 24, 37,…to 89 with increments of 13)	Study Day (5+4*k-1)*7+1	Study Days (5+4*k-1)*7+1-59 to (5+4*k-1)*7+1+58
EOT_Ext	NA	- EOT-ext visit are included if obtained within the next 14^ days of last non-0 dose intake - For the post-baseline assessments, if no data were collected at the EOT visit the last available post-baseline data will be used for EOT - Ext.
*Study Day 1 = first day of study treatment # Every 52 weeks starting from Week 101		

4.2 Month/year derivation

For all derivations, a year will be defined as 365.25 days and a month will be calculated as (365.25 / 12) = 30.4375 days. If duration is to be reported in months, duration in days will be divided by 30.4375.

4.3 Body mass index

Body mass index, in $kg/m^{2,}$ is a measure of relative weight based on an individual's mass and height.

It is calculated using the following formula, where weight is in kilograms and height is in meter:

$BMI = Weight / Height^2$

Baseline BMI will be determined using the last available height and weight prior to start of study drug.

4.4 Stratification

In this study, two randomization lists have been developed:

- Patients enrolled in the initial protocol will be randomized using a central stratified block randomization with the following stratification factor: age group (2 to <10 years versus 10 to <18 years).
- Patients enrolled after protocol amendment 1 will be randomized using a central stratified block randomization with the following stratification factors: age group (2 to <10 years versus 10 to <18 years) and prior ICT (Yes versus No).

Therefore, the FAS-1, considering only ICT naïve patients as per IRT, will include patients randomized in the following strata: 2 years to <10 years (stratification id=1), 2 to < 10 years + PICT No (stratification id=4) and 10 to < 18 years (stratification id=2) 10 to < 18 years + PICT No (stratification id=6).

4.5 Efficacy evaluations

4.5.1 Primary endpoint

An ANCOVA will be used for comparison between both treatment groups. PROC GLM procedure in SAS will be used for the primary analysis.

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

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

4.6 Safety evaluations

The text below gives more detailed instructions and rules needed for programming of the safety analyses described in Section 2.

4.6.1 Multiple assessments within post-baseline visits

For all analyses regarding abnormal assessments or analyses based on worst post-baseline value (e.g. laboratory, ECGs, vital signs), all post-baseline values will be included (scheduled, unscheduled, repeat). All unscheduled and repeat measurements will be included in listings.

4.6.2 Baseline

As defined in Section 2.7, for safety evaluations, the last available assessment before or on the date of start of study drug is defined as 'baseline' value or 'baseline' assessment.

4.6.3 Recalculated creatinine clearance

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
k = 0.55 for girls ≥ 13 years based on current age
k = 0.70 for boys ≥ 13 years based on current age

4.7 Handling of missing or partial dates

A date is considered as missing when no information at all is available, i.e. the day, the month and the year are missing.

A partial (or incomplete) date is a date for which part of date information is missing, i.e. either the day or the day and month are not available. Partial dates, if left partial, would possibly mean an event cannot be placed in time, treatment/dosage at the time of the event is unknown and the event cannot be reported/summarized appropriately – if at all. Therefore it is important to perform date imputation for selected dates to ensure that as many data events are represented as correctly as possible.

Date imputation is the creation of a new, complete date from the partial information available according to an agreed and acceptable algorithm.

4.7.1 AE date imputation

Missing and partial date for AE will be handled according to rules specified below.

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

- Completely Missing AE start dates
- AE start dates missing the year.

- Partial/missing AE end dates

For partial AE start date, the date imputation will be based on the temporal relation between the partial date and start of treatment date.

Table 4-6 provides examples of the different considered imputations for AE start date.

The full description will be provided in the PDS.

Table 4-6 AE start date imputation example scenarios

Partial AE start date	Treatment start date	Temporal relationship compared to treatment start	Imputed Date
12mmyyyy	20OCT2001	Uncertain	<blank>
ddmmm2000	20OCT2001	Before	01JUL2000
ddmmm2002	20OCT2001	After	01JAN2002
ddmmm2001	20OCT2001	Uncertain	21OCT2001
ddSEP2001	20OCT2001	Before	15SEP2001
ddOCT2001	20OCT2001	Uncertain	21OCT2001
ddNOV2001	20OCT2001	After	01NOV2001

4.7.2 Concomitant medication date imputation

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

4.7.3 Incomplete date of first/last dose of study drug

The following rule should be used for the imputation of date of last administration:

Scenario 1: If the date of last administration is completely missing and there is no EOT eCRF page, the patient is considered as on-going. The patient should be treated as on-going and the cut-off date should be used as the last dosing date.

Scenario 2: If the date of last administration is completely or partially missing and the EOT eCRF page is available (prior to any death date or withdrawal of consent date, if available):

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

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

Use Dec31yyyy

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

Use EOT date

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

- mm < the month of EOT visit:

Use last day of the Month (mm)

- mm = the month of EOT visit:

  Use EOT day.

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

Use the start date of that record.

Patients with missing start dates are to be considered missing for all study treatment component related calculations and no imputation will be made. If the date of first administration is missing, then the date of last administration should not be imputed.

Note: In order to handle partial start dates issue when identifying extension phase treatment start date, "record number" and "extension"variables will be used to identify the first DAR record in extension phase. More details in PDS.

There will be no attempt to impute any other date from eCRF DAR page.

5 References

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NOVARTIS

Clinical Development

ICL670/deferasirox/Exjade ®

CICL670F2202 / NCT02435212

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

Statistical Analysis Plan (SAP) - Final CSR

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21-Feb-2024	Prior to DB lock	Creation of final version	N/A - First version (based on SAP Amendment 3 (dated 26-Mar-2018) and CICL670F2202_SAP_End of Core Phase CSR)	NA

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List of abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATC	Anatomical Therapeutic Classification
AUC	Area under concentration-time curve
BMI	Body mass index
BP	Blood Pressure
CrCl	Creatinine Clearance
CRF	Case Report/Record Form
CSR	Clinical Study Report
DAR	Dosage Administration Record
DBP	Diastolic Blood Pressure
DRL	Drug Reference Listing
DT	Dispersible Tablet
EoC	End of Core Phase
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
PRO/ObsRO	Patient Reported Outcomes/Observer Reported Outcomes
EOT	End of Treatment
FAS	Full Analysis Set
FU	Follow Up
GCP	Good Clinical Practice
HLT	High Level Terms
IA	Interim Analysis
ICT	Iron Chelation Therapy
IRT	Interactive Response Technology
ITT	Intention To Treat
Kg	Kilogram
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable
NEU	Neutrophils
NMQ	Novartis MedDRA Queries
PAS	Pharmacokinetic Analysis Set
PDS	Programming Datasets Specifications
PK	Pharmacokinetic

PPS	Per-Protocol Set
PT	Preferred Terms
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SCIT	Satisfaction with Iron Chelation Therapy
SI	International System
SMQ	Standardized MedDRA Queries
SOC	System Organ Classes
SCr	Serum Creatinine
TBL	Total Bilirubin
TEAE	Treatment Emergent Adverse Event
TFL	Tables Figures Listings
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organization

1 Introduction

This document details the planned statistical analysis for the final CSR. The SAP from the primary analysis (CSR SAP Amendment 3, dated 26-Mar-2018) and end of core CSR (CICL670F2202_SAP_End of Core Phase CSR dated 25-Jun-2021) will be used as a reference for this SAP. The SAPs are located at the following CREDI locations:

[redacted]

Clinical Study Report (CSR) deliverables (tables, figures, listings - TFLs) and further programming specifications are described in separate documents namely TFL Shells and Programming Datasets Specifications (PDS), respectively.

An interim and the primary analysis as well as an End of Core Phase (EoC) CSR were already performed for this study.

The data cut-off date for the interim analysis was 16-Nov-2017 and included all randomized ICT naïve patients who had completed a minimum of 12 weeks of treatment exposure or discontinued from the treatment core phase by the cut-off date. The primary analysis was performed when 96 randomized ICT naive patients had completed 24 weeks of treatment or discontinued early (data cut-off date: 31-May-2018). All data collected within the core phase of the study at the time of the primary data cut-off date were reported in the primary analysis CSR.

The analyses for an EoC CSR requested by the CHMP included the cumulative data from the completed core phase and extension phase with a data cut-off date of 18-Jan-2021. This data cut-off date allowed the inclusion of all patients who have completed a minimum of 3 years of treatment or discontinued from treatment in the core or extension phase.

Completion of this study as a whole will occur upon the availability and accuracy verification of the last data point required for statistical analysis of the optional extension phase. Data collection will terminate and End of Study will be declared after all patients have completed the treatment phase of the optional extension phase (up to 305 weeks) including the safety follow-up period (30 days after treatment discontinuation). The final CSR will be based on the core and extension phase using the entire granule treatment unless mentioned otherwise. **Analyses** that were **presented in the primary CSR or EoC CSR** and **for which no additional data was collected** since previous analysis data cut-off date (e.g. baseline demographics) **will not be repeated for the final analysis.** Any analyses already presented in the primary or EoC CSR will **only be repeated** in the final CSR **in case of any additional data or data changes.**

1.1 Study design

Refer to section 1.1 of CSR SAP Amendment 3.

1.2 Study objectives, endpoints and estimands

The study objectives as outlined in the protocol version 6, Section 3 are as follows (Table 1-1). **Any analyses already presented in the primary or EoC CSR will only be repeated in the final CSR in case of any additional data or significant data changes.**

Table 1-1 Objectives and related endpoints

Objective	Endpoint	To be reported in final CSR
Primary		
• To evaluate both formulations on patient compliance, using stick pack/tablet count over 24 weeks of treatment in ICT naïve patients during core phase • To evaluate the change from baseline in serum ferritin after 24 weeks of treatment for both formulations in ICT naïve patients	• Compliance measured by stick pack/tablet count over 24 weeks of treatment (i.e. assessed at week 25 visit) • Change from baseline in serum ferritin after 24 weeks of treatment (i.e. serum ferritin at week 25 visit)	No, as it is already presented in primary CSR
Secondary (Core phase)		
To evaluate both formulations on change in serum ferritin and compliance in ICT naive patients, after 48 weeks of treatment	● Compliance measured by stick pack/tablet count after 48 weeks of treatment ● Change from baseline in serum ferritin after 48 weeks of treatment	No (presented in EoC CSR)
To evaluate both formulations on change in serum ferritin after 24 weeks and 48 weeks of treatment in ICT naïve and pre-treated patients	Change from baseline in serum ferritin after 24 weeks (i.e. assessed at week 25 visit) and 48 weeks of treatment	No (presented in EoC CSR)
To evaluate both formulations on patient satisfaction and palatability using Patient / Observer Reported Outcomes (PRO/ObsRO) questionnaires	Domain scores of treatment satisfaction and palatability over time	No (presented in EoC CSR, no extension data)
To evaluate both formulations on overall safety	Overall safety, as measured by frequency and severity of adverse events (including active monitoring for renal toxicity; including renal failure, hepatic toxicity; including hepatic failure, and gastrointestinal hemorrhage), and changes in laboratory values from baseline (serum creatinine, creatinine clearance, ALT, AST, RBC and WBC). In addition, vital signs, physical, ophthalmological, audiometric, cardiac, and growth and development evaluations will be assessed.	No (presented in EoC CSR except for Ophthalmological assessments [LOCSIII and Color fundus photographs] which will be presented in this CSR)
To evaluate compliance using a daily PRO/ObsRO questionnaire	Rate of dosing instructions deviations (doses missed / not taken at the same time every day)	No (presented in EoC CSR, no extension data)
To evaluate pre-dose PK data to support the assessment of compliance	Pre-dose deferasirox concentrations in all patients [except Egypt] at weeks 1, 3, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41 and 45 (13 samples)	No (presented in EoC CSR, no extension data)

Objective	Endpoint	To be reported in final CSR
Post-dose data to be analyzed along with pre-dose PK data	Post-dose deferasirox concentrations between 2 and 4 hours post-dose at Weeks 5 and 9 (2 samples)	No (presented in EoC CSR, no extension data)
To explore exposure-response relationships for measures of safety and effectiveness	Serum creatinine change from baseline, notable serum creatinine events, serum creatinine clearance change from baseline and notable serum creatinine clearance events, urine protein creatinine ratio change from baseline and serum ferritin change from baseline, in relationship to pre- and post-dose deferasirox concentrations.	No (presented in EoC CSR, no extension data)
Secondary (Optional Extension phase)		
To assess additional safety data about new formulation (granules) in pediatric population	Overall safety, as measured by frequency and severity of adverse events (including active monitoring for renal toxicity; including renal failure, hepatic toxicity; including hepatic failure, and gastrointestinal hemorrhage), and changes in laboratory values from baseline (serum creatinine, creatinine clearance, ALT, AST, RBC and WBC). In addition, vital signs, physical, ophthalmological, audiometric, and growth and development evaluations will be assessed.	Yes

2 Statistical methods

This section describes the analysis of the final CSR based for the entire granule treatment data. Refer to the CSR SAP Amendment 3 for additional details. **Any analyses already presented in the primary or EoC CSR will not be repeated, unless significant data changes impacting the primary and secondary analysis results presented in the primary and the EOC CSR, respectively, have occurred with the final CSR cut-off.**

Section 5 of the SAP provides statistical and programming conventions.

2.1 Data analysis general information

Data will be analyzed by Novartis Oncology Biostatistics and Statistical Programming personnel according to the data analysis section 10 of the study protocol as detailed in this analysis plan.

SAS® version 9.4 (or later version if available at time of database lock) will be used for all analyses. Data from all patients who signed informed consent and who received granule treatment will be used in the analysis. 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 per local laws).

All statistical analyses will be performed using all data (for patients who received granule treatment) collected in the database up to the last patient last visit (LPLV) date.

All events with a start date before or on the LPLV date and not having documented end date will be reported as 'ongoing'. This approach applies to adverse event and concomitant medication reports. For these events, the end date will not be imputed and therefore will not appear in the listings.

The time periods defined in Table 2-1 will be used to define the extension phase for the analysis.

Table 2-1 Definition of core and extension phases

Core phase			Extension phase		
Treatment	Start date	Stop date	Treatment	Start date	Stop date
Granules	Date of first IC signed	Date of last treatment of granules + 30 days	No treatment	Nil	Nil
DT	Date of first IC signed	Date of last treatment of DT + 30 days	No treatment	Nil	Nil
Granules	Date of first IC signed	date of first administration of granules in extension phase*– 1 day	Granules	date of first administration of granules in extension phase*	Date of the last administration of Granules in extension + 30 days
DT	Date of first IC signed	Date of first administration of granules* – 1 day	Granules	Date of first administration of Granules*	Date of the last administration of Granules in extension + 30 days

*including 0 doses for patients to identify the extension start date only

Summaries will be based on:

- Entire granule period - patients randomized to Granules combining core and extension phases (dark green rectangle in Figure 2-1) side-by-side with Granules for patients randomized to DT who switched to Granules in extension phase (light green rectangle in Figure 2-1). Cross-over treatment group corresponds to the patients randomized to DT who switched to Granules in the extension phase.

Figure 2-1 Core and extension phases

2.1.1 General analysis conventions

Pooling of centers: Unless specified otherwise, data from all study centers will be pooled for the analysis. Due to expected small number of patients enrolled at centers, no center effect will be assessed.

Qualitative/categorical data (e.g., sex, race) will be summarized by frequency counts and percentages. Percentages will be calculated using the number of patients in the relevant treatment arm as the denominator.

Continuous data (e.g., age, body weight) will be summarized using appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum, and maximum) by treatment arm. Lower and upper quartiles will also be presented when applicable.

2.1.2 Study drug and study treatment

The terms study drug and study treatment are equivalent and will refer to deferasirox granule.

2.1.3 Date of first/last administration of study drug

The date of first administration of study drug is derived as the first date when a non-zero actual dose of study drug was administered as recorded on Dosage Administration Record (DAR) Electronic Case Report Form (eCRF). The date of first administration of study drug will also be referred as 'start of study treatment'.

The date of last administration of study drug is defined as the last date when a non-zero actual dose of study drug was administered as recorded on DAR eCRF. This date will also be referred as 'last date of study treatment'.

2.1.4 Study day

The study day **for safety** (e.g. adverse event onset, laboratory abnormality occurrence, vital sign measurement, Electrocardiogram (ECG), etc.) will be calculated using the start date of study treatment as the reference. For assessments occurring

- **on or after the start date of study treatment**, the study day will be calculated as (date of safety assessment) – (start date of study treatment) + 1. Study day 1 will therefore be the first day of study treatment.
- **before the start date of study treatment**, the study day will be calculated as (date of safety assessment) – (start date of study treatment).

For example, if an adverse event starts 3 days before the start of study treatment the study day displayed on the listing will be negative, i.e. -3.

The study day will be displayed in the data listings.

2.1.5 Baseline

Baseline is considered as the result of an investigation describing the 'true' uninfluenced state of the patient.

For **safety evaluations** (e.g. laboratory, vital signs, etc.) the last available (i.e. non-missing) assessment before or on the date of start of study treatment is taken as 'baseline' value or 'baseline' assessment.

If patients have no value as defined above, the baseline result will be missing. Unscheduled assessments will be considered in the determination of baseline.

For safety assessments, if an assessment is planned to be performed prior to the first dose of study drug in the protocol and the assessment is performed on the same day as the first administration of study drug, it will be assumed that it was performed prior to study drug administration, if assessment time point is not collected or is missing.

Patients who start treatment and discontinue from the study on the same day may have 2 different sets of data collected on study Day 1, one being reported to the week 1 visit, the other reported to the End Of Treatment (EOT) visit. Data reported at the EOT visit are not eligible for baseline selection.

For analyses of the entire granule period requiring comparison to baseline value (e.g. lab shift tables, pubertal staging etc.) the baseline is defined as follows. For patients randomized to DT formulation who switched to granule formulation in the extension phase, the date of the last assessment prior or equal to the start date of granules in the extension phase will be defined as pre-granule value which will be reference value for changes in the extension time. For patients randomized to granules continuing in extension phase the initial baseline value at study start will be taken.

2.1.6 On-treatment period

The overall observation period will be divided into three mutually exclusive segments taking into account stop rules as per Table 2-1:

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

For the entire granule period, the following conventions will be taken into account while deriving the three observation periods above:

- For patients enrolled in DT formulation in the core phase, the pre-treatment period will not be derived, and their entire granule period starts from Extension phase start date mentioned in Table 2-1
- For patients enrolled in Granule formulation in the core phase, the first dose of study drug will be the day of first dose in the core phase.

2.2 Analysis sets

The Safety Set 1 will consist of all ICT naïve patients (as per eCRF) who received at least one dose of the study drug during the core phase.

The Safety Set 2 will consist of all ICT pre-treated patients (as per eCRF) who received at least one dose of study drug during the core phase.

The Safety Set 3 will consist of all patients who received at least one dose of study drug during the core phase.

Safety set 1 to 3 will only be used for the analysis of lens photography (LOCSIII) and color fundus photography. Safety set 3 is only used for disclosure related analysis, deaths and drug

dispension lisitings. Both assessments were only collected since protocol amendment 6 which was implemented after the EoC CSR.

All analysis for the final CSR will be based on Safety Set 4.

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

Patients will be analyzed according to the treatment actually received and strata information recorded in the eCRF.

Treatment actually received is defined as the treatment the patient received at the first day of study medication in the core phase

Protocol deviations

Frequency counts and percentages of patients with any protocol deviation (selection criteria not met, patient not withdrawn as per protocol, treatment deviation, prohibited concomitant medication, other Good Clinical Practice (GCP) deviation) will be tabulated by the deviation type category and treatment arm on the Safety Set 4 for the entire granule period. Patients with COVID-19 related protocol deviations will be presented separately in the table.

The full list of protocol deviations is documented in the Validation And Planning (VAP) Module 3 document. The COVID-related protocol deviations and relationship to pandemic will be identified and maintained in an independent tracker located in the document management system in the “CREDI Studies/ICL670F2202/TMF (Study Level)/Protocol Deviations” folder. The latest available tracker prior to database lock will be used.

All protocol deviations and COVID related protocol deviations will be listed on Safety Set 4.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

Listings will be produced on the Safety set 4 with a flag for extension phase data.

The summaries of patient disposition during the extension phase by treatment arm on the Safety Set 4 will show:

- Number (%) of patients who entered in the optional extension phase;
- Number (%) of patients who were not treated during the optional extension phase;
- Number (%) of patients who were treated during the optional extension phase;
- Number (%) of patients who completed the optional extension phase;
- Number (%) of patients who discontinued the optional extension phase;
- Number (%) of patients for each reason for optional extension phase discontinuation

2.3.2 Demographics and other baseline characteristics

All patients' demographic and baseline characteristics as well as enrollment status by region, country, center and treatment arm were analyzed for the primary CSR analysis and will not be repeated for the final CSR.

Demographics, disease characteristics and baseline characteristics will only be generated for safety set 4 subjects as defined in the SAP from primary analysis.

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

Safety Set 3 will be used for drug dispension listing.

2.4.1 Study treatment

Listings will be produced by treatment arm on the Safety Set 4.

Definitions of duration of exposure, total patient-years exposure. average daily dose, cumulative total dose as well as percentage of planned dose taken are defined in Table 2-2:

Table 2-2 Deferasirox: Study drug exposure

Overall duration of exposure (day):	[(date of last exposure) – (date of first study treatment) + 1]
Overall duration of exposure (months)	[(date of last exposure) – (date of first study treatment) + 1]/30.4375
Drug exposure on dose X (days)	[(date of last exposure on dose X) – (date of first study treatment on dose X) + 1]
Total patient-years (years):	Overall duration of exposure (days) / 365.25
Average dose (planned and actual, in mg/kg/day):	Mean dose over all days between first and last dose, excluding interruptions: sum of all (X dose * corresponding duration of exposure on dose X) / overall number of dosing days
Cumulative dose (planned and actual, in mg/kg):	Sum over daily doses of all days between first and last dose
Percentage of planned dose taken:	100 × [Cumulative actual dose / Cumulative planned dose]

For patients who switch from DT to granules in the extension phase, date of last exposure of study drug in core phase refers to the day prior to the date of the first administration of granules in extension phase (including a zero actual dose) as defined in Table 2-1.

For patients who switch from DT to granules, the date of the first administration of study drug (granules) refers to the first date of granules in the extension phase (including a zero actual dose) to account for treatment interruptions due to efficacy and safety reasons. The last exposure of the granules refers to the last date when a non-zero actual dose of granules was administered during the study extension phase as defined in Table 2-1.

For patients receiving granules throughout the study, the date of the first administration and last exposure of study drug refer to the first and last dates respectively when a non-zero actual dose of study drug (granules) was administered during the study.

Overall duration of exposure and total patient-years will be summarized by treatment arm for the entire granule period.

The following variables will also be summarized by treatment arm and for each phase as appropriate as:

- Duration of exposure will be categorized in the entire granule period as: <6 months, 6-<12 months, 12-<24 months, 24-<36 months, 36-<48 months and so on.

The actual dose in mg/kg/day will be obtained by dividing the actual total daily dose administered in the DAR eCRF page by the last available weight at the time of dose administration reported in the vital signs eCRF page. Average dose, average dose categories (<10.5 mg/kg/day Granule, 10.5-<17.5 mg/kg/day Granule, 17.5-<24.5 mg/kg/day Granule, ≥24.5 mg/kg/day Granule), cumulative dose and percentage of planned dose taken will only be analyzed for patients with complete dates (for all records of the patient) in DAR panel. Patients with complete DAR start and end dates for all the records of the treatment within the granule formulation will be flagged in the listings.

In addition, the number of patients who have any dose interruptions or dose changes with the corresponding reasons will be summarized as collected in the DAR panel.

2.4.2 For each patient, listings of each dose of the study drug administered along with dose change reasons will be produced. Prior, concomitant and post therapies

Prior and concomitant therapies are defined as any medication, and significant non-drug therapies administered to a subject preceding or coinciding with the study assessment period.

Medications will be coded using the World Health Organization (WHO) Drug Reference Listing (WHO DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (WHO ATC) classification system.

Concomitant therapies will include medications and significant non-drug therapies taken between the first day of study medication and up to 30 days after the last day of study medication (see Section 2.1.6 for the on-treatment period definitions).

Concomitant therapies will be summarized by ATC class, preferred term and treatment arm for the Safety Set 4. Medications starting prior to the start of study treatment and continuing after the start of study treatment will be included in this summary for the entire granule period as defined in Table 2-1.

Prior therapies will include medications or significant non-drug therapies starting and ending prior to the start of study treatment. Prior therapies were summarized in the primary CSR analysis and will not be repeated for the final CSR.

All concomitant therapies will be listed for Safety Set 4.

2.5 Analysis supporting primary objective(s)

The primary objectives of this study are to evaluate patient compliance with study treatment, as measured by the count of deferasirox granule stick packs/dispersible tablets and to evaluate the

change in serum ferritin after 24 weeks of treatment for both formulations of deferasirox in pediatric ICT naive patients with iron overload during core phase. Cumulative data up to week 24 from all ICT naive patients was analyzed in the primary CSR as well as EoC CSR (reported descriptively) and will not be repeated for final CSR.

2.6 Analysis supporting secondary objectives

Secondary variables include compliance after 48 weeks of treatment, changes in SF from baseline after 24 weeks in ICT pre-treated patients and after 48 weeks of treatment in ICT-naive and pre-treated patients, patient reported outcomes/observer reported outcomes and safety assessments (i.e. adverse events, laboratory parameters, vital signs, etc.). All secondary variables were analyzed in the EoC CSR and will not be repeated for the final CSR.

2.7 Safety analyses

All analyses will be performed on the Safety Set-4 for the entire granule period. Listings will be provided for the Safety Set-4.

Unless otherwise specified, the safety summary tables will include only assessments from the on-treatment period. For the definition of on-treatment period, please see section 2.1.6.

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.

Any COVID-19 related safety events will be flagged in listings.

2.7.1 Adverse events (AEs)

AEs will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) available prior to clinical database lock.

All aEs will be listed. Any information collected (e.g. regardless to study drug, action taken etc.) will be listed as well as the duration of the AE. The listings of all, serious adverse events, adverse events leading to study drug discontinuation, and adverse events requiring dose adjustment or interruption will also be provided.

The following adverse event summaries will be produced by treatment arm:

- Adverse events (overall and severe), regardless of study drug relationship by primary system organ class and preferred term
- 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
- Serious adverse events (overall and severe), with suspected 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
- An overall summary of type of AEs (e.g. serious, leading to study drug discontinuation, requiring dose adjustment or/and interruption) will be presented overall and by severe AEs and treatment arm.

Adverse events of special interest / grouping of AEs

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

AESI will be summarized by grouping, preferred term and treatment arm (specifying severity, SAE, relationship, leading to treatment discontinuation, leading to dose adjustment/interruption and requiring additional therapy).

A listing of all grouping levels down to the MedDRA preferred terms used to define each AESI will be generated.

2.7.2 Deaths

Deaths occurring on-treatment (i.e. within 30 days after discontinuation of study drug) as well as all deaths will be summarized by primary system organ class and preferred term. All deaths will be listed using safety set 3.

2.7.3 Disclosure related analysis

In order to provide a cumulative summary of AEs by treatment arm and by phase (core, extension) during the studyfor disclosure, the following arms need to be generated within a single XML file based on safety set 3.

- Deferasirox DT: CORE
- Deferasirox granules: CORE
- Deferasirox granules: Extension (including patients who already received granules in the core phase)
- Crossover to Deferasirox granules: Extension (including patients who received DT in core phase but crossed over to deferasirox granules during the extension phase)

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on on-treatment adverse events which are not serious adverse events with an incidence greater than 5% and on on-treatment serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.7.4 Laboratory data

2.7.4.1 Serum ferritin

Relative and absolute change from baseline in serum ferritin at every year visit during the extension period will be described for the Safety Set 4. A graphical presentation of mean and standard deviation of absolute value in serum ferritin during the study will be plotted by treatment arm and timepoint for safety set 4.

2.7.4.2 Other laboratory data

Laboratory data from all sources (central and local laboratories) will be combined. All laboratory values will be converted into International System (SI) units.

Raw values as well as absolute and relative change from baseline values for hematology, biochemistry and urinalysis laboratory parameters will be summarized descriptively per time window and treatment arm on the Safety Set 4 (see Table 5-4 for time windows definition).

Shift tables based on normal ranges to compare baseline to the worst post-baseline value will be provided by parameter and treatment arm for hematology, biochemistry and urinary laboratory data. Same shift table will be provided based on notable/extended ranges for key safety laboratory parameters defined in Table 2-4.

For notable/extended ranges below for each laboratory parameter, all patients satisfying the condition will be considered. For the other post-baseline categories, a patient will be counted only in the worst category (ie., categories are mutually exclusive).

Table 2-4 Definition of notable/extended ranges for key safety laboratory parameters

Laboratory parameters	Criteria for notable/extended 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

Laboratory parameters	Criteria for notable/extended ranges
Recalculated 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/AST	>5 x ULN and >2 x baseline (extended range >10×ULN and >2×baseline value)

Recalculated creatinine clearance will be calculated using the Schwartz formula (for pediatric population at baseline) described in Section 5.2.1. The Modification of Diet in Renal Disease (MDRD) derivation will be provided in the derived datasets only for possible future requests.

A listing of all laboratory values with values flagged to show the corresponding range classifications relative to the laboratory reference ranges will be provided by laboratory data and treatment arm based on Safety set 4. Assessment day relative to first dose of study drug will be included and all laboratory assessments collected outside of the on-treatment period will be flagged.

A listing of patients with laboratory abnormalities based on normal ranges and notable/extended ranges will also be provided for Safety set 4.

Normal ranges by laboratory parameter will also be provided in a separate listing.

Liver Function Parameters

Liver function parameters of interest are total bilirubin (TBL), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST) and alkaline phosphatase (ALP). The number (%) of subjects with worst post-baseline values as per Novartis Liver Toxicity guidelines will be summarized.

The following summaries will be produced:

- ALT > 3xULN
- ALT > 5xULN
- ALT > 8xULN
- ALT > 10xULN
- ALT > 20xULN
- AST > 3xULN
- AST > 5xULN
- AST > 8xULN
- AST > 10xULN
- AST > 20xULN
- ALT or AST > 3xULN
- ALT or AST > 5xULN
- ALT or AST > 8xULN
- ALT or AST > 10xULN
- ALT or AST > 20xULN
- TBL > 2xULN

- TBL > 3xULN
- ALT or AST > 3xULN & TBL > 2xULN
- ALT or AST > 3xULN & TBL > 2xULN & ALP >= 2xULN
- ALT or AST > 3xULN & TBL > 2xULN & ALP < 2xULN

2.7.5 Other safety data

2.7.6 Ocular evaluations

The number of patients with available assessment for each type of ocular evaluation and eye side will be provided for Safety Set 4 if not otherwise stated. The frequency and percentage of subjects with completed ocular assessments will be presented by eye side, evaluation type, timepoint, and treatment arm. Additionally, a summary for the number of ocular examinations performed at each time point will be presented by treatment arm. Overall interpretation for ocular will be listed.

As color fundus photography and Lens opacification grading (LOCSIII) was only implemented with protocol amendment 6 and never reported so far, these analyses will also be provided for Safety set 1 to 3. A separate listing for subjects with available images of color fundus photography and LOCSIII will be provided.

2.7.6.1 Visual acuity

Visual acuity will be measured using the Snellen visual acuity. This is determined by establishing the smallest optotypes that can be identified correctly by the patient at a given observation distance. Snellen visual acuity can be reported as a Snellen fraction (m/M) in which the numerator (m) indicates the test distance and the denominator (M) indicates the distance at which the gap of the equivalent Landolt ring subtends 1 minute of arc. The following formula for conversion from Snellen acuity results to the logMAR score (Holladay 1997) will be applied and the LogMAR score will be calculated for each timepoint:

$$\text{logMAR score} = -\log_{10}(m/M).$$

The logMAR scores will be categorized as follows: < 0.1, ≥ 0.1 to < 0.2, ≥ 0.2 to < 0.3, ≥ 0.3 to < 0.6, ≥ 0.6. The following shift tables will be generated using the above categories by treatment group:

- Comparing baseline and *increases* from baseline in logMAR score category at each visit by eye side (right & left)
- Comparing baseline and *decreases* from baseline in logMAR score category at each visit by eye side (right & left)

Change from baseline (logMAR) = Post Baseline Value (logMAR) – Baseline Value (logMAR)

In case both values are negative, the absolute values of Post baseline & Baseline records will be used for the calculation.

The number and percentage of subjects with the following change from baseline for logMAR categories (< 0.1, ≥ 0.1 to < 0.2, ≥ 0.2 to < 0.3, ≥ 0.3 to < 0.6, ≥ 0.6) will be summarized by treatment arm:

- the best change (decrease) in logMAR score category from baseline by eye side (right, left, best)
- the worst change (increase) in logMAR score category from baseline by eye side (right, left, worst)

The changes from baseline at each visit will be calculated for assessments done in the same correction method as at baseline.

The shift tables and summaries will be produced for the Safety set 4.

A listing with the Snellen fraction, logMAR score abnormalities and change from baseline categories will be provided for all subjects.

2.7.6.2 Slit lamp

For each considered evaluation type in the CRF page and eye side, the number & percentage of subjects with and without abnormality (normal, insignificant, clinically significant) will be provided by timepoint and treatment arm. In addition, for each slit lamp evaluation, shift tables will be generated to present the worst post-baseline changes compared to baseline by treatment arm and eye side. Further, shift tables will be generated by visit, treatment arm and eye side. A listing of patients with any abnormality will be provided.

2.7.6.3 Tonometry

Descriptive statistics for the intraocular pressure at baseline, at each post-baseline visit and changes from baseline at each post-baseline visit will be presented, by eye and treatment arm. Box plot for intraocular pressure by eye side and treatment arm will be generated for the overall period.

The number & percentage of subjects with post-baseline values listed below will be summarized by treatment arm

- *at least one post-baseline* value ≤ 5 mmHg, > 5 to ≤ 21 mmHg, > 21 to ≤ 30 mmHg, and > 30mmHg by eye side (right, left, worst)
- the Increase from baseline IOP ≥ 5mmHg to < 10 mmHg & ≥ 10mmHg by eye side (right, left, best)
- the Decrease from baseline IOP ≥ 5mmHg to < 10 mmHg & ≥ 10mmHg by eye side (right, left, worst)

A listing of patients will also be provided for this assessment.

Intraocular pressure will also be summarized in shift table (baseline and post baseline value at each time point) for each eye side considering the following categories: ≤ 5, >5 to ≤ 21, >21 to ≤ 30 and > 30 mmHg for each of the treatment arms.

2.7.6.4 Lens photography

The lens photography was collected for central reading to determine LOCSIII grade. A decimal grade using 0.1 unit intervals were assigned to the opacity by the grader. These continuous values ranging from 0.1 (clear or colorless) to 5.9 (very opaque for Cortical and Posterior

Subcapsular) or 6.9 (very opaque or brunescent for Nuclear Color, Nuclear Opalescence) were converted to standard grades using the Table 2-2 (Chylack et al., 1993).

Table 2-2 Standard grades for LOCSIII assessment

Nuclear Color (NC)	Nuclear Opalescence (NO)	Cortical (C)	Posterior Subcapsular (P)
No Opacity is >=0.1 to <1	No Opacity is >=0.1 to <1	No Opacity is >=0.1 to <1	No Opacity is >=0.1 to <1
NC1 is >=1 to <2	NO1 is >=1 to <2	C1 is >=1 to <2	P1 is >=1 to <2
NC2 is >=2 to <3	NO2 is >=2 to <3	C2 is >=2 to <3	P2 is >=2 to <3
NC3 is >=3 to <4	NO3 is >=3 to <4	C3 is >=3 to <4	P3 is >=3 to <4
NC4 is >=4 to <5	NO4 is >=4 to <5	C4 is >=4 to <5	P4 is >=4 to <5
NC5 is >=5 to <6	NO5 is >=5 to <6	C5 is >=5 to <=5.9	P5 is >=5 to <=5.9
NC6 is >=6 to <=6.9	NO6 is >=6 to <=6.9		

The worst change in grade compared to baseline for each eye, evaluation type, and treatment arm will also be presented using shift tables. For each considered evaluation type and eye side, the number & percentage of subjects for image quality will be provided by timepoint and treatment arm. A listing of subjects will be provided, additionally, listings for the findings, general comments and confidence score comments will be presented for safety set 3. As data was not analyzed so far, the analysis will be repeated for safety set 1 to 3.

2.7.6.5 Fundus oculi

For each eye side, the number & percentage of subjects with and without abnormality (normal, insignificant, clinically significant) will be provided by timepoint, eye side and treatment arm. In addition, shift table will be generated to present the worst post-baseline changes compared to baseline by eye side and treatment arm. A listing of subjects with any abnormality will be provided.

2.7.6.6 Color Fundus Photography

The Color Fundus Photography Assessment will be conducted by a central vendor though photographs. For each considered evaluation type and eye side, the number & percentage of subjects with and without abnormality will be provided by timepoint and treatment arm. For each considered evaluation type and eye side, the number & percentage of subjects for image quality will be provided by timepoint and treatment arm. A listing of subjects will be provided, additionally, listings for the findings, general comments and confidence score comments will be presented for safety set 3. As data was not analyzed so far, the analysis will be repeated for safety set 1 to 3.

2.7.7 Growth and Development

Growth velocity will be listed at EOT-extension visit and summarized using descriptive statistics by sex and age group during the entire granule period for the Safety Set 4. Listing will be produced for the entire granule period on the Safety Set 4.

The growth velocity in height which evaluates the rate of growth per year will be calculated on the difference with the previous measure of height (in cm) and the time period (in days) as:

$$\text{Growth velocity (cm / year)} = \frac{(height\ V_x - height\ V_{x-1}) * F}{date\ V_x - date\ V_{x-1}}$$

(with Vx = actual visit ; Vx-1 = previous visit ; $F = 365.25$).

2.7.7.1 SDS method

Growth data collected during the study (both core and extension phases) for safety set 4 subjects will also be summarized descriptively at each relevant time point. These data consist of BMI, height, height velocity, weight and weight velocity.

The baseline for this analysis will be the core phase baseline for both DT crossover and granule patients.

Height and BMI will be summarized at 6 months intervals, using the standard deviation scores (SDS, also called z-score), velocity and velocity SDS. The relevant height and weight values for each 6-month period are defined using time windows, as defined in Section 5.3.3. The z-scores will allow identification of potential outliers.

The formula used to calculate the SDS and height and weight velocities are provided in Section 5.6.

Note that BMI SDS are reported instead of weight SDS as no reference data for weight are provided by the WHO for age beyond 10.

Height/BMI SDS and height/weight velocity SDS will be summarized using descriptive statistics (mean, standard deviation, range) for each time window (at Baseline and thereafter allowing informal comparison of growth data), as well as by presenting number of patients with SDS values lower/higher than 5th/95th percentiles respectively. Box plots will also be plotted for each time window. In addition, a shift table to compare baseline SDS to the worst on-treatment SDS will be produced for height and BMI SDS. All height/BMI SDS, velocity and velocity SDS data will be listed, and values of SDS and velocity SDS outside of the central 95% of population values will be flagged as either High (SDS > 1.645) or Low (SDS < -1.645).

2.7.7.2 Pubertal Stage

Pubertal stage assesses the stage of physical development of sex characteristics. The characteristics breast development, pubic hair, testes and penis size are evaluated based on the Tanner scale: for each characteristic there are 5 classes (Tanner stage 1 to 5) indicating the level of development of that specific characteristic.

The age will be summarized descriptively at baseline and each annual assessment for the entire granule period by sex, characteristic, Tanner stage and treatment arm (core phase and extension phase displayed separately).

A listing will be provided including the Tanner stage as well as the individual records for each sex characteristic by visit. Patients with delayed puberty will be flagged in the listing. Delayed puberty in boys is defined as failure to attain Tanner Stage 2 (for both testis and pubic hair) by

age 14 (Crowley and Pitteloud 2012) and in girls is defined as the failure to attain Tanner Stage 2 (for both breast development and pubic hair) by age 13, or absence of menarche by age 15 or absence of menarche within 5 years of attainment of Tanner Stage 2 (Fenichel 2012).

2.7.8 Other safety data

2.7.8.1 Cardiac evaluations

Cardiac evaluations include ECG and echocardiogram. Any abnormalities at baseline were analyzed for the primary CSR analysis and will not be repeated for the final CSR. All findings of patients with new or worsened abnormalities since baseline will be listed separately for Safety Set 4.

2.7.8.2 Vital signs

The following criteria define clinically notable abnormalities for vital signs and weight values:

Table 2-5 Definition of clinically notable abnormalities for vital signs and weight values

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

[1] Systolic and diastolic blood pressure will be listed individually.

[2] Fleming S, Thompson M, Stevens R, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet 2011; published online March 15. DOI: 10.1016/S0140-6736(10)62226-X.

Descriptive statistics will be tabulated per time window and treatment arm using absolute change from baseline values for each vital sign measure, weight and BMI (see Table 5-4 for time windows definition) separately for Safety Set 4.

All vital sign assessments, weight and BMI will be listed by treatment arm, patient and parameter. In the listings, clinically notable values will also be flagged.

2.7.8.3 Other data

All data from auditory evaluation, hepatitis testing, and pregnancy test will be listed.

Patients with clinically significant abnormal interpretations or abnormal values will be flagged as well as positive pregnancy test results.

Data related to blood transfusion during treatment phase will be listed by treatment arm.

2.8 Pharmacokinetic endpoints

The assessment of pharmacokinetic parameters was characterized in the primary CSR and will not be repeated for the final CSR. For details on this analysis, refer to the primary analysis SAP.

2.9 PD and PK/PD analyses

The exposure-efficacy relationship was characterized in the primary CSR and will not be repeated for the final CSR since no additional data was collected for these endpoints after the primary CSR data cut-off. For details on this analysis, refer to the primary analysis SAP.

3 Sample size calculation

Refer to Section 2.11 of the primary analysis SAP for details

4 Change to protocol specified analyses

Table 4-1 Changes to protocol specified analysis or descriptions and rationale

Protocol section	Protocol description	Change	Rationale
10.5.4.1	Exposure-adjusted adverse event incidence, defined as number of patients with new or worsened AEs during period/[total number of days patient was on treatment summed for all patients/365.25 days], will be presented	Exposure-adjusted AE incidence will not be presented	Core phase duration is same for both arms and hence not generated for safety set 3 in EoC CSR. No comparison planned between crossover to DFX Granule in DT arm and DFX Granule arm for entire granule

	period in safety set 4 irrespective of heterogenous follow-up.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

The following rule should be used for the imputation of **date of last administration**:

Scenario 1: If the date of last administration is completely missing and there is no EOT eCRF page, the patient is considered as on-going. The patient should be treated as on-going and the cut-off date should be used as the last dosing date.

Scenario 2: If the date of last administration is completely or partially missing and the EOT eCRF page is available (prior to any death date or withdrawal of consent date, if available):

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

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

Use **Dec31yyyy**

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

Use **EOT date**

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

mm < the month of EOT visit:

Use last day of the Month (mm)

mm = the month of EOT visit:

Use EOT day.

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

Use the start date of that record.

Patients with missing start dates are to be considered missing for all study treatment component related calculations and no imputation will be made. If the date of first administration is missing, then the date of last administration should not be imputed.

Note: In order to handle partial start dates issue when identifying extension phase treatment start date, "record number" and "extension"variables will be used to identify the first DAR record in extension phase. More details in PDS.

There will be no attempt to impute any other date from eCRF DAR page.

In the rare cases that there is missing EOT eCRF pages, EOT date will be imputed using the last non-zero DAR record.

5.1.2 AE, concomitant medication, and other safety assessment date imputation

Every effort will be made to get the missing information on partial dates. However, despite best efforts, some partial dates might still exist in the database. They will be listed as is. If needed in a calculation (e.g. duration), the standard Novartis Oncology imputation rules will be used.

Table 5-1 Imputation of start dates (Adverse events, Concomitant Medications, etc.)

Missing Element	Rule
day, month, and year	• No imputation will be done for completely missing dates

day, month	• If available year = year of study treatment start date then
	  o If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY
	  o Else set start date = study treatment start date.
	• If available year > year of study treatment start date then 01JanYYYY
	• If available year < year of study treatment start date then 01JulYYYY

day	• If available month and year = month and year of study treatment start date then
	  o If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY.
	  o Else set start date = study treatment start date.
	• If available month and year > month and year of study treatment start date then 01MONYYYY
	• If available month and year < month year of study treatment start date then 15MONYYYY

Table 5-2 Imputation of end dates (Concomitant Medications)

Missing Element	Rule *=last treatment date plus 30 days non > (death date, cut-off date)
day, month, and year	• No imputation will be done for completely missing dates

Missing Element	Rule *=last treatment date plus 30 days non > (death date, cut-off date)
day, month	• If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the on-treatment period*
day	• If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period*

Any AEs and ConMeds with partial/missing dates will be displayed as such in the data listings.

Any AEs and ConMeds which are continuing as per data cut-off will be shown as 'continuing' rather than the end date provided.

5.2 Laboratory parameters

5.2.1 Derivations

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

k = 0.55 for girls ≥ 13 years based on current age

k = 0.70 for boys ≥ 13 years based on current age

The following rules will be applied for local lab data to derive the WBC differential counts when only percentages are available

Absolute value = (WBC count) * (Value (%) / 100)

The unit of this absolute value will be the unit of WBC count.

5.2.2 Handling of Special character in Laboratory data

If the values (results and ranges) of the laboratory parameters like Hematology, Biochemistry and urinalysis are provided as '<X' or '>X' (i.e. below limit of detection either lower or upper side), prior to conversion of laboratory values to SI unit, these numeric values are set to X for the analysis purposes, after removing the '<'/'>' symbol, when generating the tables and figures which are related to above mentioned laboratory parameters e.g., descriptive and shift tables of laboratory parameter. However, in case of listing actual values with '<'/'>' symbol will be reported.

5.3 Time windows

5.3.1 Study drug exposure

Study drug will be dispensed at randomization (week 1), then every four weeks. Dose adjustments based on safety are allowed at any time point during the study.

Information on study drug strength will be collected on the Dose Administration Record (DAR) eCRF and includes the planned dose (mg/kg/day), actual total daily dose (mg) taken, reason for the dose change, start date and end date.

Table 4-3 shows the defined study periods for drug exposure.

All assessments within a time period will be used to calculate the drug exposure for the corresponding period.

Table 4-3 Study periods for drug exposure

Period	Visit Period Definition
Month 1	Study Day 1 – 28
Month 2	Study Days 29 – 56
Month y (with y=3, 4, 5,…)	Study Days (y-1)*28+1 to (y)*28
Etc.	
*Study Day 1 = first day of study treatment	

5.3.2 Laboratory data and vital signs

If two or more assessments are performed within a time window then the assessment closest to the planned visit is used in analyses by time window. When two values are equidistant from the planned assessment, the later one is used in analyses. When multiple values are reported on the same day then the average value is used in analyses. For parameters with categorical results, the one from central laboratory is used in analyses. If multiple values are reported on the same day from local and central laboratory, the central laboratory value is used in analyses. If only local lab assessments are collected, then local lab values are considered for analyses.

For worst post-baseline assessment, all on-treatment values are considered regardless of time windows.

Table 5-4 shows the defined time windows.

Table 5-4 Time windows for laboratory data, vital signs, weight and BMI

Time Window	Planned Visit Timing	Time Window Definition
On treatment		
Baseline	On or before Study Day 1*	≤ Study Day 1

Time Window	Planned Visit Timing	Time Window Definition
On treatment		
Week 2**	Study Day* 8	Study Days 2 – 11 (excluded baseline assessment)
Week 3**	Study Day* 15	Study Days 12 – 18
Week 4**	Study Day* 22	Study Days 19 – 25
Week 5	Study Day* 29	Study Days 26 – 42
Every 4 weeks thereafter		
Week y=5+4*k (with k = 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12…)	Study Day (5+4*k-1)*7+1	Study Days (5+4*k-1)*7+1-14 to (5+4*k-1)*7+1+13 Notes: - EOT data visit are included if obtained within the next 7* days of last non-0 dose intake (*NA for patients continuing in extension phase).

* Study Day 1 = first day of study treatment
** where appropriate (e.g. week 2 time-window NA for serum ferritin)

5.3.3 Growth data

Table 5-5 summarizes the time windows for growth data, where windows are centered at every 6 months after start of deferasirox. If there is more than one assessment within the time window, the last available assessment in that time window will be used. Although height and weight could be collected more frequently than every 6 months, this choice of time window length was made to reflect the degree of accuracy in the reference values (every 6 months) that will be used in the calculation of summary variables of growth (Section 2.7.7).

Table 5-5 Time windows for growth data

Assessment	Time window
Baseline	Treatment Days up to 1
Month 6	Treatment Days 85 – 252
Month 12	Treatment Days 253 – 420
Month 18	Treatment Days 421 – 588
Month 24	Treatment Days 589 – 756
Month 30	Treatment Days 757 – 924
Month 36	Treatment Days 924 – 1092
Month 42	Treatment Days 1093 – 1260
Month 48	Treatment Days 1261 – 1428
Month 54	Treatment Days 1429 – 1596
Month 60	Treatment Days 1597 – 1764
etc.	

Treatment Day 1 = date of first intake of deferasirox

5.3.4 Ocular data

Ocular data will be collected at screening visit, at patient visit 11 and at end of treatment visit during the core phase and annually during the extension phase. If two or more assessments are performed within a time window then the assessment closest to the planned visit is used in analyses by time window. When two values are equidistant from the planned assessment, the later one is used in analyses.

For worst post-baseline assessment, all on-treatment values are considered regardless of time windows.

Table 5-6 and Table 5-7 show the defined time windows.

Table 5-6 Time windows for ocular data in core phase

Time Window	Planned Visit Timing	Time Window Definition
On treatment		
Baseline	On or before Study Day 1*	≤ Study Day 1
Week 25	Study Day 169	Study Days 140 – 197
EOT_Core	NA	- EOT-core visit are included if obtained within the next 14^ days of last non-0 dose intake (^NA if patients continuing in extension phase). - Week 49 visit for patients continuing into extension - For the post-baseline assessments, if no data were collected at the EOT visit the last available post-baseline data on or before the last non-zero dose will be used for EOT - Core.
*Study Day 1 = first day of study treatment		

Table 5-7 Time windows for ocular data in extension phase

Time Window	Planned Visit Timing	Time Window Definition
On treatment		
Baseline	On or before Study Day 1*	≤ Study Day 1

Time Window	Planned Visit Timing	Time Window Definition
On treatment		
Week# y=5+4*k with (k = 24, 37,…to 89 with increments of 13)	Study Day (5+4*k-1)*7+1	Study Days (5+4*k-1)*7+1-59 to (5+4*k-1)*7+1+58
EOT_Ext	NA	- EOT-ext visit are included if obtained within the next 14 days of last non-0 dose intake - For the post-baseline assessments, if no data were collected at the EOT visit the last available post-baseline data on or before the last non-zero dose will be used for EOT - Ext.
*Study Day 1 = first day of study treatment # Every 52 weeks starting from Week 101		

5.4 Month/year derivation

For all derivations, a year will be defined as 365.25 days and a month will be calculated as (365.25 / 12) = 30.4375 days. If duration is to be reported in months, duration in days will be divided by 30.4375.

5.5 Body mass index

Body mass index, in kg/m^2, is a measure of relative weight based on an individual's mass and height.

It is calculated using the following formula, where weight is in kilograms and height is in meter:

BMI = Weight / Height^2

Baseline BMI will be determined using the last available height and weight prior to start of study drug.

5.6 Growth data

SDS will be calculated using the current formulae provided by the WHO as follows:

1. Calculate $z_{ind} = \frac{\left(\frac{X}{M}\right)^L - 1}{LS}$
2. If $|z_{ind}| \leq 3$, SDS = z_{ind}
   If $z_{ind} > 3$, SDS = 3 + (X – SD3*pos*) / SD23*pos*
   If $z_{ind} < -3$, SDS = -3 + (X – SD3*neg*) / SD23*neg*

where:

- *X* is height in centimeters or BMI in kilograms/m^2,
- *L*, *M* and *S* are height or BMI-, sex- and age-specific reference values from the WHO Growth Charts.

- SD3*pos* is the cutoff 3SD calculated by the LMS method:
  $SD3pos = M * (1 + LS*3)^{1/L}$
- SD3*neg* is the cutoff -3SD calculated by the LMS method:
  $SD3neg = M * (1 + LS*(-3))^{1/L}$
- SD23*pos* if the difference between the cutoffs 3SD and 2SD:
  $SD23pos = M * (1 + LS*3)^{1/L} - M * (1 + LS*2)^{1/L}$
- SD23*neg* if the difference between the cutoffs -2SD and -3SD:
  $SD23neg = M * (1 + LS*(-2))^{1/L} - M * (1 + LS*(-3))^{1/L}$

Height-for-age and BMI-for-age L, M and S reference values for males and females are available under http://www.who.int/childgrowth/standards/en/ (for patients aged between 0 to 5 years old) and http://www.who.int/growthref/en/ (for patients aged between 5 to 19 years old). These correspond to the latest available international references available at this time and described in the 2007 Bulletin of the World Health Organization (Mercedes de Onis et al 2007). The age category immediately above the patient's exact age should be used. SDS is actually a Z score that measures the distance from the population mean in units of standard deviations. That is, SDS < 0 refers to values lower than the population mean, and for example SDS ≤ -1.645 refers to values in the lowest 5%. (The usual percentile more commonly used in the clinical practice can be derived from the z-score by a normal distribution).

Note that BMI is reported instead of weight as no reference data are provided by the WHO for age beyond 10.

Height velocity is defined as follows:

Height velocity (cm/6-months) = (height in time window *k* – height in time window *k-1*) ÷ ([assessment date in time window *k* – assessment date in time window *k-1*] x [365.25/2]),

and similarly for weight velocity.

Velocity SDS is calculated as (velocity – mean) / SD, where mean and SD are obtained as the height-, weight-, sex- and age-specific values (Baumgartner et al 1986)), where the age category immediately above the patient's exact age (at the assessment date in time window *k*) should be used. Velocity SDS will only be calculated for time window *k* if data also exists for time window *k-1*, since calculating across multiple units of 6 months requires more than one reference value to be taken into account.

6 Reference

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