NOVARTIS

Clinical Development

ICL670 (Deferasirox)

CICL670A2421 / NCT01868477

An open-label, phase II, randomized, pilot study to assess the effect in term of erythroid improvement of deferasirox combined with erythropoietin compared to erythropoietin alone in patients with low- and int-1-risk myelodysplastic syndrome

RAP Module 3 – Detailed Statistical Methodology

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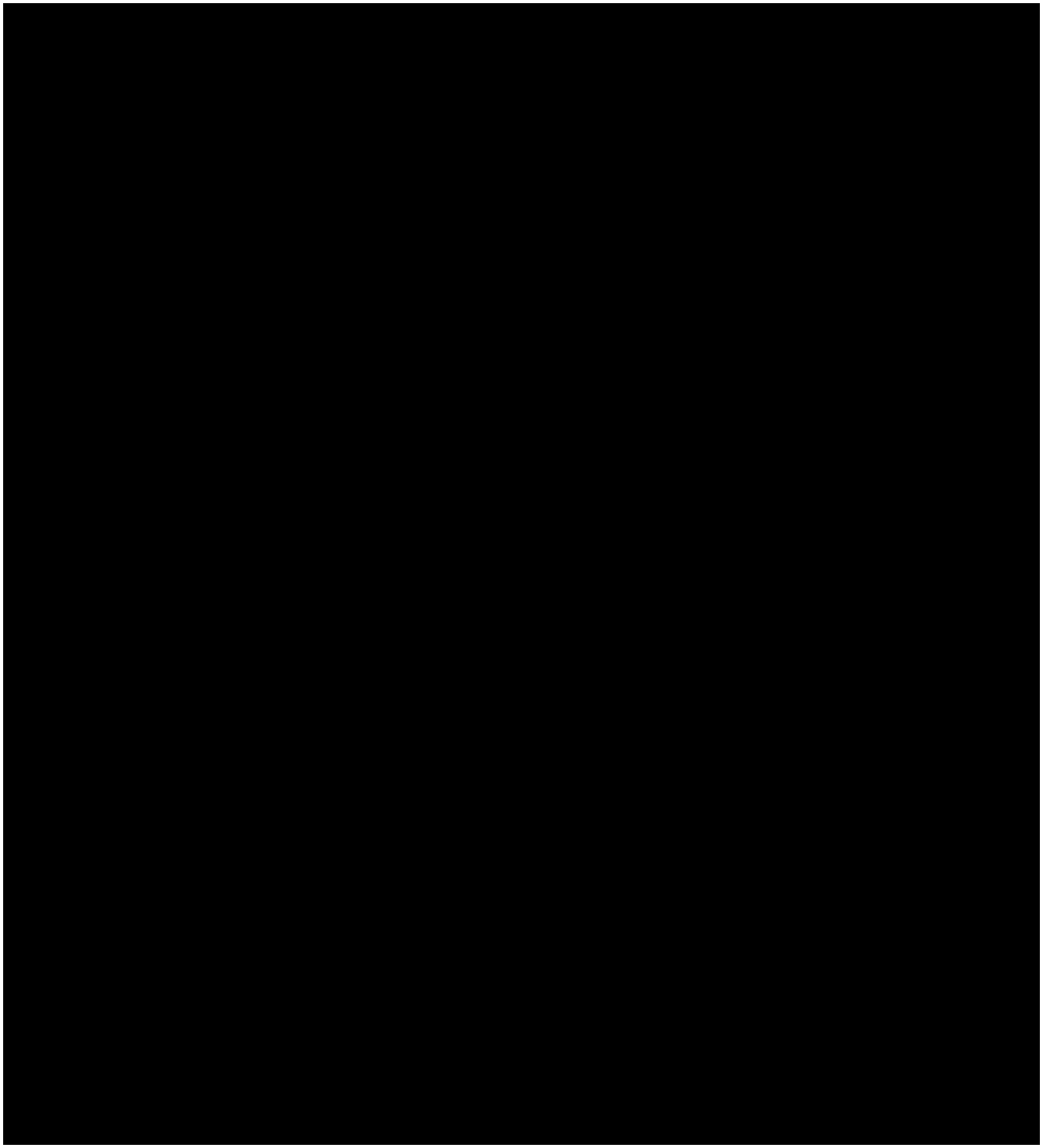

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List of Abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
BMI	Body Mass Index
[redacted]	[redacted]
CRF	Case Report Form
[redacted]	[redacted]
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events v3.0
CTT	Clinical Trial Team
CV	Coefficient of Variation
DFX	Deferasirox
DT	Dispersible Tablet
ECG	electrocardiogram
eCRF	electronic Case Report Form
EOS	End of Study Evaluation Completion
EOT	End of Study Treatment
EPO	Erythropoietin
FAB	French-American-British Cooperative Group
FAS	Full Analysis Set
FCT	Film-Coated Tablet
g/dL	grams per deciLiter
Hb	hemoglobin
IWG	International Working Group
IWR	Interactive Web Response Technology
MDS	Myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligrams
mg/m^2	milligrams / meter squared
mg/kg/day	milligrams / meter squared / day
NCI-CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
p.o.	per os/by mouth/orally
PD	Protocol Deviation
PP	Per Protocol
PT	Preferred Term
RAP	Report analysis plan
s.c	Subcutaneous(ly)
SAE	Serious Adverse Event
SOC	System Organ Class

TEAE	treatment-emergent Adverse Event
ULN	Upper limit of normal
WHO	World Health Organization

1 Introduction

1.1 Document content

This Report and Analysis Plan (RAP) module describes the planned statistical methods for all efficacy and safety analyses for phase II study CICL670A2421 which is an open-label, phase II, randomized, pilot study to assess the effect in term of erythroid improvement of deferasirox (DFX) combined with erythropoietin (EPO) compared to EPO alone in patients with low- and int-1-risk myelodysplastic syndrome (MDS).

It is structured as:

- A draft of Section 9.7 (Statistical methods planned in the protocol and determination of sample size)
- A draft of Appendix 16.1.7 and 16.1.9 (Documentation of statistical methods) of the CSR.

It is written in future tense. It will be reviewed and updated (including conversion to past tense) for entry into the clinical study report after the analysis has taken place.

The shells for the in-text tables and figures, post-text tables, figures and listings, and the table of contents will be in Module 7. Programming specifications, including derivations and imputation dates will be given in Module 8.

2 Clinical Study Report Section 9.7 - Statistical methods planned in the protocol and determination of sample size

2.1 CSR Section 9.7.1 – Statistical and analytical plans

All data will be analyzed by [redacted], and reviewed by Novartis, according to the data template analysis section 10 of the study protocol which is available in Appendix 16.1.1 of the CSR. Important information is given in the following sections and details are provided, as applicable, in Appendices 16.1.7 and 16.1.9 of the CSR template. Analysis data sets and statistical outputs will be produced using the most recent SAS® Version, and stored in [redacted].

2.2 Data included in the analyses

Data will be collected on patients aged ≥ 18 years or older with low- and-int-1-risk MDS, randomized in 1:1 ratio to DFX+EPO or EPO alone. If after 12 weeks of treatment with EPO alone, Hb increase is < 1 g/dL and total Hb is < 12 g/dL, the patient will switch to combination therapy of EPO and DFX. The study treatment duration is 24 weeks.

As per the current protocol, no interim analysis is planned. All interim (if required) and final CSRs will have a documented medical review by [redacted].

2.3 Analysis sets

The analysis will consider the following populations:
Full Analysis Set: The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned by randomization (EPO or EPO+DFX). According to the intent to treat principle, patients will be analyzed according to the treatment they have been assigned to during the randomization procedure.

Safety Set: The Safety Set includes all randomized patients who received at least one dose of study medication, i.e. either EPO or EPO+DFX, and with at least one post-baseline safety assessment (e.g. lab, vital signs, AEs) and the statement that a subject did not experience an AE can currently be regarded as a valid safety assessment.

2.4 Protocol Deviations

The number and percentage of patients with any relevant CSR reportable protocol deviations (PDs) will be tabulated. All relevant CSR reportable PDs will be also listed. PD criteria are specified in the **Validation Analysis Plan Module 3 "**Protocol Deviations" document.

ICH E3 defines the categories into which most CSR reportable PDs will fall:

- Eligibility: Subject entered study even though they did not satisfy the entry criteria.
- Withdrawal: Subject developed study/treatment withdrawal criteria during the study but was not withdrawn.
- Study drug: Subject received the wrong treatment or incorrect dose.

- Concomitant medication: Subject took an excluded concomitant medication.
- Others: Important deviations which do not align with one of the above categories and which might jeopardize the safety or rights of the subject or which may impact the scientific value of the trial.

Refer to section 4.4. with regard to describing actions against protocol violations.

2.5 Statistical methods and data analysis

Categorical parameters

Categorical (qualitative) data (e.g., gender, race, etc) will be presented as frequencies and percentages. A missing category for categorical data will be presented where applicable. Unless otherwise noted, percentages will be based on the number of patients in the relevant population or subgroup as the denominator. Categorical variables will be summarized by absolute and relative frequencies where applicable.

Continuous parameters

Continuous (quantitative) data (e.g., age, body weight, etc.) will be summarized by number of patients, mean, standard deviation, median, minimum, and maximum. The lower and upper quartiles may also be used under special circumstances.

2.6 Patient disposition, background and demographic characteristics

All analyses described in this section will be conducted using the FAS.

2.6.1 Patient disposition

This analysis will provide the number and percentage of patients who:

1. Have been randomized (Treated/ Untreated),
2. Have completed the study (patient who completes treatment duration as per protocol as per the EOT [777] page of CRF and also completes the follow up phase as per protocol in the EOS [778] page of CRF),

The number (%) of patient by reason of study treatment discontinuation will be provided for those patients who have discontinued the study treatment. Similarly, this will be performed for study discontinuation. Protocol deviations will be summarized and listed.

The study will end when the last patient will have either withdrawn (including follow-up of 30 days) from the study or completed the study (24 weeks + follow up period of 30 days) from the start of treatment (EPO or EPO+DFX), whichever occurs earlier.

Listings will be provided for screen failure patients (with reasons for screen failure). Screen failures are patients who have been screened (patients who have signed ICF) and who failed to be randomized and treated for any reason (i.e. failing to meet inclusion or exclusion criteria or any other screening procedure).

2.6.2 Background and demographic characteristics

The FAS will be used for all baseline and demographic summaries and listings.

Basic demographic data

Demographic data (gender, predominant race, ethnicity, age, height, weight, BMI) and other baseline data (baseline serum ferritin, EPO levels at screening, baseline Hb) will be summarized descriptively and listed.

While being analyzed as continuous variables, age, baseline serum ferritin, baseline Hb, EPO levels at screening will also be reported using categories.

Age (years) category will consider the following categories: <65 and ≥65.

EPO levels at screening will consider the following categories: 0 - < 20, 20 - < 50, 50 - < 200, 200 - < 500 and >= 500.

BMI (kg/ m^2) will be calculated as weight [kg] / (height^2 [m^2]).

History of disease

The French-American-British Cooperative Group (FAB) classification at screening will be tabulated and listed.

The FAB originally classified MDS into 5 different types (see protocol Table 1-1). However, the World Health Organization (WHO) has revised this classification and now identifies 8 different orders (see protocol Appendix 1).

The FAB classifications for subjects with MDS to be considered in this study are:

- Refractory Anemia (RA),
- Refractory Anemia with Ringed Sideroblasts (RARS) and
- Refractory Anemia with Excess of Blasts (RAEB).

The information can be obtained from the HIS panel of the CRF.

History of blood transfusion

History of blood transfusions (number of prior transfusions, time since last transfusion) will be summarized and listed. Time since last transfusion is the time interval from the last blood transfusion to start of study), ie.,

Time since last transfusion (years) = (Screening 1 visit date – Date of last transfusion received +1) / 365.25.

Time since diagnosis of MDS

Time since diagnosis of MDS as obtained from the CND panel (Relevant medical history/current medical conditions) of the CRF with MDS being the active problem will be

summarized and listed. Time since diagnosis of MDS is the time interval between the date of diagnosis of MDS to start of study, i.e.,

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

Other baseline characteristics

Childbearing potential and serum pregnancy test results will be listed. Overall interpretation in audiometric test (normal or clinically significant or insignificant abnormality), overall interpretation in ocular exam (normal or clinically significant or insignificant abnormality), and clinically significant abnormality in electrocardiogram (ECG) (yes or no), will be summarized and listed.

Baseline summary for serum ferritin will be provided. Baseline categories (described in RAP M7) will be provided for serum creatinine, creatinine clearance, ALT and AST.

2.6.3 Medical History

The FAS will be used for all medical history and current medical conditions including cancer-related conditions and symptoms, which will be summarized and listed. Separate summaries will be presented for current and historical medical conditions. The summaries will be presented by primary system organ class (SOC) and preferred term (PT) based on latest available Medical Dictionary for Regulatory Activities (MedDRA) dictionary version at time of database lock. The MedDRA version used for reporting the study will be specified as a footnote in the related tables/listings.

2.7 Study treatment

The investigational study drugs used in this trial are deferasirox (DFX DT) provided as dispersible tablet or deferasirox (DFX FCT) provided as film-coated tablet for oral use and erythropoietin alpha (EPO) for subcutaneous injection.

The study treatment is DFX + EPO or EPO alone.

At the time when DFX FCT study drug becomes available at a study site, all new patients who are randomized to combination therapy will receive the DFX FCT. Patients who are ongoing and receive DFX DT will continue with the DT. It is not permitted to change formulation during treatment.

Table 2-1 EPO Dosing

Initial Treatment	**EPO 40,000 units/week**	**EPO 40,000 units/week + DFX DT 10 mg/kg day or DFX FCT 7 mg/kg day**
Week 4	Hemoglobin status	Action
	Hb increased < 1 g/dL from baseline and Hb < 12 g/dL	Increase EPO to 60,000 units/week *
	Hb increase is ≥ 1 g/dL and Hb < 12 g/dL	Continue EPO 40,000 units/week *
	Hb increase is ≥ 1 g/dL and Hb ≥ 12 g/dL	Hold EPO treatment *
Week 12	Hemoglobin status	Action
	Hb increased < 1 g/dL from baseline and Hb < 12 g/dL	If patient is in the combination arm: Discontinue from the study or If patient is in the EPO monotherapy arm: Switch to the combination EPO + DFX
	Hb increase is ≥ 1 g/dL and Hb < 12 g/dL	
	Hb increase is ≥ 1 g/dL and Hb ≥ 12 g/dL	Hold EPO treatment *

* Patients in combination arm will continue DFX DT 10 mg/kg/day or DFX FCT 7 mg/kg/day treatment

2.7.1 Exposure to study treatment

For all analysis described in this section, the Safety Set will be used.

Duration of exposure

The *duration of exposure to study drug* is defined as the time interval from first (non-zero) dose of study drug administration to last study drug administration date (i.e. last known study drug administration date), and it will be calculated using the following formula:

Duration of exposure (days) = [(last date of exposure to the study drug) – (date of first administration of the study drug) + 1 day], where:

- 'Date of first administration of the study drug' is defined as the first date when a non-zero dose of study treatment is administered. For the sake of simplicity, the date of first administration of study treatment is referred to **start date of study treatment.**
- 'Last date of exposure to the study drug' is the date of last administration of this study treatment which is defined as the last date when a non-zero dose of study treatment is administered. This date will also be referred as **last date of study treatment.**

The duration of exposure includes the periods of temporary study drug interruption.

For patients who did not take any study drug, the duration of exposure is defined as zero.

The duration of exposure excluding the temporary study drug interruption will also be computed, only time interval where the drug was known to be taken will be considered. It will be computed using the following formula:

Duration of exposure excluding temporary study drug interruption (days) = Duration of exposure (days) – number of days during this time interval where the actual dose was zero.

Both the duration of exposure and duration of exposure excluding interruptions will be summarized as continuous variables and by days as <28, 28 to <56, 56 to <84, 84 to <140, 140 to <164 and ≥ 164.

Percentage of exposure

The percentage of exposure is defined as 100×(duration of exposure excluding interruptions)/(duration of exposure).

It will be summarized as a continuous variable and by the following categories as <20%, 20% to <40%, 40% to <60%, 60% to <80% and 80% to ≤100%.

2.7.2 Dose exposure

For all analysis described in this section, the Safety Set will be used.

The dose exposure will be provided for both DFX and EPO in the following way:

- *For patients randomized to EPO and those who do not switch to combination after 12 weeks: Duration of exposure to EPO for 24 weeks.
- For patients randomized to EPO+DFX: Duration of exposure to EPO for 24 weeks (with suitable exposure categories described in RAP M7) and duration of exposure to DFX DT or DFX FCT for 24 weeks (duration unit expressed as number of days with suitable exposure categories described in RAP M7).
- For patients randomized to EPO and switched to combination after 12 weeks: Duration of exposure to EPO for 24 weeks and duration of exposure to DFX DT or DFX FCT for 12 weeks (week 13 to week 24).

Note: Patients randomized to EPO and switched to combination after 12 weeks, will not be counted in *. The patient population as described in * will be exclusively those patients who were randomized to EPO and remained in the EPO arm for 24 weeks.

2.7.2.1 Deferasirox

Exposure to DFX DT or DFX FCT will be summarized descriptively using the following parameters: average planned daily dose (mg/kg/day) and average actual daily dose (mg/kg/day).

The actual daily dose is calculated in the following way:

Actual daily dose per kg of weight (mg/kg/day) = actual daily dose (mg/day) / last available weight prior to the dose administration (kg)

The cumulative dose is calculated in the following way which is used later to calculate average actual dose.

Cumulative dose (mg/kg) = sum of all (actual daily dose Z (mg/kg/day) × duration of dose Z administration (days)); where Z is the specific dose level considered, e.g. 10 mg/kg/day for DFX DT or 7 mg/kg/day for DFX FCT.

The following formulae will be used to compute the average daily planned and the average actual daily doses.

1. *Average planned dose (mg/kg/day)* = sum of all (planned dose (mg/kg/day) × corresponding planned dose exposure) / overall drug exposure (days),

   where the planned dose is the dose reported in the CRF page for a given time interval.

2. *Average actual dose (mg/kg/day)* = Cumulative dose (mg/kg) / overall drug exposure (days).

2.7.2.2 Erythropoietin

Similarly, the exposure to EPO will be summarized in the following way:

Cumulative dose (units/week) = sum of all (actual weekly dose Z (units/week) × duration of dose Z administration (week)); where Z is the specific dose level considered, e.g. 40,000 units/week.

The following formulae will be used to compute the average weekly planned and the average actual weekly doses.

1. *Average planned dose (units/week)* = sum of all (planned dose Z (units/week) × corresponding planned dose Z exposure) / overall drug exposure (weeks),
2. *Average actual dose (units/week)* = Cumulative dose (unit/week) / overall drug exposure (weeks).

2.7.3 Dose reductions and interruptions

The number of patients with dose reductions or interruptions, as well as the reasons leading to study drug dose reduction or to study drug interruption will be tabulated.

The number of dose interruptions and dose reductions will be tabulated by treatment group. Both of dose reduction and dose interruption will be calculated with regards to DFX DT or DFX FCT and EPO. Patients randomized to EPO arm or EPO+DFX arm may have an AE related to either EPO and/or DFX and thus the drug may be stopped or the dose may be reduced till the AE severity reduces.

An **interruption** is defined as a dose equal to zero on one or more days as reported in the CRF. A missing dose will not be considered as zero. A zero dose will not be considered as an interruption if it is the last dose administration record for a patient.

An interruption during consecutive days for the same reason is counted once.

If an interruption occurs for more than one consecutive day due to different reasons, then it will be counted for each reason.

A **dose reduction** is defined as a decrease in dose from the protocol planned starting dose or a decrease from the previous non-zero dose, even if this decrease has been directly preceded by an interruption. If, due to a dosing error, a patient receives higher dose than protocol planned starting dose and moves down to the planned starting dose then this is not be counted as a reduction. However if they move directly from a higher than planned starting dose down to a lower than protocol planned starting dose, then this is counted as a reduction.

A **dose increase** is defined as an increase in dose from the protocol planned starting dose or an increase from the previous non-zero dose, even if this increase has been directly preceded by an interruption.

2.8 Concomitant medication

For all analysis described in this section, the Safety Set will be used.

Concomitant therapy is defined as any interventions (therapeutic treatments, procedures or significant non-drug therapies) other than the study treatment administered to a patient coinciding with the study treatment period.

Concomitant or prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Dictionary Enhanced (DDE) ATC term according to the latest version during the time of analysis of data.

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 will be listed and summarized by ATC class, preferred term and treatment arm by means of frequency counts and percentages. 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 medications, procedures or significant non-drug therapies starting and ending prior to the start date of study treatment will be listed.

2.9 Efficacy evaluation

2.9.1 Primary objective

The primary objective will be to assess the effect of treatment with DFX+EPO vs. EPO alone on erythropoiesis after 12 weeks of treatment.

2.9.1.1 Variable

The primary variable is the difference in proportion of patients achieving an erythroid response after 12 weeks of treatment between the two arms according to modified IWG 2006 criterion (increase in Hb from baseline $\geq$ 1.5 g/dL).

Patients meeting the criterion at any time within the first 12 weeks period will be considered erythroid responders.

2.9.1.2 Statistical hypothesis, model, and method of analysis

A patient is defined as an erythroid responder if the criterion of Hb increase from baseline ≥ 1.5 g/dL is met at any time within the first 12 weeks period.

Baseline is defined as the last available value within windows of 4 weeks prior to or on treatment start date. No imputation will be performed for missing Hb value.

Difference in proportions between treatment groups with its 95% Agresti-Caffo (Agresti-Caffo 2000) confidence interval will be provided. Erythroid response proportion will be also summarized by treatment group with its 95% Clopper-Pearson confidence intervals (Clopper and Pearson 1934). Analysis will be performed on FAS.

2.9.2 Secondary objectives

The following secondary endpoints will be analyzed by treatment arms.

2.9.2.1 To assess the effect of treatment with DFX+EPO and EPO alone on hematologic response within 24 weeks of treatment

This analysis includes patients who were randomized to EPO and EPO+DFX and remained in their respective treatment arms.

Hematological response will be assessed on this subset of patients and hematological responder is defined as patient meeting at least one of the following modified IWG 2006 criteria:
Hematological response:

- Hb increase from baseline ≥ 1.5 g/dL and Hb < 11 g/dL at baseline (All patients on study per inclusion criterion 5, cf. study protocol section 5.2).
- Neutrophil response: increase from baseline of ≥ 100% and increase > 0.5 x 10^9 /L and neutrophils < 1.0 × 10^9 /L at baseline.
- Platelet response: increase from baseline of ≥ 30 x 10^9/L and platelets < 100 × 10^9/L at baseline.

Patients who met at least one of the 3 conditions of hematological response at any time between first day of treatment and week 12 or 24 will be considered as responders.

Supportive analyses (proportion of patients, descriptive statistics on the related parameters, change from baseline) will also be provided for patients who do not satisfy the IWG 2006 pre-treatment conditions for neutrophil and/or platelet response (i.e., these patients have baseline neutrophils ≥ 1.0 × 10^9/L and baseline platelets ≥ 100 × 10^9/L) but show hematologic improvement with respect to neutrophils (increase from baseline > 0.5 × 10^9/L) and/or platelets (increase from baseline ≥ 30 × 10^9/L).

Proportion of patients achieving a hematological response within 12 weeks and within 24 weeks of treatment with DFX combined with EPO and EPO alone will be calculated along with 95% Clopper-Pearson confidence interval. Descriptive statistics will be provided for

hematological improvement response, as well as for all hematological improvement of myeloid cell lineages subcomponents (hemoglobin, erythrocytes, neutrophils and platelets). Analysis will be performed on FAS.

Hematologic response and improvement within 12 weeks and 24 weeks will be analyzed separately.

Table 2-2 summarizes the distinction between response and improvement as being used for supportive analyses:

Table 2-2 Criteria for hematological response and hematologic improvement

	Pre-treatment conditions	**Post-baseline**	**Response**
Hematological response: If a patient fulfills at least erythroid or platelet or neutrophil response as well as it's corresponding pre-treatment condition	Hb< 11 g/dL at baseline	Hb increase from baseline by ≥ 1.5 g/dL	Erythroid response
	Platelet < 100 ×10^9 /L at baseline	Increase from baseline ≥ 30 × 10^9/L	Platelet response
	Neutrophil < 1.0 × 10^9/L at baseline	Increase from baseline > 100% and increase from baseline > 0.5 × 10^9/L	Neutrophil response
Hematologic improvement: If a patient fulfills at least hemoglobin or platelet or neutrophil improvement response without it's corresponding pre-treatment condition	Hemoglobin < 11 g/dL at baseline	Increase from baseline by ≥ 1 g/dL	Hemoglobin improvement
	Platelet ≥ 100 ×10^9/L at baseline	Increase from baseline ≥ 30 ×10^9/L	Platelet improvement
	Neutrophil ≥ 1.0 × 10^9/L at baseline	Increase from baseline > 0.5 × 10^9/L	Neutrophil improvement

2.9.2.2 To assess the effect of treatment on erythropoiesis within 24 weeks in patients who were non-responder to EPO alone after 12 weeks and switched to DFX+EPO

Patients who are non-responders to erythroid at week 12 in the EPO group will have to switch to combination therapy, if they continue to participate in the study.

Patients meeting the criterion (Hb increase from baseline ≥ 1.5 g/dL) at any time between week 12 and week 24 will be considered as erythroid responders.

Proportion of erythroid responders between week 13 and 24 will be reported along with its 95% Clopper-Pearson confidence interval. Descriptive statistics will be provided for erythroid response. Analysis will be performed on FAS.

2.9.2.3 To assess the effect of treatment with EPO alone on erythropoiesis within 24 weeks of treatment

This analysis includes patients who started with the EPO alone and are not switched to combination therapy.

Patients meeting the criterion (Hb increase from baseline ≥ 1.5 g/dL) at any time between week 1 and week 24 will be considered as erythroid responders. Proportion of erythroid responders who starts with EPO alone and are not switched to combination therapy will be reported along with its 95% Clopper-Pearson confidence interval.

Descriptive statistics will be provided for erythroid response. Analysis will be performed on FAS.

2.9.2.4 To assess iron parameters in patients randomized to EPO alone, DFX+EPO and in patients randomized to EPO alone and switched to DFX+EPO after 12 weeks

This analysis will include patients randomized either to EPO or DFX+EPO at baseline as well as patients who are non-responders to erythroid at week 12 in the EPO group switched to combination therapy. The time-course of serum ferritin and its absolute/relative changes from baseline will be summarized by descriptive statistics by visit and erythroid response. Data will be summarized on FAS.

Note: Patients randomized to EPO and not switching after 12 weeks to EPO+DFX, will consist of only responders.

2.9.2.5 To assess Hb parameters in patients randomized to EPO alone, DFX+EPO and in patients randomized to EPO alone and switched to DFX+EPO after 12 weeks

This analysis will include patients randomized either to EPO or DFX+EPO at baseline as well as patients who are non-responders to erythroid at week 12 in the EPO group switched to combination therapy. The time-course of Hb and its absolute/relative changes from baseline will be summarized by descriptive statistics by visit and erythroid response. Data will be summarized on FAS.

Note: Patients randomized to EPO and not switching after 12 weeks to EPO+DFX, will consist of only responders.

2.10 Safety evaluation

For all safety analyses, the Safety Set will be used. All listings and tables will be presented by treatment group.

2.10.1 Analysis set and grouping for the analyses

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

1. pre-treatment period: from day of patient's informed consent to the day before first dose of study medication

2. on-treatment period: from the day of first dose of study medication to 30 days after last dose of study medication
3. Post-treatment period: starting at day 31 after last dose of study medication.

If dates are incomplete in a way that clear assignment to pre-, on-, post-treatment period cannot be made, then the respective data will be assigned to the on-treatment period.

The assessment of safety will be based mainly on frequency of AEs and on the number of laboratory values that fall outside of pre-determined ranges.

The safety summary tables will include on-study assessments (with the exception being the prior concomitant medications, laboratory parameters with baseline value taken prior to start of study drug). All safety assessments will be listed and those collected outside of the on-study period will be flagged appropriately.

In all safety listings, a column will be added to provide the true treatment (EPO alone, EPO+DFX DT or EPO+DFX FCT, DFX DT or DFX FCT alone, no treatment) at onset of AE or at time of any other safety assessment and the original treatment assigned.

2.10.2 Adverse events (AEs)

The reporting of AEs and AEs of special interest will be reported in the following periods based on the treatment received as follows:

- For patients receiving EPO during the first 12 weeks and for those continuing with EPO after 12 weeks (no switching to EPO+DFX arm), the safety data will be reported based on the corresponding treatment group: EPO. The safety data will be reported in period 1-12 weeks, 13-24 weeks and 1-24 weeks.
- For patients receiving EPO+DFX DT or EPO+DFX FCT from week 1 and continuing with EPO+DFX DT or EPO+DFX FCT after 12 weeks or with DFX DT or DFX FCT alone after 12 weeks, the safety data will be reported based on the corresponding treatment group EPO+DFX. The safety data will be reported in period 1-12 weeks and 1-24 weeks.
- For patients receiving EPO alone and switched to EPO+DFX after 12 weeks of treatment, the safety data will be reported only in period 13-24 weeks.

Overall summary will be reported for AEs occurred in period 1-12 weeks of treatments and 1-24 weeks for patients receiving EPO alone and patients receiving EPO+DFX DT or EPO+DFX FCT.

Overall summary, SAE and AEs leading to study drug discontinuation will be reported for in the corresponding treatment: EPO, DFX DT, DFX FCT, EPO+DFX DT and EPO+DFX FCT.

All AEs will be coded using the latest version of MedDRA at the time of analyzing data using the Safety Set. The severities of the AE will be coded as mild/moderate/severe as documented in the CRF.

Summary tables for AEs have to include only AEs that started or worsened during the on-study period, the treatment-emergent AEs, i.e. TEAEs. However, all safety data (including

those from the pre and post-study periods) will be listed and those collected during the pre-study and post-study period will be flagged.

If an AE deteriorates or improves over time, new event will be reported accordingly with new severity.

The incidence of treatment-emergent AEs (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (mild/moderate/severe), type of AE and relation to study treatment.

Deaths reportable as SAEs and non-fatal serious AEs will be listed by patients and tabulated by type of AE.

Additionally, AEs and SAEs with suspected relationship to study drug, requiring dose adjustment, leading to drug interruption/discontinuation, requiring significant additional therapy will be specifically tabulated and listed.

AEs of special interest (AESIs) will be listed and summarized by grouped term and preferred term as shown in: [redacted]. It should be noted that this is a live document and may get updated with time and only the latest updated version should be used during the time of analyzing the data.

Also the AESI list to be used should have been updated based on the latest version of the case retrieval sheet (CRS) in terms of using the updated MedDRA version for identifying the AEs.

As mentioned above only the most recent version of the AESI list and CRS will be used for this study. AEs of special interest (AESIs) will be listed and summarized by group term and preferred term.

2.10.2.1 General rules for AE reporting

The number and percentage of patients reporting any AE will be summarized by primary SOC, PT overall and by treatment group. The most common AEs reported (≥ xx% in any group for each preferred term; xx% depends on the total number of AEs) will be presented in descending frequency according to its incidence in EPO and EPO+DFX starting from the most common event.

Additional summaries will be provided by severity and relationship to study treatment.

If a patient reported more than one AE with the same preferred term, the AE with the greatest severity will be presented. If a patient reported more than one AE within the same primary system organ class, the patient will be counted only once with the greatest severity at the system organ class level, where applicable.

2.10.3 Laboratory data

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

Note that, Hemoglobin (g/dL) and Serum Ferritin (ng/mL) are the only exceptions which will be reported in US-units (if appropriate).

Table 2-4 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	>113.1 mg/mmol at two consecutive measurements at least 7 days apart

The frequency of laboratory abnormalities will be displayed by parameter and treatment group. Laboratory data will be summarized by presenting summary statistics of raw values at baseline and changes from baseline (absolute) to worst post-baseline value and by treatment group.

Laboratory data will be summarized by presenting **shift tables** showing baseline versus most extreme post-baseline result by notable range.

Box plots of absolute value will be provided for selected parameters.

Listings of all laboratory data with values flagged corresponding to normal/notable/extended ranges will be provided. The listing of all laboratory values will be provided by planned and actual dose along with the columns for treatment arm to which the patient was randomized and the treatment arm where the patient belongs at the time of the assessment will be provided.

Hematology:

Box plots on absolute value for Hb, neutrophil and platelets corresponding to each visit will be provided.

Absolute change from baseline to worst post-baseline value (the lowest for hematology parameters) will be provided for Hb, neutrophil and platelets.

Absolute change from baseline to last available value at the time of EOT will be provided for Hb, neutrophil and platelets.

Listings will be provided for Hb, platelets and neutrophils as well.

Only listings will be provided for the parameters: Hematocrit, red blood cell (RBC) count, reticulocyte count, mean corpuscular volume (MCV), White blood cell (WBC) count with differential.

Blood chemistry

Absolute change from baseline to worst post-baseline value (the highest for blood chemistry parameters except creatinine clearance, which the lowest value is considered to be the worst) will be provided for serum ferritin, ALT, AST, total bilirubin, serum creatinine, creatinine clearance and urinary protein/creatinine ratio.

Absolute change from baseline to last available value at the time of EOT will be provided for serum ferritin, ALT, AST, total bilirubin, serum creatinine, creatinine clearance and urinary protein/creatinine ratio.

Shift tables from baseline to post-baseline value will be provided for serum ferritin, ALT, AST, serum creatinine, creatinine clearance and urinary protein/creatinine ratio in the following way:

Serum ferritin - Baseline categories: ≤ 270 ng/mL, > 270 – 500 ng/mL, > 500 – 1650 ng/mL, > 1650 ng/mL and Missing;

Serum ferritin - Post-baseline categories: ≤ 270 ng/mL, > 270 – 500 ng/mL, > 500 – 1650 ng/mL, > 1650 ng/mL.

ALT/AST - Baseline categories: ≤ ULN, > ULN - ≤ 5×ULN, > 5×ULN - ≤ 10×ULN, > 10×ULN and Missing;

ALT/AST - Post-baseline categories: ≤ ULN, > ULN - ≤ 5×ULN, One value > 5×ULN, One value > 10×ULN, Two consecutive values measured at least 7 days apart > 5×ULN, Two consecutive values measured at least 7 days apart > 10×ULN, > 5×ULN and 2× Baseline value, > 10×ULN and 2× Baseline value and Missing.

Serum creatinine - Baseline categories: ≤ULN, >ULN and Missing;

Serum creatinine - Post-baseline categories: ≤ ULN, One value > ULN, Two values >ULN, Two consecutive values measured at least 7 days apart > ULN, Two consecutive values measured at least 7 days apart > ULN, both > 33% increase from baseline and Missing-

Urinary protein/creatinine ratio – Baseline categories: ≤ 22.62 mg/mmol, >22.62 - ≤ 113.1 mg/mmol, > 113.1 mg/mmol and Missing; Post-baseline categories: ≤ 113.1 mg/mmol, One value > 113.1 mg/mmol, Two values > 113.1 mg/mmol, Two consecutive values measured at least 7 days apart > 113.1 mg/mmol and Missing.

Creatinine clearance - Classification I:

Creatinine clearance - Baseline categories: < 40 mL/min, 40 - < 60 mL/min, 60 - < 90 mL/min, 90 - < 160 mL/min, ≥ 160 mL/min and Missing;

Creatinine clearance - Post-baseline categories: Two consecutive values measured at least 7 days apart < 60 mL/min, One value < 60 mL/min, Two consecutive values measured at least 7 days apart 60 - <90 mL/min, One value 60 - <90 mL/min, two consecutive values measured at least 7 days apart 90 - < 160 mL/min, One value 90 - <160 mL/min, ≥ 160 mL/min and Missing.

Creatinine clearance - Classification II:

Creatinine clearance - Baseline categories: < 40 mL/min, 40 - < 60 mL/min, 60 - < 90 mL/min, 90 - < 160 mL/min, ≥ 160 mL/min and Missing;

Creatinine clearance - Post-baseline categories: Two consecutive values measured at least 7 days apart < 40 mL/min, One value < 40 mL/min, Two consecutive values measured at least 7 days apart 40 - <60 mL/min, One value 40 - <60 mL/min, ≥ 40 mL/min and Missing

Calculation for CrCl:

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

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

CrCl (mL/min) =

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

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

Note 1: The recalculated creatinine clearance in derived Lab data and standard UNITCONV data:

- Parameter names (PARNAM1C) as 'CRCLSCG' for Cockcroft-Gault formula.
- Preferred (PREUNT1C) and Converted (CNVUNT1C) unit 'mL/min' for Cockcroft Gault formulae.
- Zero Precision (CNVPCS1N) for converted values.

Note 2: For Height and Weight, last available values at the time of assessments should be used. Current age should be derived at the time of assessments.

Listings will also be provided for serum ferritin, ALT, AST, total bilirubin, serum creatinine, creatinine clearance and urinary protein/creatinine ratio.

A listing of all laboratory values will be flagged as appropriate and will be provided along with planned and actual dose (EPO and EPO + DFX). Assessment day relative to first dose of study drug will be included.

All other blood chemistry parameters apart from the ones mentioned above will only be listed.

For the laboratory result on serum pregnancy: β-HCG and on urine pregnancy, listings will be provided.

2.10.4 Vital signs, weight and body mass index

Absolute change from baseline to highest and lowest post-baseline for systolic blood pressure, diastolic blood pressure, pulse rate and weight will be summarized by treatment group (EPO and EPO+DFX), A listing will be provided for systolic blood pressure, diastolic blood pressure, pulse rate weight and BMI. Notable systolic blood pressure, diastolic blood pressure, pulse rate and weight values will be flagged.

Note: Baseline is defined as the last available value prior to or on the day of first dose of study drug.

The criteria for notably vital signs and weight values is displayed in the table below.

The criteria for clinically notable abnormalities were defined as follows:

Clinically notable elevated values:

- Systolic BP: ≥ 160 mmHg or increase ≥ 20 mmHg from baseline
- Diastolic BP: ≥ 100 mmHg or increase ≥ 15 mmHg from baseline
- Weight: Increase from baseline of ≥ 7%
- Pulse: ≥ 100 bpm or increase from baseline of ≥ 15 bpm

Clinically notable below normal values:

- Systolic BP: ≤ 90 mmHg or decrease ≥ 20 mmHg from baseline
- Diastolic BP: ≤ 60 mmHg or decrease ≥ 15 mmHg from baseline
- Weight: decrease from baseline of ≥ 7%
- Pulse: ≤ 60 bpm or decrease from baseline of ≥ 15 bpm

2.10.5 Other safety data

Ocular and auditory examination will be collected at screening, nevertheless the examination(s) can be performed at any time if there is a need to be repeated. Data from these assessments will be flagged as appropriate and will be listed and summarized by treatment group. [redacted]

2.11 CSR Section 9.7.2: Sample size and power considerations

This is a pilot study that was planned to enroll approximately 60 patients considering site capabilities. No formal sample size calculation based on primary endpoint assumptions is performed.

However to give an idea regarding primary endpoint analysis, for a given number of 60 patients, under scenarios, where considering a minimal detectable differences of 20%, 30% and 40% assuming a reference response rate of 40% at 5% level of significance gives a 95% Agresti-Caffo confidence interval of (-0.04, 0.44), (0.068, 0.53) and (0.18, 0.62).

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Appendix 16.1.7: Randomization scheme and codes

Document type: Clinical Study Report - Appendix 16.1.7

3 Clinical Study Report – Appendix 16.1.7 Randomization scheme and codes

This section of the RAP document presents a short account of the randomization procedures.

3.1 Randomization scheme and codes

Each patient will be identified in the study by a Patient Number, that will be assigned when the patient will be first enrolled for screening and will be retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Patient Number consists of the [redacted], so that each patient will be numbered uniquely across the entire database.

Upon signing the informed consent form, the patient is assigned to the next sequential Patient Number.

The investigator or designated staff will contact the Interactive Web Response Technology (IWR) and provide the requested identifying information for the patient to register them into the IWR. Once assigned, the Patient Number must not be reused for any other patient and the Patient Number for that individual must not be changed, even if the patient is re-screened. If the patient fails to be randomized or start treatment for any reason, the reason will be entered into the Screening Log.

IWR must be notified within 2 days that the patient was not randomized.

3.2 Treatment assignment or randomization

Patients will be assigned to one of the 2 treatment arms in a ratio of 1:1.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IWR provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication randomization list will be produced by or under the responsibility of [redacted] using a validated system that automates the random assignment of medication numbers to medication packs containing each of the study treatments.

Prior to dosing, all patients who fulfill all inclusion/exclusion criteria will be randomized via IWR to one of the treatment arms. The investigator or his/her delegate will call or log on to the IWR and confirm that the patient fulfills all the inclusion/exclusion criteria.

3.3 Treatment blinding

This is an open-label study and the CTT is unblinded to the study treatment.

4 Clinical Study Report – Appendix 16.1.9 Documentation of statistical methods

This section of the RAP document presents further detail about the statistical methods not given in Section 9.7 of the Clinical Study Report (CSR).

4.1 Appendix 16.1.9 – Documentation of statistical methods

The statistical methods used to perform the analyses presented in the clinical study report will be described in Section 9.7. Section 16.1.9 will provide further details of the statistical methods not already provided in Section 9.7.

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Appendix 16.1.9: Documentation of statistical methods

Document type: Clinical Study Report - Appendix 16.1.9

4.2 Definitions

4.2.1 Study drug and study treatment

Study treatments refers to EPO and EPO+DFX DT or EPO+DFX FCT.

Study drugs are DFX and EPO.

4.2.2 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 will be administered. For the sake of simplicity, the date of first administration of study treatment is referred to **start date of study treatment**. Start date of study treatment is defined by first non-zero dose administration date of EPO or EPO+DFX DT or EPO+DFX FCT.

The date of first administration for EPO and EPO+DFX DT or EPO+DFX FCT will be recorded on the corresponding "dosage administration record" (DAR) eCRF page.

4.2.3 Date of last administration of study drug

The date of last administration of study drug is defined as the last date when a non-zero dose of study treatment EPO or EPO+DFX DT or EPO+DFX FCT is administered and recorded on the DAR of the CRF. The date of last administration of study treatment is referred to **end date of study treatment or last date of study treatment**.

Note: For patients either randomized to EPO+DFX DT or EPO+DFX FCT or for patients who switch to EPO+DFX DT or EPO+DFX FCT after 12 weeks, the end date of study treatment could be the last date when a non-zero dose of DFX DT or DFX FCT is administered since EPO is administered weekly and the patient may have received the EPO 6 days before the last non-zero dose of DFX DT or DFX FCT is given.

4.2.4 Study start date

The start date of study should be considered to be the date when the first patient signs the informed consent form.

4.2.5 End of treatment

For a given patient the End of treatment will be defined as the **last day** when the patients received the study drug while still being on study.

4.2.6 Definition of End of study

The study will end when the last patient will have either withdrawn (including follow-up period of 30 days) from the study or completed the study (24 weeks + follow up period of 30 days) from the start of treatment (EPO or EPO+DFX DT or EPO+DFX FCT), whichever occurs earlier.

4.2.7 Study Day definition

For safety variables and analyses that requires using the safety set, study day will be defined as the number of days since the date of first dose of study drug (after randomization or enrollment). For a particular date on or after first dose, it will be calculated as:

Study day = Assessment date – Date of first dose of study drug + 1.

Therefore, the date of the first dose of study drug will be **Day 1** by definition.

The day before this day will be defined to be Day -1, i.e., there will be no Day 0. Study days before first dose of study drug will be calculated as

Study day = Assessment date – Date of first dose of study drug.

4.2.8 Treatment period

Having completed the screening period, patients are enrolled and randomized to receive either DFX DT or DFX FCT plus EPO or EPO alone. Study treatment is defined as DFX DT 10 mg/kg/day p.o. or DFX FCT 7 mg/kg/day p.o. plus EPO 40,000 units/week s.c. once weekly or EPO 40,000 units/week once weekly s.c.. EPO dose changes are allowed in both arms according to the EPO guidelines (see Appendix 3 of the CSP). For details on study design and dose adjustments, see Section 4.1 of the protocol. The study treatment duration is 24 weeks. After randomization, patient visits will occur weekly during the first month because key safety assessments need to be performed weekly in the first month of treatment and then every 4 weeks thereafter until week 24. In case of a dose increase of EPO after 4 weeks of treatment, an additional visit needs to be performed after 2 weeks of dose increase. For details of assessments, see Table 7-1 and Table 7-2 of the CSP.

4.2.9 Baseline

In general, for safety variables, the baseline value is defined to be the last available value prior to or on the day of first dose of study drug. For efficacy variables, the baseline value is defined to be the last available value prior to or on the day of randomization.

This definition does not apply for the following exceptions, where a specific definition was used:

- Serum creatinine: baseline value is defined as the mean of visit 1 and 2.
- Serum ferritin: baseline value is defined as the mean of visit 1 and 2.

4.2.10 Calculation of change

Baseline value will be the value collected during the baseline assessment as per the specific definition applying to the parameter, e.g. lab value

Absolute change from baseline will be the absolute difference between value a time point t (post-baseline) and value at baseline assessment, it will be calculated as:

- Absolute change from baseline = post-baseline value – baseline value

Relative change from baseline, or Percentage change from baseline, will be calculated as:

- Relative change from baseline (%) = (absolute change / baseline value) × 100

4.2.11 Visit Windows

A year = 365.25 days.

A month = 365.25/12=30.4375 days.

Month 1 = Day (1;45] and then floor(n×30.4375) days±15 days, n=2, 3, 4,… that is Month 2 = Day (45;75]; Month 3 = Day (75;106]; etc.

For each parameter (i.e., hematologic and erythroid response), time windows will be used to identify data to be considered for the specific analysis at a specific time point. If there is more than one assessment within the time window, the last available assessment in that time window will be used. For all windows after baseline, only values after first dose of study drug will be used. Time windows are defined based on date of randomization (=study day 1; Visit 3 according to VES of protocol).

The following table shows the time windows for the analyses of responses based on planned assessment schedule.

Table 4-1 Visit windows

Planned assessment	Time window	Nominal day for visit
Baseline	**Baseline; see definition 4.2.6**	**Baseline**
Visit 3: Date of Randomization	**Day 1**	**Day 1**
Visit 4	**Day 4 to Day 10***	**Day 7**
Visit 5	**Day 11 to day 17***	**Day 14**
Visit 6	**Day 18 to Day 24***	**Day 21**
Visit 7	**Day 25 to Day 31***	**Day 28**
Visit 8	**Day 35 to Day 49***	**Day 42**
Visit 9	**Day 50 to Day 63***	**Day 56**
Visit 10	**Day 77 to Day 91***	**Day 84**
Visit 11	**Day 105 to Day 119***	**Day 112**
Visit 12	**Day 133 to Day 147***	**Day 140**

The End of Treatment visit time window is Day 161 to Day 175 with nominal day of visit is Day 168 considering Visit 3 as Day 1.

In case of early treatment discontinuation or end of visit 12, the follow up will be 27 -33 days from the last date when a non-zero dose of study treatment is administered (Last date of study treatment).

Considering, a patient has received EPO only and received a response. This patient will hold EPO until study end. However, Follow-up visit for them will be 30 days (+/- 3 days after EOT) and not 27-33 days from the last date when a non-zero dose of study treatment is administered.

4.3 Data handling conventions

Partial dates will be listed as partial dates. For computing time/duration, the following rules will be used to impute partial dates: if the day and month is missing, it will be replaced by 30th of June (to be used only for prior events, e.g., medical history), if only the day is missing it will be replaced by 15th of that month. For dates known to be within the trial period, if this imputation makes the date later than trial completion date, then the trial completion date will be used; if the imputed date is earlier than the first medication date, then the first medication date will be used. The same rules of assigning AE start and end dates will apply for study medication start and end dates for subjects with missing or partial date of or with duplicate records of study medication.

Partially or completely missing AE onset dates and concomitant medication dates are imputed according to the standard Novartis imputation rules as described in the following:

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

A partial date is simply an incomplete date e.g.,

ddOCT2001 the days are missing from this DDMMMYYYY date

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

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

Therefore it is important to perform date imputation to ensure that as many data events are represented as correctly as possible. Of course partial and/or missing dates should *also* be caught as edit checks and passed back to the investigator for resolution.

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 4-2 explains the abbreviations used.

Table 4-2 AE/Treatment Date Abbreviations

	Day	**Month**	**Year**
Partial Adverse Event Start Date	<not used>	AEM	AEY
Treatment Start Date (TRTSTD)	<not used>	TRTM	TRTY

Table 4-3 describes the possible combinations and their associated imputations. In the light grey boxes the upper text indicates the imputation and the lower text the relationship of the AE start date to the treatment start date (TRTSTD).

Table 4-3 Imputation algorithm

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

The legend to the above table is shown in Table 4-4.

Table 4-4 Relationship and Imputation Legend

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

Few examples are shown in Table 4-5.

Table 4-5 Example Scenarios

Partial AE start date	**Treatment start date**	**Relationship**	**Imputation Calculation**	**Imputed Date**
12mmyyyy	20OCT2001	Uncertain	NC	<blank>
ddmmm**2000**	20OCT2001	Before	(D)	01JUL2000
ddmmm**2002**	20OCT2001	After	(E)	01JAN2002
ddmmm**2001**	20OCT2001	Uncertain	(B)	21OCT2001
dd**SEP2001**	20OCT2001	Before	(C)	15SEP2001
dd**OCT2001**	20OCT2001	Uncertain	(B)	21OCT2001
dd**NOV2001**	20OCT2001	After	(A)	01NOV2001

For any continuing events (e.g. AEs, concomitant medication, etc) which needs to be summarized for annual reports (or any interim analyses), when a date cut-off date is used an indication in the listings will be done to inform that the event is continuing. For patients who discontinue the study with ongoing events, the discontinuation date will be used as the completion date of the event.

Vital sign, Study Completion, CMP, ECG and laboratory assessment dates will be imputed in associating visit date from Visit-based event date imputation (AVIS) (see RAP Module 8).

Any event which has a partial date and requires imputing but has no specific imputation rule will be described in the RAP Module 8 and the imputed will be as follows:

- If the day and month is missing, it will be replaced by 1st of July. If only the day is missing it will be replaced by the 1st of that month. Partial dates will remain partial in the data listings.
- Missing day information for start date of prior chelation therapy or start date of history of blood transfusions will be imputed by the 15th of the Month. If the month will be missing it will be imputed by July.

A missing category for categorical data will be presented where applicable. Unless otherwise noted, percentages will be based on the number of patients in the relevant population or subgroup.

4.4 Protocol deviations

The complete list of PDs, which is usually described in a Novartis VAP Module 3, is described in the following tables:

Table 4-6 CSR Reportable Protocol Deviation Categories

Violation Code	Protocol ID	Description of CSR Reportable Category
Inclusion Criteria	Ixx	Subject enrolled despite selection criteria not being met
Exclusion Criteria	Exx	Subject enrolled despite selection criteria not being met
Withdrawal	Dxx	Subject developed withdrawal criteria during the study but was not withdrawn
Treatment	Sxx	Subject received the wrong treatment or incorrect dose
Prohibited Medication	Mxx	Subject took an excluded concomitant medication
Other	Gxx	For deviations which jeopardize the safety or rights of the individual trial subjects, or jeopardize the scientific value of the trial may be reported under this category, should it not align with any of the 4 categories. Protocol deviations captured under this category should be reviewed during a PD meeting for CSR- Reportable validity and must be reported in CSR if appropriate.

The table below specifies the actions to be taken if any of the deviations listed in the VAP occur:

Table 4-7 Protocol Deviations List

Deviation Code	Protocol Deviation description	Action taken
I01	Patient has not provided consent prior to study start	Report as PD, include in FAS and Safety Set.
I24	Written informed consent not provided at all	Report as PD, Exclude from all analyses.
I25	Patient signed incorrect version of informed consent	Report as PD, include in FAS and Safety Set.
I02	Subject is < 18 years or age missing	Report as PD, include in FAS and Safety Set.
I03	Patient does not suffer from MDS	Report as PD, include in FAS and Safety Set.
I04	MDS is not lasting ≥ 3 months or < 3 years	Report as PD, include in FAS and Safety Set.
I05	MDS is secondary to treatment with radiotherapy, chemotherapy, and/or immunotherapy for malignant or autoimmune disease	Report as PD, include in FAS and Safety Set.
I06	Patient has no low- and Int-1- risk MDS	Report as PD, include in FAS and Safety Set.
I07	Hemoglobin is ≥ 10.5 g/dL at Screening Visit 1 and/or Screening Visit 2	Report as PD, include in FAS and Safety Set.
I08	Hemoglobin is < 7.6 g/dL at Screening Visit 1 and/or Screening Visit 2	Report as PD, include in FAS and Safety Set.
I09	Patient has history of ≥ 10 times RBC transfusions in total	Report as PD, include in FAS and Safety Set.
I27	Patient has history of ≥ 10 units of RBC transfusions in total	Report as PD, include in FAS and Safety Set.
I10	ANC < 500/mm^3 at Screening Visit 1 and/or Screening Visit 2	Report as PD, include in FAS and Safety Set.
I11	Platelet count < 30,000/mm^3 at Screening Visit 1 and/or Screening Visit 2	Report as PD, include in FAS and Safety Set.
I12	Serum creatinine > 1.5 times ULN in mean value of measurements at Screening Visit 1 and Screening Visit 2	Report as PD, include in FAS and Safety Set.
I13	Patients with creatinine clearance < 40 mL/min.	Report as PD, include in FAS and Safety Set.

I20	Creatinine clearance below the concentration limit locally approved PI at Screening Visit 1 and/or Screening Visit 2	Report as PD, include in FAS and Safety Set.
I14	AST and ALT > 2.0 times ULN at Screening Visit 1 and/or Screening Visit 2	Report as PD, include in FAS and Safety Set.
I15	Serum total bilirubin ≥ 3.0 mg/dL at Screening Visit 1 and/or Screening Visit 2	Report as PD, include in FAS and Safety Set.
I16	FE/TIBC (TSAT) < 20% at Screening Visit 1	Report as PD, include in FAS and Safety Set.
I17	SF is ≤ 270 ng/mL at Screening Visit 1 and/or Screening Visit 2	Report as PD, include in FAS and Safety Set.
I18	SF is ≥ 1650 ng/mL at Screening Visit 1 and/or Screening Visit 2	Report as PD, include in FAS and Safety Set.
I19	SF is ≥ 1100 ng/mL at Screening Visit 1 and/or Screening Visit 2	Report as PD, include in FAS and Safety Set.
I21	Endogenous EPO levels ≥ 500 units/L at Screening Visit 1	Report as PD, include in FAS and Safety Set.
I22	Patient received cytotoxic chemotherapeutic agents or experimental agents for treatment of MDS within 8 weeks prior Screening	Report as PD, include in FAS and Safety Set.
I23	Patient is transfusion dependent (> 2U RBC/4 weeks at any time during the last 12 weeks period prior to study entry)	Report as PD, include in FAS and Safety Set.
I26	Patient is transfusion dependent (≥ 2U RBC/month during the past 3 months)	Report as PD, include in FAS and Safety Set.
E01	Patient has MDS with isolated del(5q)	Report as PD, include in FAS and Safety Set.
E02	Prior EPO treatment or other recombinant growth factors with reported outcome, for ≥ 4 weeks or within 3 month before Screening	Report as PD, include in FAS and Safety Set.
E03	Patient receiving steroids or immunosuppressive therapy for the improvement of hematological parameters	Report as PD, include in FAS and Safety Set.
E04	B12 or folate deficiency with or without clinical symptoms	Report as PD, include in FAS and Safety Set.

E05	Uncontrolled seizures	Report as PD, include in FAS and Safety Set.
E06	Uncontrolled hypertension	Report as PD, include in FAS and Safety Set.
E07	History of other malignancies and has not been confirmed disease free for ≥ 3 years	Report as PD, include in FAS and Safety Set.
E08	Significant medical condition interfering with the ability to partake in this study	Report as PD, include in FAS and Safety Set.
E09	Thromboembolic event within the past 3 years	Report as a PD, include in FAS and Safety Set.
E10	Known allergic reaction to EPO or human serum albumin	Report as PD, include in FAS and Safety Set.
E11	Clinical or laboratory evidence of active Hepatitis B or Hepatitis C (HBsAg in the absence of HBsAb OR HCV Ab positive with HCV RNA positive)	Report as PD, include in FAS and Safety Set.
E12	Patient has known HIV-1 seropositivity	Report as PD, include in FAS and Safety Set.
E13	Clinically significant anemia resulting from iron deficiencies, autoimmune or hereditary hemolysis, or gastrointestinal bleeding	Report as PD, include in FAS and Safety Set.
E14	Active bleeding	Report as PD, include in FAS and Safety Set.
E15	Patient is pregnant or nursing	Report as PD, include in FAS and Safety Set.
E16	Female of childbearing potential with missing serum HCG test	Report as PD, include in FAS and Safety Set.
E17	Patient with child-bearing potential without adequate birth control	Report as PD, include in FAS and Safety Set.
E19	Hepatic impairment fulfilling criteria of Child-Pugh Class B or C	Report as PD, include in FAS and Safety Set.
G04	Blood Sample for Hematology not collected for analysis at the required visit	Report as PD, include in FAS and Safety Set.
S01	Patient not exposed to study medication	Report as PD, include in FAS and Safety Set.
S02	Epo dose is not stopped as per protocol for more than 1 week but Hb increase is ≥1 g/dL and total Hb ≥ 12 g/dL in period week 1-24	Report as PD, include in FAS and Safety set.

S19	Epo dose is stopped for more than 1 week but Hb increase is not ≥1 g/dL and total Hb not ≥ 12 g/dL in period week 1-12	Report as PD, include in FAS and Safety Set.
S20	Epo dose is stopped for more than 1 week but Hb increase is not ≥1 g/dL and total Hb not ≥ 12 g/dL in period week 13-24	Reported as PD, include in FAS and Safety Set.
S21	Epo dose reduced below assigned dose as per protocol for more than 1 week in period week 1-12	Report as PD, include in FAS and Safety Set.
S22	Epo dose reduced below assigned dose as per protocol for more than 1 week in period week 13-24	Report as PD, include in FAS and Safety Set.
S23	Epo dose increased above assigned dose as per protocol for more than 1 week in period week 1-12	Report as PD, include in FAS and Safety Set.
S24	Epo dose increased above assigned dose as per protocol for more than 1 week in period week 13-24	Report as PD, include in FAS and Safety Set
S03	Epo dose maintained at 40.000 units/week and not increased to 60.000 units/week after 4 weeks as per protocol for more than 1 week but Hb increase < 1g/dL and total Hb < 12 g/dL	Report as PD, include in FAS and Safety Set.
S05	Epo dose increased to 60.000 units/week and not maintained at 40.000 units/week after 4 weeks as per protocol for more than 1 week but Hb increase ≥ 1 g/dL and total Hb < 12 g/dL	Report as PD, include in FAS and Safety Set.
S06	Patient randomized to monotherapy not switched to combination therapy as per protocol or switch delayed for more than 1 week after 12 weeks of treatment but Hb increase < 1 g/dL and total Hb < 12 g/dL	Report as PD, include in FAS and Safety Set.
D12	Patient randomized to combination therapy not discontinued after 12 weeks of treatment as per protocol or discontinuation delayed for more than 1 week but Hb increase < 1 g/dL and total Hb < 12 g/dL	Report as PD, include in FAS and Safety Set.
S10	Patient randomized to combination therapy stopped DFX treatment for more than 1 week in period week 1-12 not as per protocol	Report as PD, include in FAS and Safety Set.
S25	Patient assigned to combination therapy stopped DFX treatment for more than 1 week in period week 13-24 not as per protocol	Reported as PD, include in FAS and Safety Set.
M01	Forbidden concomitant medication as per	Report as PD,

	protocol	include in FAS and Safety Set.
M02	Patient received iron chelation therapy other than the study treatment	Report as PD, include in FAS and Safety Set.
D01	Transfusion during the study but not withdrawn	Report as PD, include in FAS and Safety Set.
D02	Pregnancy during the study, but not withdrawn	Report as PD, include in FAS and Safety Set.
S11	Patient randomized but received wrong study drug	Report as PD, include in FAS and Safety Set.
D03	≥50% decrement from maximum response levels in granulocytes or platelets but patient not withdrawn	Report as PD, include in FAS and Safety Set.
D04	Reduction of Hb level ≥1.5g/dL compared to best response but patient not withdrawn	Report as PD, include in FAS and Safety Set.
D05	Consent withdrawn but patient not withdrawn	Report as PD, Exclude from all analyses.
S12	Deferasirox dose was not reduced despite serum creatinine increase of ≥33% above baseline and above ULN at 2 consecutive occasions	Report as PD, include in FAS and Safety Set.
S13	Deferasirox treatment was not interrupted despite severe case of skin rash	Reported as PD, include in FAS and Safety Set.
S14	Deferasirox treatment was not interrupted despite persistent and progressive increase in serum transaminase levels that cannot attributed to other causes	Report as PD, include in FAS and Safety Set.
S15	Deferasirox treatment was not interrupted despite unexplained cytopenia	Report as PD, include in FAS and Safety Set.
S16	Deferasirox dose not recalculated despite > 10% change in body weight	Report as PD, include in FAS and Safety Set.
S17	Deferasirox treatment was not interrupted despite severe hypersensitivity reactions	Reported as PD, include in FAS and Safety Set.
S18	Deferasirox treatment was not permanently discontinued despite suspected Stevens Johnson syndrome	Report as PD, include in FAS and Safety Set.
G01	Use of local laboratory instead of central laboratory	Report as PD, include in FAS and Safety Set.
G03	Patient was randomized with missing central lab results and/or based on local lab results	Reported as PD, include in FAS and Safety Set.

The RAP module 8 will include variables that will flag the missing values at baseline for the laboratory parameters or flag corresponding to certain assessments which leads to the exclusion of the patient from any analyses.

4.5 Other rules

Percentages in shift tables cross-tabulating baseline versus post-baseline values will be based on all patients with a non-missing post-baseline value in the respective analysis set.

4.6 Number of decimals

Whenever possible, minimum and maximum will be presented to the same precision as the raw data. Mean and median will be presented to one more decimal place and standard deviation to two more decimal places.

Unless stated otherwise, no imputation for missing data will be performed.

5 References

Agresti and Caffo (2000). Simple and Effective Confidence Intervals for Proportions and Differences of Proportions Result from Adding Two Successes and Two Failures. The American Statistican, Vol 54, No. 5.

Cheson BD, Greenberg PL, Bennett JM, et al (2006). Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood; 108:419-25.

Clopper, C. J., and Pearson, E. S. (1934), 'The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial', Biometrika 26, 404–413.

6 SAS procedure used for inferential analysis

6.1 Clopper-Pearson (Exact) CI for response rate

The 100 × (1 – *alpha level*) % Pearson-Clopper CI for the proportion of responders (binary outcome = 1 or "Yes"), for a given treatment group **X**, is obtained from the following:

```
PROC FREQ data = dataset;
WHERE group = 'X';
TABLE binary event /binomial (exact level='Yes')
alpha = alpha level;
```

When there are no responders for treatment group **X**, SAS does not produce a CI by default. To obtain a CI in this situation, PROC FREQ is used as specified above except changing **level**="No". From the results of this modified procedure, the values in percent of the LCL and UCL of a 0% response rate are calculated as follows:

- $LCL_{LEVEL="Yes"}$ (%) = 100% - $UCL_{LEVEL="No"}$ (%)
- $UCL_{LEVEL="Yes"}$ (%) = 100% - $LCL_{LEVEL="No"}$ (%)

6.2 Agresti-Caffo CI for difference in proportions

The Agresti-Caffo confidence limits for the risk difference are computed as:

$$\tilde{d} \pm (z_{\alpha/2} \times \text{s.e}\,(\tilde{d}))$$

where $\tilde{d} = \tilde{p}_1 - \tilde{p}_2$, $\tilde{p}_i = (n_{i1} + 1)/(n_{i\cdot} + 2)$,

$$\text{se}(\tilde{d}) = \sqrt{\tilde{p}_1(1-\tilde{p}_1)/(n_{1\cdot}+2) + \tilde{p}_2(1-\tilde{p}_2)/(n_{2\cdot}+2)}$$

and $z_{\alpha/2}$ is the $100(1-\alpha/2)$ percentile of the standard normal distribution.

That is: $\widetilde{p_1}$ = (n_{11}+ 1)/(n_1+ 2) and $\widetilde{p_2}$ = (n_{22}+ 1)/(n_2+ 2)

	Column 1	Column 2	Total
Row 1	n_{11}	n_{12}	$n_{1\cdot}$
Row 2	n_{21}	n_{22}	$n_{2\cdot}$
Total	$n_{\cdot 1}$	$n_{\cdot 2}$	n

The Agresti-Caffo interval adjusts the Wald interval for the risk difference by adding a pseudo-observation of each type (success and failure) to each sample. See Agresti and Caffo (2000) for more information.

This CI calculation is available in SAS Version 9.3 using the CL=AC options as follows:

```
ods select  PdiffCLs;
ods output PdiffCLs=ciac;
proc freq data= dataset;
    tables group*response /riskdiff (CL=AC);
run;
```