NOVARTIS

Clinical Development

ICL670/Deferasirox/Exjade®

Study Number: CICL670A2302 / NCT00940602

A multi-center, randomized, double-blind, placebo-controlled clinical trial of deferasirox in patients with myelodysplastic syndromes (low/int-1 risk) and transfusional iron overload (TELESTO)

RAP Module 3- Detailed Statistical Methodology

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Document History – Changes compared to previous final version of RAP M3

Date	Version	Outcome/changes
11Mar2015	Final	• RAP M3
04Apr2017	Amendment 1	• The previous final RAP was lean and did not include standard sections. Examples include, study design, definitions of baseline, etc. The amendment is an adaptation of the new SAP template. Section numbers listed in the current RAP amendment follow the current M3 template. • Per new template, added study design (Section 1.1) • Tabulated study objectives and endpoints (Section 1.2) • Added a few definitions including last contact date (Section 2.1.2.4) • Clarified baseline definition (Section 2.1.2.8) • Added two observational periods: study evaluation period and survival follow-up period (Section 2.1.2.9) • Elaborated and added the criteria for Per Protocol Set (PPS) associated with severity code 1 (Section 2.2.2) • Deleted randomized population set (Section 2.2.3) • Modified the language for disposition table (Section 2.3) • Added analysis language for relevant medical history and current medical condition and also for hemoglobin history (Section 2.3) • Included time-intervals for duration of exposure categories (Section 2.4) • Clarified primary endpoint definition (Section 2.5.1) • Clarified that statistical significance level is indeed 2.5% in a one sided test (Section 2.5.2.1) • Clarified HI (Hematologic Improvement) definition (Section 2.7.1.1) • Elaborated time-to event analysis in terms of what will be displayed (Section 2.7.1.1) • Added the definition of treatment emergent AEs and also list of AE tables (Section 2.8.1) • Included two AE tables for the requirement of ClinicalTrials.gov and EudraCT: Non-serious adverse

Date	Version	Outcome/changes
		events and deaths due to SAEs suspected to be study drug related (Section 2.8.1) • Explained AESI mapping from the AESI search table with the notable adverse event groupings (Section 2.8.1.1) • Added notable criteria for total bilirubin (Section 2.8.3) • Elaborated the ECG notable values (Section 2.8.6) • Added criteria for notable vital signs (Section 2.8.6.1) • Added auditory and ophthalmic data listings (Section 2.8.6.2) • Explained imputation rules for study drug administration date (Section 5.1.1); AE date (Section 5.1.2); Concomitant medication start date (Section 5.1.3); prior and post-therapy start and end date (Section 5.1.3.1 and 5.1.3.2), and other dates, such as death date (Section 5.1.3.3) • Elaborated STRATA options in Cox's proportional hazard model (Section 2.5.2.3 and 5.5.1.1)
March5, 2018	Amend ment 2	• Revised per protocol set by updating prohibited concomitant medication (Section 2.2.2) • Deleted age specific subgroup analysis (Section 2.2.4) per DMC comment. Note that age specific subgroup analyses are not required by the protocol. • Revised disposition table by deleting analysis of "Number (%) for the primary reason of the end of study completion except completion per protocol and death" (Section 2.3) • Deleted analysis for drug accountability analysis due to fact that it is not required by HA (Section 2.4) • Added descriptive analysis for deaths and non-fatal events, adjudicated by the Endpoint Adjudication Committee (Section 2.5.4) • Clarification added regarding nominal p-value for overall survival analysis by DMC comment (Section 2.7.1.1) • Clarified what to be included in the safety tables and listings and corrected the neutrophils count criteria (Section 2.8)

Date	Version	Outcome/changes
April 9, 2018	Amendment 3	• Added time to event analysis for the first occurrence of serum ferritin > 2 times the baseline value (section 2.5.3.6 and section 2.7.1.7) as this is a secondary endpoint • Deleted the reason of not performing the time to event analysis for the first occurrence of serum ferritin > 2 times the baseline value from section 4 • Added analysis for moderate or severe anemia (section 2.8)
April 19, 2018	Amendment 4	• Added repeated time-to-event analyses for the primary endpoint excluding patients from one site for data integrity issue (section 2.5.4)

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List of abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase/serum glutamic pyruvic transaminase/SGPT
AML	Acute Myeloid Leukemia
AST	Aspartate aminotransferase/serum glutamic oxaloacetic transaminase/SGOT
BMI	Body Mass Index
CI	Confidence Interval
CrCl	Creatinine Clearance
CTC	Common terminology criteria
CTCAE	Common Terminology Criteria for Adverse Events
CRF	Case report/record form
DFX	Deferasirox/ICL670/Exjade®
DFO	Deferoxamine/Desferal®
DMC	Data monitoring committee
EAC	Endpoint Adjudication Committee
eCRF	Electronic case report/record form
FAS	Full Analysis Set
FPG	Fasting plasma glucose
HI	Hematological Improvement
HR	Hazard Ratio
ICL670	Deferasirox/Exjade®
IPSS	International Prognostic Scoring System
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
KM	Kaplan-Meier
LIC	Liver iron concentration
LVEDVI	Left ventricular end-diastolic volume index
LVEF	Left Ventricular Ejection Fraction
LVESVI	Left ventricular end-systolic volume index
LVMI	Left ventricular mass index
LVIDD	Left Ventricular Internal diameter end-diastole
LVISD	Left Ventricular Internal diameter end-systole
MDRD	Modification of Diet in Renal Disease
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
OGTT	Oral Glucose Tolerance Test
PPS	Per Protocol Analysis Set
RAP	Reporting and Analysis Plan
PRBC	Packed Red Blood Cells
RBC	Red Blood Cells
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SCr	Serum Creatinine
SD	Standard deviation
SI	System International (or International System)
SSC	Study steering committee
T4	Thyroxine
TSH	Thyroid Stimulated Hormone

1 Introduction

The purpose of this Reporting and Analysis Plan (RAP) is to describe the implementation of the statistical analysis specified in the protocol. The final Clinical Study Report (CSR) will be written based on this RAP. It is not intended to produce any other report resulting from this RAP. The current RAP is written following the finalized protocol version 5, disease area standards, and Exjade project-specific standard TFLs.

1.1 Study design

This is a prospective, randomized, double-blind, placebo-controlled, parallel group design study. Two-hundred and ten patients (per protocol amendment 5) are planned to be enrolled in this study. A screening period lasting up to 35 days with two screening visits (Visit 1 and Visit 2 - at least 14 days apart.) will be used to assess patient eligibility. Eligible patients will be randomized in 2:1 ratio in deferasirox and placebo arms respectively. Randomization will be stratified by IPSS (low or int-1), as well as by geographical region (Asian versus non-Asian countries). All patients who are randomized in this study will start study treatment at 10 mg/kg/day and may be titrated up to 40 mg/kg/day based on dose modification guidelines (see protocol section 6.7.1).

The primary endpoint is a composite endpoint including death and non-fatal events related to cardiac and liver function. Patients who meet a non-fatal events (see protocol Section 3.1.1 for the definition of non-fatal events) will be discontinued from the study treatment. After treatment termination, all patients will be followed for safety (28 days) and then evaluated with visits every three months. Subsequent to the Evaluation period, or at the end of treatment if a patient and treating physician decide that a patient will not participate in the evaluation period, patients will be followed by phone monitoring every 6 months for their need for iron chelation therapies and overall survival ("Survival Follow-up") until study end.

Patients not meeting a non-fatal event will continue study treatment as long as the patient and the treating physician feel it is in the best interest for the patient. Following discontinuation from study treatment, they will be followed for safety (28 days). They may choose to be evaluated with visits every three months, then subsequent to the Evaluation period, or at the end of treatment, if a patient and treating physician decide that a patient will not participate in the evaluation period, patients will be followed every 6 months by phone for their need for iron chelation therapies and overall survival ("Survival Follow-up").

An external Data Monitoring Committee (DMC) will monitor patient safety and trial conduct and will receive a blinded summary of serious adverse events as detailed in the DMC Charter.

A complete analysis following the specifications in the RAP document will be done subsequent to the last visit at least 3 years after the last-patient-first-visit unless all patients will have met the endpoint or discontinued the study earlier.

There will be no interim analysis for this study.

1.2 Study objectives and endpoints

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

Table 1-1 Study objectives and endpoints

Objective	Endpoint
Primary	
The primary objective is to evaluate deferasirox and placebo for event-free survival (a composite primary endpoint including death and non-fatal events related to cardiac and liver function, and transformation to AML) in low and int-1 risk MDS patients with transfusional iron overload.	Composite primary endpoint (event-free survival) : Time from date of randomization to date when death or any of the non-fatal events defined below has been reached (event-free survival): ● Death ● Non-fatal event: 1. Echocardiographic evidence of worsening cardiac function based on the following criteria: at least > 15% absolute decrease in left ventricular ejection fraction (LVEF) from screening value at two consecutive assessments at least two weeks apart OR LVEF below institutional limits of normal and at least > 10% absolute decrease from LVEF screening value at two consecutive assessments at least two weeks apart. 2. Hospitalization for congestive heart failure defined as follows: Overnight stay (i.e., change in calendar day) due to congestive heart failure confirmed by the presence of the following: a) At least one of the following symptoms: ● Paroxysmal nocturnal dyspnea ● Orthopnea ● Dyspnea on exertion AND b) Two or more of the following signs consistent with heart failure: ● Pulmonary edema by radiography ● Rales ● Enlarged heart by radiography - Peripheral edema - S3 gallop - Hepatojugular reflux ● Neck vein distention ● Rapid weight gain ● Elevated brain natriuretic peptide (BNP) AND c) Treatment with either intravenous diuretics, intravenous vasodilators, intravenous inotropes, mechanical fluid removal (e.g., ultrafiltration or dialysis), or insertion of an intra-aortic

	balloon pump for hemodynamic compromise. Initiation of oral diuretics or intensification (doubling) of the maintenance diuretic dose will also qualify. 3. Liver function impairment reflected by: ● ALT or AST > 2 times the baseline value and > 3.5 times ULN AND ● Total bilirubin > 2 mg/dL at two consecutive visits 4. Liver cirrhosis confirmed by: ● The presence of at least one of the following symptoms/signs: cirrhosis-related ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, variceal bleeding due to portal hypertension OR ● Abdominal ultrasonography (if clinically indicated) OR ● Liver biopsy (if clinically indicated) 5. Progression to Acute Myeloid Leukemia (confirmed by bone marrow biopsy or aspirate)
Secondary	
Hematologic improvement (HI) in terms of erythroid response	Proportion of patients with hematologic improvement in terms of erythroid response
Overall survival	Overall survival
Change in endocrine function (thyroid and glycemic control)	• Proportion of patients with hypothyroidism as assessed by annual TSH and free T4. • Proportion of patients with a worsening of glucose metabolism from baseline as assessed by annual oral glucose tolerance test (OGTT)
Disease progression (which includes MDS progression and progression to AML)	Time to disease progression, i.e. either MDS progression defined as a transition into a higher MDS risk group based on IPSS scoring or progression to AML defined as >20% blasts in the bone marrow
Change in serum ferritin level	Time to first occurrence of serum ferritin > 2 times the baseline value at two consecutive assessments (at least two weeks apart) (See Section 4 for details)
Change in cardiac function	• Time to at least a 10% increase from baseline in left ventricular end-diastolic internal dimension (LVIDD) at two consecutive assessments at least two weeks apart • Time to at least a 10% increase from baseline in left ventricular internal systolic diameter (LVISD) at two consecutive assessments at least two weeks apart

Frequency of infections requiring intravenous antimicrobials	Frequency and rate of infections requiring intravenous antimicrobials
Assess the levels of increased risk for pre-specified adverse events (renal dysfunction, neutropenia, thrombocytopenia, gastrointestinal bleeding, and laboratory abnormalities) that would be clinically unacceptable in the context of the level of benefit that is likely to be provided by iron chelation using deferasirox in MDS patients with iron overload (see Fleming 2008 for general approach).	• Proportion of patients with significant renal dysfunction defined as serum creatinine ≥ 2 times ULN at two consecutive assessments (at least 7 days apart) • Proportion of patients with newly occurring severe (CTCAE Grade 4) neutropenia or thrombocytopenia • Proportion of patients with major gastrointestinal bleeding • Time to study drug discontinuation due to an adverse event or laboratory abnormality • Incidence of other adverse events and laboratory abnormalities

2 Statistical methods

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

2.1 Data analysis general information

Data will be analyzed by Novartis according to the data analysis section 10 of the study protocol as detailed in this analysis plan. SAS version 9.4 or later (upon availability) will be used. As specified in the protocol, a complete analysis following the specification in this RAP documentation will be done subsequent to last visit at least three years after last-patient-first-visit unless all patients will have met an endpoint or discontinued from the study earlier.

2.1.1 General presentation of descriptive summaries

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

Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (e.g., mean, standard deviation, median, minimum, and maximum).

2.1.2 General definitions

2.1.2.1 Investigational drug and study treatment

Investigational drug, will refer to the deferasirox only; whereas, ***investigational treatment*** will refer to deferasirox or placebo treatment. In this document, the term investigational treatment will be referred as ***study treatment*** and will be used throughout this document.

2.1.2.2 Date of first administration of study treatment

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

2.1.2.3 Date of last administration of study treatment

The date of last administration of study treatment is defined as the last date when a non-zero dose of study treatment was administered as per Dose Administration eCRF.

2.1.2.4 Last contact date

The last contact date will be derived for patients not known to have died at the analysis cut-off date using the latest complete date among the following:

- All assessment dates, such as vital signs, physical, audiometry, ophthalmologic exam and third-party assessment date, such as central laboratory, ECG, ECHO, ultrasound, and liver biopsies
- Medication dates including study medication, concomitant medications, iron chelation therapies administered after study treatment discontinuation, and transfusions during the study
- Adverse events start/end dates
- Last contact date collected on the 'Survival information' eCRF
- Study treatment start/end date
- Randomization date

Only dates associated with patient visits (scheduled or unscheduled) or actual examinations of the patient will be used in the derivation. Dates associated with a technical operation unrelated to patient status, such as the date a blood sample was processed, will not be used. An imputed partial date will not be used to derive the last contact date. The assessment dates after the cutoff date will not be applied to derive the last contact date. The last contact date will be used for censoring of patients in the analysis of overall survival.

2.1.2.5 Screening failure

Screening failures are patients who enrolled and failed screening criteria in a study. These patients are never randomized. Patients who are randomized, but never received study treatment in a randomized study, are not screening failures.

2.1.2.6 Study day

The study day ***for safety assessments*** (e.g. adverse event onset, laboratory abnormality occurrence, vital sign measurement, dose interruption etc.) will be calculated as the difference between the date of the event (onset date of an event, assessment date etc.) and the start of study treatment plus 1. The first day of study treatment is therefore study day 1. If an event starts after the start date of study treatment, the study day will be calculated as:

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

If an event date is before the treatment start date, the study day will be calculated using the below formula:

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

The study day ***for efficacy assessments*** will be calculated as:

Study day = The date of the assessment / event - randomization date + 1

In other words, all efficacy, including time-to-event variables (event-free survival, overall survival, time to disease progression), will be calculated from the date of randomization.

For any assessment or events, such as baseline disease characteristics or medical history (e.g., time since diagnosis of disease) collected prior to randomization date, the study day will be negative and will be calculated as:

Study Day = Event date - Randomization date.

The study day will be displayed in the data listings.

2.1.2.7 Month

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

2.1.2.8 Baseline

Unless otherwise specified below, for ***efficacy evaluations***, the baseline value is defined as the last available measurement before or on the day of randomization (including results from unscheduled visits analyzed by the central laboratory). It is assumed that assessments scheduled for Visit 3 – the randomization visit – were done prior to randomization in order to be interpreted as *prior to or on the day of randomization* (e.g. physical examination, chest x-ray). If an assessment is done at both screening visits, Visit 1 and Visit 2, the value of Visit 2 is considered the baseline value.

Differing definitions for baseline values were specified for the following assessments or parameters:

- Serum creatinine, creatinine clearance, ALT/AST, serum ferritin, total and direct bilirubin: the baseline value is defined as the mean of the Visit 1 and Visit 2 values. If additional measurements analyzed by the central laboratory are available from

unscheduled visits in the screening period, they will be included in the average. Only the central lab values between -35 days and day 1 from randomization date will be considered to determine baseline.

- Transfusion history: data of platelet and PRBC transfusion records in the 6-month period prior to study start (randomization) will be used to establish baseline transfusion frequency and hematologic counts.

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

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

2.1.2.9 On-treatment assessment/event and observation periods

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

1. ***pre-treatment period***: before the first administration of study treatment
2. ***on-treatment period***: from date of first administration of study treatment to 28 days after date of last actual administration of any study treatment (including start and stop date)
3. ***post-treatment period***: starts on day 28+1 after last administration of study treatment.

Per study design, there will be two additional observation periods:

4. ***study evaluation period:*** starts on day 29 after last administration of study treatment until study evaluation completion period (visit frequency every three months)
5. ***survival follow-up period:*** starts after study evaluation completion visit until LPFV plus three years or death. If a patient declines to participate in the evaluation period, the survival follow-up period will start on day 29 after last administration of study treatment until LPFV plus three years or death (visit frequency is every 6 months).

2.2 Analysis sets

The following three analysis sets were defined for analyses in the study protocol.

2.2.1 Full Analysis Set

The Full Analysis Set (FAS) includes all patients to whom study treatment has been assigned by randomization. According to the intention to treat principle, patients will be analyzed according to the study treatment and strata they were assigned to during the randomization procedure (IVRS).

2.2.2 Per Protocol Analysis Set

The per protocol analysis set (PPS) is a subset of the FAS and comprises all randomized patients:

- Whose first administered study medication is in accordance with the randomized assignment, and

- Without protocol deviations regarding inclusion or exclusion criteria with respect to underlying disease, such as:
  - No low or intermediate-1 MDS according to IPSS score in the eCRF,
  - Serum ferritin ≤ 1000 µg/L at Screening,
  - More than 3 years since patient began receiving regular transfusions,
  - LVEF < 50%,
  - Diagnosis of liver cirrhosis

Also patients with the following protocol deviation will be excluded from the PPS:

- No bone marrow biopsy within 6 months of entering study
- Stratum assignment differs from MDS risk and / or country reported by investigator
- Patient randomized but received wrong study drug (first administered study medication)
- Prohibited concomitant medications:
  - Aluminium containing antacid therapies (aluminium hydroxide and magnesium hydroxide)
  - Use of bile sequestrants (e.g. cholestyramine, colesevelam, colestipol)
  - Use of any other chelation therapy (e.g. deferoxamine, deferiprone)
  - Any investigational drugs other than study medication.
  - Use of hormonal contraceptive (oral or injected)

Patients will also be excluded from per-protocol set according to VAP M3.

2.2.3 Safety Analysis Set

The Safety Analysis Set (SAS) includes all randomized patients who received at least one dose of study medication. Patients will be analyzed according to the study treatment they actually received (defined as the study medication administered first) and according to strata information (MDS risk score/IPSS score) recorded in the eCRF.

The FAS is the primary analysis set for the statistical analyses of efficacy. The PPS will be used as the secondary analysis set to perform sensitivity analyses of the primary efficacy endpoint. All analyses of safety are based on the safety analysis set.

2.2.4 Subgroup of interest

The following subgroups will be considered for selected figures and tables:

- IPSS low risk and Asian; IPSS low risk and Non-Asian; IPSS Intermediate 1 risk and Asian; IPSS Intermidiate1 and Non-Asian

For efficacy subgroups, stratification factors i.e., IPSS score (low vs Int-1 risk) and geographical region (Asian countries vs non-Asian Countries) as in the randomization (IVRS) will be used. Asian countries are China, Hong Kong, Malaysia, Thailand, and Taiwan.

For safety subgroups, definition of strata is based on IPSS score and geographical region as in the eCRF.

2.3 Patient disposition, demographics and other baseline characteristics

A breakdown of reasons will be provided for patients excluded during screening.

The number and percentage of patients randomized will be summarized by region, country, center and treatment arm.

Patient disposition will be summarized for the treatment period, as well as for evaluation and survival follow-up period using the FAS. The disposition table will include:

- Number (%) of treated and untreated patients
- Number (%) of patients who completed the end of treatment
- Number (%) for the primary reason of the end of treatment completion
- Number (%) of patients followed for evaluation period
- Number (%) for the reason of evaluation period completion
- Number (%) of patients entering the survival follow-up
- Number (%) for the primary reason of study evaluation completion
- Number (%) of patients alive at last contact

The number and percentage of patients with any protocol deviation will be tabulated by the deviation type and treatment arm using FAS.

Demographic data and baseline characteristics will be summarized descriptively based on the FAS. Demographic data include age, age group, gender, race, and ethnicity. Age will be presented by region (Asian countries vs non-Asian Countries). Age will be calculated based on patient's first screening date. Baseline characteristics are weight group (<35 kg, $35 - <55$ kg, $55 - <75$ kg, $75 - < 95$ kg, ≥ 95 kg), and IPSS score (low vs int-1 risk as in randomization) and will be summarized categorically by treatment arm and for all patients. Height, weight will be summarized continuously using FAS by each treatment arm and for all patients.

Relevant medical histories and current medical condition will be summarized and listed. The summaries will be presented by primary system organ class and preferred term. (Medical history/current medical conditions are coded using MedDRA) using FAS.

Hemoglobin history will be listed using FAS. The listing will include hemoglobin value, unit, sample collection date and study day.

2.4 Treatments (study treatment, compliance)

Duration of study treatment exposure (days), average planned daily dose (mg/kg/day), and average actual daily dose (mg/kg/day) will be summarized by treatment arm and for all

patients. Duration of exposure will be categorized into time intervals. The upper limit of each time interval is calculated based on 364 days (defined as 52 weeks x 7 days) +/- 14 days for each year (< 379 days; 379- <743 days; 743- <1107 days; 1107- <1471 days, 1471- <1835 days; >=1835 days). Frequency counts and percentages will be presented for the number of patients in each interval. Total patient years will also be reported.

Average (actual) and planned dose (mg/kg/day) will be summarized similarly.

The frequency in changes of planned dose (reductions and increases), overall and by reason for change, will be summarized. Reasons for interruptions (actual dose zero) will also be summarized by treatment arm and for all patients.

Listings of all doses of the study treatment along with dose change and dose interruption reasons will be produced.

The percentage of total dose taken will be used as an assessment of a patient's compliance and calculated as the amount of medication (deferasirox/placebo) taken versus the planned amount of study medication. Percentage of total dose taken will be summarized by treatment arm and for all patients.

The Safety Analysis Set will be used for all summaries and listings of study treatment.

2.4.1 Duration of exposure

The following algorithm will be used to calculate the duration of study treatment exposure for patients who took at least one dose of any study treatment (DFX or placebo):

Duration of exposure (days) = [(date of last administration of study treatment) - (date of first administration of study treatment) + 1]

The date of last administration of study treatment (treatment component) is taken from the DAR eCRF. The calculation of 'duration of exposure 'does not consider the potential lagging effect' from the last dose.

Duration includes the periods of temporary interruption of the study treatment for any reason. 'Date of first administration of study treatment 'and 'date of last administration of study treatment' are defined in Section 2.1.2.2 and Section 2.1.2.3 respectively.

Exposure duration excluding interruption will also be calculated using the following algorithms:

Duration of exposure excluding interruption = duration of exposure (days) – number of days drug being interrupted (0 dose)

2.4.2 Cumulative dose

Cumulative dose (mg/kg) is defined as sum over daily doses of all days between first and last dose. For patients who did not take any drug, the cumulative dose is by definition equal to zero. In this study, dose is weight adjusted.

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

2.4.3 Average planned and actual dose

Average planned and actual dose are defined by the following algorithm:

> Average planned dose (mg/kg/day) = [Cumulative planned dose during the time of exposure]/Duration of exposure (days)
>
> Average actual dose (mg/kg/day) = [Cumulative actual dose during the time of exposure]/Duration of exposure (days)

2.4.4 Percent dose taken

Percent dose taken = 100 times ratio of average (actual) dose and average planned dose

2.4.5 Concomitant, prior and post therapies

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) besides the study treatment that were administered to a subject preceding or coinciding with the study assessment period.

Concomitant medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List to allow for categorization by preferred term. In addition to categorizing medication data by preferred term, drugs are classified according to their ATC classification in order to present and compare how they are being utilized.

Concomitant medications and significant non-drug therapies taken concurrently with the study drug(s) will be listed and summarized categorically by Anatomical Therapeutic Chemical (ATC) class and preferred term for each treatment arm. These summaries will include medications starting on or after the start of study treatment or medications starting prior to the start of study treatment and continuing after the start of study treatment.

Any prior concomitant medications or significant non-drug therapies starting and ending prior to the start of study treatment will be listed separately.

Patients discontinue from study drug may receive post-treatment chelation therapy. Statistical analysis for post-treatment chelation therapy will be outlined in Section 2.4.5.2.

2.4.5.1 Prior chelation therapy

History of iron chelation therapy and blood transfusions will be collected retrospectively six months prior to study entry.

Duration of iron chelation prior to study entry will be categorized into time intervals (< 1, 1-<3, 3-<6 months of cumulative therapy). Frequency counts and percentages will be presented for the number of patients in each interval. The number of patients who received different prior iron chelators will also be summarized by treatment and for all patients.

Prior chelation therapy will be listed using FAS.

2.4.5.2 Chelation therapy after discontinuation of study treatment

The number of patients chelated since discontinuation of study drug will be summarized and categorized as reported within 28 days since discontinuation or later. In the summary table, deferoxamine mesilate will be displayed as “deferoxamine”.

Chelation therapy after discontinuation of study treatment will be listed using the FAS.

2.4.5.3 Blood transfusion

The number of blood transfusions during the study will be summarized by type of transfusion, e.g., packed red blood cells (PRBC), platelets, or whole blood. Statistics on average hematocrit per patient, total number of units transfused during the study, and total number of transfusion received six months prior to study start will also be provided using the FAS. To calculate the total volume, only PRBC and whole blood will be taken into account. 450 mL of whole blood is assumed to correspond to 185 mL of PRBC and will be considered as one unit.

Data on blood transfusions will be presented in a listing using FAS.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

Event-free survival is the composite primary endpoint which is defined by the time from the date of randomization to the date of the first documented non-fatal event or death due to any cause. Non-fatal events comprise:

- Echocardiographic evidence of worsening cardiac function
- Hospitalization for congestive heart failure (CHF)
- Liver function impairment
- Liver cirrhosis
- Progression to Acute Myeloid Leukemia (AML) confirmed by bone marrow biopsy

Criteria for these events are detailed in Section 3.1.1 of the study protocol. All events which could potentially fulfill the criteria for one of the components of the endpoint (except death)

will be reported to the Endpoint Adjudication Committee (EAC) for blinded assessment. Evaluation by the EAC is decisive for the analysis, i.e. the analysis only takes those events into account that are confirmed by the EAC.

2.5.2 Statistical hypothesis, model, and method of analysis

The sample size of 210 patients does not provide sufficient power for testing confirmatory statistical hypotheses. The analysis will therefore concentrate on estimating the treatment effect of deferasirox relative to placebo to evaluate potential event-free survival benefit and other descriptions of the survival functions.

Statistical tests will be performed in an exploratory sense only. There will be no procedures to control multiple/family-wise type-I-error probabilities regarding the different endpoints.

2.5.2.1 Statistical hypotheses (exploratory)

Suppose that $S_D(t)$ and $S_P(t)$ denote the event-free survival function for deferasirox and placebo, respectively. The null hypothesis:

H_0: $S_D(t) = S_P(t)$ for all $t \geq 0$ (identical survival functions for both groups)

will be tested against the one-sided alternative hypothesis:

H_A: $S_D(t) > S_P(t)$ for all $t \geq 0$ and $S_D(t) > S_P(t)$ for at least some $t > 0$ (event-free survival benefit in the deferasirox group over the placebo group).

The significance level will be 2.5%, and it will be a one-sided test.

2.5.2.2 Estimation of survival functions for event-free survival

A graphical estimate of the survival function for each treatment group will be obtained separately by the Kaplan-Meier (KM) product-limit method as implemented in SAS PROC LIFETEST.

If available, median survival for each treatment group will be obtained by SAS PROC LIFETEST along with 2-sided 95% confidence intervals calculated using the method of (Brookmeyer and Crowley 1982).

KM estimates with 2-sided 95% confidence intervals at days 364, 728, 1092 and 1456 will be provided. The confidence intervals will be constructed using Greenwood's formula (Collett 1994) for the standard error of the Kaplan-Meier estimate.

2.5.2.3 Stratified unadjusted Cox proportional hazards regression model

For the primary analysis, an unadjusted Cox model will be used. Hazard ratio as a treatment effect measure for time to event endpoints will be derived from the ***Cox proportional hazards model*** using SAS procedure PHREG (with TIES=EXACT option in the MODEL statement as explained in Section 5.5.1.1). STRATA options will be used to account for variations in baseline hazards across strata.

2.5.2.4 Statistical hypothesis test (exploratory)

A stratified log-rank test with stratification variables used in the randomization, i.e. IPSS (low or int-1) and geographical region (Asian versus non-Asian countries), will be implemented as follows: For each of the K strata, a BY statement will be used with the SAS LIFETEST procedure, while a STRATA statement including a variable for identifying the treatment group will be used to obtain the rank statistic S_k and variance $var(S_k)$ where $k = 1, 2, \ldots, K$.

The final test statistic will then be constructed as:

$Z = [S_1 + \ldots + S_K]/\sqrt{[var(S_1) + \ldots + var(S_k)]}$.

Under the null hypothesis, the test statistic Z is approximately normally distributed (Z^2 is approximately chi-square distributed with one degree of freedom). A one-sided (exploratory) p-value will be obtained using the Z statistic:

p = P(Z>z) = 1-Probnorm(z)

where z is the observed value of Z and Probnorm denotes the inverse of the normal cumulative distribution function.

2.5.3 Handling of missing values/censoring/discontinuations

Event-free survival

For the primary analysis of event-free survival, the following censoring rules will be applied:

- Patients who have not experienced any of the non-fatal events from the composite primary endpoint and have not stopped study participation at the time of data cut-off (end of study) will be censored - irrespective of adherence to study treatment - considering the following dates for the components and taking the earliest (minimum) of these as the censoring date:
    - Worsening of cardiac function: the last date when echocardiography results will be available
    - Hospitalization for congestive heart failure: the data cut-off date
    - Liver function impairment: the last date when laboratory values for ALT, AST and bilirubin will be available
    - Liver cirrhosis: the data cut-off date
    - Progression to AML: the data cut-off date
- Patients who have not experienced any of the non-fatal events from the composite primary endpoint, but have stopped study participation before the time of data cut-off, will be censored - irrespective of adherence to study treatment - considering the following dates for the components and taking the earliest (minimum) of these as the censoring date:
    - Worsening of cardiac function: the last date when echocardiography results will be available
    - Hospitalization for congestive heart failure: the last date when the patient will have some documented personal contact (visit or phone call) with the investigator
    - Liver function impairment: the last date when laboratory values for ALT, AST and bilirubin will be available

- Liver cirrhosis: the last date when the patient had documented personal contact (visit or phone call) with the Investigator regarding imaging, laboratory data, or biopsy results regarding cirrhosis
- Progression to AML: the last date when the patient will have some documented personal contact (visit or phone call) with the Investigator. Suspected progression to AML without confirmation by bone marrow biopsy or aspiration does not constitute an event and censoring will be applied at last contact.

2.5.3.1 Worsening of cardiac function

For the analysis of worsening of cardiac function, patients who have not experienced a worsening of cardiac function will be censored at the last date when echocardiography results are available.

2.5.3.2 Hospitalization for congestive heart failure

For the analysis of hospitalization for congestive heart failure, patients who have not experienced any hospitalization for congestive heart failure will be censored at the last contact date.

2.5.3.3 Liver function impairment

For the analysis of liver function impairment, patients who have not experienced any liver function impairment will be censored at the last date when laboratory values for ALT, AST and bilirubin are available.

2.5.3.4 Liver cirrhosis

For the analysis of liver cirrhosis, patients who have not experienced liver cirrhosis will be censored at the last contact date.

2.5.3.5 Progression to AML

AML progression will be determined by the bone marrow aspirate. In case of AML suspicion, bone marrow aspirate will be performed to confirm AML at any time until study evaluation completion. Thus, for the analysis of progression to AML, patients who have not experienced progression to AML will be censored at the last contact date.

2.5.3.6 Increase in serum ferritin

For the analysis of time from randomization to the first occurrence of serum ferritin > 2 times the baseline value at two consecutive assessments (at least two weeks apart), patients who did not experience such an increase in serum ferritin will be censored at the last date when serum ferritin was available or at the date of randomization if no post baseline serum ferritin is available.

2.5.4 Sensitivity and supportive analyses

The two main sensitivity analyses for the primary efficacy analysis (event-free survival) will be based on the two alternative censoring rules. Otherwise, the same statistical methods will be used for the primary analysis of event-free survival. A third sensitivity analysis using the

same methodology will address the issue of partial data for the composite endpoint (i.e., a patient with some missing data but not all of the components of composite endpoints).

For the first main sensitivity analysis patients with premature discontinuation of randomized study treatment and subsequent treatment with marketed iron chelation therapy (including Exjade®) will be censored at the date of first administration of the subsequent iron chelation therapy.

For the second main sensitivity analysis patients with premature discontinuation of randomized study treatment (regardless of whether they were subsequently treated with marketed iron chelation therapy) will be censored at the date of last administration of randomized study treatment.

The third sensitivity analysis will employ the following censoring rules:

- If an event is documented after three or more consecutive missing biochemistry laboratory assessments (regarding results for ALT, AST, and total bilirubin), the event-free survival time of these patients will be censored at the date of the last assessment with complete information for ALT, AST, and total bilirubin.
- If an event is documented after two or more consecutive missing echocardiogram (ECHO) assessments (for left ventricular ejection fraction), the event-free survival time of these patients will be censored at the date of the last ECHO assessment.
- If an event is documented after at least three consecutive missing biochemistry laboratory assessments (ALT, AST, and total bilirubin) and at least two consecutive missing ECHO assessments simultaneously, the event-free survival will be censored at the date of the last assessment with both biochemistry laboratory and ECHO assessments completed.
- As the three other components, 'hospitalization for congestive heart failure', 'liver cirrhosis' and 'Progression to AML', i.e. assessed in unscheduled examinations, missing assessments for them cannot be determined.

Sensitivity analyses include:

- Point estimate and two-sided 95% confidence interval for the adjusted HR from a Cox proportional hazard regression model stratified for the randomization factors with adjustment for demographic or baseline characteristics of clinical interest. The adjustment will be made for age (≥65 vs < 65), Asian vs non-Asian, MDS risk group (low vs intermediate).
- Statistical analyses based on the PPS instead of the FAS.

Supportive analyses include:

- KM curves by treatment and unadjusted HR (point estimate and two-sided 95% confidence interval) for each of the strata defined by the randomization factors.
- KM curves by treatment and unadjusted HR (point estimate and two-sided 95% confidence interval) for each component of event-free survival (overall survival is also a secondary efficacy endpoint, see Section 2.7.1.1).
- Number of deaths and non-fatal events adjudicated by the endpoint adjudication committee

- Primary endpoint analyses will be repeated for the FAS excluding patients from one site due to data integrity issue. The time to event analyses will be performed and will include:
  - Stratified log-rank test and Cox-regression model for event-free survival
  - Overall summary of event free survival

These patients will be excluded from per-protocol set for the sensitivity analyses.

2.6 Analysis of the key secondary objective

There is no key secondary objective for this study.

2.7 Analysis of secondary efficacy objective(s)

2.7.1 Secondary efficacy endpoints

All analyses of secondary efficacy endpoints will be based on the FAS.

If applicable, nominal significance levels will be set to one-sided alpha = 0.025; all confidence intervals will be two-sided using an ordinary confidence level of 95%.

2.7.1.1 Hematologic improvement

Hematologic improvement (HI) in terms of erythroid response during treatment will be assessed based on International Working Group (IWG) criteria (Cheson 2006).

The variable used in the analysis of HI will be the proportion of patients who satisfy the erythroid response criteria; namely,

- Hemoglobin increased $\geq$ 1.5 g/dL

OR

- Reduction of $\geq$ 4 units of RBC transfusions over 8 weeks, in comparison to 8 weeks' pre-treatment values, and lasting at least 8 weeks.

For purposes of calculating the reduction in transfusions component of this endpoint, a transfusion unit is defined as 185 mL of PRBC (Cohen Glimm Porter 2008). According to IWG criteria, HI is measured in patients with pre-treatment hemoglobin levels of less than 11 g/dL or RBC transfusion dependence. The definition of transfusion dependency is based on IWG criteria (Cheson 2006). All patients included in this study are transfusion dependent. In order to measure hemoglobin increase, the last hemoglobin value measured prior to randomization will be used as the pretreated value. If 2 pre-treated (prior randomization) hemoglobin values are available and each is at least 7 days after any transfusion, an average of the 2 values will be used to determine the pre-treatment hemoglobin level. All RBC transfusions regardless of pre-transfusion hemoglobin level, will count in the RBC transfusion response criteria. If any pre-treatment hemoglobin value or transfusion history over 8-week period cannot be determined, they will not be a part of risk set and will not be included in the percentage calculation.

All episodes of HI in the patient will be considered.

The percentage of responders will be summarized for the two treatment groups and 100(1-α)% confidence intervals with α of 0.05 will be provided. The 95% confidence limits for the difference of two proportions will be derived by the Wilson score test (see Section 5.5.3).

Overall survival

Overall survival (OS) will be evaluated in patients treated with either deferasirox or placebo. The variable used in the analysis of overall survival is time to death measured in days. It is defined as date of death (irrespective of cause) minus date of randomization plus 1.

Censoring is described in Section 2.7.3.1. The estimation of survival functions and the Cox model to estimate the HR are defined in Section 2.5.2.2 and Section 2.5.2.3. An exploratory statistical test will be performed analogously to the description in Section 2.5.2.4.

The Kaplan-Meier curves, medians, and Kaplan-Meier estimates with 95% confidence intervals at specific time points will also be displayed by treatment and stratum.

In Kaplan-Meier plots, statistics such as p-value, hazard ratio, etc. will also be displayed. Note that only nominal p-values are provided with no statistical interpretation.

Survival information will be listed. The listing will include if patients survived (Yes/No), last contact date, study day, date of death if not survived and principal cause of death.

Unless otherwise specified, all time-to-event analysis will be analyzed in a similar fashion.

2.7.1.2 Proportion of patients with hypothyroidism

Hypothyroidism will be evaluated by the annual measurement of TSH and free T4. The proportion of patients with normal thyroid function, primary hypothyroidism, secondary hypothyroidism or subclinical hypothyroidism will be determined at each time point (i.e. 1, 2, …, years after randomization).

Definitions:

- normal thyroid function: serum TSH and free T4 within normal limits;
- primary hypothyroidism: serum TSH >ULN and free T4 <LLN;
- secondary hypothyroidism: serum TSH <ULN and free T4 <LLN;
- subclinical hypothyroidism: TSH >ULN and a free T4 within normal limits.

Frequency of newly occurring hypothyroidism and shift tables will be provided for each treatment group. Results will also be shown separately for each year since randomization. A combined listing for hypothyroidism and glucose metabolism will be provided.

2.7.1.3 Proportion of patients with worsening of glucose metabolism

An annual oral glucose tolerance test will be carried out to evaluate changes of glucose metabolism compared to the baseline status. The proportion of patients with an increase in glucose metabolism category (normal, impaired glucose metabolism, diabetes mellitus) based on the American Diabetes Association criteria (American Diabetes Association 2009) compared to their baseline result will be determined at each time point, i.e. 1, 2, …, years

after randomization. For this classification, fasting and 2-hour post-prandial plasma glucose levels will be measured.

Criteria for impaired glucose metabolism:

- fasting plasma glucose (FPG) levels ≥ 100 mg/dL (5.6 mmol/L) but <126 mg/dL (7.0 mmol/L)

  OR

- 2-h values in the oral glucose tolerance test (OGTT) of ≥ 140 mg/dL (7.8 mmol/L) but <200 mg/dl (11.1 mmol/L)

Criteria for diabetes mellitus:

- non-fasting plasma glucose ≥ 200 mg/dL (11.1 mmol/L)

OR

- FPG ≥ 126 mg/dL (7.0 mmol/L). Fasting plasma glucose is defined as no caloric intake for at least 8 hours

  OR

- 2 hour post load glucose ≥ 200 mg/dL (11.1 mmol/L) during an OGTT. As described by WHO, the test use a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water

Frequency and shift tables will be provided for each treatment group. Results will also be shown separately for each year since randomization.

2.7.1.4 Disease progression

An evaluation of the time from randomization to either MDS progression or progression to AML in the treatment groups will be done based on date of diagnosis of MDS progression or date of first diagnosis of AML minus date of randomization plus 1.

MDS progression will be defined as a transition into a higher MDS risk group based on IPSS scoring (see Section 5.3.2). Progression to AML will be defined based upon the most current classification guidelines (Vardiman 2009), as 20% or more blasts seen in the bone marrow collected by biopsy or aspirate.

The time-to-event analysis follows the description given in Section 2.5.2.2. Censoring for patients with neither MDS progression nor progression to AML at last contact is described in Section 2.7.3.2 and Section 2.5.3.5.

2.7.1.5 Time to at least a 10% increase from baseline in LVIDD

An evaluation of the time from randomization to the first occurrence of an increase of at least 10% from the baseline value of LVIDD (Left Ventricular Internal end-diastolic dimension) will be performed based on the following variable:

- date of echocardiography assessment where a minimum of 10% increase first occurred minus date of randomization plus 1.

The time-to-event analysis follows the description given in Section 2.5.2.2. Censoring for patients without such an increase in LVIDD will be at the time of last LVIDD assessment (Section 2.7.3.3).

2.7.1.6 Time to at least a 10% increase from baseline in LVISD

An evaluation of the time from randomization to the first occurrence of an increase of at least 10% from the baseline value of LVISD (Left Ventricular Internal end-systolic dimension) will be performed based on the following variable:

- date of echocardiography assessment where a minimum of 10% increase first occurred minus date of randomization plus 1.

The time-to-event analysis follows the description given in Section 2.5.2.2. Censoring for patients without such an increase in LVISD will be at the time of a last LVISD assessment (Section 2.7.3.3).

2.7.1.7 Time to first occurrence of serum ferritin > 2 times the baseline value

An evaluation of the time from randomization to the first occurrence of serum ferritin > 2 times the baseline value at two consecutive assessments (at least two weeks apart) will be performed per treatment group based on the following variable:

- date of the first of the two consecutive laboratory assessment fulfilling the criterion of SF > 2 × baseline value minus date of randomization plus 1

The time-to-event analysis follows the description given in Section 2.5.2.2. Censoring for patients without such a serum ferritin increase is described in Section 2.5.3.6.

2.7.1.8 Infections

Infections requiring intravenous antimicrobials during the treatment period (until the 28 day follow-up visit) will be evaluated separately for each treatment group.

Definitions:

- Infections will be determined from the reported adverse events with system organ class "Infections and infestations" and action taken “Concomitant medication taken”.
- Antimicrobial therapy will be determined from the reported concomitant medications for patients who had an infection AE. The medications will be based on a pre-specified list of WHO low level ATC codes. The route of administration needs to be specified as “intravenous (i.v.)”.
- Identified events will be combined with medications (of the same patient) based on the following criterion: start date of medication ≥ start date of AE and start date of medication ≤ minimum (start date of AE + 1, end date of AE).

The total number of infections requiring intravenous antimicrobials will be counted and summarized per treatment group. For this number, one patient can contribute more than one infection event. To account for different lengths of observation time in the two groups, the rate of infections will be calculated with the number of recorded infections treated with intravenous antimicrobials divided by the total number of patient-years of follow-up. The relative risk of infection will be calculated as the rate of infection in the treatment group compared with the rate in the placebo group.

2.7.2 Statistical hypothesis, model, and method of analysis

No hypothesis will be tested for secondary endpoints.

2.7.3 Handling of missing values/censoring/discontinuations

2.7.3.1 Overall survival

For the analysis of overall survival (see Section 2.7.1.1), patients will be censored at the last contact date.

2.7.3.2 Disease progression to MDS

For the analysis of time to disease progression (see Section 2.7.1.4), patients who did not experience an MDS progression will be censored at the last contact date.

2.7.3.3 Increase in LVIDD or LVISD

For the two analyses of time from randomization to the first occurrence of an increase of at least 10% from the baseline value of LVIDD and time from randomization to the first occurrence of an increase of at least 10% from the baseline value of LVISD (see Section 2.7.1.5 & 2.7.1.6), respectively, patients who did not experience such an increase will be censored at the last date when LVIDD (or LVISD, respectively) was available.

2.8 Safety analyses

As stated in the protocol (Section 3.2), one of the secondary objectives was to evaluate safety, in particular to assess the levels of increased risk for pre-specified adverse events (renal dysfunction, neutropenia, thrombocytopenia, gastrointestinal bleeding, and laboratory abnormalities) that would be clinically unacceptable in the context of the level of benefit that is likely to be provided by iron chelation using deferasirox in MDS patients with iron overload.

Endpoints for the secondary safety objectives are as follows:

1. Proportion of patients with significant renal dysfunction
2. Proportion of patients with newly occurring moderate or severe neutropenia or thrombocytopenia
3. Proportion of patients with major gastrointestinal bleeding
4. Time to study drug discontinuation due to an adverse event or laboratory abnormality
5. Incidence of other adverse events and laboratory abnormalities

The first four endpoints are defined and evaluated as follows:

Endpoint	Analysis
Proportion of patients with significant renal dysfunction defined as serum creatinine ≥ 2 times ULN at two consecutive assessments (at least 7 days apart)	Frequency tables by treatment group will be prepared along with a two-sided 95% confidence interval for evaluation of DFX in contrast to placebo. Results will also be

Endpoint	Analysis
Proportion of patients with newly occurring neutropenia (absolute neutrophils count $<1.0\times10^9$/L) or thrombocytopenia (platelets $<50\times10^9$/L) Proportion of patients with major gastrointestinal bleeding.	provided for annual time intervals.
Time to study drug discontinuation due to an AE or laboratory abnormality, more specifically date of study drug discontinuation due to an AE or laboratory abnormality minus date of randomization plus 1.	The time-to-event analysis follows the description given in Section 2.5.2.2 The statistical test will be exploratory in nature. For the analysis of time from randomization to study drug discontinuation due to an AE or laboratory abnormality (see Section 2.8.3), patients who did not discontinue study medication due to an AE or laboratory abnormality will be censored at the date of study drug discontinuation.

Proportion of patients with moderate or severe anemia will be analyzed like newly occurring neutropenia.

Other analyses and other safety data (ocular and auditory examinations, electrocardiogram, and vital signs) will be also considered.

Safety summary includes baseline and on-treatment period. All safety data (including those from the post-treatment period) will be listed and those collected during the pre-treatment and post-treatment periods will be flagged.

2.8.1 Adverse events (AEs)

All AEs recorded during the study are coded using the latest version of the medical dictionary for regulatory activities (MedDRA) and summarized by treatment group and overall. Adverse events are not assessed according to the common terminology criteria for AEs (CTCAE); instead, AE severity (mild, moderate, severe) is used to report treatment-emergent AEs starting on or after the date of first study medication (including AEs that start within 28 days after the discontinuation of the study medication).

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

Frequency tables will display at least the MedDRA system organ class and preferred term, AE severity (mild, moderate, severe), and relationship to study drug. The following tables will be generated:

- Adverse events, regardless of study drug relationship

- Serious adverse events, regardless of study drug relationship
- Serious adverse events, suspected to be study drug relationship
- Adverse events leading to study drug discontinuation, regardless of study drug relationship
- Adverse events requiring dose adjustment or interruption, regardless of study drug relationship
- Adverse events requiring additional therapy, regardless of study drug relationship
- Adverse events, suspected to be study drug related
- Adverse events which are not serious adverse events, regardless of study drug relationship

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

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

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

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

The number of deaths resulting from SAEs suspected to be related to study treatment will be tabulated by SOC and PT and a listing will be generated.

2.8.1.1 Adverse events of special interest / grouping of AEs

Specific groupings of adverse events of special interest will be considered and the number of patients with at least one event in each grouping will be reported. Such groups consist of adverse events for which there is a specific clinical interest in connection with deferasirox treatment. Note that certain adverse events may be reported within multiple groupings/AESIs.

AESIs are defined by MedDRA terms. Definition for retrieval (maintenance of terms considered AESI) is in a separate document in the Novartis Documentum management system at the path “CREDI Projects/I/ICL670A/Integrated Medical Safety”. The MedDRA codes will be used to generate the outputs.

The AESI search table will be used to map reported adverse events to the notable adverse events groupings. The list of adverse events of special interest may be updated during the

course of the trial based on accumulating safety data. Therefore the clinical study report will list the AE groupings used and provide a listing of the corresponding AESI search table.

AESI will be summarized regardless of study drug relationship, by grouping, preferred term and treatment arm.

2.8.2 Deaths

Separate summaries for on-treatment and all deaths *(including post-treatment deaths)* will be produced by treatment arm, system organ class, and preferred term using the Safety set.

All deaths will be listed for the safety set, and post-treatment deaths will be flagged. A separate listing of deaths prior to starting treatment will be provided for all screened subjects.

2.8.3 Laboratory data

All laboratory values are generally converted into SI units and the severity grade calculated using notable and extended ranges as available in the deferasirox program standards. All values from central laboratory will be used to evaluate the primary and secondary endpoints. Any tests that are performed at local laboratories will not be used for either secondary or primary endpoints evaluation; however, collected local laboratory values will be listed along with central laboratory results and also for safety tables, all values for central and local laboratory results will be considered.

The frequency of laboratory abnormalities is displayed by parameter and treatment group. Laboratory data is summarized by presenting summary statistics of raw values and absolute and relative change from baseline.

Shift tables from baseline to highest (or lowest) post baseline value are provided for hematology: hemoglobin, WBC count, absolute neutrophils and platelets, biochemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine and creatinine clearance and urinalysis: urinary total protein/creatinine ratio using normal or extended ranges. Standard oncology shift tables for laboratory parameters, based on normal ranges, are also provided.

Box plots of absolute value and the absolute change from baseline in absolute neutrophils, platelets, ALT, AST, serum creatinine, creatinine clearance and urinary total protein/creatinine ratio by time points are provided. The last available value in a time point window is used.

Criteria for clinically notable and extended laboratory ranges

Parameter	Criteria
Absolute neutrophils	$<1.5\times10^9$/L (extended range $<0.5\times10^9$/L)
Platelets	$<100\times10^9$/L (extended range $<50\times10^9$/L)
ALT/AST	>5×ULN and >2×baseline value (extended range >10×ULN and >2×baseline value)
Serum creatinine	>33% increase from baseline and >ULN at two consecutive measurements at least 7 days apart
Creatinine clearance	<60 mL/min at two consecutive measurements at least 7 days apart (extended range <40 mL/min)
Urinary total protein/creatinine ratio	>1.0 mg/mg at two consecutive measurements at least 7 days apart
Total bilirubin	>2.0 mg/dL (>34.2 umol/L)

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

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

2.8.4.1.1 Data handling

In case the study requires ECG replicates at any assessment, the average of the ECG parameters at that assessment should be used in the analyses.

2.8.4.1.2 Data analysis

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

The number and percentage of subjects with notable ECG values will be presented by treatment arm.

- QT, QTcF and QTcB
  - New value of >450 and ≤480 ms
  - New value of >480 and ≤500 ms
  - New value of >500 ms
  - Increase from baseline of >30 ms to ≤60 ms
  - Increase from baseline of >60 ms
- HR
  - Increase from baseline >25% and to a value >100 bpm
  - Decrease from baseline >25% and to a value <50 bpm
- PR
  - Increase from baseline >25% and to a value >200 ms
  - New value of >200 ms

- QRS
  - Increase from baseline >25% and to a value >120 ms
  - New values of QRS >120 ms

A listing of all ECG assessments will be produced by treatment arm and notable values will be flagged. A separate listing of only the subjects with notable ECG values may also be produced. In the listing, assessments collected during the post-treatment period will be flagged.

2.8.4.2 Vital signs

Vital sign assessments are performed in order to characterize basic body function. The following parameters are collected: height (cm), weight (kg), body temperature (°C), respiratory rate (beats per minute), sitting systolic and diastolic blood pressure (mmHg).

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

A listing will be provided for all vital signs and BMI (Body Mass Index). Notable vital signs are flagged. The criteria for notable abnormal vital signs are displayed in Table 2-1.

Table 2-1 Definition of notable ranges for blood pressure 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
Weight	≥ 10% increase or decrease from baseline weight

2.8.4.3 Auditory and ophthalmic findings

Auditory and ophthalmic overall interpretation data will be summarized using shift tables comparing baseline result to most extreme post-baseline value.

Auditory data will be listed using the Safety set. The listing will include when tests are performed, overall interpretation, and any clinical significant abnormality findings.

Ophthalmic data includes visual acuity, slit lamp findings, tonometry, and fundus oculi. Results will be listed by test date using Safety Set.

2.9 Pharmacokinetic endpoints

Not applicable.

2.10 Patient-reported outcomes

Not applicable.

2.11 Biomarkers

Not applicable.

2.12 Other Exploratory analyses

No exploratory analyses are planned for this study.

2.13 Interim analysis

No interim analysis will be performed.

3 Sample size calculation

The sample size of 210 patients randomized in a ratio of 2:1 in favor of deferasirox is based on the feasibility of enrolling the patients and consultations with the Health Authorities. As noted earlier, this study is not powered for any confirmatory primary or secondary endpoints.

4 Change to protocol specified analyses

The following change was made:

- Newly occurring thrombocytopenia and neutropenia was redefined using the definition of the corresponding notable laboratory abnormalities

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

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

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

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

Impute date= Dec31yyyy

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

Impute date=EOT date

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

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

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

Impute date= the start date of that record.

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

5.1.2 AE date imputation

Date imputation is the creation of a new, complete date from a partial one according to an agreed and acceptable algorithm. The missing date for AEs will be handled according to STL (Standard Tables and Listings) standard.

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

Partial adverse event start dates, if left partial, will ultimately mean the following
It will not be possible to place the adverse event in time.
Therefore, the treatment/dosage at the time of the event will be unknown.
Therefore, the event could not be reported/summarized appropriately - if at all.
There **will be no** attempt to impute the following

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

Table 5-1 AE/treatment date abbreviations

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

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

Table 5-2 AE partial date imputation algorithm

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

Table 5-3 AE/treatment date relationship and imputation

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

The following Table 5-4 gives a few examples.

Table 5-4 Example Scenarios

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

5.1.3 Concomitant medication date imputation

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

5.1.3.1 Prior therapies date imputation

Start date:

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

End date:

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

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

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

5.1.3.2 Post therapies date imputation

Start date

Imputed date = max (last date of study drug + 1, first day of the month), if day is missing;

Imputed date = max (last date of study drug + 1, 01JAN), if day and month are missing.

End date: No imputation.

5.1.3.3 Other imputations

Incomplete date for death

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

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

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

5.2 AEs coding/grading

Major gastrointestinal bleeding

Major gastrointestinal bleeding (See Section 2.8) is defined as an AE that may include one of the following MedDRA preferred terms:

Gastric haemorrhage
Gastrointestinal haemorrhage
Small intestinal haemorrhage
Oesophageal haemorrhage
Large intestinal haemorrhage
Rectal haemorrhage
Melaena
Duodenal ulcer haemorrhage
Gastric ulcer haemorrhage
Peptic ulcer haemorrhage
Large intestinal ulcer haemorrhage
Oesophageal ulcer haemorrhage
Haematochezia

Infections requiring intravenous antimicrobials- definition (Section 2.7.1.8)

- Infections will be determined from the reported adverse events with system organ class "Infections and infestations" and action taken “Concomitant medication taken”.
- Antimicrobial therapy will be determined from the reported concomitant medications for patients who had an infection AE.
- The selection of medications will be based on the following categories of WHO low level ATC codes: D01, D04, J01, J02, J04, J05, P01, and P02.
- The route of administration must be specified as “intravenous (i.v.)”.
- Contemplable events will be combined with medications (of the same patient) based on the following criteria: start date of medication ≥ start date of AE and start date of medication ≤ minimum (start date of AE + 1, end date of AE).

5.3 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 or later. The calculation of laboratory CTC grades will be based on the observed laboratory values only; clinical assessments will not be taken into account.

For laboratory tests where grades are not defined by CTCAE 4.03 or latest version, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 is not applicable. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

5.3.1 Creatinine clearance estimation

An estimated creatinine clearance based on the Schwartz or Cockroft-Gault formula will be used. The modification of diet in renal disease (MDRD) derivation is provided in derived datasets only for possible future requests.

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

Cockroft-Gault formula, CrCl (mL/min)=

Male patients: (140-age)×weight/(815×0.001×SCr)

Female patients: (140-age)×weight×0.85/(815×0.001×SCr)

Abbreviated MDRD formula, CrCl (mL/min/1.73m^2)=

$186.3\times(SCr\times0.01131)^{-1.154}\times age^{-0.203}\times E\times S$ where,

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

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

5.3.2 Terminology IPSS score and MDS risk group

In the study protocol, both "IPSS score" and "MDS risk group" are used. In the randomization (IVRS) system, the baseline IPSS score is collected. However, the eCRF collects "MDS risk group" to "indicate patient's MDS Risk Group by International Prognostic Scoring System".

Post-text supplement 1 of the protocol includes the following table:

MDS Risk Group	Total score
Low	0
int-1	0.5 – 1.0
int-2	1.5 – 2.0
High	≥ 2.5

The total score is derived by summing up the score for each prognostic variable (Marrow Blasts, Karyotype, and Cytopenia). The score for each prognostic variable is given in table below:

	Score				
Prognostic Variable	**0**	**0.5**	**1.0**	**1.5**	**2.0**
Marrow Blasts (%)[1]	<5	5-10	--	11-20	21-30
Karyotype[2]	Good	Intermediate	Poor		
Cytopenia[3]	0/1	2/3			

[1] Patients with 21-30% blasts may be considered as MDS or AML

[2] Cytogenetics: Good = Normal, -Y, del(5q), del(20q); Poor = Complex (≥ 3 abnormalities) or chromosome 7 anomalies; Intermediate = other abnormalities

[3] Cytopenias: neutrophil count < 1.8 10E9/L, platelets < 100 10E9/L, hemoglobin < 10 g/dL

5.4 Dose interruption and modification

The following definitions will be used to define dose interruption and dose change:

Term	Details
Interruption	An interruption is a period with a zero actual dose preceded and followed by a period with a non-zero actual dose.
Dose change	A planned dose reduction is where 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 where 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).

5.5 Statistical models

5.5.1 Primary analysis

5.5.1.1 Stratified unadjusted Cox model

The stratified unadjusted Cox model and its assumptions are described by

$$h(t, x_{jk1,}\beta_1) = h_{0k}(t).\exp(x_{jk1}.\beta_1)$$

where h (.) is the hazard function as a function of time (relative to date of randomization), the randomized study treatment of patient j in stratum k and the unknown regression parameter.

$h_{0k}(t)$ be the unspecified baseline hazard function for stratum k at time t.

x_{jk1} is the randomized study treatment for patient j in stratum k coded as 0 for placebo and 1 for deferasirox.

β_1 is the unknown regression parameter for the treatment effect on the log-scale (the log hazard ratio), to be estimated.

The hazard ratio (HR) is a multiplicative constant, $\exp(\beta_1)$, comparing the hazard function in the deferasirox group relative to the hazard function in the placebo group. The latter is called the baseline hazard function which is allowed to vary across strata. However, the HR comparing study treatments is assumed to be common across strata. A HR <1 would indicate a decreased hazard for deferasirox as compared to placebo.

The Cox proportional hazards model will be evaluated by using SAS PROC PHREG with the TIES = EXACT option in the MODEL statement. STRATA options will be used to account for variations in baseline hazards across strata. The HR point estimate will be based on the partial maximum likelihood function, and a two-sided 95% on confidence interval based on Wald test will be generated by the RISKLIMITS option. The detailed SAS code will be provided in the programming note in RAP M7.

5.5.2 Key secondary analysis

Not applicable

5.5.3 Confidence interval for the difference of proportions

The 95% confidence limits for the difference of two proportions will be derived as the Wilson score confidence limits, i.e. in Proc Freq riskdiff-option: CL=WILSON(CORRECT).

5.5.4 Treatment switching to new chelator(s)

If there is a high differential in the proportion of patients (more than 10%) of switching to new chelation therapy prior to experiencing event-free survival event in the placebo arm compared to Deferesirox arm, then a set of additional analyses may be performed: descriptive summaries of a selected set of baseline and disease characteristics and a model-based analysis such as IPCW or RPSFT to account for potential confounding of new chelation therapy.

5.5.5 Time point windows

For summaries by time periods (e.g. Year or Quarter), windows are based on scheduled days and separating time between visits into halves as in table below. Day of randomization will be considered as Day 1:

Visit Description	First day in window	Scheduled day in window	Last day in window	Quarter	Year
Baseline	-35		1		
Week 2	2	14	21	1	1
Week 4	22	28	42	1	1
Week 8	43	56	70	1	1
Week 12	71	84	98	1	1
Week 16	99	112	126	2	1
Week 20	127	140	154	2	1
Week 24	155	168	182	2	1
Week 28	183	196	210	3	1
Week 32	211	224	238	3	1
Week 36	239	252	266	3	1
Week 40	267	280	294	4	1
Week 44	295	308	322	4	1
Week 48	323	336	350	4	1
Week 52	351	364	378	4	1
Week 56	379	392	406	1	2
Week 60	407	420	434	1	2
Week 64	435	448	462	1	2
Week 68	463	476	490	2	2
Week 72	491	504	518	2	2
Week 76	519	532	546	2	2
Week 80	547	560	574	3	2
Week 84	575	588	602	3	2
Week 88	603	616	630	3	2
Week 92	631	644	658	4	2
Week 96	659	672	686	4	2
Week 100	687	700	714	4	2
Week 104	715	728	742	4	2
Week 108	743	756	770	1	3
Week 112	771	784	798	1	3
Week 116	799	812	826	1	3
Week 120	827	840	854	2	3
Week 124	855	868	882	2	3
Week 128	883	896	910	2	3
Week 132	911	924	938	3	3
Week 136	939	952	966	3	3
Week 140	967	980	994	3	3
Week 144	995	1008	1022	4	3
Week 148	1023	1036	1050	4	3
Week 152	1051	1064	1078	4	3
Week 156	1079	1092	1106	4	3
Week 160	1107	1120	1134	1	4
Week 164	1135	1148	1162	1	4

Visit Description	First day in window	Scheduled day in window	Last day in window	Quarter	Year
Week 168	1163	1176	1190	1	4
Week 172	1191	1204	1218	2	4
Week 176	1219	1232	1246	2	4
Week 180	1247	1260	1274	2	4
Week 184	1275	1288	1302	3	4
Week 188	1303	1316	1330	3	4
Week 192	1331	1344	1358	3	4
Week 196	1359	1372	1386	4	4
Week 200	1387	1400	1414	4	4
Week 204	1415	1428	1442	4	4
Week 208	1443	1456	1470	4	4
Week 212	1471	1484	1498	1	5
Week 216	1499	1512	1526	1	5
Week 220	1527	1540	1554	1	5
Week 224	1555	1568	1582	2	5
Week 228	1583	1596	1610	2	5
Week 232	1611	1624	1638	2	5
Week 236	1639	1652	1666	3	5
Week 240	1667	1680	1694	3	5
Week 244	1695	1708	1722	3	5
Week 248	1723	1736	1750	4	5
Week 252	1751	1764	1778	4	5
Week 256	1779	1792	1806	4	5
Week 260	1807	1820	1834	4	5
Week 264	1835	1848	1862	1	6
Week 268	1863	1876	1890	1	6
Week 272	1891	1904	1918	1	6
Week 276	1919	1932	1946	2	6
Week 280	1947	1960	1974	2	6
Week 284	1975	1988	2002	2	6
Week 288	2003	2016	2030	3	6
Week 292	2031	2044	2058	3	6
Week 296	2059	2072	2086	3	6
Week 300	2087	2100	2114	4	6
Week 304	2115	2128	2142	4	6
Week 308	2143	2156	2170	4	6
Week 312	2171	2184	2198	4	6
Week 316	2199	2212	2226	1	7
Week 320	2227	2240	2254	1	7
Week 324	2255	2268	2282	1	7
Week 328	2283	2296	2310	2	7
Week 332	2311	2324	2338	2	7
Week 336	2339	2352	2366	2	7

Visit Description	First day in window	Scheduled day in window	Last day in window	Quarter	Year
Week 340	2367	2380	2394	3	7
Week 344	2395	2408	2422	3	7
Week 348	2423	2436	2450	3	7
Week 352	2451	2464	2478	4	7
Week 356	2479	2492	2506	4	7
Week 360	2507	2520	2534	4	7
Week 364	2535	2548	2562	4	7
Week 368	2563	2576	2590	1	8
Week 372	2591	2604	2618	1	8
Week 376	2619	2632	2646	1	8
Week 380	2647	2660	2674	2	8
Week 384	2675	2688	2702	2	8
Week 388	2703	2716	2730	2	8
Week 392	2731	2744	2758	3	8
Week 396	2759	2772	2786	3	8
Week 400	2787	2800	2814	3	8
Week 404	2815	2828	2842	4	8
Week 408	2843	2856	2870	4	8
Week 412	2871	2884	2898	4	8
Week 416	2899	2912	2926	4	8
Week 420	2927	2940	2954	1	9
Week 424	2955	2968	2982	1	9
Week 428	2983	2996	3010	1	9
Week 432	3011	3024	3038	2	9
Week 436	3039	3052	3066	2	9
Week 440	3067	3080	3094	2	9
Week 444	3095	3108	3122	3	9
Week 448	3123	3136	3150	3	9
Week 452	3151	3164	3178	3	9
Week 456	3179	3192	3206	4	9
Week 460	3207	3220	3234	4	9
Week 464	3235	3248	3262	4	9
Week 468	3263	3276	3290	4	9

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