NOVARTIS

Clinical Development

ICL670/deferasirox

CICL670AIC04 / NCT02720536

Open-label, multicenter, single arm, phase III study to collect additional safety and efficacy data with deferasirox film-coated tablets in patients completing study CICL670F2201

Statistical Analysis Plan (SAP) Amendment 1

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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
24AUG2018	Prior to DB lock	Creation of final version	N/A - First version	NA
26AUG2019	Prior to DB lock	Working hyperlinks	Update hyperlinks	All
		Insufficient patient numbers for main underlying disease subgroup analysis	Removed main underlying disease as a subgroup of interest	Section 2.2.1 Subgroup of interest
		Insufficient patient numbers for age subgroup analysis	Removed age as a subgroup of interest	Section 2.2.1 Subgroup of interest
		Align baseline creatinine clearance categories with shift table categories	Updated the baseline categories for creatinine clearance	Section 2.4.2 Background and demographic characteristics
		Current unit does not accurately present the data	Updated time since last blood transfusion to be in days rather than years	Section 2.4.2 Background and demographic characteristics
		Insufficient patient numbers for age subgroup analysis	Removed the summary of the relative consumed tablet count by age group	Section 2.5.1 Study treatment/ compliance
		Inconsistency in definition of concomitant medication in SAP vs TFL shells	Clarified definition of concomitant medication	Section 2.5.2 Prior and concomitant therapies

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		Insufficient patient numbers for age subgroup analysis	Removed the summary of the incidence of AEs, regardless of study drug relationship, by age group	Section 2.9.1 Adverse events (AEs)
		Insufficient patient numbers for age subgroup analysis	Removed the summary of AESIs by age group	Section 2.9.1.1 Adverse events of special interest/ grouping of AEs
		Implication of more than one treatment group in a single arm study	Removed the text “and treatment group”	Section 2.9.3 Laboratory data
		Clarification of definition of baseline serum ferritin	Added text to clarify the definition of baseline serum ferritin	Section 4 Change from protocol specified analyses

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List of abbreviations

AE	Adverse event
ALT/SGPT	Alanine aminotransferase/serum glutamic pyruvic transaminase
AST/SGOT	Aspartate aminotransferase/serum glutamic oxaloacetic transaminase
ATC	Anatomical Therapeutic Classification
BMI	Body mass index
C-G	Cockcroft-Gault
CI	Confidence interval
CL	Confidence level for limits
CrCl	Creatinine Clearance
CSR	Clinical study report
DAR	Dosage Administration Record
DFX	Deferasirox
DRP	Data review plan
DT	Dispersible tablet
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EOT	End of treatment
F	Frequency
FAS	Full Analysis Set
FCT	Film-coated tablet
gMean	Geometric mean
HBsAg	Hepatitis B surface antigen
HBsAb	Hepatitis B surface antibody
HCV	Hepatitis C virus
HLT	High level term
ICT	Iron chelation therapy
IDMS	Isotope dilution mass spectrometry
IPSS-R	Revised International Prognostic Scoring System
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Drug Regulatory Affairs
n	Number of non-missing observations
NMQ	Novartis MedDRA queries
PD	Protocol deviation
PK	Pharmacokinetics
PLS	Product Lifecycle Services
PRBC	Packed red blood cells
PRO	Patient-reported outcomes
PT	Preferred term
Q1	Lower quartile
Q3	Upper quartile
RBC	Red blood cell
SAE	Serious adverse event

SAP	Statistical analysis plan
SCr	Serum Creatinine
SD	Standard deviation
SE	Standard error
SI	Standard international
SMQ	Standardized MedDRA queries
SOC	System organ class
SOP	Standard Operating Procedure
TEAE	Treatment emergent adverse event
TFLs	Tables, figures, and listings
ULN	Upper limit of normal range
UPC	Urine protein/creatinine ratio
WBC	White blood cell
WHO	World Health Organization

1 Introduction

This statistical analysis plan (SAP) describes the statistical analysis planned in Section 10 of the study protocol (Clinical Trial Protocol CICL670AIC04 Amended Protocol Version 1, 25 October 2017) along with any additional analyses, specifications, or deviations from the protocol planned before unmasking of the data. This may be used as a first draft of Section 9.7 (Statistical methods planned in the protocol and determination of sample size) and Appendix 16.1.9 (Documentation of statistical methods) of the Clinical Study Report (CSR).

Determination of sample size is specified in Section 3.

This document is written in the future tense. The SAP text will be reviewed and updated (including conversion to past tense) for entry into the CSR after the analysis has taken place.

The data will be analyzed by Novartis Product Lifecycle Services (PLS). Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

1.1 Study design

This is an open-label, multicenter, single arm, phase III study aimed at collecting additional data on safety and tolerability as well as data on efficacy of the film-coated tablet (FCT) formulation in patients with transfusion-dependent thalassemia or myelodysplastic syndrome (MDS) (very low, low or intermediate risk) when treated for more than 24 weeks in CICL670F2201.

Patients from Region Europe participating sites in CICL670F2201who have completed the 24 week treatment period with ongoing tolerance to deferasirox (DFX) (in the investigator's opinion) and fulfilling all other eligibility criteria will be given the opportunity to continue study treatment and follow-up assessments in this study. This will include patients from Region Europe who completed 24 weeks of treatment with either DFX FCT or DFX dispersible tablet (DT) in CICL670F2201; and patients with a lag period between completion of CICL670F2201 and start of this study, i.e. those patients who completed CICL670F2201 and have already switched to commercially available DFX DT or another iron chelation therapy (ICT).

In CICL670F2201, iron-chelation naïve patients were assigned either DFX DT 20 mg/kg once daily or DFX FCT 14 mg/kg once daily. All iron chelation pre-treated patients were assigned a DFX DT or an equivalent FCT starting dose corresponding to their pre-washout dose. At the start of this study, the following was planned to occur:

- Patients continuing directly from CICL670F2201 who were originally randomized to the DFX FCT formulation will continue treatment at the same dose they were assigned at the end of CICL670F2201.
- Patients continuing directly from CICL670F2201 who were originally assigned to the DFX DT formulation will be switched to the DFX FCT formulation and will be assigned a DFX FCT dose equivalent to the DFX DT dose they were assigned at the end of CICL670F2201.
- Patients completing CICL670F2201 who had switched to commercially available DT or other ICT will have to undergo a 5-day washout period and then be assigned an equivalent FCT starting dose corresponding to their last DFX dose on CICL670F2201.

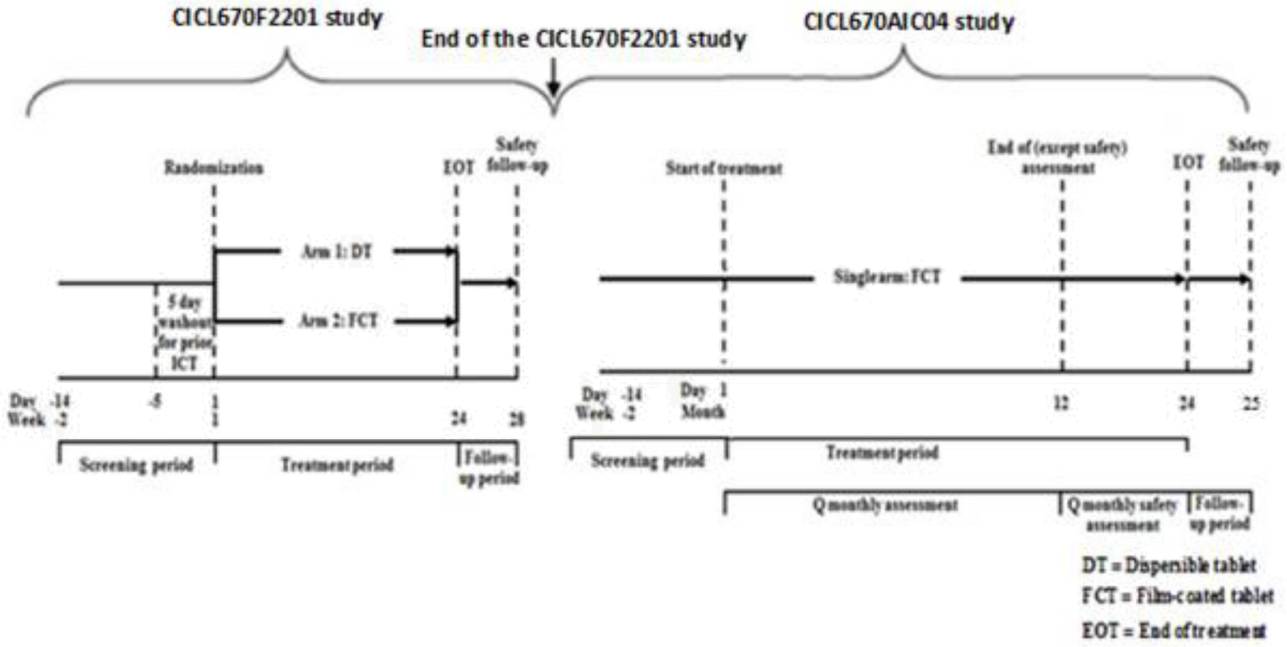
However, no patient for this study continued directly from CICL670F2201.

Study treatment should be administered by the patient once per day, preferably at the same hour. Following enrolment (Visit 3/Day 1) patients will return to the site at 2 week intervals until Visit 5 (Month 1). Thereafter scheduled visits will be monthly. Patients may return to the study center more frequently at the physician's discretion as clinically indicated or as per standard of care. The planned duration of study treatment in this study is for a maximum of 24 months.

According to enrolment of CICL670F2201 in Region Europe, a maximum of 90 patients should be eligible for enrollment in this study. However as only three countries (Austria, Greece, and Italy) are participating in this study which is less than originally foreseen, it is planned to enroll a maximum of 58 patients.

There is no interim analysis planned for this study.

Figure 1-1 Study design



1.2 Study objectives and endpoints

The study objectives and related endpoints are detailed in the following table (Table 1-1).

Table 1-1 Objectives and endpoints

Objective	Endpoint
Primary	
To evaluate the overall safety of DFX FCT formulation in patients with transfusion-dependent thalassemia or MDS at very low, low or intermediate risk	Overall safety, as measured by frequency and severity of adverse events (AEs) and changes in laboratory values of interest i.e. serum creatinine and creatinine clearance*
Secondary	

Objective	Endpoint
To evaluate efficacy of DFX FCT on serum ferritin levels (decrease or maintenance, according to the individual therapeutic goal)	Absolute and relative change of serum ferritin level over time

* Schwartz et al 1987

2 Statistical methods

2.1 Data analysis general information

This study will be conducted under the sponsorship of Novartis.

All analyses will be performed using SAS® statistical software (Version 9.4 or a more recent version) unless otherwise noted.

Data will be summarized with respect to demographic and baseline characteristics, primary, and secondary assessments, along with safety observations.

Descriptive statistics (the number of non-missing observations [n], mean, median, standard deviation [SD], lower quartile [Q1], upper quartile [Q3], minimum, and maximum values) will be presented for continuous variables. The following number of decimal places will be used: mean, median, Q1, and Q3 values to 1 more decimal place than the raw data; minimum and maximum to the same number of decimal places as the raw data and SD to 2 more decimal places than the raw data. If required, the geometric mean (gMean) will be derived by calculating the mean of the natural log transformed individual values. This value will then be back transformed to give the gMean.

For categorical variables, the number and percentage of each category within a variable will be calculated for non-missing data. If a count of zero is obtained for categorical data, only the zero count will be displayed. If no treatment group satisfies a category, then the category will be displayed, unless stated otherwise. A row (category) denoted 'Missing' will be included in count tabulations if a non-zero count of missing values is present. In addition, the corresponding percentage for this row will be displayed.

The safety observation period (days) for treated patients begins at the first administration of study treatment within this study (refer to Figure 1-1). It finishes at:

- the date of the Month X visit for patients that attend it (for patients who have not discontinued study treatment or study prior to the Month X visit)
- the latest day in the window for the Month X for patients who have not discontinued (study treatment or study) prior to the Month X visit but do not attend that visit
- the date of the last visit (including the study discontinuation visit) for patients who have discontinued study treatment prior to the Month X visit

where Month X is the last scheduled visit in the study.

Safety observation period (days) is defined as:

- (date of last administration of study treatment - date of first administration of study treatment) + 31 (i.e. 30 days after last administration of study treatment)

The study day for a baseline or post-baseline scheduled or unscheduled visit is defined as:

- Study day = (Date of visit) - (Date of baseline visit) + 1

For visits prior to baseline, the study day is defined as:

- Study day = (Date of visit) - (Date of baseline visit)

Date of baseline visit is the date of first administration of study treatment.

Change from baseline and relative change from baseline will only be summarized for patients with both baseline and post-baseline data for the relevant visit and will be calculated using the following formulae:

- Change from baseline = Post-baseline value − baseline value
- Relative change from baseline (%) = 100 × ([Post-baseline value − baseline value]/ baseline value)

All data will be listed by center and patient number, unless stated otherwise.

2.1.1 General definitions

All analyses will be based on assessments according to the investigator. This study will consist of the following epochs (refer to Figure 1-1):

- a pre-treatment period
  - from day of patient's study informed consent for this study to the day before first administration of study treatment within this study
- an on-treatment period
  - from day of first administration of study treatment within this study to 30 days after last administration of study treatment
- a follow-up period
  - starting at day 31 after last administration of study treatment within this study to the date of the last assessment collected in this study

Study treatment refers to:

- DFX FCT (Exjade®)
  - The investigational open-label treatment will be provided as 90 mg, 180 mg, and 360 mg DFX FCT for oral use.
  - Treatment visits will occur at Visit 3 (Day 1), then every 2 weeks until Visit 5 (Month 1). Thereafter visits will be monthly until end of treatment (EOT) (Visit 28/Month 24).
  - The planned duration of study treatment in this study is for a maximum 24 months.

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

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

2.2 Analysis sets

The **Full Analysis Set** (FAS) comprises of all patients enrolled in this study.

The **Safety Set** includes all enrolled patients who received at least one dose of study treatment (DFX FCT) and had at least one safety assessment on or after Visit 3 (Day 1). An entry on the AE eCRF page of 'no AE' constitutes a safety assessment.

The safety analyses will be performed on the Safety Set and the efficacy (serum ferritin) on the FAS.

The number of patients within each of the analysis sets used in this study will be summarised.

Frequency counts and percentages of patients in the FAS will be tabulated by protocol deviation (PD) type. The results will be grouped using the broad categories defined in the current Standard Operating Procedure (SOP) which are:

- Patient did not satisfy entry criteria
- Patient received the wrong treatment or incorrect dose
- Patient developed study/treatment withdrawal criteria during the study, but was not withdrawn
- Patient took an excluded concomitant medication
- Others

All PDs will be listed by center and patient number for the FAS.

Note: There is no per protocol set in this study. Therefore no PD will lead to exclusion from any of the analysis sets (defined earlier within this section).

2.2.1 Subgroup of interest

The subgroups of interest for this study are:

- actual average daily dose (< 7, 7 to < 21, ≥ 21 mg/kg/day)
  Note: The actual total daily dose is collected on the DAR eCRF in mg, day is implied as it is a daily dose (mg/day). This dose will then be adjusted for the current weight (kg). The current weight is the weight prior or on the date of the start of each dosage record. If there are multiple weight assessments taken on the same day, then the mean value of these records will be used for the current weight.
- prior chelation therapy (DFX, any other ICT)

2.3 Assessment windows, baseline and post-baseline definitions, missing data handling

2.3.1 Definition of baseline date

Baseline date is referred to as Day 1 of the study. It is defined as the date of first administration of study treatment in this study on Day 1 for treated patients.

2.3.2 Baseline and post-baseline definitions

The baseline value for efficacy and safety variables is the last available, non-missing, (scheduled or unscheduled) value collected prior to first administration of study treatment on Day 1 of this study (or the first date when a non-zero actual dose of study drug was administered), unless otherwise stated.

Some baseline assessments may be recorded on the day of the baseline visit (Visit 3/Day 1). However the time of each of these assessments may not be recorded in the eCRF. In this case, only the assessments which, according to the protocol, should have been conducted pre-dose on Day 1 will be assumed to have been done prior to administration of study treatment on Day 1 when deriving baseline values recorded on the day of the baseline visit (Visit 3/Day 1).

All data collected after baseline (see Section 2.3.1 for definition of baseline date) are defined as post-baseline.

2.3.3 Time windows

2.3.3.1 Study drug exposure

Study drug will be dispensed at Visit 3 (Day 1), then every 2 weeks until Visit 5 (Month 1) and monthly thereafter. Dose adjustments based on safety are allowed at any time point during the study.

An appropriate number of DFX FCT tablets, depending on the patient's calculated dose, will be dispensed to the patient. Information on study drug strength will be collected on the DAR eCRF and includes the planned dose (mg/kg/day), actual total daily dose (mg/day) taken, reason for the dose change, start date, and end date of each treatment dose.

Table 2-1 shows the defined study periods for drug exposure, where a month is regarded as 4 weeks.

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

Table 2-1 Study periods for drug exposure

Study period	Study period definition	Study period categories
[Week 1 to Month 1]	Study Day 1 to Study Day 28	<4 weeks
[Month 1 to Month 2]	Study Day 29 to Study Day 56	4 to < 8 weeks
[Month 2 to Month 3]	Study Day 57 to Study Day 84	8 to < 12 weeks
[Month 3 to Month 4]	Study Day 85 to Study Day 112	12 to < 16 weeks
[Month 4 to Month 5]	Study Day 113 to Study Day 140	16 to < 20 weeks
[Month 5 to Month 6]	Study Day 141 to Study Day 168	20 to < 24 weeks
[Month 6 to Month 7]	Study Day 169 to Study Day 196	24 to < 28 weeks
[Month 7 to Month 8]	Study Day 197 to Study Day 224	28 to < 32 weeks
[Month 8 to Month 9]	Study Day 225 to Study Day 252	32 to < 36 weeks
[Month 9 to Month 10]	Study Day 253 to Study Day 280	36 to < 40 weeks
[Month 10 to Month 11]	Study Day 281 to Study Day 308	40 to < 44 weeks
[Month 11 to Month 12]	Study Day 309 to Study Day 336	44 to < 48 weeks

Study period	Study period definition	Study period categories
[Month 12 to Month 13]	Study Day 337 to Study Day 364	48 to < 52 weeks
[Month 13 to Month 14]	Study Day 365 to Study Day 392	52 to < 56 weeks
[Month 14 to Month 15]	Study Day 393 to Study Day 420	56 to < 60 weeks
[Month 15 to Month 16]	Study Day 421 to Study Day 448	60 to < 64 weeks
[Month 16 to Month 17]	Study Day 449 to Study Day 476	64 to < 68 weeks
[Month 17 to Month 18]	Study Day 477 to Study Day 504	68 to < 72 weeks
[Month 18 to Month 19]	Study Day 505 to Study Day 532	72 to < 76 weeks
[Month 19 to Month 20]	Study Day 533 to Study Day 560	76 to < 80 weeks
[Month 20 to Month 21]	Study Day 561 to Study Day 588	80 to < 84 weeks
[Month 21 to Month 22]	Study Day 589 to Study Day 616	84 to < 88 weeks
[Month 22 to Month 23]	Study Day 617 to Study Day 644	88 to < 92 weeks
[Month 23 to Month 24]	Study Day 645 to Study Day 672	92 to < 96 weeks
[Month 24 to Month 25]	Study Day 673 to Study Day 700	96 to < 100 weeks
[Month 25 to Month 26]	Study Day 701 to Study Day 728	100 to < 104 weeks
[Month 26 to Month 27]	Study Day 729 to Study Day 756	104 to < 108 weeks
[Month 27 to EOT]	Study Day ≥ 757	≥ 108 weeks

2.3.3.2 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, regular patient visits, and EOT.

If two or more assessments are performed within a time window then the assessment closest to the planned visit will be used in analyses by time window. When two values are equidistant from the planned assessment, the later one will be used in analyses.

Note: For worst post-baseline assessment, all on-treatment values are considered regardless of time windows. Table 2-2 shows the defined time windows, where a month is regarded as 4 weeks.

Table 2-2 Time windows for laboratory and vital signs 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 15	Study Day 2 to Study Day 21
Month 1	Study Day 29	Study Day 22 to Study Day 43
Month 2	Study Day 57	Study Day 44 to Study Day 71
Month 3	Study Day 85	Study Day 72 to Study Day 99
Month 4	Study Day 113	Study Day 100 to Study Day 127
Month 5	Study Day 141	Study Day 128 to Study Day 155
Month 6	Study Day 169	Study Day 156 to Study Day 183
Month 7	Study Day 197	Study Day 184 to Study Day 211
Month 8	Study Day 225	Study Day 212 to Study Day 239
Month 9	Study Day 253	Study Day 240 to Study Day 267

Time window	Planned visit timing	Time window definition
Month 10	Study Day 281	Study Day 268 to Study Day 295
Month 11	Study Day 309	Study Day 296 to Study Day 323
Month 12	Study Day 337	Study Day 324 to Study Day 351
Month 13	Study Day 365	Study Day 352 to Study Day 379
Month 14	Study Day 393	Study Day 380 to Study Day 407
Month 15	Study Day 421	Study Day 408 to Study Day 435
Month 16	Study Day 449	Study Day 436 to Study Day 463
Month 17	Study Day 477	Study Day 464 to Study Day 491
Month 18	Study Day 505	Study Day 492 to Study Day 519
Month 19	Study Day 533	Study Day 520 to Study Day 547
Month 20	Study Day 561	Study Day 548 to Study Day 575
Month 21	Study Day 589	Study Day 576 to Study Day 603
Month 22	Study Day 617	Study Day 604 to Study Day 631
Month 23	Study Day 645	Study Day 632 to Study Day 659
Month 24	Study Day 673	Study Day 660 to Study Day 687
Month 25	Study Day 701	Study Day 688 to Study Day 715
Month 26	Study Day 729	Study Day 716 to Study Day 743
Month 27	Study Day 757	Study Day 744 to Study Day 771
Month 28	Study Day 785	≥ Study Day 772
EOT		
EOT	N.A.	Note: if no data were collected at the EOT visit the last post-baseline (extension) available data obtained before EOT will be used.

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

2.4 Patient disposition, demographics and other baselinecharacteristics

Patient disposition, background and demographic characteristics will be reported for the FAS, unless otherwise specified.

No inferential tests for differences in background and demographic characteristics will be performed.

2.4.1 Patient disposition

The number of patients screened will be summarized by country and center.

The number and percentage (based on the number of patients in the FAS) of patients who complete the study will be displayed. The primary reason for premature study discontinuation will also be displayed.

The total number of patients screened and the number of patients screened, but did not start treatment will be shown. The primary reason for screening failure will be summarized.

All patient disposition data will be listed by center and patient number for the FAS.

2.4.2 Background and demographic characteristics

Demographic, background data and key efficacy variables at baseline will be summarized for the FAS.

The time since diagnosis of disease will be derived using the following formula:

Time since diagnosis (years) = (Date of informed consent − Date of diagnosis)/365.25

Demographics

Categorical variables

- age (< 18, 18 to < 50, 50 to < 65, ≥ 65 years)
- child bearing potential (Able to bear children, Premenarche, Post menopausal, Sterile – of child bearing age)
  - Note: Child bearing potential will only be completed for patients where gender is marked as female.
- ethnicity (Hispanic/Latino, Chinese, Indian [Indian subcontinent], Japanese, Other)
- sex (Male, Female)
- predominant race (Caucasian, Black, Asian, Native American, Pacific Islander, Other)
- weight (< 20, 20 to < 35, 35 to < 55, 55 to < 75, ≥ 75 kg)

Continuous variables

- age (years)
- height (cm)
- weight (kg)
- body mass index (BMI) (kg/m^2)

Disease characteristics

Categorical variables

- hepatitis B surface antigen (HBsAg) (Negative, Positive, Indeterminate/Borderline)
- hepatitis B surface antibody (HBsAb) (Negative, Positive, Indeterminate/Borderline)
- hepatitis C virus (HCV) antibody positive (Negative, Positive, Indeterminate/Borderline, Below detectable limit)
- HCV RNA positive (Negative, Positive, Indeterminate/Borderline, Below detectable limit)
- hepatitis status (Hepatitis B, Hepatitis C, Hepatitis B and C, No Hepatitis)
  - Hepatitis B is defined as HBsAg in the absence of HBsAb (i.e. HBsAg is positive and HBsAb is negative). HBsAg and HBsAb must be measured from the same sample, otherwise Hepatitis B status cannot be determined.
  - Hepatitis C is defined as HCV antibody positive with HCV RNA positive. HCV antibody positive and HCV RNA positive must be measured from the same sample, otherwise Hepatitis C status cannot be determined.

  - Note: If there is no confirmatory assessment of HCV RNA measured from the same sample as HCV antibody, then the status of Hepatitis C will be regarded as Unknown/Undetermined.
- hematologically stable since last bone marrow examination (Yes, No)
- history of ICT (Yes, No)
- history of splenectomy (Yes, No)
  - Note: Patients with history of splenectomy are defined as those patients with a splenectomy recorded before Visit 3 (Day 1) (started before first administration of study treatment) in Relevant medical history/Current medical conditions eCRF (Preferred term [PT]: Splenectomy).
- main underlying disease (MDS with very low risk as per the Revised International Prognostic Scoring System [IPSS-R], MDS with low risk as per the IPSS-R, MDS with intermediate risk as per the IPSS- R, Thalassemia)
- formulation of the ICT received during CICL670F2201 (DFX DT, DFX FCT)
- type of last ICT prior to the study (Deferoxamine, Deferiprone, Combination therapy of Deferoxamine and Deferiprone, DFX, Combination therapy of Deferoxamine and DFX, Combination therapy of DFX and Deferiprone, Other)

Continuous variables

- time since diagnosis (years)
- time since last bone marrow examination (years)
- time since last blood transfusion (days)
- total number of blood transfusions received since last 12 months

Hepatitis data (HBsAg, HBsAb, HCV antibody positive, HCV RNA positive, Hepatitis status) will also be summarized by visit (see Table 2-2 for time windows definition). Hepatitis status was planned to be determined at Visit 3 (Day 1) however there is an option if some information was not collected then this can be collected at a later time-point.

Baseline abnormalities in ECG, audiometric test, and ocular exam

Categorical variables

- clinically significant abnormality in ECG (Yes, No)
- overall interpretation in audiometric test (Normal, Clinically insignificant abnormality, Clinically significant abnormality)
- overall interpretation in ocular exam (Normal, Clinically insignificant abnormality, Clinically significant abnormality)

Baseline laboratory values

Categorical variables

- Alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT) (≤ Upper limit of normal range (ULN), > ULN to 5×ULN, > 5×ULN)

- Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT) (≤ ULN, > ULN to 5×ULN, > 5×ULN)
- Serum creatinine (≤ ULN, > ULN)
- Creatinine clearance (< 40, 40 to < 60, ≥ 60 mL/min)
- Urine protein/creatinine ratio (UPC) (≤ 0.2, > 0.2 to ≤ 1.0, > 1.0 mg/mg)

Continuous variables

- ALT/SGPT (U/L)
- AST/SGOT (U/L)
- Serum creatinine (umol/L)
- Creatinine clearance (mL/min)
- UPC (mg/mg)

All demographic and baseline data will be listed by center and patient number for the FAS.

2.4.3 Medical history

Relevant medical history and current medical conditions will be tabulated by system organ class (SOC) and PT of the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (version 19.1 or a more recent version) for the FAS. The SOCs will be presented in alphabetical order. PTs will be sorted by decreasing proportion and alphabetical order.

Furthermore, medical history data will be listed by center and patient number for the FAS.

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

Unless otherwise stated, all analyses will be based on patients in the Safety Set.

2.5.1 Study treatment/compliance

Study treatment

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 the following table (Table 2-3).

Table 2-3 Study drug exposure

Term	Definition
Overall drug exposure (days)	[(date of last administration of study treatment) − (date of first administration of study treatment) + 1]
Drug exposure on dose X (days)	[(date of last administration of study treatment on dose X) − (date of first administration of study treatment on dose X) + 1]
Average dose (planned [mg/kg/day] or actual [mg/kg/day]	Mean dose over all days between first and last dose, including interruptions: sum of all (X dose × corresponding drug exposure on dose X) ⁄ overall drug exposure

Term	Definition
Final dose (planned [mg/kg/day] or actual [mg/kg/day])	Last non-zero dose record
Cumulative dose (planned [mg/kg] or actual [mg/day])	Sum of daily doses over all days between first administration of study treatment and last administration of study treatment
Total patient-years (years)	Overall duration of exposure (days) ／ 365.25
Percentage of planned dose taken (%)	100 × (Cumulative actual dose [mg/kg] ／Cumulative planned dose [mg/kg])

Note:
(1) The actual dose will be adjusted for the current weight (kg). The current weight is the weight prior or on the date of the start of each dosage record. If there are multiple weight assessments taken on the same day, then the mean value of these records will be used for the current weight.
(2) Cumulative dose is the sum of daily doses hence day is not part of the unit.

Descriptive statistics for the number of days a patient was on study treatment will be provided for the Safety Set. The table will also provide the total patient-years that all patients were on treatment. The frequency and percentage of patients belonging to each categorical range of exposure weeks will be provided (see Table 2-1 for definition of study period categories).

In addition, summary statistics (frequency and percentage of patients for categorial varaibles; descriptive statistics for continuous variables) of dosage will be provided for:

Categorical variables

- average planned dose (< 10.5, 10.5 to < 17.5, 17.5 to < 24.5, ≥ 24.5 mg/kg/day)
- average actual dose (< 10.5, 10.5 to < 17.5, 17.5 to < 24.5, ≥ 24.5 mg/kg/day)
- final planned dose (< 10.5, 10.5 to < 17.5, 17.5 to < 24.5, ≥ 24.5 mg/kg/day)
- final actual dose (< 10.5, 10.5 to < 17.5, 17.5 to < 24.5, ≥ 24.5 mg/kg/day)

Continuous variables

- average planned dose (mg/kg/day)
- average actual dose (mg/kg/day)
- final planned dose (mg/kg/day)
- final actual dose (mg/kg/day)
- cumulative planned dose (mg/kg)
- cumulative actual dose (mg/kg)
- percentage of planned dose taken (%)
- duration of actual dose (days)
  - The duration of actual dose refers to the number of days in the study where actual dose is non-zero.
- relative duration of actual dose (%)
  - The relative duration of actual dose is defined as the ratio of duration of actual dose (days) to overall drug exposure (days).

Futhermore, the frequency and percentage of patients with dose decreases, increases in planned dose, or dose interruptions, the corresponding reasons, and average length of dose interruptions will be summarized. A shift table to compare final planned dose to final actual dose will also

be provided. A planned dose reduction is when a planned dose is lower than the previous planned dose, a planned zero dose is included as a dose reduction record. A planned dose increase is when a planned dose is higher than the previous planned dose. Patients with more than one reason for planned dose change are counted once per reason in each category (reduction or increase). A dose interruption is when an actual dose is recorded as zero.

Average actual daily dose will be also graphically presented using a box plot over time (see Table 2-1 for study period definition).

Study treatment data will be listed by center and patient number for the Safety Set.

Study compliance

The patient compliance with DFX FCT will be evaluated using the count of DFX FCT by the relative consumed tablet count (%). The relative consumed tablet count is defined as the ratio of total count consumed to total count prescribed, where

- Total count consumed is derived from cumulative dispensed and returned counts:
  The total count consumed is calculated as the sum of counts dispensed minus the sum of counts returned.
- Total count prescribed is cumulative prescribed count:
  The prescribed count corresponds to the count prescribed by the investigator for the period that the patient should have taken the study treatment during this period. For each strength (90 mg, 180 mg, and 360 mg tablets), the prescribed count for a period is calculated from the daily prescribed count at the beginning of this period multiplied by the duration (days) of this period. The daily prescribed count is the sum of counts prescribed per strength. The duration of a period will be calculated using the following formula:
  (end date of the period) - (start date of the period) + 1
  The subsequent period duration calculation will exclude the start day (i.e., a day will be not be counted in subsequent periods). The total count prescribed is the sum of counts prescribed over all periods.

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

Descriptive statistics including 95% confidence interval (CI) for the mean relative consumed tablet count will be provided.

In addition, the persistence of DFX FCT will be summarised at Month 3, Month 6, Month 9, and Month 12. Persistence is defined as the continuous use of DFX FCT without a gap of ≥ 30 or ≥ 60 days over a fixed time interval of interest. A gap will be calculated as the time between two consecutive dates of study drug administration when study drug was administered (i.e. actual dose is non-zero) within the fixed time interval of interest.

Furthermore, a listing will be provided including dispensed/returned and prescribed counts as well as the relative consumed tablet count by center and patient number for the Safety Set.

2.5.2 Prior and concomitant therapies

The number and percentage of patients taking prior and concomitant therapies will be summarized for the Safety Set.

Summaries will be presented separately for prior and/or concomitant medications. Concomitant therapies will include medications and significant non-drug therapies taken between the first and last day with study medication + 30 days, excluding medications that 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 in this study. Medications starting prior to the start of study treatment in this study and continuing after the start of study treatment will be counted in both summaries.

Prior or concomitant medication will be identified based on recorded or imputed start dates of medication taken in this study. The rules for imputing incomplete start dates are described in Section 5.1.2.

Medications will be identified by Anatomical Therapeutic Chemical (ATC) class and PT according to the World Health Organization (WHO) Drug Reference List dictionary (201603 or a more recent version). Tables will show the overall frequency and percentage of patients receiving at least one dose of the therapy.

A listing of prior and concomitant therapies will be provided by center and patient number for the Safety Set.

2.5.3 Rescue medication

Rescue medication is not planned in this study.

2.6 Analysis of the primary objective

The primary objective of this study is to evaluate the overall safety of the DFX FCT formulation, as measured by frequency and severity of AEs and changes in laboratory parameters, in patients with transfusion-dependent thalassemia or MDS at very low, low or intermediate risk.

2.6.1 Primary endpoint

The primary variables are:

- treatment emergent AEs (TEAEs)
  - An AE is defined as treatment emergent if its onset date is on or after (≥) the first administration of study treatment within this study or events present prior to start of study treatment but increased in severity on or after (≥) the first administration of study treatment within this study but not later than 30 days after the last study treatment in this study (i.e. during the safety observation period, see Section 2.1 for definition).
- changes from baseline at Months 6 and 12 for the following laboratory assessments:
  - serum creatinine
  - creatinine clearance
  - ALT/SGPT
  - AST/SGOT
  - red blood cell (RBC)
  - platelets

- white blood cell (WBC)

2.6.2 Statistical hypothesis, model, and method of analysis

No hypotheses will be tested. All analyses will be descriptive in nature.

The incidence of any TEAEs overall and by severity will be summarized using frequency counts, percentages of patients, and 95% CIs for percentages obtained using Clopper-Pearson method.

Laboratory data will be summarized using descriptive statistics including 95% CI of the mean for raw values and absolute change from baseline at each visit (see Table 2-2 for time windows definition). Furthermore, mean and standard error (SE) values will be plotted over time (see Table 2-2 for time windows definition) for each of the laboratory parameters of interest (serum creatinine, creatinine clearance, ALT/SGPT, AST/SGOT, RBC, platelets, WBC total).

The analysis of the primary variables will be performed on the Safety Set.

2.6.3 Handling of missing values/censoring/discontinuations

No missing values will be imputed however missing partial AE dates will be imputed following the rules outlined in Section 5.1.1.

2.6.4 Supportive analyses

Overall AEs and selected laboratory parameters (serum creatinine and creatinine clearance) of the primary objective will be analyzed separately by the subgroups of interest outlined in Section 2.2.1.

2.7 Analysis of the key secondary objective

There is no key secondary objective for this study.

2.8 Analysis of secondary efficacy objective(s)

The secondary objective of this study is to evaluate the efficacy of DFX FCT on serum ferritin levels (decrease or maintenance, according to the individual therapeutic goal).

2.8.1 Secondary endpoints

The secondary variables are:

- serum ferritin level at baseline, Month 6 (Visit 10), and Month 12 (Visit 16)
- change from baseline in serum ferritin at Month 6 (Visit 10) and Month 12 (Visit 16)

It should be noted that the maximum serum ferritin provided by certain laboratories is 4500 ng/mL with values above 4500 ng/mL represented as “>4500”. If there is an occurrence of “>4500”, the site will record this value in the electronic data capture (EDC) system as 4500 ng/mL. For derivations and table summaries, the value of 4501 will be used; for listings this value will be shown as “>4500”.

2.8.2 Statistical hypothesis, model, and method of analysis

No hypotheses will be tested. All analyses will be descriptive in nature.

Serum ferritin will be summarized using descriptive statistics of raw values, absolute change from baseline, and relative change from baseline at each visit (see Table 2-2 for time windows definition). The summaries will include n, mean with respective 95% CI, SD, minimum, Q1, median, Q3, and maximum.

The analysis of the secondary variables will be performed on the FAS.

2.8.3 Handling of missing values/censoring/discontinuations

No missing values will be imputed.

2.9 Safety analyses

The safety evaluations during the study will be summarized for the Safety Set, unless otherwise specified.

No inferential tests for differences in safety analyses will be performed.

2.9.1 Adverse events (AEs)

All AEs occurring before first administration of study treatment in this study will be assigned to the pre-treatment period and those occurring after last drug intake + 30 days will be assigned to the follow-up period (for listings only). Only TEAEs will be summarized.

AEs will be coded by primary SOC and PT according to the MedDRA dictionary (version 19.1 or a more recent version).

The following AE summaries will be presented:

- AEs, regardless of study drug relationship
- AEs by maximum severity grade (mild, moderate, severe), regardless of study drug relationship
- AEs, suspected to be related to the study treatment
- serious AEs (SAEs), regardless of study drug relationship
- AEs leading to study drug discontinuation, regardless of study drug relationship
- AEs requiring study drug dose adjustment or interruption, regardless of study drug relationship
- AEs requiring additional therapy, regardless of study drug relationship

In addition 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 maximum severity grade. An overall summary of AEs will also be presented overall and by maximum severity grade using frequency and percentage of patients along with 95% CIs for percentages obtained using Clopper-Pearson method.

AEs will be summarized by presenting the frequency and percentage of patients having at least one AE, and having at least one AE by primary SOC and/or PT, severity, and relationship to

study drug by treatment group. A patient with multiple occurrences of an AE will be counted only once in the AE category.

For the legal requirements of clinicaltrials.gov and EudraCT, two required tables on TEAEs which are not SAEs with an incidence greater than 5% and on treatment emergent SAEs and SAEs suspected to be related to study treatment will be provided by primary SOC and PT.

If for the same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same primary 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.

In addition exposure-adjusted AE incidence will be presented by PT. It is defined as:

$$\frac{(Number\ of\ patients\ with\ new\ or\ worsened\ AEs\ during\ the\ on-treatment\ period)}{(Total\ number\ of\ days\ a\ patient\ is\ on\ treatment\ summed\ over\ all\ patients\ /\ 365.25\ )}$$

Furthermore, all AEs (AEs during the pre-treatment period, TEAEs, AEs during the follow-up period) will be listed by center and patient number for the FAS. This will also include details of the AE (e.g., verbatim given by the investigator as well as the primary SOC and PT), onset date, end date, severity, and relationship to study treatment.

2.9.1.1 Adverse events of special interest/grouping of AEs

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

All AESI groupings are defined through the use of PT, High Level Terms (HLT), primary 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 will be used.

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

AESIs will be summarized regardless of study drug relationship, by grouping and PT.

In addition, AESIs during the first 6 and 12 months of treatment during this study will be summarized regardless of study drug relationship, by grouping and PT.

2.9.1.2 Selected gastrointestinal TEAEs

The incidence of any gastrointestional TEAE as well as selected gastrointestional TEAEs will be summarized by using frequency and percentage of patients along with 95% CIs for percentages obtained using Clopper-Pearson method.

Selected gastrointestional AEs include the following PTs: diarrhoea, constipation, nausea, vomiting, and abdominal pain.

2.9.2 Deaths

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

In addition, the primary and contributing reason for death will be listed for all deaths by center and patient number.

2.9.3 Laboratory data

Hematology, serum chemistry, and urinalysis parameters will be presented using standard international (SI) units and the severity grade calculated using the low/normal/high classifications based on laboratory normal ranges, and for selected parameters by notable/extended ranges.

Raw values as well as absolute and relative change from baseline values for hematology, biochemistry, and urinalysis laboratory parameters will be summarized descriptively by visit (see Table 2-2 for time windows definition).

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

- shift tables using normal/notable/extended ranges to compare baseline to the worst on-treatment value
- listing of all laboratory data with values flagged to show the corresponding normal/notable/extended ranges

All data, including data from unscheduled visits, will be considered when identifying abnormal values.

Shift tables based on normal ranges to compare baseline to the worst post-baseline value will be provided by parameter for hematology, biochemistry, and urinary laboratory data.

A similar shift table will be provided based on notable/extended ranges for key safety laboratory parameters defined in Section 10.5.2.2 (Clinical Trial Protocol CICL670AIC04 Amended Protocol Version 1, 25 October 2017).

2.9.4 Other safety data

2.9.4.1 ECG and cardiac imaging data

All data from ECG will be listed by center and patient number for the FAS. Patients with clinically significant abnormal interpretations or abnormal values will be flagged. A listing of patients with new or worsened clinically significant ECG abnormality compared to baseline will be provided.

2.9.4.2 Vital signs

Vital signs (sitting blood pressure [systolic blood pressure, diastolic blood pressure], weight, and BMI) will be summarized for the Safety Set using descriptive statistics, by visit for raw values and absolute change from baseline.

Clinically notable values for certain vital sign measurements are defined in Section 10.5.2.3 (Clinical Trial Protocol CICL670AIC04 Amended Version 1, 25 October 2017). The frequency and percentage of patients with clinically notable values values will be presented for the Safety Set.

Patient listings of vital signs data will be provided by center and patient number for the FAS. Values which are clinically notable will be flagged.

2.9.4.3 Other safety assessments

Serum and urine pregnancy test results (if applicable) will be listed for female patients. All data from chest X-ray examination, auditory test, ocular assessment, hepatitis testing, and pregnancy test will be listed for the FAS.

Descriptive statistics for blood transfusion data during the treatment phase (on-treatment period) will be provided by visit (see Table 2-2 for time windows definition) for the Safety Set:

- platelets (amount transfused [mL], hematocrit of blood transfused [%])
- packed RBC (PRBC) (amount transfused [mL], hematocrit of blood transfused [%])
- whole blood (amount transfused [mL], hematocrit of blood transfused [%])

Summary statistics for the number of transfusions (platelets, PRBC, whole blood) per patient will be presented by frequency distribution (number of patients with 1 unit transferred, number of patients with 2 units transferred, on up to the maximum number of units transferred for any one patient) and visit (see Table 2-2 for time windows definition).

Note: Each blood transfusion will be recorded separately on the Blood transfusion - During treatment phase eCRF, therefore the sum of each of the blood tranfusion parameters of interest which occur during the time window of interest will be presented.

Data related to blood transfusion during the treatment phase will be listed by center and patient number for the FAS.

2.10 Pharmacokinetic endpoints

There are no pharmacokinetic (PK) endpoints in this study.

2.11 Pharmacodynamic and PK/Pharmacodynamic analyses

There are no pharmacodynamic and PK/pharmacodynamic analyses planned in this study.

2.12 Patient-reported outcomes

There are no patient-reported outcomes (PRO) analyses planned in this study.

2.13 Biomarkers

There are no biomarker analyses planned in this study.

2.14 Other exploratory analyses

There are no other exploratory analyses planned in this study.

2.15 Interim analysis

There are no interim analyses in this study.

3 Sample size calculation

No formal sample size has been calculated. All patients enrolled into CICL670F2201 who have completed 24 weeks treatment will be offered participation in this current protocol and those consenting to participate will contribute to the pool of data.

According to enrolment of CICL670F2201 in Region Europe, a maximum of 90 patients should be eligible for enrollment in this study. However as only three countries (Austria, Greece, and Italy) are participating in this study which is less than originally foreseen, it is planned to enroll a maximum of 58 patients.

4 Change to protocol specified analyses

Due to insufficient patient numbers in the categories for the subgroups: age and main underlying disease, it was agreed to remove the planned age and main underlying disease subgroup analyses.
Within the protocol, it is stated that the Baseline serum ferritin value will be defined as the average of the 2 measurements obtained during the Screening period. It was clarified that this statement is in reference to the eligibility criteria and baseline serum ferritin should be derived for analysis purposes as outlined in Section 2.3.2.

5 Appendix

5.1 Imputation rules

5.1.1 AE date imputation

5.1.1.1 AE end date

For the purpose of date imputation, the study treatment follow-up period date is defined as the last available visit date, i.e. including unscheduled visits after the end of study visit.

1. If the AE end date month is missing, the imputed end date should be set to the earliest of the (study treatment follow-up period date, 31DECYYYY, date of death).
2. If the AE end date day is missing, the imputed end date should be set to the earliest of the (study treatment follow-up period date, last day of the month, date of death).
3. If AE year is missing or AE is ongoing, the end date will not be imputed.

If the imputed AE end date is less than the existing AE start date then use AE start date as AE end date.

5.1.1.2 AE start date

AEs with completely missing onset dates will be considered to be treatment emergent. AEs with partially missing onset dates will also be included as treatment emergent when the month (if it exists) and the year occur on or later than the month and year of first administration of study treatment within this study.

Partial AE start dates are imputed with reference to the first administration of study treatment (TRTSTD) within this study as outlined in the table below.

The date value is split into day, month, year sections and referenced in the imputation table as outlined below

	Day	Month	Year
Partial AE Start Date	Not used	MON	YYYY
Treatment Start Date (TRTSTD)	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

Comparison of month section	MON missing	MON<TRTM	MON=TRTM	MON>TRTM
YYYY missing	NC	NC	NC	NC
YYYY<TRTM	(D) = 01JULYYYY Before Treatment Start	(C) = 15MONYYYY Before Treatment Start	(C) = 15MONYYYY Before Treatment Start	(C) = 15MONYYYY Before Treatment Start
YYYY=TRTY	(B) = TRTSTD+1 Uncertain	(C) = 15MONYYYY Before Treatment	(A) = TRTSTD+1 Uncertain	(A) = 01MONYYYY After Treatment

Comparison of month section	MON missing	MON<TRTM	MON=TRTM	MON>TRTM
YYYY>TRTY	(E) = 01JANYYYY After Treatment Start	Start (A) = 01MONYYYY After Treatment Start	(A) = 01MONYYYY After Treatment Start	Start (A) = 01MONYYYY After Treatment Start

The following table is the legend to the logic matrix.

Relationship	
Before Treatment start	Partial date indicates AE start date prior to Treatment Start Date in this study
After Treatment start	Partial date indicates AE start date after Treatment Start Date in this study
Uncertain	Partial date insufficient to determine relationship of AE start date to Treatment Start Date in this study
Imputation calculation	
NC/Blank Uncertain	No convention
(A) After Treatment Start or Uncertain	MAX(01MONYYYY, TRTSTD+1)
(B) Uncertain	TRTSTD+1
(C) Before Treatment Start	15MONYYYY
(D) Before Treatment Start	01JULYYYY
(E) After Treatment Start	01JANYYYY

Before imputing the AE start date, find the AE start reference date.

- If the AE end date is complete and the (imputed) AE end date < TRTSTD then AE start reference date = min (study informed consent date, earliest visit date).
- Else AE start reference date = TRTSTD

To impute AE start date:

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

a. If the AE month is missing, the imputed AE start date is set to the year start point (01JANYYYY).
b. Else if the AE month is not missing, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

4. If the AE start date year value is equal to the study treatment start date year value:
   a. And the AE month is missing the imputed AE start date is set to the AE reference start date + 1 day.
   b. Else if the AE month is less than the study treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).
   c. Else if the AE month is equal to the study treatment start date month or greater than the study treatment start date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

If complete (imputed) AE end date is available and the imputed AE start date is greater than the (imputed) AE end date, then imputed AE start date should be set to the (imputed) AE end date.

5.1.2 Concomitant medication date imputation

5.1.2.1 Concomitant medication end date

To impute concomitant end date:

1. If the concomitant end date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the concomitant end year value is missing or ongoing, the imputed concomitant end date is set to NULL.
2. Else, if the concomitant end date month is missing, the imputed end date should be set to the earliest of the (study treatment follow-up period date, 31DECYYYY, date of death).
3. If the concomitant end date day is missing, the imputed end date should be set to the earliest of the (study treatment follow-up period date, last day of the month, date of death).

If the imputed concomitant end date is less than the existing concomitant start date, use the concomitant start date as the imputed concomitant end date.

5.1.2.2 Concomitant medication start date

Concomitant treatments with partial start dates will have the date or dates imputed. Partial concomitant treatment start dates are imputed with reference to the first administration of study treatment (TRTSTD) within this study in accordance with the rules outlined below.

	Day	Month	Year
Partial AE Start Date	Not used	MON	YYYY
Treatment Start Date (TRTSTD)	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

Comparison of month section	MON missing	MON<TRTM	MON=TRTM	MON>TRTM
YYYY missing	(C) Uncertain	(C) Uncertain	(C) Uncertain	(C) Uncertain

Comparison of month section	MON missing	MON<TRTM	MON=TRTM	MON>TRTM
YYYY<TRTM	(D) = 01JULYYYY Before Treatment Start	(A) = 15MONYYYY Before Treatment Start	(A) = 15MONYYYY Before Treatment Start	(A) = 15MONYYYY Before Treatment Start
YYYY=TRTY	(C) Uncertain	(A) = 15MONYYYY Before Treatment Start	(C) Uncertain	(B) = 01MONYYYY After Treatment Start
YYYY>TRTY	(E) = 01JANYYYY After Treatment Start	(B) = 01MONYYYY After Treatment Start	(B) = 01MONYYYY After Treatment Start	(B) = 01MONYYYY After Treatment Start

The following table is the legend to the logic matrix.

Relationship	
Before Treatment start	Partial date indicates CMD start date prior to Treatment Start Date in this study
After Treatment start	Partial date indicates CMD start date after Treatment Start Date in this study
Uncertain	Partial date insufficient to determine relationship of CMD start date to Treatment Start Date in this study
Imputation calculation	
NC/Blank Uncertain	No convention
(A) Before Treatment Start	15MONYYYY
(B) After Treatment Start	MAX(01MONYYYY, TRTSTD+1)
(C) Uncertain	IF CMDTYP1C IN (1, 3) THEN TRTSTD-1 ELSE IF CMDTYP1C IN (. 2) THEN TRTSTD+1
(D) Before Treatment Start	01JULYYYY
(E) After Treatment Start	01JANYYYY

To compute concomitant start date:

1. If the concomitant start date year value is missing, the imputed concomitant start date is set to one day prior to study treatment start date.
2. If the concomitant start date year value is less than the study treatment start date year value, the concomitant medication started before study treatment. Therefore:
   a. If the concomitant month is missing, the imputed concomitant start date is set to the mid-year point (01JULYYYY).

   b. Else if the concomitant month is not missing, the imputed concomitant start date is set to the mid-month point (15MONYYYY).
3. If the concomitant start date year value is greater than the study treatment start date year value, the concomitant started after study treatment. Therefore:
   a. If the concomitant month is missing, the imputed concomitant start date is set to the year start point (01JANYYYY).
   b. Else if the concomitant month is not missing, the imputed concomitant start date is set to the month start point (01MONYYYY).
4. If the concomitant start date year value is equal to the study treatment start date year value:
   a. And the concomitant month is missing or the concomitant month is equal to the study treatment start date month, then the imputed concomitant start date is set to one day prior to study treatment start date.
   b. Else if the concomitant month is less than the study treatment start date month, the imputed concomitant start date is set to the mid-month point (15MONYYYY).
   c. Else if the concomitant month is greater than the study treatment start date month, the imputed concomitant concomitant start date is set to the month start point (01MONYYYY).

If complete (imputed) concomitant end date is available and the imputed concomitant start date is greater than the (imputed) concomitant end date, then imputed concomitant start date should be set to the (imputed) concomitant end date.

5.1.3 Medical history date of diagnosis imputation

Completely missing dates and partially missing end dates will not be imputed. Partial dates of diagnosis will be compared to the treatment start date.

- If DIAG year < study treatment start date year and DIAG month is missing, the imputed DIAG date is set to the mid-year point (01JULYYYY)
- Else if DIAG month is not missing, the imputed DIAG date is set to the mid-month point (15MONYYYY)
- If DIAG year = study treatment start date year and (DIAG month is missing OR DIAG month is equal to study treatment start month), the imputed DIAG date is set to one day before study treatment start date

5.1.4 Other imputations

5.1.4.1 Age

The age of patients with a completely missing date of birth will be set to missing. If a patient's date of birth is partially missing then

- If the year is missing then the age will be set to missing
- Else if the month is missing then the day will be set to 01 and the month will be set to July
- Else if the day is missing then the day will be set to 15.

If a patient has a partially missing date of birth and an imputed age of 17 years then this will be set at 18 years. However, if the imputed age were 16 years then the imputed age will remain at 16 years.

5.1.4.2 Dose interruptions, dose delays, and dose changes

This section provides additional details to those included in Section 2.5.1.

Dose interruption

A dose interruption will be indicated in the eCRF by a dosing record with an actual total daily dose of 0 mg for one or more days. In order not to over count interruptions, dosing records with 0 mg entered as last dosing record will not be counted as interruptions. Those represent the reason for permanent discontinuation and will therefore be presented in the reason for treatment discontinuation analysis.

Dose reduction

A reduction is defined as a decrease from the previous non-zero dose. For example, in the sequence of planned dose (mg/kg/day) 25-0-15, the 15 mg/kg/day dose will be counted as a reduction. The planned zero dose is also counted as a dose reduction record. The reduction will be determined using the eCRF 'planned dose'. If the planned dose is reduced as described above, a reduction will be counted.

5.2 Statistical models

Clopper Pearson CI

CL = Confidence level for limits in % (i.e. 95)

F = Frequency (i.e. number of successes)

N = Number of patients

&pl. = Lower CL

&pu. = Upper CL

```
%macro exactcl(cl,f,n,pl,pu);
 _P=&F./&N.;    _PCT=100*_P;
 Z=PROBIT(1-(100-&CL.)/200);
 XX2=FINV((100-&CL.)/200,2*&F.,2*(&N.-&F.+1),0);
 XX3=FINV((100+&CL.)/200,2*(&F.+1),2*(&N.-&F.),0);
 IF _P=0   THEN &pl.=0;
        ELSE &pl.=100*&F.*XX2/(&N.-&F.+1+&F.*XX2);
 IF _P=1   THEN &pu.=100;
        ELSE &pu.=100*(&F.+1)*XX3/(&N.-&F.+(&F.+1)*XX3);
%mend exactcl;
```

5.3 Rule of exclusion criteria of analysis sets

Table 5-1 Protocol deviation categories used

PD Category	PD Code
Eligibility	E
Discontinuation of treatment/ study	D
Prohibited Concomitant Medication	M
Study drug (incorrect dose, wrong treatment)	S
Other	O

The full list of PDs are defined in the data review plan (DRP) which is located in the document management system in the following folder:

- 'CREDI Projects/I/ICL670A/CREDI Studies/ICL670AIC04/Administrative Files (study level)/Validation and Planning documents'

Table 5-2 Patient classification

Analysis Set	PD ID that cause patients to be excluded	Non-PD criteria that cause patients to be excluded
FAS	I03	Not enrolled
SAF	I03, D05	Not in FAS; No study drug taken during the study; Not having at least one post-baseline safety assessment on or after Visit 3 (Day 1)

6 References

Cheng WJ et al (2018) Adherence to iron chelation therapy in patients who switched from deferasirox dispersible tablets to deferasirox film-coated tablets. Current Medical Research and Opinion; DOI: 10.1080/03007995.2018.1470500

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.