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Clinical Development

ICL670/deferasirox/Exjade®

CICL670F2203 / NCT03203850

A phase II, multicenter, open-label, randomized two-year study to evaluate the efficacy and safety of deferasirox film-coated tablet versus phlebotomy in patients with Hereditary Hemochromatosis

Statistical Analysis Plan (SAP)

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18-May-2023	Prior to DB lock	Creation of amendment 1	SAP was updated to reflect the latest changes as per the SAP template version 6.	all
		Creation of amendment 1	Addition of location of the SAP in CREDI	Section 1 - Introduction
		Creation of amendment 1	Addition of purpose of the study and HA commitment	Section 1.1 – Study design
		Creation of amendment 1	Ocular assessment was included in the safety evaluation.	Section 2.1.1-General definitions.
		Creation of amendment 1	Addition of definition of average actual daily dose, average planned daily dose; Clarification of definition of cumulative dose were added; Addition of new definition of dose change; dose reduction; dose increase.	Section 2.3.1-Study treatment/compliance

		Creation of amendment 1	Addition of box plot for serum ferritin	Section 2.4.2 – Statistical hypothesis, model, and method of analysis
		Creation of amendment 1	Removal of supportive analysis	Section 2.4.4 – Supportive analysis
		Creation of amendment 1	Addition of treatment emergent definition. Addition of clear categories of ocular AESI	Section 2.5.2 - Statistical hypothesis, model, and method of analysis
		Creation of amendment 1	Following updates and clarifications added to for the of Ocular data analyses to address HA request: - Clarification of definition of Ocular examinations; summary table ; additional of swimmers plot for key ocular assessment on treatment periods and post treatment periods; Clarification of LogMAR conversion method and	Section 2.6.2 – Ocular examinations

			detailed analysis for Visual acuity ; Addition of clear analysis of Slit lamp, summary table, shift table, listing for abnormalities, listing for MedDRA coded term. Addition of clear analysis of Fundus Oculi, Table and listing for other abnormal findings MedDRA coded term; Addition of analysis - summary table and listing for the color fundus photography with and without abnormalities, Additional listing for findings; general comments and confidence score comments.	
		Creation of amendment 1	Clear specification of AEs Analysis; summary tables	Section 2.6.3 – Adverse Event (AEs)

			for different categories. Addition of separate table of secondary safety objective on the evaluation of safety and tolerability of deferasirox FCT in subjects who interrupt to SF ≤ 100 µg/L and re-initiate therapy when ≥ 300 µg/L. Additional analysis related to COVID-19 AEs.	
		Creation of amendment 1	clear specification of AESI Analysis, summary tables.	Section 2.6.5 - Adverse Event of Special Interest (AESI)
		Creation of amendment 1	Addition of disclosure related output	Section 2.6.6 – Disclosure related outputs
		Creation of amendment 1	Addition of descriptive statistics for the lab results.; redefinition of notable range for Hemoglobin, creatinine clearance. Addition of conversion factor for the lab parameter – urinary protein / creatinine ratio. Addition of summaries of	Section 2.6.7 – Laboratory data

			individual liver function parameters like ALT, AST etc.	
		Creation of amendment 1	redefinition of notable range vital sign(weight)	Section 2.6.8 - Vital Signs and Weight
		Creation of amendment 1	Addition of analysis related to COVID-19 AEs.	Section 4 – Change to protocol specified analyses
		Creation of amendment 1	Addition of Date imputation for AE, LB, CM etc.	Section 5.1 – Imputation rules
		Creation of amendment 1	Update on End of treatment for Time windows for laboratory assessment	Section 5.3.1 – Safety laboratory assessments
		Creation of amendment 1	Addition of Ocular assessment analysis and window period	Section 5.3.2 – Ocular assessments
		Creation of amendment 1	Addition of reference	Section 6 - Reference

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List of Abbreviations

AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
ALP	Alkaline Phosphatase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Classification
BCVA	Best Corrected Visual Acuity
CRS	Case Retrieval Sheet
CSR	Clinical Study report
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	Full Analysis Set
DAR	Dose Administration Record
DI	Dose Intensity
DRL	Drug Reference Listing
FCT	Film-Coated Tablet
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOT	End Of Treatment
EOS	End of study
HGLT	High Level Group Term
HLT	High Level Term
IVR	Interactive Voice Response
MedDRA	Medical Dictionary for Drug Regulatory Affairs
NMQ	Novartis MedDRA Queries
PDI	Planned Dose Intensity
PT	Preferred Term
RDI	Relative Dose Intensity
RR	Response Rate
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SF	Serum Ferritin
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
TFLs	Tables, Figures, Listings
TBL	Total Bilirubin
TTR	Time To Response
WHO	World Health Organization

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses for the clinical study report (CSR) of study CICL670F2203, a phase II, multicenter, open-label, randomized two-year study to evaluate the efficacy and safety of deferasirox film-coated tablet versus phlebotomy in subjects with Hereditary Hemochromatosis.

The content of this SAP is based on protocol CICL670F2203 version 01. All decisions regarding final analysis, as defined in the SAP document, have been made prior to database lock of the study data.

The CSR SAP is located at the following CREDI location:

/CREDI Projects/I/ICL670F/CREDI Studies/ICL670F2203/Administrative Files (study level)/RAP or RAMP Meeting – CICL670F2203_SAP (Statistical Analysis Plan)

1.1 Study Design

This is a randomized, multicenter, open-label, two-year, Phase II study to evaluate the efficacy and safety of deferasirox Film-Coated Tablet (FCT) versus phlebotomy in subjects with Hereditary Hemochromatosis with iron overload.

Eligible subjects will be identified during a 4-week screening period, then randomized to either deferasirox FCT or phlebotomy beginning on Day 1 and treated for 24 months (104 weeks). A total of 150 adults were planned to be randomized in a 2:1 ratio (100 subjects to deferasirox FCT and 50 subjects to phlebotomy). The present study is being conducted to fulfill post-marketing requirements for EXJADE.

After end of treatment (EOT), there is a standard 30-day safety follow-up. If a subject discontinues from treatment in either arm and has completed at least 6 months of assessments, they will be encouraged to continue in a Post-treatment Ocular Follow-up phase and undergo ocular exams every 6 months as scheduled to receive a total of at least 5 ophthalmological examinations. End of study (EOS) occurs after the last subject has completed last visit which includes a 30-day safety follow-up. This last subject may have either completed 24 months (104 weeks) of treatment, or prematurely discontinued and completed ocular assessments. After completing the study or discontinuing from study treatment, subjects will receive standard of care.

The primary analysis will be conducted on all subjects' data after final database lock. No interim analysis is planned.

The present study is being conducted to fulfill post-marketing commitments/ requirements for EXJADE PMC 750-10, NDA 021882) and JADENU (PMR 2888-8, NDA 206910). [redacted]

1.2 Study Objectives and Endpoints

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		Refer to
Assess the response rate in the deferasirox FCT and phlebotomy treatment arms where response is defined by achieving target SF ≤ 100 µg/L on or before 24 months.	Proportion of Subjects achieving target SF ≤ 100 µg/L for the first time.	Section 2.5
Key Secondary		Refer to
Characterize the ocular safety of deferasirox FCT and phlebotomy over 24 months.	Incidence of ocular AEs overall and by severity, type of AE, and relation to study treatment.	Section 2.6
Secondary		Refer to
Evaluate the safety and tolerability of deferasirox FCT and phlebotomy over 24 months.	Incidence of AEs, AEs leading to discontinuation from study, laboratory abnormalities, and deaths.	Sections 2.8
Assess the change from baseline in visual acuity, intra-ocular pressure, retina or/and optic nerve abnormalities, and lens abnormalities at months 6, 12, 18, and 24 of deferasirox FCT and phlebotomy.	Change from baseline at months 6, 12, 18 and 24 in visual acuity, tonometry, slit lamp, and fundus exams.	Section 2.8.1
Assess the safety and tolerability of deferasirox FCT in subjects who interrupt and re-initiate treatment due to SF levels ≤ 100 µg/L and ≥ 300 µg/L.	Incidence of AEs in subjects who interrupt due to reaching target SF ≤ 100 µg/L, then re-initiate therapy at ≥ 300 µg/L.	Sections 2.8
Assess the first time to response (defined as SF ≤ 100 µg/L) between the deferasirox and phlebotomy treatment groups.	Time to reach target SF ≤ 100 µg/L in the deferasirox and phlebotomy arms for the first time.	Section 2.7

2 Statistical Methods

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 to perform all data analyses and to generate tables, figures, and listings.

Data Included in the Analysis

Data from all subjects who signed informed consent will be used in the analysis. All statistical analyses described hereafter will be performed using all data collected in the database up to the final database lock date. The final database lock date will be established after all randomized

subjects have completed 24 months of treatment including safety follow-up if applicable, or have discontinued from the study (see Protocol Section 4.3 for more details) .

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 subjects 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 subjects 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.

2.1.1 General Definitions

Study Treatment

The term study treatment/treatment group will refer both to Deferasirox FCT (DFX) or Phlebotomy.

Date of First/Last Administration of Study Treatment

For Deferasirox FCT:

- The date of first administration of study treatment is derived as the first date when a non-zero actual dose of study treatment was administered as recorded on Dose Administration Record (ZQ) Electronic Case Report Form (eCRF).
- The date of last administration of study treatment is defined as the last date when a non-zero actual dose of study treatment was administered as recorded on ZQ eCRF.

For Phlebotomy:

- The date of first administration of study treatment is derived as the first date when a non-zero volume of blood removed was recorded on Phlebotomy Record eCRF (FAZU) on or after the randomization date.
- The date of last administration of study treatment is defined as the last date when a non-zero volume removed of blood was recorded on Phlebotomy Record eCRF (FAZU). This date will also be referred as ‘last date of study treatment’.

Study Day

The study day **for safety assessments** (e.g. adverse event onset, laboratory abnormality occurrence, vital sign measurement, Electrocardiogram (ECG), Ocular, 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** (i.e. serum ferritin) 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.

Time Unit

A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375.

Baseline

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

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

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

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

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

Subjects 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 Day 1 visit, the other reported to the EOT visit. Data reported at the EOT visit are not eligible for baseline selection.

On-treatment Period

The overall observation period (for both Deferasirox and Phlebotomy) will be divided into three mutually exclusive segments:

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

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). For additional details refer to specific section – Section 2.6.3 details on AEs and Section 5.3.2 on Ocular assessments.

However, all safety data (including those from the post-treatment period) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

Analysis sets

Full Analysis Set

The Full Analysis Set (FAS) comprises all subjects to whom study treatment has been assigned by randomization. According to the intent to treat principle, subjects will be analyzed according to the treatment they have been assigned to during the randomization procedure.

Safety Set

The Safety Set includes all subjects who received at least one administration of study treatment. Subjects will be analyzed according to the study treatment received, where treatment received is defined as the randomized treatment if the subject took that treatment (at least one administration or phlebotomy) or the first treatment received if the randomized treatment was never received.

Screen Failures

Screen failures are subjects who have signed the informed consent and who failed to be randomized for any reason (i.e. failing to meet inclusion or exclusion criteria or any other screening procedure).

Withdrawal of Informed Consent

Any data collected in the clinical database after a subject withdraws informed consent from all further participation in the trial, will not be included in the analysis. The date on which a subject withdraws full consent is recorded in the eCRF.

Death events may be used in the analysis if captured from public records (registers), local law and subject informed consent permitting.

2.1.2 Subgroup of Interest

NA

2.2 Disposition, Demographics and Other Baseline Characteristics

The FAS will be used for all baseline and demographic summaries and listings, unless otherwise specified. Summaries will be reported by treatment arm and for all subjects and listings will be reported by treatment arm to assess baseline comparability. No inferential statistics will be provided.

2.2.1 Subject Disposition

Enrollment by country and center will be summarized by treatment arm using the FAS. The number (%) of randomized subjects included in the FAS will be presented overall and by treatment group. The total number of screen failures will also be displayed in listings. The number (%) of subjects in the FAS who discontinued the study phases and the reason for discontinuation will be presented overall and by treatment group.

The following summaries will be provided (with % based on the total number of FAS subjects):

- Number (%) of subjects who were randomized (based on data from IRT system)
- Number (%) of subjects who were randomized but not treated (based on 'ZQ' & "FAZU" eCRF page)
- Number (%) of subjects who were treated (based on 'ZQ' & "FAZU" eCRF pages of each study treatment component completed with non-zero dose administered)
- Number (%) of subjects who discontinued the study treatment phase (based on the 'End of Treatment Phase' page)
- Primary reason for study treatment phase discontinuation (based on the 'End of Treatment Phase' page)
- Number (%) of subjects who have entered the post-treatment follow-up (based on the 'End of Treatment Phase' page)
- Number (%) of subjects who have discontinued from the post-treatment follow-up (based on the End of Post-treatment follow-up page)
- Reasons for discontinuation from the post-treatment follow-up (based on End of Post-treatment follow-up page)

Listings will also be generated for the subject disposition.

Protocol Deviations

The number (%) of subjects in the FAS with any protocol deviation will be tabulated by deviation category (as specified in the study Data Handling Plan) overall and by treatment group for the FAS.

All protocol deviations will be listed based on FAS. Subjects with COVID-19 related protocol deviations will be presented separately in the table and listing for FAS by category and relationship.

The full list of protocol deviations is documented in the Study Specification Document (SSD). 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/ICL670F2203/TMF (Study Level)/Protocol Deviations" folder. The latest available tracker prior to database lock will be used.

Analysis Sets

The number (%) of subjects in each analysis set (defined in Section 2.1.1) will be summarized by treatment group.

2.2.2 Demographics and Other Baseline Characteristics

The FAS will be used for all subject demographic and baseline characteristic summaries and listings, unless otherwise specified.

Basic Demographic Data

All demographic and baseline disease characteristics data will be summarized and listed by treatment arm. Categorical data (e.g. gender, age groups: 18 to <65 and ≥65 years, race, and ethnicity) will be summarized by frequency counts and percentages; the number and percentage of subjects with missing data will be provided. Continuous data (e.g. age and weight) will be summarized by descriptive statistics (N, mean, median, standard deviation, minimum and maximum).

The number of subjects by sex and age categories and the number of subjects by race will be tabulated.

Phlebotomy History

Summary statistics will be provided for the volume of blood removed (average of the volume removed per subject) and the frequency (number of procedures per subject) of phlebotomy procedure (based on records reported before the randomization date in 'Phlebotomy Record' page).

Average Volume Removed per subject = Sum of Volume removed/frequency
A listing will also be provided.

Medical History

Medical history and ongoing conditions entered on (e) CRF will be summarized and listed by treatment arm. Separate summaries will be presented for ongoing and historical medical conditions. The summaries will be presented by primary system organ class (SOC), preferred term (PT) and treatment arm. Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.

Ocular medical history and ongoing conditions will be summarized and listed by treatment arm.

Other Baseline Characteristics

Descriptive statistics, frequency counts and percentages will be tabulated by treatment arm, as appropriate for history of cirrhosis (yes or no), clinically significant abnormality in ECG (yes or no) and overall interpretation in audiometric test (normal or clinically significant or insignificant abnormality) on the Safety set.

The Serum Ferritin at baseline will be summarized as both continuous (descriptive statistics) and categorical variable. It will be categorized as: <1000, ≥1000 to 2000, >2000 µg/L

All data collected will be listed.

2.3 Treatments (Study Treatment, Rescue Medication, Concomitant Therapies, Compliance)

The Safety Set will be used for medication data summaries and listings, unless otherwise specified.

2.3.1 Study Treatment / Compliance

Deferasirox FCT

Duration of exposure, daily dose, cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized by treatment arm. Duration of exposure will be categorized into time intervals; frequency counts and percentages will be presented for the number (%) of subjects in each interval. The number (%) of subjects who have dose reductions, increases, or interruptions, and the reasons, will be summarized by treatment group.

Subject level listings of all doses administered on treatment along with dose change reasons will be produced.

The safety set will be used for all summaries and listings of study treatment.

1. Duration of Exposure & Daily Dose

- **Duration of exposure to DFX FCT (days)** = (date of last administration of study treatment) – (date of first administration of study treatment) + 1.

Summary of duration of exposure of DFX FCT in appropriate time units will include categorical summaries based on <12, 12-<24, 24-<52, 52-<76 and >76 weeks and continuous summaries (i.e. mean, standard deviation etc.).

- **Average Actual Daily Dose (mg/kg/day)** = Sum of all ((Dose X/current weight) * Corresponding duration of exposure on dose X) / overall duration of exposure
- **Average Planned Daily Dose (mg/kg/day)** = Sum of all (Dose X * Corresponding duration of exposure on dose X) / overall duration of exposure

Average daily dose is the dose over all days between first and last dose, excluding interruptions. 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. The planned dose in the eCRF is reported in mg/Kg unit, and therefore the dose is already adjusted for the subject weight when calculating the average planned daily dose.

2. Cumulative Dose

The planned daily dose of a subject is collected on the CRF page as dose prescribed in mg/kg/day and the actual daily dose is calculated by dividing the total daily dose collected on the CRF page in mg by the current weight (kg) corresponding to that visit. The current weight is equal to the weight on the same visit when dose had been administered or the last available weight before the dosing visit if the same visit weight is missing. Cumulative dose (mg/kg) is defined as the sum over the daily doses of all days between first and last dose.

Cumulative dose = sum of (daily dose at a visit * (end date of dose –start date of dose +1).

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

For subjects who did not take any drug the cumulative dose is by definition equal to zero.

The actual cumulative dose is the sum of the non-zero doses recorded over the dosing period and the planned cumulative dose is the planned starting dose summed over the same dosing period.

3. Dose Intensity and Relative Dose Intensity

- **Actual Dose Intensity (DI)** for subjects with non-zero duration of exposure is defined as follows:

  DI (mg/kg/day) = Actual Cumulative dose (mg/kg) / Duration of exposure to DFX FCT (day).

For subjects who did not take any drug the DI is by definition equal to zero. The denominator for DI, i.e., duration of exposure includes days of 0 doses.

- **Planned Dose Intensity (PDI)** is defined as follows:

  PDI (mg/kg/day) = Planned Cumulative dose (mg/kg) / Duration of exposure to DFX FCT (day).

- **Relative Dose Intensity (RDI)** is defined as follows:

  RDI = [DI (mg/kg/day) / PDI (mg/kg/day)]*100.

The actual dose intensity and relative dose intensity will be summarized using descriptive statistics using the Safety Set. Additionally, categories of the RDI (<= 75%, >75% -90%, >90%-110%, >110%) will be summarized through frequency and percentage.

Dose Reduction/ Increases, Interruptions or Permanent Discontinuations

The number of subjects who have dose reductions, increases, permanent discontinuations or interruptions, and the reasons, will be summarized separately for each of the study treatment components in the DFX arm only.

'Dose Changed', 'Dose interrupted', and 'Dose permanently discontinued' fields from the DAR CRF pages will be used to determine the dose reductions, dose interruptions, and permanent discontinuations, respectively.

The corresponding fields 'Reason for dose change/dose interrupted' and 'Reason for permanent discontinuation' will be used to summarize the reasons.

A dose change is either 'change in prescribed dose level' or 'change in actual dose administered' where the dose is different from previous visit (increase or decrease). 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 these mentioned multiple entries on consecutive days, then it will be counted as one interruption.

Dose Reduction: When in the DAR CRF page, dose change field is equal to 'yes' and the reason for dose change is present, then a dose reduction is considered if the non-zero actual daily dose administered (mg) , after weight adjustment in mg/kg, is *lower* (>15%) than the previous non-zero actual daily dose administered (mg), and after weight adjustment in mg/kg (threshold of >15% is applied to the dose adjusted for weight in mg/kg, see below, received by the subject or if the non-zero actual daily dose administered (after weight adjustment in mg/kg) is *lower* (>15%) than the dose amount based on the prescribed dose (mg/kg).

Dose Increases: When in the DAR CRF page, dose change field is equal to 'yes' and the reason for dose change is present, then a dose increase is considered if the non-zero actual daily dose administered (mg), after weight adjustment in mg/kg, is *higher* (>15%) than the previous non-zero actual daily dose administered (mg), and after weight adjustment in mg/kg (threshold of >15% is applied to the dose adjusted for weight in mg/kg, see below, received by the subject or if the non-zero actual daily dose administered (after weight adjustment in mg/kg) is *higher* (>15%) than the dose amount based on the prescribed dose (mg/kg).

Any dose change to correct a dosing error will not be considered a dose reduction (subject goes back to previous prescribed/actual dose after a dose change due to dosing error) or a resumption of dose as per protocol after an interruption (subject goes back to previous prescribed/actual dose after a dose interruption as per protocol). The threshold of 15% is applied to the percentage change of dose calculated by $(D_{previous}\text{-}D_{current}/D_{previous}) \times 100$.

For example, due to weight adjustments when calculating actual dose differences between current and previous dose, 15% increment or decrement is checked when comparing current non-zero actual dose with previous non-zero actual dose when checking for dose resumption after an interruption as per protocol.

Dose reductions/increases will be derived programmatically, and number of dose reductions/increases will be reported.

Phlebotomy

Summary statistics will be provided for duration of exposure, average volume of blood (mL) removed and average frequency of procedure by treatment arm.

For each subject, listing of each phlebotomy administered along with the volume removed and the hematocrit record will be produced. Any subjects from DFX FCT arm with Phlebotomy during post treatment follow up will be flagged.

2.3.2 Prior and Concomitant Therapies

Concomitant Medications

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) other than the study treatment administered to a subject coinciding with the study treatment period. Concomitant therapy includes medications (other than study treatments) starting on or after the start date of study treatment or medications starting prior to the start date of study treatment and continuing after the start date of study treatment.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Reference Listing (DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (ATC) classification system and summarized by ATC level 2 and preferred term using frequency counts and percentages. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and preferred term. These summaries will include:

1. Medications starting on or after the start of study treatment but no later than 30 days after start of last dose of study treatment and
2. Medications starting prior to start of study treatment and continuing after the start of study treatment.

All concomitant therapies will be listed. Any concomitant therapies starting and ending prior to the start of study treatment or starting more than 30 days after the last date of study treatment will be flagged in the listing. The safety set will be used for all concomitant medication tables and listings.

Prior Therapies

Prior medication is defined to be drugs starting and ending prior to the first dose of study medication. The number and percentage of subjects who received any prior medications will be listed and summarized by treatment arm by lowest ATC class, preferred term, and treatment.

The above analyses will be performed using the FAS.

2.4 Analysis of the Supporting Primary Objective

The primary objective of this study is to assess the response rate (RR) of deferasirox FCT and phlebotomy treatment arms where response is defined by achieving target Serum Ferritin (SF) $\leq$ 100 μg/L on or before month 24 (week 104).

2.4.1 Primary Endpoint

The primary endpoint is the RR by month 24 (week 104) , i.e. the proportion of subjects whose SF ≤ 100 µg/L for the first time on or before month 24 (week 104) . All post-baseline SF values collected until week 104 (EOT) will be considered to derive the primary endpoint (including unscheduled and repeat measurements).

The primary analysis will be carried out in the FAS.

2.4.2 Statistical Hypothesis, Model, and Method of Analysis

RR is defined as the proportion of subjects whose SF ≤ 100 µg/L at any time on or before month 24 and the response rate will be summarized (proportion) by treatment arm along with two-sided exact binomial 95% CIs [Clopper and Pearson 1934]. The analyses will be descriptive only. No formal hypothesis testing is planned.

In addition, a box plot for serum ferritin by timepoint and treatment arm and line graph for individual subject values for serum ferritin by timepoint and treatment arm will be plotted.

2.4.3 Handling of Missing Values/ Discontinuations

For the primary analysis, subjects are considered responders if they meet response criteria for the primary endpoint on or before month 24 (week 104). Any subject who discontinues treatment prematurely before meeting such criterion is counted as non-responder. Any subjects with unknown or missing SF (no viable post-baseline SF assessment during the study) by 24 months will also be counted as non-responder.

2.5 Analysis Supporting Secondary Objectives

The key secondary objective for this study is to characterize the ocular safety of deferasirox FCT and phlebotomy over 24 months.

2.5.1 Key Secondary Endpoint

The key secondary endpoint is the Ocular Adverse Event as defined by AESI of "Lens disorders, retinal disorders and optic neuritis". This analysis will be carried out in the Safety Set.

2.5.2 Statistical Hypothesis, Model, and Method of Analysis

To characterize long-term ocular safety, the incidence of treatment-emergent ocular AEs (new or worsening from baseline) will be summarized (along with two-sided exact binomial 95% CIs [Clopper and Pearson, 1934]) by preferred term, overall and by severity, type of AE (e.g. serious, leading to study drug discontinuation, requiring dose adjustment or/and interruption), and relation to study treatment.

Treatment-emergent AEs are defined as AEs started during on-treatment period: from the day of the first dose of study medication or the first phlebotomy to 30 days after the last dose of study medication or last phlebotomy.

All ocular AEs included under "Lens disorders, retinal disorders and optic neuritis" Adverse Event of Special Interest (AESI, listed in the compound case retrieval strategy) will be reported.

The above analysis will also be repeated for the overall period (on-treatment & post-treatment).

The analyses will be descriptive. No formal hypothesis testing is planned for this key secondary objective.

A listing of Ocular AEs will also be generated, and post-treatment events will be flagged.

2.6 Analysis of Secondary Efficacy Objective

The secondary efficacy objective is to assess the first time to response of achieving SF ≤ 100 µg/L between the deferasirox and phlebotomy treatment arms.

2.6.1 Secondary Efficacy Endpoint

The secondary efficacy endpoint of the study is the time from the date of randomization to the date of the first time the SF is achieving a value ≤ 100 µg/L on or before month 24 (week 104) , defined as Time To Response (TTR). This analysis will be carried out in the FAS.

TTR (in months) will be listed and summarized by treatment arm. The distribution of time to response will be estimated using the Kaplan-Meier method and the median time to response will be presented along with 95% confidence interval only if a sufficient number of responses is observed.

No inferential analysis that compares time to response between the two treatment arms will be performed.

Subjects who do not achieve SF ≤ 100 µg/L will be censored as follows:

- at the last serum ferritin assessment date on or before month 24 (week 104),
- at the day of randomization if a subject does not have any post-baseline serum ferritin value,
- at the death date

Secondary Safety Objectives

Secondary safety objectives include:

- Assessment of change from baseline in visual acuity, intra-ocular pressure, retina or/and optic nerve abnormalities, and lens abnormalities at months 6, 12, 18, and 24.
- Evaluation of safety and tolerability of deferasirox FCT and phlebotomy over 24 months
- Evaluation of safety and tolerability of deferasirox FCT in subjects who interrupt due to SF ≤ 100 µg/L and re-initiate therapy when ≥ 300 µg/L.

Unless otherwise specified, the following analyses will be performed by treatment arm on the Safety Set. All data, regardless of observation period, will be listed by treatment arm. Safety assessments starting during the pre-treatment or post-treatment period will be flagged in the listings. Safety assessments starting prior to study day 1 will appear with negative study day in the listings.

2.6.2 Ocular Examinations

Each ocular examination will be analyzed by eye side and treatment arm separately for the overall (on-treatment and post-treatment) period. 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. Furthermore, swimmer plots for key ocular assessments of interest will be generated along with dosing information to delineate the ocular assessments which were on the on-treatment and post-treatment periods. See additional details in (Ocular Assessments Section 5.3.2)

Visual Acuity

The visual acuity will be measured using an Early Treatment Diabetic Retinopathy Study (ETDRS) chart. A letter score is calculated based on the number of letters that can be correctly identified from specified distances. The ETDRS score entered into the CRF pages accounts for the distance at which the measurement was made (Section 1.1 of Manual of Ophthalmic Procedures for CICL670F2203); there will be no further adjustment while calculating logMAR. For low luminance and standard acuity measures, visual acuity will be described on a logMAR scale for all measures. For including acuity obtained with the ETDRS letters, the values will be converted to a logMAR scale, using the following formula (Beck et al, 2003):

$$\text{logMAR} = 1.7 - 0.02 * \text{ETDRS score},$$

where ETDRS score is the visual acuity ETDRS score. Finger counting, hand motion, and light perception will be assigned logMAR values of 2.0, 2.3, and 2.6 respectively (with a 0.3 logMAR increment per step). No light perception will be assigned a logMAR value of 2.9 (based on Lange et al, 2009).

The following shift tables will be generated using the categories (<0.1, ≥0.1 to <0.2, ≥0.2 to <0.3, ≥0.3 to <0.6, ≥0.6) 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)

Swimmer plots will be generated to show the change in the categories of logMAR at baseline versus scheduled visits by treatment arm and eye side. The on- treatment period will also be displayed on the plot.

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 for the overall period -

- 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.

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

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 subjects 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.

Slit Lamp

For each considered evaluation type (Lids, Cornea, Conjunctiva, Iris, Anterior chamber, Aqueous flare, Aqueous inflammatory cells, Lens) and eye side, the number & percentage of subjects with and without abnormality (normal, insignificant, clinically significant) will be provided by timepoint and treatment arm. Further, shift tables will be generated for each eye, evaluation type, and treatment arm by time point separately. 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. A listing of subjects with any abnormality will be provided. Subjects with abnormalities recorded in free text of "Abnormalities" section of the "Ophthalmic Examinations - Slit Lamp Exam" CRF for the following eye parts - lids/lashes, cornea, conjunctiva, iris & anterior chamber will be coded using MedDRA (version 26.0) and these coded ocular terms will be summarized using frequency counts and percentages by timepoints. Further, subjects with abnormalities recorded in free text of "Abnormalities" section of the "Ophthalmic Examinations - Slit Lamp Exam" CRF abnormalities for the following eye parts – aqueous flare, aqueous inflammatory cells, lens will be reported as recorded in CRF by frequency and percentages. A listing for the MedDRA coded ocular terms will also be presented.

Lens Opacification

The Lens opacification will be measured by the LOCSIII with categories as mentioned in the CRF. These assessments will be summarized using shift tables – the changes in LOCSIII grade will be presented for each eye, evaluation type (Nuclear Color, Nuclear Opalescence, Cortical, Posterior Subcapsular) and treatment arm by time point. Additionally, the worst change in grade compared to baseline for each eye, evaluation type, and treatment arm will also be presented using shift tables. Swimmer plots will be generated to show the categories of LOCSIII at baseline versus scheduled visits for each of the evaluation types by treatment arm and eye side. The treatment duration will also be displayed on the plot. A listing of subjects will be provided.

Fundus Oculi

For each considered evaluation type (Peripheral Retina, Macula, Optic Nerve, & Vitreous Hemorrhage) and eye side, the number & percentage of subjects with and without abnormality 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. Subjects with abnormalities recorded in free text of "Other Findings (Abnormalities)" section of the "Dilated Fundus Examination" CRF will be coded using MedDRA (version 26.0) and these coded ocular terms will be summarized by timepoints using frequency counts and percentages. A listing for the MedDRA coded ocular terms will also be presented.

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. A listing of subjects will be provided; additionally, listings for the findings, general comments and confidence score comments will be presented.

2.6.3 Adverse Events (AEs)

Adverse Event summaries will include all AEs occurring during on treatment period (see Section 2.1.1).

In AE summaries, the primary system organ class will be presented alphabetically, and the preferred terms will be sorted within primary SOC in descending frequency. The sort order for the preferred term will be based on their frequency in the Deferasirox FCT arm.

The following adverse event summaries will be produced by treatment arm. A subject with multiple occurrences of an AE will be counted only once in the respective AE category.

- Adverse events, regardless of study treatment relationship by primary system organ class, preferred term, and severity (mild, moderate & severe)
- Adverse events with suspected study treatment relationship by primary system organ class, preferred term, and severity

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

To assess the secondary safety objective on evaluation of safety and tolerability of deferasirox FCT in subjects who interrupt due to SF ≤ 100 µg/L and re-initiate therapy when ≥ 300 µg/, the number (%) of subjects who met the criteria of interruption due to SF ≤ 100 µg/L and re-initiation of therapy when ≥ 300 µg and interruption due to SF ≤ 100 µg/L will be summarized respectively.

The summaries from above (barring the last two) will be repeated for subjects who interrupted deferasirox FCT at least once due to SF ≤ 100 µg/L and re-initiated ≥ 300 µg/L will be tabulated. If less than 10 subjects meet the above criteria, only listings will be generated.

AEs will be summarized by presenting the number and percentage of subjects having at least one AE, and having at least one AE by system organ class and preferred, severity and relation to study treatment by arm. A subject with multiple occurrences of an AE will be counted only once in the worst AE category (if it occurs in multiple categories).

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.

Additionally, for those with dose interruptions (FCT re-initiation), the overall summary for the AEs will generated as described above.

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.

Summaries of COVID related adverse events as defined in the eCRS will be provided by treatment arm. A listing of COVID related AEs and deaths will also be generated.

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

2.6.4 Deaths

Separate summaries for on-treatment and all deaths (including post-treatment death) will be produced by treatment arm, system organ class and preferred term (primary reason of death).

All deaths will be listed, pre-treatment (if any) and post treatment deaths will be flagged.

2.6.5 Adverse Events of Special Interest (AESI)

An adverse event of special interest is a grouping of adverse events that are of scientific and medical concern specific to compound ICL670. These groupings are defined in the eCRS using MedDRA terms, SMQs, HGLTs (high level group terms), HLT and PTs. Customized SMQs (NMQ) may also be used. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad. The latest version of the eCRS available at the time of the analysis will be used.

For each specified AESI, number and percentage of subjects with at least one event of the AESI occurring during on treatment period will be summarized.

Summaries of these AESIs will be provided for each of the two treatment arms by grouping and preferred term –

- AESIs, regardless of study treatment relationship
- AESIs, with suspected study treatment relationship
- Serious AESIs regardless of study treatment relationship
- Serious AESIs with suspected study treatment relationship
- AESIs leading to study treatment discontinuation
- AESIs requiring dose adjustment or study treatment interruption
- AESIs requiring additional therapy
- AESIs Outcomes – Recovered or Recovering
- Deaths (all and on-treatment)

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

2.6.6 Disclosure Related Outputs

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables will be produced for the Safety Set 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 subject, 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 AEs in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

2.6.7 Laboratory Data

On analyzing laboratory, data from all sources (central and local laboratories) will be combined. The summaries will include all assessments available for the lab parameter collected no later than 30 days after the last study treatment administration date (see Section 2.1.1).

The following summaries will be produced for hematology, urinary, and biochemistry laboratory data (by laboratory parameter and treatment):

- Descriptive Statistics for lab results and change by from baseline time point and treatment arm
- Shift tables using notable/extended ranges to compare baseline to the worst on-treatment value for key lab parameters (see Table 2-1)
- Shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.
- Trends of key lab parameter values over time (baseline and selected on-treatment timepoints) will be displayed via boxplots based on time windows and corresponding tables displaying the statistics used for the box plots by the selected time points.

The following listings will be produced for the laboratory data:

- Listings of all laboratory data, with classification relative to the laboratory normal range.
- Listing of all lab abnormalities based on notable/extended ranges

Table 2-1 Definition of notable/extended ranges for key safety laboratory parameters

Parameter	Criteria
Absolute neutrophils	< 1.5×10^9/L (extended range < 0.5×10^9/L)
Platelets	< 100×10^9/L (extended range < 50×10^9/L)
Hemoglobin	< 100 g/L
ALT and AST	> 5× ULN and > 2× baseline (extended range > 10× ULN and > 2× baseline)
Total bilirubin	> 2 x ULN
Serum creatinine	> 33% increase from baseline and > ULN at 2 consecutive measurements at least 7 days apart
Creatinine clearance	< 60 mL/min at 2 consecutive measurements at least 7 days apart (extended range < 40 mL/min at least 7 days apart)
Urinary protein/creatinine ratio*	≥ 1.0 mg/mg at 2 consecutive measurements at least 7 days apart

* If the unit of the parameter (Urinary protein/creatinine ratio) is in mg/mmol then will have to use a conversion factor as 0.00885 to convert into mg/mg unit for further derivation.

For all analyses, creatinine clearance will be re-derived using the Cockcroft-Gault equation described in Section 5.2.1.

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

A figure displaying time course of hepatic function tests (ALT, AST, TBL, ALP) in subjects with Hy's law (ALT or AST > 3xULN & TBL > 2xULN & ALP < 2xULN) will be displayed in the Safety Set.

2.6.8 Vital Signs and Weight

Vital signs collected on treatment will be summarized. Values measured outside of on treatment period will be flagged in the listings.

For analysis of vital signs the clinically notable vital sign criteria are provided in Table 2-2 below and the windowing for vital signs are in Table 5-3.

Table 2-2 Definition of notable ranges for vital signs and weight

Parameter	Criteria for notable ranges
Systolic blood pressure	≥ 180 mmHg / ≤ 90 mmHg with increase / decrease from baseline ≥ 20 mmHg
Diastolic blood pressure	≥ 105 mmHg / ≤ 50 mmHg with increase / decrease from baseline ≥ 15 mmHg
Pulse rate	≥ 120 bpm / ≤ 50 bpm with increase / decrease from baseline ≥15 bpm
Weight	≥ 10% increase or decrease

The number and percentage of subjects with notable vital sign values (high/low) will be presented by treatment arm.

A listing of all vital sign assessments will be produced by treatment arm and notable values will be flagged. In the listing, the assessments collected outside of on-treatment period will be flagged.

2.6.9 Other Safety Data

The number and percentage of subjects with clinically significant abnormalities in ECG test and auditory evaluation will be presented by treatment arm. A listing of all ECG and auditory assessments will be produced by treatment arm and the assessments collected during the post-treatment period will be flagged.

Results from pregnancy tests will be listed and positive results will be flagged.

3 Sample Size Calculation

The primary objective of the study is to estimate response rates and therefore the sample size is not based on power calculations. Sample size calculations were performed for the deferasirox FCT and phlebotomy arms to estimate the response rate with reasonable accuracy (half-width of 95% confidence interval).

Based on the Exjade study ICL670A2202, the subject dropout rate at month 6 (core study) is 24% and 12% at month 12 (optional extension phase). Assuming decreasing dropout rate over time and expected better subject compliance with deferasirox FCT formulation, a sample size of 100 subjects in the FCT arm is expected to have at least 60 subjects followed for 24 months to fulfil the FDA post-marketing requirement with regard to the ocular toxicity assessment in subjects receiving deferasirox.

With a sample size of 100 on deferasirox FCT and 50 subjects on phlebotomy, the projected half-widths of the 2-sided 95% confidence interval assuming various response rates are displayed in Table 3-1. The 95% confidence interval half-width extends at most to 0.096 and 0.136 in the deferasirox FCT and phlebotomy arms, respectively.

Table 3-1 Half-width of 95% CI of response rates in deferasirox FCT and phlebotomy arms

Response rate (RR)	Half-width of the 95% CI for deferasirox FCT N=100	Half-width of the 95% CI for phlebotomy N=50
0.60	0.096	0.136
0.65	0.093	0.132
0.70	0.090	0.127
0.75	0.085	0.120
0.80	0.078	0.111
0.85	0.070	0.099
0.90	0.059	0.083

4 Change to protocol specified analyses

Additional analysis related to COVID-19 related AEs and COVID-19 specific protocol deviations (Section 2.2.1 and Section 2.6.3) added. Due to COVID-19, the scheduled assessments had delays and consequently the subjects' assessments were unscheduled. Therefore, the Ocular windowing for the scheduled assessments was updated (see details in Section 5.3.2).

5 Appendix

5.1 Imputation Rules

5.1.1 Study Treatment

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 subject is considered as on-going. The subject 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 this latter date should be used.

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

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).

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.

Subjects 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 ZQ page.

5.1.2 AE, Concomitant medications and safety assessment date Imputation

Table 5-1 Imputation of start dates (AE, CM) and assessments (LB, EG, VS)

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 (AE, CM)

Missing Element	Rule (*=last treatment date plus <30> days not > (death date, cut-off date, withdrawal of consent date))
day, month, and year	Completely missing end dates (incl. ongoing events) will be imputed by the end date of the on-treatment period*
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 ‘ongoing’ rather than the end date provided.

5.1.3 Prior and Concomitant Medication Date Imputation

The imputation of the start date of concomitant medication will follow the same conventions as for AE start date.

5.1.4 Incomplete Date of Diagnosis of Hemochromatosis History

Incomplete dates for date of diagnosis 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.

5.2 Laboratory Parameters Derivations

5.2.1 Re-derived Creatinine Clearance

The re-derived creatinine clearance will be calculated using the Cockcroft-Gault equation.

In the formulae below, CrCl denotes Creatinine Clearance in mL/min, 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.

Cockcroft-Gault formula (≥18 years of age),

CrCl (mL/min)=
Male subjects: (140-age (years)) ×weight (kg)/(815×0.001×SCr (µmol/L))
Female subjects: (140-age (years)) ×weight (kg)×0.85/(815×0.001×SCr(µmol/L))

5.2.2 Multiple Assessments Within Post-Baseline Visits

All scheduled/unscheduled assessments should be assigned to time windows. In case of multiple values per window, the one closest to the planned visit date should be used. If 2 values are equidistant to the planned visit date, the selection should be made by selecting the one assessed by central (if any) and otherwise - for multiple central assessments equidistant to the planned visit - the last value. When multiple values are reported on the same day then the average value is used in analyses.

For worst post-baseline assessment, all on-treatment values are considered regardless of time windows. All unscheduled and repeat measurements will be included in listings.

5.3 Time-Windows

5.3.1 Safety Laboratory Assessments

Safety laboratory data (biochemistry, hematology, and urinary parameters as well as serum creatinine, creatinine clearance and proteinuria) will be collected at screening visits, at each regularly subject 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.

Table 5-3 shows the defined time windows.

Table 5-3 Time windows for safety laboratory data

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 4	Study Day* 22	Study Days 19 – 25
Every 4 weeks thereafter		
Week y=4+(4*k) (with k = 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11,…,25)	Study Day (4+4*k-1)*7+1	Study Days (5+4*k-1)*7+1-14 to (5+4*k-1)*7+1+13
End of treatment	NA	Data collected at EOT visit are included if obtained within the next 30 days of last non-0 dose for DFX intake / non 0 volume removed for Phlebotomy
*Study Day 1 = first day of study treatment		

5.3.2 Ocular Assessments

Ocular data will be collected at screening visit, at week 24, 52, 76, 104 (EOT) visits. If two or more assessments 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. The windowing defined is applicable for both on-treatment & post-treatment time periods. For the summaries by time point, we will be presenting the time points as defined below (Table 5-3).

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

Table 5-4 shows the defined time windows.

Table 5-4 Time windows for Ocular data

Time point (Weeks)	Study Day	Lower Limit (day)	Upper Limit (day)
Baseline (Screening)	1*	-30	1
Week 24	162	2	259
Week 52	358	260	441
Week 76	526	442	623
Week 104	722	624	819

End of Treatment - Data collected at the EOT visit if conducted within 30 days of EOT date on disposition (DS) page in CRF.

For the post-baseline assessments among discontinued subjects, if no data were collected at the EOT visit the last available post-baseline on-treatment data will be used for EOT.

***Study Day 1 =** first day of study treatment

6 Reference

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