NOVARTIS

Clinical Development

Deferasirox (ICL670, Exjade®)

Clinical Trial Protocol 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)

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List of abbreviations

AE	Adverse Event
ALT/SGPT	alanine aminotransferase/glutamic pyruvic transaminase/GPT
AML	Acute Myeloid Leukemia
ANCOVA	Analysis of Covariance
AST/SGOT	aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
BL	Baseline Visit
BNP	Brain Natriuretic Peptide
CBC	Complete Blood Count
CHF	Congestive Heart Failure
CK	Creatine Kinase
CoMed	Concomitant Medication
CPO	Country Pharma Organizations
Cr	Creatinine
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DAR	Dosage Administration Record
DFO	Deferoxamine
DMC	Data Monitoring Committee
DS&E	Drug Safety and Epidemiology
DSM	Drug Supply Management
EAC	Endpoint Adjudication Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EPO	Erythropoietin
FAS	Full Analysis Set
FPFV	First Patient First Visit
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transpeptidase
GI	Gastrointestinal
HDPE	High Density Polyethylene
HI	Hematologic Improvement
HR	Hazard Ratio
IB	Investigators' Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICT	Iron Chelation Therapy
IN	Investigator's Notification
IO	Iron Overload
IPSS	International Prognostic Scoring System
IRB	Institutional Review Board
IRT	Interactive Response Technology
IVRS	Interactive Voice Response System

[redacted]

IWG	International Working Group
IWRS	Interactive Web Response System
KM	Kaplan-Meier
LDH	Lactase Dehydrogenase
LIC	Liver Iron Concentration
LVEF	Left Ventricular Ejection Fraction
LVIDD	Left Ventricular Internal end-diastolic dimension
LVISD	Left Ventricular Internal end-systolic dimension
MCV	Mean Corpuscular Volume
MDRD	MoDification of Renal Disease
MDS	Myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
OGTT	Oral Glucose Tolerance Test
OS	Overall Survival
PD	Pharmacodynamics
PK	Pharmacokinetics
PPS	Per Protocol Analysis Set
PRBC	Packed Red Blood Cells
PSB	Program Safety Board
RAEB	Refractory Anemia with Excess Blasts
RAP	Report and Analysis Plan
RBC	Red Blood Count
REB	Research Ethics Board
SAE	Serious Adverse Event
SC	Steering Committee
SD	Standard Deviation
SF	Serum Ferritin
SUSAR	Suspected Unexpected Serious Adverse Reactions
TSH	Thyroid Stimulating Hormone
UGT	Uridine 5'-diphospho-glucuronosyltransferase
ULN	Upper Limit of Normal
UPCR	Urine Protein: Urine Creatinine Ratio
WBC	White Blood Count
WHO	World Health Organization

[redacted]

Amendment 5

Amendment rationale

At the time of this amendment, 192 patients have been randomized in the study and 175 patients failed screening.

The purpose of amendment 5 is to clarify exclusion criteria and provide guidance regarding dose modifications, concomitant medications, and contraception as detailed below.

The exclusion criteria and dose modification guidelines were updated to exclude patients with moderate and severe hepatic impairment (Child-Pugh Class B and C). In addition, guidance on treating patients who develop moderate hepatic impairment (Child-Pugh Class B) during the trial and immediate discontinuation if severe hepatic impairment (Child-Pugh Class C) or Stevens-Johnson syndrome occurs is being provided, in alignment with the Exjade prescribing information.

Guidance is included on the use of contraception. Effective contraception is required in alignment with the Exjade prescribing information. Highly effective contraception was inadvertently added to amendment 4 of this protocol. Embryo-fetal development animal studies did not show evidence of teratogenicity and there were no developmental effects noted at doses that were not toxic to the maternal animals. Guidance is updated in this amendment to correct this administrative error.

Additional guidance was added regarding treatment discontinuation of patients with creatinine clearance < 40 mL/min or serum creatinine > 2 time the age appropriate ULN, and caution in patients with creatinine clearance between 40 and less than 60 mL/min, in alignment with the Exjade prescribing information.

Guidance was added regarding the concomitant administration of deferasirox with compounds metabolized through CYP3A4, CYP2C8, and CYP1A2; and the concomitant use of UGT inducers and bile acid sequestrants in alignment with the Exjade prescribing information.

Clarification to the visit schedule, adverse events, and collection and reporting bone marrow assessments was also added. In addition, modification in hematologic improvement analysis was provided for clarification.

Changes to the protocol amendment 5

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

Changes to Protocol Synopsis

- Inclusion/exclusion criteria: Child-Pugh Class B and C were added as hepatic diseases which would prevent study treatment.

[redacted]

Changes to Section 5.1 Inclusion criteria

- Contraception requirements were modified to clarify that effective contraception methods are required in line with the known safety profile of deferasirox. The Highly effective methods were removed as their addition was an administrative error in the previous amendment (4).

Changes to Section 5.2 Exclusion criteria

- Child-Pugh Class B and C were added to "Systemic diseases which would prevent study treatment" as hepatic conditions that would prevent study treatment.

Changes to Section 6.7.1.3 Elevations in serum creatinine

- Caution regarding treatment of patients with creatinine clearance between 40 and less than 60 mL/min, and guidance for discontinuation of study medication in case serum creatinine is >2 times the age-appropriate upper limit or if creatinine clearance <40 mL/min, were added.

Changes to Section 6.7.1.6 Skin Rash

- Guidance was included requiring immediate and permanent discontinuation of study drug if Stevens-Johnson Syndrome is suspected. Sections 6.7.1.6.1 and 6.7.1.6.2 were added to separate Stevens-Johnson syndrome from other rashes.

Changes to Section 6.7.1.7 Elevated liver function tests

- Title of this section was changed from "Elevated liver function tests" to "Liver function abnormalities".
- Dose modification rules were added related to moderate hepatic impairment (Child-Pugh Class B). In the event Child Pugh B criteria are met, study drug dosing will be interrupted. If liver disease prognosis improves, study medication can be introduced at 10 mg/kg/day or 50% of the previous dose, whichever is less. At the Investigator's discretion, the dose may then be increased by 5 mg/kg/day every 2 weeks to a maximum of 50% of the patient's previous dose.
- Guidance was included requiring immediate and permanent discontinuation of study drug if Child Pugh Class C is suspected.

Sections 6.7.1.8, 6.7.1.9 and 6.7.1.10 added

- Guidance was added for dose modifications related to auditory (decreased hearing) and ocular (lens opacities) disturbances, hypersensitivity reactions, and cytopenias, to reflect the Exjade prescribing information.

Changes to Section 6.7.4 Other concomitant medications

- Section 6.7.4.1 "Concomitant therapy requiring caution and/or action" was added.
- Section 6.7.4.1 "The concomitant administration of deferasirox and vitamin C has not been formally studied. Doses of vitamin C up to 200 mg/d have not been associated with adverse consequences" was moved from Section 6.7.4 to Section 6.7.4.1.
- Section 6.7.4.1 "Aluminum containing antacid therapies should be avoided because they may bind to deferasirox" was moved from Section 6.7.4 to Section 6.7.4.1.

[redacted]

- Section 6.7.4.1 cautions that taking study drug in combination with medications with known ulcerogenic potential may increase the risk of gastrointestinal irritation and bleeding.
- Section 6.7.4.1 cautions that deferasirox may potentially decrease serum levels of substances metabolized through CYP3A4 and may increase serum concentrations of substances metabolized through CYP2C8.
- Section 6.7.4.1 cautions that concomitant administration of deferasirox with CYP1A2 substrates that have a narrow therapeutic index is not recommended. If deferasirox and theophylline are used concomitantly, monitoring or theophylline dose reductions should be considered.
- Section 6.7.4.1 cautions that the use of bile acid sequestrants decreases deferasirox systemic exposure.
- Section 6.7.4.1 cautions that the use of potent UGT may result in a decrease in deferasirox efficacy.

Changes to Section 6.7.6.1 End of Treatment

- Additional reasons for study drug discontinuation were added to align with newly released eCRF.

Changes to Section 6.7.6.2 Study evaluation completion

- Additional reasons for the end of study evaluation were added to align with newly released eCRF.

Changes to Table 7-1 Visit evaluation schedule

- A column and footnote were added to the table to show and describe the timing and requirements for the 28-day follow up (Visit 501). Footnotes “b” through “d” were amended to account for the addition of the visit description.
- Evaluation period was altered to show that it begins on visit 502.
- Minor change to footnote #4. “Hematological response” was changed to “hematological improvement”.
- Urine pregnancy test was added for women of child bearing potential at the End of Treatment visit (777).

Changes to Section 7.5.1 Adverse events

- Clarification was added that MDS is not an adverse event in this study. MDS is a required condition for study entry and disease progression (including MDS progression and progression to AML) is a secondary efficacy endpoint.

Changes to Section 7.5.5.5 Pregnancy Test

- Urine pregnancy testing will be performed locally at the End of Treatment visit and if menses are delayed for more than 7 days in a female patient capable of becoming pregnant.

Changes to Table 7-2 Laboratory evaluations

- Urine pregnancy testing added to table for the End of Treatment visit (777) for female patients capable of becoming pregnant.

[redacted]

Changes to Section 7.5.9 Bone marrow biopsy

- Title of this section was changed from "Bone marrow biopsy" to "Bone marrow biopsy or aspirate" and clarification added regarding bone marrow assessments for Disease progression including MDS progression and progression to AML.

Changes to Section 10.5.1.1 Secondary efficacy variables and related analyses

- Clarification was added that the last pre-treatment hemoglobin value measured prior to the first dose of study medication will be used as the pre-treatment hemoglobin value (If 2 pre-treatment 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 value). "Only RBC transfusions given for hemoglobin levels of equal to or less than 9 g/dL pre-treatment" was changed to "all RBC transfusions regardless of pre-transfusion hemoglobin level" will count in the RBC transfusion response evaluation". "Only the first episode of HI" was changed to "all episodes of HI" in the patient will be considered.
- Clarification was added for bone marrow collected by biopsy or aspirate.

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

[redacted]

Summary of previous amendments

Amendment 4

Amendment rationale

The purpose of amendment 4 is to adjust the sample size, statistical analysis, and duration of the study and to add two secondary endpoints. Editorial and administrative changes are being made to ensure consistency and clarity in the protocol as a result of these changes.

Since the initiation of this study in November 2009 the enrollment projections of 630 patients could not be met and as of July 2013 only 124 patients were enrolled. A reduction in the sample size to 210, which is based on the enrollment projection until December 2014, will support a timely completion of the study.

The sample size of 210 patients does not provide sufficient power for testing statistical hypotheses. The statistical analysis has been revised accordingly to concentrate on evaluating the treatment effect of deferasirox relative to placebo, and the study phase designation has been changed to Phase II. The end of the study is no longer defined by the number of events for the primary endpoint, instead, the study will continue for three years from the date the last patient is enrolled. The individual patient treatment duration of at least three years remains unchanged. Overall survival has been changed from key secondary to secondary endpoint because of the reduction in sample size and statistical power.

Two secondary endpoints have been added to assess the efficacy of treatment:

- Hematologic improvement (HI) in terms of erythroid response
  The International Working Group 2006 (IWG 2006) criteria for hematologic improvement-erythroid (HI-E) as defined by improvement in hemoglobin levels or reduction in transfusion requirement are both particularly relevant in transfusion-dependent patients with MDS (Cheson 2006).
- Frequency and rate of infections requiring intravenous (IV) antimicrobials
  Infections are recognized as a cause of morbidity and mortality in MDS patients and the reduction of infections which require intravenous antimicrobials is therefore of relevance for those patients (Dayyani 2010). Iron availability is known to be essential for proliferation of microbes and the development of infections (Schaible 2004). The effect of chelation therapy or placebo on the frequency of infections requiring IV antimicrobials will be evaluated.

As of July 2013, 124 patients had been enrolled in the study. Data will be available to support the analysis of the additional secondary endpoints for patients enrolled prior to the implementation of amendment 4. Upon approval of the amendment, patients will sign a new consent form and continue the appropriate visit schedule.

Changes to the protocol amendment 4

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

Changes to Protocol Synopsis

- Study phase: The study phase was changed from phase III to phase II.
- Purpose/rationale: The purpose of the study was changed to evaluate clinical benefit instead of demonstrating superiority.
- Objectives: The primary objective was changed from statistical comparison to descriptive evaluation of the effect of deferasirox and placebo with regard to event-free survival. Overall survival was changed from key secondary to secondary endpoint. Hematological function expressed in transfusion requirements was incorporated in the added hematologic improvement endpoint based on IWG criteria. MDS progression and progression to AML was renamed to disease progression. Frequency of infections requiring IV antimicrobials was added.
- Endpoints (efficacy, safety): Overall survival was changed from key secondary to secondary endpoint. Hematological function expressed in frequency/total amount of blood transfusions was incorporated in the added endpoint of proportion of patients with hematologic improvement. Time to MDS progression and progression to AML was renamed to time to disease progression. Frequency and rate of infections requiring IV antimicrobials was added.
- Study design: Interim analyses were removed. The recruitment period was updated from a duration of 24 months to completion of recruitment in December 2014. The duration of study is no longer events driven. The study will be completed 3 years after the last patient is enrolled.
- Population: The number of patients to be enrolled has been changed to at least 210.
- Efficacy evaluation(s): Hematologic improvement was added to be evaluated.
- DMC: Text related to the conduct of the interim analyses has been removed as well as the possibility to prematurely stop the study for evidence of a favorable risk/benefit relationship of deferasirox compared to placebo.
- Statistical methods and data analysis: As there will be no key secondary endpoint, the analysis done for the per protocol analysis set was removed. The description related to the significance level and control of the overall type I error was removed as was any mention of the interim analyses. The confirmatory significance test was removed. The difference in survival functions will be tested in an exploratory sense only. Two sensitivity analyses will no longer be conducted because of the reduced sample size and expected number of events (structural-nested failure time model, non-proportional hazards model). Assumptions for and calculation of the sample size from the original protocol was removed and the new sample size stated.

Changes to Section 3 Objectives

The purpose of the study was changed to evaluate clinical benefit instead of demonstrating superiority.

Changes to Section 3.2 Secondary objectives

Changes as addressed above, in the protocol synopsis.

Changes to Section 3.2.1 Endpoints for secondary objectives

Changes as addressed above, in the protocol synopsis.

Changes to Section 4 Study design

Changes as addressed above, in the protocol synopsis. In addition, the required number of 244 events has been removed from the explanation of adjudication of events.

Changes to Section 5 Population

The number of patients to be enrolled has been changed to at least 210, and Oceania has been added to the regions.

Changes to Section 5.2 Exclusion criteria

New pregnancy language was included in criterion for patients of child-bearing potential and in the definition under the "Women of child-bearing potential" subheading. Both include details regarding the use of highly effective methods of contraception.

Changes to Section 6.5 Treatment blinding

In the description of accessibility of randomization data prior to unblinding of the final database, the two exceptions related to the interim analyses (DMC as well as independent statistician and programmer) have been removed. The DMC has also been removed from the occasions of unblinding in the last sentence. The DMC may be unblinded on special request only.

Changes to Table 7-1

Week number of End of Treatment was changed from 260 to 372 to reflect the change in study duration specified in newly added footnote 'a'. Study Evaluation Completion (visit 778) column was added to the table.

Changes to Section 9.4 Data Monitoring Committee

Text related to the conduct of the interim analyses has been removed as well as the possibility to prematurely stop the study for evidence of a favorable risk/benefit relationship of deferasirox compared to placebo.

Changes to Section 10.1 Populations for analysis

Key secondary endpoint was removed from analyses done for the per protocol analysis set.

Changes to Section 10.4 Primary objective

The primary objective was changed from comparison (statistical test) to evaluation (description).

[redacted]

Changes to Section 10.4.2 Statistical hypothesis, model, and method of analysis

A paragraph was added explaining the change in statistical analysis.

Changes to Section 10.4.2.1 Statistical hypotheses

The description of the statistical hypotheses was moved after the paragraphs on estimation. They were denoted as exploratory.

Changes to Section 10.4.2.2 Statistical hypothesis test

The description of the statistical test was moved to the end of Section 10.4.2. The test was denoted as exploratory.

Changes to Section 10.4.2.3 Estimation of survival functions for event-free survival

Text related to the interim analyses was removed.

Changes to Section 10.4.2.4 Stratified unadjusted Cox proportional hazards regression model

The last sentence about adjusting the estimates for the group-sequential design has been deleted.

Changes to Section 10.4.3 Handling of missing values/censoring/discontinuations

Text for the case of censoring at the time of interim analysis has been deleted.

Changes to Section 10.4.4 Supportive and sensitivity analyses

The description of the following sensitivity analyses was removed: structural-nested failure time model, analysis considering non-proportional hazards, analyses based on the PPS.

Changes to Section 10.5.1 Secondary efficacy objectives

Test about overall survival as key secondary endpoint as well as description of the testing strategy was removed. Overall survival will only be tested in an exploratory sense.

Changes to Section 10.5.1.1 Secondary efficacy variables and related analyses

The analysis of overall survival and further time to event endpoints was changed from testing to estimation of hazard ratio. Tests will only be performed in an exploratory sense.

Hematologic improvement in terms of erythroid response and infections were added as secondary endpoints.

MDS progression or progression to AML was renamed “Disease progression”.

Changes to Section 10.5.2.2 Secondary safety variables and related analyses

The analysis of time to study drug discontinuation will concentrate on estimating the hazard ratio. The test will be exploratory only.

Changes to Section 10.6 Interim analysis

The interim analyses foreseen in the original protocol will not be performed due to the reduced sample size. The description was removed from the section and a statement inserted that no interim analyses will be done.

[redacted]

Changes to Section 10.7 Sample size calculation

The sample size calculation from the original protocol was removed and the new sample size stated.

Changes to Section 10.8 Power for analysis of critical secondary variables

Text related to the power of the key secondary endpoint was removed.

IRB/IEC

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Amendment 3

Amendment rationale

The purpose of amendment 3 is to modify some of the inclusion and exclusion criteria, to modify the liver function component of the composite endpoint, to incorporate the specific wording regarding the sponsor standard Interactive Response Technology (IRT) eligibility criteria, and to correct typographical errors and inconsistencies.

The inclusion/exclusion criteria are being modified to address the most common reasons for the 60% screen failure rate observed among patients that are being screened for the study and are in alignment with the study steering committee discussions. This would also allow MDS patients that are more commonly seen in the real-world setting as described by the investigators to be enrolled, hence allowing more patients to participate in the study. The upper limit of serum ferritin inclusion criterion is being removed so that patients qualify for inclusion if their serum ferritin is >1000 mcg/L. The liver transaminases ALT/AST exclusion criterion is being changed from >2.5 x ULN at screening to ALT/AST > 3.5 x ULN at screening. The bilirubin exclusion criterion is being changed from total bilirubin > ULN at screening to total bilirubin > 1.5 x ULN at screening. The serum creatinine exclusion criterion is being changed from serum creatinine > 1.2 x ULN at screening to serum creatinine > 1.5 x ULN at screening.

The change in ALT/AST exclusion criterion is supported by an analysis of pooled data from MDS patients enrolled in four studies (Studies A0108 A2204 A2409 US02) that show that patients with elevated ALT values up to and including 3.5 X ULN at study entry were not at higher risk of notable ALT increase when treated with deferasirox. The shift table below shows that only 1 out of 38 (2.6%) treated patients who had baseline ALT >ULN and ≤3.5 × ULN worsened to >3.5 x ULN to 5 × ULN at the end of treatment, whereas 15 patients (39.5%) remained at >ULN to ≤3.5 x ULN and 22 patients (57.9%) improved to ≤ULN. Baseline ALT was >3.5 x ULN - 5 × ULN in one patient and >5 × ULN in another, and both patients improved to >ULN - ≤3.5 x ULN at end of treatment. This change in ALT/AST exclusion criteria is further supported by previously published data in MDS patients showing

[redacted]

that the decrease in serum ferritin with deferasirox treatment is associated with a decrease in ALT indicating a possible association between reduction of iron overload and improvement in liver function (Gatterman 2010)

The serum creatinine exclusion criterion is slightly increased from >1.2 x ULN to > 1.5 ULN according to the CTCAE grade 1 which is supported by data from the US03 study.

Among patients with normal (Grade 0) creatinine at baseline (N = 149), 48 patients (32.2%) had shifts to Grade 1 and 4 patients (2.7%) had shifts to Grade 2. A total of 12 patients having a Grade 1 serum creatinine at baseline had a Grade 2 value post-baseline; this represented 54.5% of the 22 patients with a Grade 1 baseline value. Thus, the incidence of treatment emergent shifts from baseline in serum creatinine levels was 37.4% (64/171). Shifts of more than one grade occurred for just those patients with a normal baseline.

The component of the composite endpoint defining liver function impairment as reflected by ALT or AST changes is being modified in correspondence with the change in ALT/AST exclusion criterion from being > 2 x the baseline value and > 3 x ULN to > 2 x the baseline value and > 3.5 x ULN. The part of the component related to total bilirubin is left unchanged. The component of the secondary efficacy endpoint defining "time to first occurrence of serum ferritin" has been modified to correspond with the change in the serum ferritin inclusion criterion.

Shift table of ALT (U/L) from baseline value to end of study value (Pooled MDS data (A0108 A2204 A2409 US02) - Per Protocol Set)

	End of study					
Baseline	**≤ ULN** n (%)	**> ULN – ≤ 3.5 × ULN** n (%)	**> 3.5 × ULN – ≤ 5 × ULN** n (%)	**> 5 × ULN** n (%)	**> 5 × ULN and > 2 × BL** n (%)	**Total** n (%)
≤ ULN	28 (90.3)	3 (9.7)	0 (0.0)	0 (0.0)	0 (0.0)	31 (100.0)
> ULN – ≤ 3.5 × ULN	22 (57.9)	15 (39.5)	1 (2.6)	0 (0.0)	0 (0.0)	38 (100.0)
> 3.5 × ULN – ≤ 5 × ULN	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
> 5 × ULN	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
Total	50 (70.4)	20 (28.2)	1 (1.4)	0 (0.0)	0 (0.0)	71 (100.0)

As of this amendment, 42 patients have been enrolled in the study, 81 have failed screening. With the implementation of this amendment, more patients are expected to meet the eligibility criteria to participate in the study.

The most frequent reason for screen failure due to laboratory assessment are summarized in the table on the next page.

[redacted]

Reason for screen failure due to laboratory assessment

Reason for Screen failure	Number of Patients
ALT or AST >2.5 x ULN	15
Total Bilirubin > ULN	17
Ferritin > 3500 mcg/L	5
Ferritin < 1000 mcg/L	14
Serum Creatinine > 1.2 x ULN	1
Creatinine Clearance < 40 ml/min	5
Significant Proteinuria	4

Changes to the protocol amendment 3

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

Changes to List of Abbreviations

- Abbreviations updated to reflect additions and deletions

Changes to Protocol Synopsis and Inclusion/Exclusion Criteria (Sections 5.1 & 5.2)

- The inclusion and exclusion criteria have been modified to remove the upper limit of serum ferritin at screening, to increase the ALT or AST exclusion criterion to > 3.5 x ULN at screening, to increase the bilirubin exclusion criterion to 1.5xULN at screening, and to increase the serum creatinine exclusion criterion to 1.5 x ULN at screening.

Changes to Section 3.1.1 Endpoints for primary objective

- ALT or AST > 2 times the baseline value and >3**.5** times ULN

Changes to Section 4 Study design

- Table 4-1 changed to Figure 4-1

New study design figure included

- 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.
- After 3 months of treatment, **at the dose of 20mg/kg/day**, dose may be adjusted by 5 to 10 mg/kg/day up to 40 mg/kg/day based on serum ferritin response.

Changes to Section 5 Population

- Male or female patients, > 18 years of age with low/int-1 MDS, as determined by IPSS score, who have serum ferritin >1000 mcg/L at screening

Changes to Section 5.1 Inclusion Criteria

- Serum ferritin will be measured at Screening Visit 1 and Screening Visit 2 (at least 14 days apart) and the mean value will be used for eligibility criteria.

Changes to Section 5.2 Exclusion Criteria

- Serum creatinine will be measured at Screening Visit 1 and Screening Visit 2 (**at least 14 days apart**) and the mean value will be used for eligibility criteria.

[redacted]

Changes to Section 6.1.2.1 Study Drug

After 3 months of **treatment at the dose of 20 mg/kg/day**, the dose can be adjusted by 5 or 10 mg/kg/day up to 40 mg/kg/day based on serum ferritin response.

Changes to Section title 6.7.1.3

- Elevations in serum creatinine

Changes to Section 6.7.6 Premature patient withdrawal

- If such withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the **Study Evaluation Completion** (778) eCRF and notify IVRS.

Changes to Section 7 Visit schedule and assessments

- Following registering in IRT for screening, patient eligibility will be checked once all screening procedures are completed. The eligibility check will be embedded in the IRT system. Detailed guidelines to be followed can be found in the IRT manual.

Changes to Table 7-1 Footnote 4

- Repeat bone marrow aspiration and cytogenetics, iron stains and biopsy recommended at the time of major hematological response per IWG criteria.

Changes to Section 7.5.5 Laboratory Evaluations

- Safety laboratory parameters monitored at Screening Visit 1 and Weeks 2 – **Study Evaluation Completion** (778) will include…

Changes to Section 7.5.5.1 Biochemistry

- Blood samples will be sent to the central laboratory for chemistry analysis at the screening Visit 1 and Weeks 2 – **End of Treatment (777).**

Change to Section 7.5.5.2 Urinalysis/Proteinuria

- During Weeks 2-260 and **End of Treatment (777),** a midstream, non-first voided…

Changes to Section 7.5.5.3 Transfusion requirements, hematologic counts

- Complete blood counts will be drawn at screening Visit 1 and Weeks 2-260 and **End of Treatment (777)**.

Changes to Sections 7.5.6 Electrocardiogram and 7.5.7 Echocardiogram

- Weeks 12, 24, 36, 52, 64, 76, 88, 104, **116, 128, 140**, 156, **168, 180, 192**, 208, 220, 232, 244, 260, and **End of Treatment Visit (777).**

Changes to Section 13 References (available upon request)

- Gattermann N. Finelli C, Porta MD, et al (2010). Deferasirox in iron-overloaded patients with transfusion-dependent myelodysplastic syndromes: Results from the large 1-year EPIC study. Leuk Res 34:1143-1150

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IRB/IEC

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The changes described in this amended protocol require IRB/IEC approval prior to implementation. These changes do not affect the global informed consent, If these changes affect the country-specific informed consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

Amendment 2

Amendment rationale

This protocol has been updated to include changes to the inclusion/exclusion criteria, to clarify the frequency of assessments listed in Table 7-1 (visit evaluation schedule) and all relevant sections, to update the screening visit procedures, to update laboratory evaluation parameters and to address several administrative errors.

The inclusion/exclusion criteria are being changed due a greater than 90% pre-screen failure rate in patients being considered for the study, and after discussions with the Study Steering Committee members. The notable changes to the inclusion criteria include allowing patients into the trial that have been previously iron chelated for no more than six months cumulatively (such as daily deferasirox (Exjade) or deferiprone or 5x/week deferoxamine from only including those who were chelation naïve. The minimum number of transfused units of blood is being changed from 20 units to 15 units and patients entering the study must be transfused with at least 8 units of PRBC annually from 8 times annually. The serum creatinine entry criteria is being changed from requiring serum creatinine >ULN at screening to serum creatinine >1.2x ULN at screening. The exclusion criteria of prior diagnosis of liver cirrhosis is being defined as either an established diagnosis or diagnosis by liver biopsy or central ultrasound reading. The exclusion criteria pertaining to left ventricular ejection fraction <50% by echocardiography must be confirmed by the central reading facility used in this trial. Lastly, patients with a history of another malignancy within the past five years, with the exception of basal cell skin carcinoma or cervical carcinoma *in situ*, has been expanded to include completely resected colonic polyps carcinoma *in situ*.

The visit evaluation schedule is being revised to clarify the procedures required at the week 260 visit (end of treatment visit) to allow for local laboratories to be used for weekly assessments that are required at the initiation of treatment and at the time of dose adjustments, as well to as to note that those patients who have a diagnosis of diabetes requiring treatment with medication do not require a 2 hour fasting glucose tolerance test to be performed.

The screening visit period is being revised to allow for a 35 day screening window. This amendment also serves to outline the details of the screening visit and further define late/missed visits.

This first center was initiated on 1-December-2009 in Canada. As of 12-November-2010, 15 subjects have been screened and 5 subjects has been randomized to the trial.

[redacted]

Changes to the protocol Amendment 2

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike-through red font for deletions, **red** (bold) for insertions.

Changes to List of Abbreviations

- Abbreviations updated to reflect additions and deletions

Changes to Section Protocol Synopsis, Inclusion/Exclusion Criteria

- Criteria have been amended to allow for ≤6 months of cumulative iron chelation therapy (such as daily deferasirox (Exjade) or deferiprone or 5x/week deferoxamine (intermittent deferoxamine doses in association with blood transfusions are not exclusionary regardless of duration of such treatment), to increase the serum creatinine value, to broaden the history of the transfusion range, to clarify transfusion requirements, to specify the central reading of echocardiography, to clearly define the liver cirrhosis criteria, and to expand the history of malignancies.

Changes to Section 3.1.1

- This section is being amended to make it clearer to the reader and to expand the details around the screening criteria.

Changes in Section 4

- This section is being amended to include further details on the screening procedures.

Change to Section 5

- This section is being amended to reflect the revised inclusion/exclusion criteria.

Changes in Section 5.1

- Changes as addressed above, in the protocol synopsis.

Changes in Section 5.2

- Changes as addressed above, in the protocol synopsis.

Changes to Tables 6-1- 6-8

- This section is being amended due to an administrative error.

Changes to Section 6.4

- This section is being amended to reflect the updates made in the IVRS process and to further define missed/late study visits.

Changes to Section 6.6.1.1

- This section is being amended to delete the statement on mixing cups.

Changes to Section 6.7.5.1

- This section is being amended to clarify discontinuation of study treatment.

Changes to Section 6.7.5.2

- This section is being amended to clarify discontinuation of study treatment.

[redacted]

Changes to Table 7-1

- Table 7-1 is being amended to correct administrative errors found in the table and footnotes section as well as to clarify the use of local laboratories, and to update glucose tolerance testing and BNP parameters.

Changes to Section 7.1

- This section is being amended to include pre-screening log details and re-screening procedures.

Changes to Section 7.2

- Changes as addressed above, in the protocol synopsis.

Changes to Section 7.5.4

- This section is being amended due to an administrative error.

Changes to Section 7.5.5

- This section is being amended to clarify the use of local laboratories.

Changes to Section 7.5.5.2

- This section is being amended to clarify serum ferritin testing.

Changes in Table 7-2

- This section is being amended to provide details on the oral glucose tolerance testing.

Changes in Section 7.5.7

- This section is being amended to clarify the echocardiogram (ECHO) central reading process.

Changes in Section 7.5.9

- This section is being amended to include the specific bone marrow assessments that are required.

Changes in Section 7.5.10

- This section is being amended to clarify the liver ultrasound central reading process.

Changes in Section 8.2

- This section is being amended to update the pregnancy outcome criteria, since female partners of those males participating in the trial are not consented.

Changes in Section 10.4.3

- This section is being amended to include “Progression to AML”

IRB/IEC/REB Approval

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are

[redacted]

required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

Amendment 1

Amendment rationale

This protocol has been updated to include changes to the inclusion/exclusion criteria, changes to Table 7-1 (visit evaluation schedule) and all relevant sections, to update the Study Design section and to update the composite primary endpoint, as well as to incorporate changes to the statistical analysis agreed upon with the FDA.

The inclusion/exclusion criteria are being changed due a greater than 90% pre-screen failure rate in patients being considered for the study. The notable changes are that the maximum serum ferritin level for inclusion is being raised from 2500 to 3500 mcg/L with a concurrent increase of the maximum number of transfused units of blood from 50 to 75. Additionally, the exclusion criteria of more than 3 years from diagnosis of MDS is being changed to more than 3 years from the time the patient became transfusion dependent.

The visit evaluation schedule is being revised to clarify the need for baseline BNP assessment and for a baseline chest x-ray, as well as to allow for local laboratories to be used for weekly serum creatinine assessments that are required at the initiation of treatment and at the time of dose adjustments.

The composite primary endpoint is being updated to include transformation to AML as one of the parameters that composes the primary endpoint. Based upon recent data (Sanz 2008), iron overload may play a role in AML transformation in patients with MDS as patients with serum ferritin levels of ≥1000 ng/ml had a significantly higher rate of AML transformation than patients with serum ferritin levels of < 1000 mg/ml. Given that progression to AML is an extremely significant medical event in terms of both morbidity and mortality, it is appropriate to include as part of the composite primary endpoint.

Changes to the protocol Amendment 1

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike-through red font for deletions, **red** (bold) for insertions.

Changes to List of Abbreviations

- Abbreviations updated to reflect additions and deletions

Changes to Endpoint section

- The composite primary endpoint has been updated to include transformation to AML as one of the parameters that compose the primary endpoint.

Changes to Secondary Endpoint section

- This section has been amended to further define the progression of AML.

[redacted]

Changes to Section Protocol Synopsis, Inclusion/Exclusion Criteria

- Criteria have been amended to allow for an expanded weight range, to increase the upper limit of Serum Ferritin and to increase the number of transfusions. The time since diagnosis of MDS criteria has been expanded upon and the left ventricular ejection fraction value has been decreased. Other exclusion criteria have been clarified.

Changes to Section Protocol Synopsis, Supply, preparation, and administration

- This section has been amended to address an administrative error.

Changes to Protocol Synopsis, Patient Numbering

- This section has been amended to address an administrative error

Changes to Protocol Synopsis, Efficacy Assessments

- This section has been modified to add the bone marrow biopsy performed to confirm the diagnosis of the AML transformation.

Changes to Section Protocol Synopsis, Statistical methods and data analysis,

- The statistical section has been updated.

Changes to Special safety assessment(s) Section, Protocol Synopsis

- This section has been amended to address an administrative error.

Changes to Section 1.2

- This section has been amended to address an administrative error.

Changes to Section 2

- This section has been amended to address an administrative error.

Change to Section 3.1

- Changes as addressed above, in the protocol synopsis.

Changes to Section 3.2.1

- Changes as addressed above, in the protocol synopsis.

Changes to Section 4

- This section has been amended to make it more clear to the reader.

Change to Section 5.1

- Changes as addressed above, in the protocol synopsis.

Changes to Section 6.3

- This section has been amended in order to make the IVRS process more defined.

Changes to Section 6.4

- This section has been amended in order to make some administrative changes.

Changes to Section 6.6.1

- This section was amended to clarify the IVRS procedures.

[redacted]

Changes to Section 6.6.1.1

- This section was amended to further clarify patient dosing procedures.

Changes to Section 6.7

- This section was amended to clarify permitted study dosage changes.

Changes to Section 6.7.1.2

- This section was amended to provide guidance surrounding the need to discontinue study drug.

Changes to Section 6.7.1.3

- This section was amended to clarify the instructions for a specific visit procedure.

Changes to Section 6.7.1.4

- See changes to Section 6.7.1.2

Changes to Section 6.7.1.5

- See changes to Section 6.7.1.2

Changes to Section 6.7.1.6

- See changes to Section 6.7.1.2

Changes to Section 6.7.1.7

- See changes to Section 6.7.1.2

Changes to Section 6.7.4

- This section was amended due to an administrative error.

Changes to Section 6.7.5

- This section was amended to clarify the end of study procedures.

Changes to Section 6.7.5.2

- See Section 6.7.5.

Changes to Section 6.7.6.1

- See Section 6.7.5.

Changes to Section 6.7.6.2

- See Section 6.7.5.

Changes to Table 7-1

- Table 7-1 was amended to add procedures as well as to make the visit schedule and all procedures more clear.

Changes to Section 7.1

- This section was amended to include the word “screening.”

Changes to Section 7.2

- This section was amended to include further blood tests.

Changes to Section 7.3

- This section was amended to include further descriptive information.

Changes to Section 7.5.2

- This section was amended due to administrative error.

Changes to Section 7.5.3

- This section was amended to include further descriptive information.

Changes to Section 7.5.4

- This section was amended to include further descriptive information.

Changes to Section 7.5.5.2

- This section was amended to include further descriptive information.

Changes to Section 7.5.5.3

- This section was amended to provide guidance surrounding the need to discontinue study drug.

Changes to Section 7.5.5.4

- This section was amended to include further descriptive information.

Changes to Table 7-2

- This section was amended due to administrative error.

Changes to Section 7.5.6

- This section was amended to correct the visit numbering.

Changes to Section 7.5.7

- This section was amended to correct the visit numbering.

Changes to Section 7.5.8

- This section was amended to provide guidance on when chest x-rays need to be performed.

Changes to Section 7.5.9

- This section was amended to include language surrounding the addition of the primary composite endpoint.

Changes to Section 7.5.10

- This section was amended to include further descriptive information.

Changes to Section 8.1

- This section was amended to reflect the change from IMS to DS&E.

Changes to Section 8.2

- This section was amended for clarification purposes.

Changes to Section 10

- This section was amended to further describe the statistical analysis.

[redacted]

Changes to Section 10.4

- This section was amended for clarification purposes.

Changes to Section 10.4.3

- This section was amended to further describe the statistical analysis.

Changes to Section 10.4.4

- This section was amended to further describe the statistical analysis.

Changes to Section 10.5.1.1

- This section was amended to further describe the statistical analysis.

Changes to Section 10.5.2.4

- This section was amended to further describe the statistical analysis.

Changes to Section 10.7

- This section was amended to further describe the statistical analysis.

Changes to Reference Section 13

- Reference has been added.

IRB/IEC/REB Approval

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

[redacted]

Oncology clinical study protocol synopsis

Investigational drug	Deferasirox (ICL670, Exjade®)
Protocol no.	CICL670A2302
Study phase	II
Study title	A multi-center, randomized, double-blind, placebo-controlled, clinical trial of deferasirox in patients with Myelodysplastic Syndromes (Low/Intermediate-1 Risk) and transfusional iron overload.
Background	Myelodysplastic syndromes (MDS) are clonal stem cell disorders characterized by ineffective hematopoiesis in one or more cell lineages and has the potential to evolve to acute myeloid leukemia (AML). Treatment goals for patients with low/int-1 risk MDS primarily involve managing cytopenias. While specific therapies and the use of growth factors may alleviate transfusion requirements in some patients, 60-80% of patients do not respond and require ongoing platelet and red blood cell (RBC) transfusions due to impaired hematopoiesis. In many patients, this leads to chronic RBC transfusion therapy and the development of secondary iron overload (IO). Liver dysfunction, cirrhosis and endocrinopathies have been described in multi-transfused MDS patients (even with a short-term duration of transfusion), where even mild liver function abnormalities have been associated with marked hepatic iron overload and portal fibrosis on biopsy (Schafer 1981, Jaeger 1992). Cardiac complications of iron overload secondary to long-term transfusion therapy are well-described in β-thalassemia major, but have not yet been well-described for the MDS population. Iron chelation therapy (ICT) has a long history in transfusion-dependent patients with hemoglobinopathies, primarily β-thalassemia major, with demonstrated improvement in organ dysfunction and survival in patients who are compliant with therapy (Olivieri 1997). Use of deferoxamine (DFO) in iron-overloaded MDS patients has been reported to improve organ dysfunction (Jensen 2003, Schafer 1985), and even improve cytopenias (Jensen 1996). With the use of ICT, there have also been reports of improvements in glucose metabolism in iron-overloaded thalassemia major patients (Farmaki 2006), and reduced insulin requirements in MDS patients (Schafer 1985). However, poor patient compliance associated with the necessity of repeated subcutaneous infusions, as well as the potential for increased bruising/bleeding in patients with thrombocytopenia and/or platelet dysfunction are significant problems with DFO, particularly with elderly MDS patients. Therefore, the need exists for an iron chelator which could be administered via the more convenient oral route. Iron overload may impact survival in MDS, which is especially relevant for low-risk patients. A recent retrospective analysis of 467 MDS patients demonstrated that cardiac failure and liver cirrhosis constituted 51% and 8%, respectively, of the non-leukemic causes of death (Malcovati 2005). Moreover, secondary iron overload, reflected by a serum ferritin level greater than 1,000 ng/mL, was associated with a poorer overall survival (OS). Recent, uncontrolled studies suggest a benefit of ICT upon survival in MDS (Leitch 2007, Rose 2010, Sanz 2008). Leitch et al. reported results of a retrospective review of 178 MDS patients (60% with low/int-1 MDS). Eighteen patients received ICT for a median of 15 months. In low/int-1 patients, the median OS was 40 months for those not receiving ICT compared with a median OS not reached at 160 months for patients receiving ICT. Also, 80% of patients receiving ICT survived to 4 years from the time of diagnosis compared to 44% without ICT. In a non-randomized, prospective 2 year follow-up of 165 MDS patients (59% low/int-1 risk) in an outpatient setting, Rose reported a median survival from time of diagnosis of 115 months in patients receiving ICT compared with 51 months in those who did not receive ICT. Sanz reported that the development of iron overload and transfusion dependency were strongly associated with AML transformation risk in MDS.These studies included patients with a wide range of transfusional iron intake, time since diagnosis of MDS and co-morbidities.

[redacted]

	Deferasirox (Exjade®) is approved for the treatment of transfusional iron overload in over 90 countries. Data on 47 MDS patients were included in the registration dossier (Study CICL670A0108). Efficacy was demonstrated based on changes in serum ferritin and liver iron content. The relationship between serum ferritin levels and clinical outcome is well described in patients with β-thalassemia (Cappellini 2006), but has not been well described in a prospective study until now.
Purpose/rationale	Use of iron chelation therapy has demonstrated benefits in terms of morbidity and mortality for chronically-transfused thalassemia patients with iron overload. Recent retrospective data (Leitch 2007, Rose 2010, Sanz 2008) suggest that overall survival may be improved in adult patients with MDS who receive iron chelation therapy. The purpose of this study is to evaluate in low/int-1 risk MDS patients, treated as per standard practice, the clinical benefit of deferasirox versus placebo, while rigorously monitoring relevant clinical parameters (cardiac and liver function and transformation to Acute Leukemia AML) potentially affected by iron overload complications.
Objectives	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. The secondary objectives are to evaluate: ● Hematologic improvement (HI) in terms of erythroid response ● Overall survival ● Change in endocrine function (thyroid and glycemic control) ● Disease progression (which includes MDS progression and progression to AML) ● Change in serum ferritin level ● Change in cardiac function ● Frequency of infections requiring intravenous antimicrobials ● 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 (see Fleming 2008 for general approach).
Endpoints (efficacy, safety)	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

[redacted]

	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) All events which could potentially fulfill the criteria for one of the components of the composite primary endpoint, will be reported to the Endpoint Adjudication Committee (EAC) for assessment. **Secondary endpoints:** **Efficacy:** Proportion of patients with hematologic improvement in terms of erythroid response Overall survival 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) 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. Time to first occurrence of serum ferritin > 2 times the baseline value at two consecutive assessments (at least two weeks apart) 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 and rate of infections requiring intravenous antimicrobials

	Safety: 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
Study design	This is a prospective, randomized, double-blind, placebo-controlled, parallel group design study. The recruitment period is planned to last until December 2014. Patients will be assigned to either deferasirox or matching placebo (2:1 ratio in favor of deferasirox) by stratified randomization using an interactive voice response system (IVRS) and strata defined by IPSS (low vs int-1 MDS risk patients) and geographical region (Asian countries versus non-Asian countries) since the Asian population have a longer survival. (Matsuda 2005). The study will continue for 3 years from the date the last patient is enrolled. The end of study treatment may occur if a patient meets any non-fatal component of the composite primary endpoint (confirmed by the EAC). His/her individual randomized study treatment will be unblinded and discontinued at that time. The subsequent iron chelation treatment is subject to patient's and the investigator's decision. Patients will continue to be followed every 6 months for iron chelation therapies and overall survival once he/she discontinues from the study treatment. Patients who discontinue study treatment without meeting a non-fatal component of the composite primary endpoint will continue to be evaluated every 3 months. Once patients stop study evaluations they will be followed for at least every 6 months for overall survival and any iron chelation therapies they are receiving up to the end of study. The EAC is responsible for ensuring whether pre-specified endpoint criteria were met for all non-fatal events. The role of the EAC is to ensure that all events that have been reported by the sites are judged uniformly using the same criteria. The EAC is blinded to study treatment allocation.
Population	At least 210 adult patients with low or intermediate (int-1) MDS (Greenberg 1997) from approximately 126 centers will be enrolled in this protocol. Patients receiving locally approved treatment for MDS (e.g.,5'-azacitidine, lenalinomide, decitabine, EPO) are allowed to be randomized.
Inclusion/exclusion criteria	**Key Inclusion criteria:** ● Male or female patients, ≥18 years of age ● Patient must weigh between 35-135 kg ● Patients with low or intermediate (int-1) risk MDS, as determined by IPSS score. This must be confirmed by a bone marrow examination within 6 months prior to study entry and must be hematologically stable ● Ferritin > 1000 mcg/L at screening ● History of transfusion of 15 to 75 PRBC units ● Anticipated to be transfused with at least 8 units of PRBCs annually during the study **Key Exclusion criteria:** ● More than 6 months of cumulative iron chelation therapy (such as daily deferasirox (Exjade®) or deferiprone or 5x/week deferoxamine) ● Intermittent deferoxamine doses in association with blood transfusions are not exclusionary regardless of duration of such treatment.

[redacted]

	● More than 3 years since patient began receiving regular transfusions (2 units per 8 weeks or 4 units received in a 3 month period) ● Creatinine clearance <40 mL/min ● Serum creatinine > 1.5 x ULN at screening ● Serum creatinine will be measured at Screening Visit 1 and Screening Visit 2 and the mean value will be used for eligibility criteria. ● Significant proteinuria as indicated by a urinary protein/creatinine ratio > 0.5 mg/mg in a non-first void urine sample at Visit 1 or Visit 2 (or alternatively in two of three samples obtained for screening) ● ECOG performance status > 2 ● Left ventricular ejection fraction < 50% by echocardiography as per the central reading assessment ● A history of hospitalization for congestive heart failure ● Systemic diseases which would prevent study treatment (e.g. uncontrolled hypertension, cardiovascular, renal, hepatic (including Child-Pugh Class B and C), metabolic, etc.) ● Clinical or laboratory evidence of active Hepatitis B or Hepatitis C (HBsAg in the absence of HBsAb OR HCV Ab positive with HCV RNA) ● History of HIV positive test result (ELISA or Western blot) ● Treatment with systemic investigational drug within 4 weeks or topical investigational drug within 7 days of study start ● ALT or AST > 3.5×ULN at screening ● Total bilirubin > 1.5× ULN at screening ● Diagnosis of liver cirrhosis (either established diagnosis or diagnosis by liver biopsy or central ultrasound reading) ● Patients participating in another clinical trial other than an observational registry study ● Patients with a history of another malignancy within the past five years, with the exception of basal cell skin carcinoma or cervical carcinoma *in situ* or completely resected colonic polyps carcinoma *in situ*. ● History of non-compliance to medical regimens, or patients who are considered potentially unreliable and/or not cooperative ● Presence of a surgical or medical condition which might significantly alter the absorption, distribution, metabolism or excretion of study drug ● Pregnant, or breast-feeding patients or patients of child-bearing potential not employing an effective method of birth control ● History of drug or alcohol abuse within the 12 months prior to enrollment.
Patient numbering	IVRS will be utilized for stratified randomization (see Study Design section). Patient identification will incorporate a center number and subject number.
Investigational and control drugs	Investigational drug: ICL670 (deferasirox): ● Drug formulation: dispersible tablets ● Strength: - 125 mg, 250 mg, 500 mg ● Mode of administration: oral use (suspension can be prepared in water, orange or apple juice) Control drug: placebo matching deferasirox

[redacted]

Dose, regimen, treatment cycle	Having completed the screening period, patients enrolled and randomized to deferasirox (ICL670, Exjade®) or matching placebo will begin study treatment. The following dosing schedule is to be followed: ● 10 mg/kg/day (once daily) for 2 weeks, followed by 20 mg/kg/day (once daily) ● After 3 months of treatment at the dose of 20mg/kg/day the dose can be adjusted by 5 or 10 mg/kg/day up to 40 mg/kg/day based on serum ferritin response
Supply, preparation, and administration	When the patient has signed the informed consent form, the investigator or his/her staff will telephone the IVRS and provide the requested identifying information for the patient. The IVRS will then assign the medication number. During the scheduled visits, the investigator or pharmacist will dispense the appropriate number of drug bottles (125 mg, 250 mg or 500 mg tablets) to the patient. The number of tablets of each strength, the medication numbers, visit number and date of dispensation will be recorded in the drug-dispensing log.
Visit schedule and assessments	Refer to the attached table.
Efficacy assessment(s)	An ongoing evaluation of criteria for the composite primary efficacy endpoint must be completed for all patients randomized in this trial by the EAC. Left heart ventricle function measured by echocardiography at screening and then approximately every 3 months. Liver function determined by assessment of ALT/AST and total bilirubin at screening, and then monthly throughout the study. Endocrine function as determined by oral glucose tolerance test, TSH and free T4 performed at screening and then annually. Hematologic improvement in terms of erythroid response (HI-E) based on change in Hgb or transfusion requirements pre-treatment and during the study will be evaluated. Bone Marrow biopsy or aspiration will be performed to confirm diagnosis of AML transformation, if suspected based upon results of peripheral blood analysis. Complete blood counts will be drawn at screening, then monthly throughout the study. Serum ferritin will be analyzed by a central laboratory, using a validated standard kit assay, on samples collected at screening (Visit 1) and prior to commencing study treatment (Visit 3), and then monthly during study. Infections requiring IV antimicrobials will be identified from the adverse events and the concomitant medication page.
Special safety assessment(s)	Clinical symptoms of cardiac dysfunction during the study. Hematology, liver enzymes (AST/SGOT and ALT/SGPT) and serum chemistry will be determined by a central laboratory at Visit 1 (screening) and then monthly during study. Serum creatinine at Visits 1 and 2 (screening) and then monthly during study. Proteinuria (urinary protein /creatinine ratio) at Visit 1 (screening) and then monthly during study. Ocular and auditory examinations will be performed at Visit 1(screening) and then annually until Study Evaluation Completion, unless otherwise indicated.
Patient reported outcomes	Not planned
Pharmacokinetics	Not planned
Biomarker assessments	Not planned

[redacted]

Exploratory Biomarker pharmacodynamic studies involving tumor samples	Not planned
Optional Biomarker studies on additional or remaining samples	Not planned
DMC	An independent Data Monitoring Committee will be established. It will include experts in hematology, cardiology, hepatology and biostatistics (the experts will be external to Novartis and will not otherwise be involved in this study). The DMC charter will be approved prior to enrollment of the first patient. The DMC will monitor patient safety and trial conduct, and receive a blinded summary of serious adverse events on a regular basis. The composition, frequency of the meetings, and roles will be detailed in the DMC charter (in appendix). The DMC may recommend to the Sponsor: ● To continue the study as planned ● To continue the study with modifications ● To prematurely stop the study for unfavorable safety profile of deferasirox compared to placebo The DMC will give recommendations to the sponsor on any changes in study conduct. The DMC will meet prior to First Patient First Visit to finalize the DMC charter describing roles and responsibilities.
Statistical methods and data analysis	**Analysis sets:** ● The Full Analysis Set (FAS) comprises 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 treatment and strata they were assigned to during the randomization procedure. The FAS will be the primary analysis set for all statistical analyses of efficacy. ● The Per Protocol Analysis Set (PPS) is a subset of the FAS and comprises all randomized patients whose first administered study medication was in accordance with the randomized assignment, and without protocol deviations regarding inclusion criteria with respect to underlying disease (e.g., low or intermediate-1 MDS according to IPSS and serum ferritin > 1000 mcg/L at screening). The PPS will be used as the secondary analysis set to perform statistical analyses of the primary efficacy endpoint. ● The Safety Analysis Set 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 recorded in the (e)CRF. All statistical analyses of safety and tolerability will be based on the Safety Analysis Set. **Significance level:** No confirmatory hypothesis tests will be performed. Two-sided 95% confidence intervals will be provided for estimating treatment effects of deferasirox relative to placebo. For some endpoints tests will be performed in an exploratory sense only. **Statistical analysis methods:** Patient demographics and baseline characteristics will be summarized by treatment group. Primary statistical analysis method for the primary endpoint: For the primary analysis, the following censoring rule will be applied: Patients not known to have experienced any event from the composite primary endpoint at the time of a data cut-off will be censored - irrespective of adherence to study treatment - at the last date when there has been evidence for being event-free (details in the full protocol). A point estimate and two-sided confidence interval for an unadjusted hazard ratio will be obtained from a Cox proportional hazard regression model stratified for the

[redacted]

	randomization factors IPSS and geographical region (Asian countries versus non-Asian countries). For each treatment group, survival functions for time from randomization to the composite primary endpoint (event-free survival) will be estimated and displayed by the Kaplan-Meier method. Sensitivity/supportive/exploratory analyses for the primary endpoint: ● Point estimate and two-sided confidence interval for an adjusted hazard ratio from a Cox proportional hazard regression model stratified for the randomization factors; adjustment for (partly data driven) demographic and/or baseline characteristics of clinical interest; ● Unadjusted hazard ratio estimates for each of the strata defined by the randomization factors; ● Analysis analog to the primary statistical analysis but patients with premature discontinuation of randomized study treatment will be censored at the day of last administration of randomized study treatment; ● Summary of the types of events observed; ● Statistical analyses based on the PPS instead of the FAS. Statistical analysis methods for secondary efficacy endpoints: Analyses will be described in the full clinical study protocol. Statistical analysis methods for safety endpoints: Following (Fleming 2008), the goal of this exploratory trial is not to determine whether there is significant evidence to rule out the null hypothesis of no increased risk. In contrast, the objective here is to exclude levels of increased risk (for pre-specified adverse events mentioned in the Endpoints section) 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. Therefore, two-sided 95% confidence intervals for risk (or hazard, if applicable) ratios will be calculated. Incidences of treatment emergent (serious) adverse events (including combinations of MedDRA terms as defined by Standardized MedDRA Queries) will be summarized by treatment group. Laboratory data will be summarized using descriptive statistics and shift tables (using CTCAE classification where available) by treatment group. **Sample size:** The sample size of 210 patients randomized in a ratio of 2:1 in favor of deferasirox is based on the enrollment projection.

[redacted]

1 Background

1.1 Overview of myelodysplastic syndrome (MDS)

Myelodysplastic syndromes (MDS) are clonal stem cell disorders characterized by ineffective hematopoiesis in one or more cell lineages and by potential for evolution to acute myeloid leukemia (AML). Treatment goals for patients with lower risk MDS primarily involve managing cytopenias. While specific therapies and the use of growth factors may alleviate transfusion requirements in some patients, 60-80% of patients do not respond and require ongoing platelet and red blood cell (RBC) transfusions due to impaired hematopoiesis.

In many patients, this leads to chronic RBC transfusion therapy, and the development of secondary iron overload (IO). Liver dysfunction, cirrhosis and endocrinopathies have been described in multi-transfused MDS patients (even with a short-term duration of transfusion), where even mild liver function abnormalities have been associated with marked hepatic iron overload and portal fibrosis on biopsy (Schafer 1981, Jaeger 1992). Cardiac complications of iron overload secondary to long-term transfusion therapy are well-described in β-thalassemia major, but have not yet been well-described for the MDS population.

Iron chelation therapy (ICT) has a long history in transfusion-dependent patients with hemoglobinopathies, primarily β-thalassemia major, with demonstrated improvement in organ dysfunction and survival in patients who are compliant with therapy (Olivieri 1997). Use of deferoxamine (DFO) in iron-overloaded MDS patients has been reported to improve organ dysfunction (Jensen 2003, Schafer 1985), and even improve cytopenias (Jensen 1996).

With the use of ICT, there have also been reports of improvements in glucose metabolism in iron-overloaded thalassemia major patients (Farmaki 2006), and reduced insulin requirements in MDS patients (Schafer 1985). However, poor patient compliance associated with the necessity of repeated subcutaneous infusions, as well as the potential for increased bruising/bleeding in patients with thrombocytopenia and/or platelet dysfunction are significant problems with DFO, particularly with elderly MDS patients. Therefore, the need exists for an iron chelator which could be administered via the more convenient oral route. Iron overload may impact survival in MDS, which is especially relevant for low-risk patients. A recent retrospective analysis of 467 MDS patients demonstrated that cardiac failure and liver cirrhosis constituted 51% and 8%, respectively, of the non-leukemic causes of death (Malcovati 2005). Moreover, secondary iron overload, reflected by a serum ferritin level greater than 1,000 ng/mL, was associated with a poorer overall survival (OS).

Recent, uncontrolled studies suggest a benefit of ICT upon survival in MDS (Leitch 2007, Rose 2010, Sanz 2008). Leitch et al. reported results of a retrospective review of 178 MDS patients (60% with low/int-1 MDS). Eighteen patients received ICT for a median of 15 months. In low/int-1 patients, the median OS was 40 months for those not receiving ICT compared with a median OS not reached at 160 months for patients receiving ICT. Also, 80% of patients receiving ICT survived to 4 years from the time of diagnosis compared to 44% without ICT. In a nonrandomized, prospective 2 year follow-up of 165 MDS patients (59% low/int-1 risk) in an outpatient setting, Rose reported a median survival from time of diagnosis of 115 months in patients receiving ICT compared with 51 months in those who did

not receive ICT. Both studies included patients with a wide range of transfusional iron intake, time since diagnosis of MDS and co-morbidities. Sanz reported that the development of iron overload and transfusion dependency were strongly associated with AML transformation risk in MDS

A recent review of safety data in 584 MDS patients pooled from Novartis-sponsored clinical trials confirms the current safety profile of deferasirox in the approved label regarding the most frequent adverse events associated with deferasirox such as gastrointestinal disorders (abdominal pain, diarrhea, nausea, vomiting) and renal disorders (increased blood creatinine). The overall profile of adverse events in the reviewed population was consistent with the clinical features of MDS such as age-related co-morbidities, MDS-related clinical symptoms and laboratory abnormalities.

1.2 Overview of deferasirox (ICL670)

Deferasirox (ICL670, Exjade®) is an N-substituted bis-hydroxyphenyl-triazole, a representative of a new class of tridentate iron chelators (Nick 2003) that has been developed by Novartis for treating transfusional iron overload. Two molecules of deferasirox form a complete complex with Fe^{3+}. The high potency of deferasirox in mobilizing tissue iron and promoting iron excretion was demonstrated both *in vitro* and *in vivo* model systems (Nick 2003). Deferasirox is eliminated from the body by hepatic glucuronidation and biliary excretion. Preclinical studies also revealed that deferasirox did not affect fertility and it is neither teratogenic nor carcinogenic.

To date, deferasirox has been approved in more than 90 countries, including the European Union, the USA, Switzerland, and Japan for the treatment of chronic iron overload due to blood transfusions in adult and pediatric patients. Within this indication, deferasirox is approved for use in transfusion-dependent MDS patients, based on data demonstrating efficacy in reducing liver iron concentration (LIC) and serum ferritin.

Detailed information on preclinical and clinical evaluation of deferasirox is provided in the current [Investigators' Brochure].

Deferasirox is formulated as a dispersible tablet for oral suspension which facilitates administration of the appropriate quantity of drug substance to both pediatric and adult patients. Deferasirox is supplied as 125 mg, 250 mg and 500 mg tablets which can be dispersed in water, orange juice or apple juice. Bioavailability studies indicate that absorption is highly variable when deferasirox is taken together with food. Therefore, it is recommended that deferasirox is taken in the morning on an empty stomach, at least 30 minutes prior to food.

More than 800 pediatric and adult patients aged 2 to 80 years were enrolled in randomized controlled trials evaluating the safety and efficacy of deferasirox in the treatment of transfusional iron overload. At least 500 patients received deferasirox. The studies showed deferasirox to effectively chelate iron in patients with transfusional iron overload as demonstrated by decreases in liver iron concentration (LIC) and serum ferritin (Porter 2008), (Cappellini 2006), (Vichinsky 2007).

The efficiency of deferasirox in chelating iron appears to be constant at all doses ranging from 5 to 40 mg/kg/day and is not affected by age, gender, baseline LIC or underlying anemia (Porter 2005).

[redacted]

1.3 Safety profile

Deferasirox has demonstrated acceptable safety and tolerability in adult and pediatric patients with transfusional iron overload (Cappellini 2006), (Vichinsky 2007). The most frequent reactions reported during the first year of treatment with deferasirox in adult and pediatric patients included gastrointestinal (GI) disturbances in about 26% of patients (mainly nausea, vomiting, diarrhea, or abdominal pain), and skin rash in about 7% of patients. These reactions were dose-dependent, mostly mild to moderate, generally transient and mostly resolved even if treatment was continued. In addition, there have been rare reports of upper GI hemorrhage and/or ulceration in patients receiving deferasirox. There have been very occasional postmarketing reports of erythema multiforme, leukocytoclastic vasculitis and hypersensitivity reactions (including anaphylaxis and angioedema). Alopecia, usually comprising thinning of the hair, has been occasionally reported in patients receiving deferasirox.

Mild, non-progressive increases in serum creatinine, mostly within the normal range, occurred in about 36% of patients during the first year of treatment. These were dose-dependent, often resolved spontaneously and were sometimes alleviated by reducing the dose. Rare cases of acute renal failure, defined as a serum creatinine increases $\geq 2 \times$ ULN, and usually reversible after treatment interruption (and sometimes a brief course of hemodialysis), have been reported following the prescription use of deferasirox.

Elevations of liver transaminases were reported as an adverse reaction in about 2% of patients. These were not dose-dependent and most of these patients had elevated levels prior to receiving deferasirox. Elevations of transaminases $>10 \times$ ULN were uncommon (0.3%). There have been postmarketing reports of hepatic failure, mostly in patients with severe baseline liver disease.

There have been reports of cytopenias, mostly in patients with pre-existing blood disorders which are frequently associated with failure of the bone marrow to produce sufficient amounts of blood cells.

High frequency hearing loss and lenticular opacities (early cataracts) have been uncommonly observed in patients treated with deferasirox.

As with other iron chelator treatment, the risk of toxicity of deferasirox may be increased when inappropriately high doses are given in patients with a low iron burden or with serum ferritin levels that are only slightly elevated.

In summary, deferasirox is a once-daily oral iron chelator that has been developed for treating transfusional iron overload, with demonstrated efficacy in the reduction or maintenance of body iron stores, and an acceptable safety profile.

2 Study rationale/purpose

The primary purpose of this study is to prospectively assess the efficacy and safety of iron chelation therapy with deferasirox compared to placebo in patients with myelodysplastic syndromes (low/int-1 risk) and transfusional iron overload.

[redacted]

It is well understood how excess iron damages organs and tissues, and deferasirox has been clearly demonstrated to reduce iron burden, as measured by LIC and serum ferritin. Data on the correlation between serum ferritin and morbidity and mortality come mainly from the thalassemia population, so the relevance of serum ferritin as a surrogate for clinical benefit has not been definitively proven in the MDS setting. Recent retrospective data (Leitch 2007), (Rose 2010) suggest that overall survival may be improved in adult patients with MDS who receive iron chelation therapy.

3 Objectives

The purpose of this study is to evaluate in low/int-1 risk MDS patients, treated as per standard practice, the clinical benefit of deferasirox versus placebo, while rigorously monitoring relevant clinical parameters (cardiac and liver function) potentially affected by iron overload complications.

3.1 Primary objective

The primary objective is to evaluate deferasirox and placebo with regard to 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.

3.1.1 Endpoints for primary objective

The primary endpoint is a composite primary endpoint (event-free survival) defined as time from date of randomization to date of death or any of the non-fatal events defined below has been reached:

- Death
- Non-fatal event (fulfilling the following criteria):

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

[redacted]

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 (AML) confirmed by bone marrow biopsy or aspirate.

All events which could potentially fulfill the criteria for one of the components of the composite primary endpoint, will be reported to the Endpoint Adjudication Committee (EAC) for assessment. Details for reporting events to the EAC will be outlined in both the investigative site manual and EAC manual. A summary describing the role of the EAC is located in Section 11 of this protocol.

[redacted]

3.2 Secondary objectives

The secondary objectives are to evaluate:

- Hematologic improvement (HI) in terms of erythroid response
- Overall survival
- Change in endocrine function (thyroid and glycemic control)
- Disease progression (which includes MDS progression and progression to AML)
- Change in serum ferritin level
- Change in cardiac function
- Frequency of infections requiring intravenous antimicrobials
- 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 (see Fleming 2008 for general approach).

3.2.1 Endpoints for secondary objectives

Endpoints for the secondary efficacy objectives are as follows (detailed definitions are given in Section 10.5.1.1):

- Proportion of patients with hematologic improvement in terms of erythroid response
- Overall survival
- 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)
- Time to disease progression, i.e. either MDS progression defined as a transition into a higher MDS risk group based on IPSS scoring or to progression to AML as defined in Section 7.5.9.
- Time to first occurrence of serum ferritin > 2 times the baseline value at two consecutive assessments (at least two weeks apart)
- 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 and rate of infections requiring intravenous antimicrobials (Fenaux 2009)

Endpoints for the other secondary safety objectives are as follows (detailed definitions are given in Section 10.5.2.2):

- 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 moderate (CTCAE Grade 3) or severe (CTCAE Grade 4) neutropenia or thrombocytopenia

[redacted]

- 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

4 Study design

This is a prospective, randomized, double-blind, placebo-controlled, parallel group design 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. Should the 35 day screening period be exceeded due to delays in scheduling exams as outlined in the protocol (such as ocular exams, audiometry testing, ECHO, etc.) this delay will not be considered a protocol deviation and all laboratory assessments outlined in Visit 1 must be repeated. In the event that it is more convenient for the site, confirmatory laboratory assessments may be collected by a local laboratory. Prior to a patient being randomized in the study (Visit 3), both the inclusion and exclusion criteria must be evaluated and documented in the source documents as being met and the results of all screening assessments must be available and reviewed by the investigator. At the randomization visit (Visit 3), patients will be randomized to 10 mg/kg/day of either deferasirox or matching placebo in a 2:1 manner in favor of deferasirox. As a control medication, placebo matching to each of the strength of the active compound will be utilized.

Randomization will be stratified using an interactive voice/web response system (IVRS/IWRS). The stratification will be defined by IPSS (low or int-1) as well as by geographical region (Asian versus non-Asian countries) since the Asian population have a longer survival (Matsuda 2005). Details on stratification will be outlined in the study manual provided by the IVRS vendor. Starting from Day 1, patients will receive either deferasirox 10 mg/kg/day or matching placebo for 2 weeks. At Week 2, the dose will be increased to 20 mg/kg/day deferasirox or matching placebo in all patients. This dose should be maintained through Week 14 unless there is a safety related issue (see Section 6.1.2.1). After **3 months** of treatment, at the dose of 20mg/kg/day, dose may be adjusted by 5 to 10 mg/kg/day up to 40 mg/kg/day based on serum ferritin response.

Study treatment should be administered by the patient once per day. During the treatment period, patients will return every 4 weeks to the site for routine procedures and for follow-up to monitor safety, efficacy and compliance with therapy. Should a patient require dose adjustments at any point during the trial, the patient may be asked to return more frequently to monitor safety and efficacy.

The recruitment period is planned to last until December 2014. The study will continue for 3 years from the date the last patient is enrolled.

Patients meeting a non-fatal component of the composite primary endpoint

The end of study treatment will occur if a patient meets any non-fatal component of the composite primary endpoint (Section 3.1.1) confirmed by the Endpoint Adjudication Committee (EAC). His/her individual randomized study treatment will be unblinded and discontinued at that time. The subsequent iron chelation treatment is subject to the patient's

[redacted]

and the investigator's decision. After termination of study treatment, all patients will continue to be followed for safety and non-fatal components of the primary endpoint during the evaluation period at visits occurring 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 every 6 months for iron chelation therapies and overall survival ("Survival Follow-up").

All suspected endpoint events will be reviewed and adjudicated by the EAC; however, only the first confirmed endpoint for a patient will be counted for the composite primary endpoint. The role of the EAC is to ensure that all events that have been reported are judged uniformly using the same criteria. The EAC is blinded to study treatment.

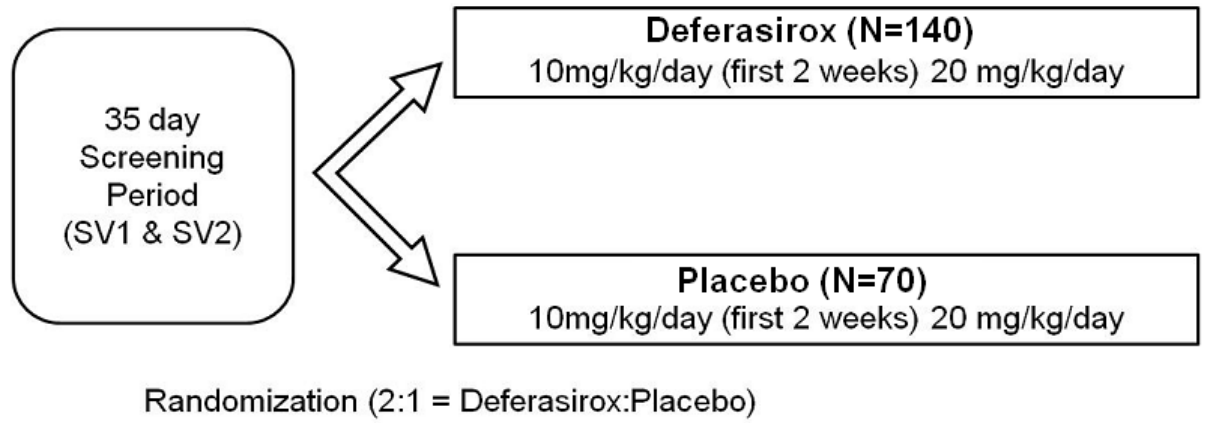
Patients not meeting a non-fatal component of the composite primary endpoint

For patients who do not meet a non-fatal component of the composite primary endpoint, study treatment will continue as long as the patient and treating physician feel it is in the best interest of the patient, or until the study terminates. There is no planned unblinding for patients who terminate study treatment without meeting a non-fatal component of the composite primary endpoint. After termination of study treatment, all patients will continue to be followed for safety and endpoints during the evaluation period at visits occurring 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 every 6 months 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. The DMC may issue the following recommendations to the sponsor:

- To continue the study as planned
- To continue the study with modifications
- To prematurely stop the study for unfavorable safety profile of deferasirox compared to placebo.

Figure 4-1 Study design



[redacted]

5 Population

Male or female patients, ≥ 18 years of age with low/int-1 MDS, as determined by IPSS score, who have serum ferritin >1000 mcg/L at screening.

At least 210 patients will be enrolled from North America, Latin America, Europe, Oceania and Asia. Patients who drop out from the study will not be replaced with additional patients.

Patients must have eligibility evaluation performed prior to Visit 3 (randomization). Principal investigator must ensure that each patient signed an Informed Consent Form prior to any study related procedures and all inclusion/exclusion criteria are met prior randomization/enrollment of each patient into the study. The eligibility check will be done automatically via IVRS. Details on the patient eligibility review process can be found in the IVRS/IWRS site manual. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations, and all regulatory requirements for informed consent. Written informed consent must be obtained from all patients prior to enrollment. The following criteria apply to all patients enrolled in the study unless otherwise specified:

Inclusion/exclusion criteria

5.1 Inclusion criteria

- Male or female patients, ≥ 18 years of age
- Patient must weigh between 35–135 kg
- Patients with low or intermediate (int-1) risk MDS, as determined by IPSS score. This must be confirmed by a bone marrow examination within 6 months prior to study entry and must be hematologically stable
- Ferritin > 1000 mcg/L at screening
  - Serum ferritin will be measured at Screening Visit 1 and Screening Visit 2 (at least 14 days apart) and the mean value will be used for eligibility criteria.
- History of transfusion of 15 to 75 PRBC units
- Anticipated to be transfused with at least 8 units of PRBCs annually during the study
- Women of child-bearing potential using effective methods of contraception during dosing of study treatment (see 'Women of Child-bearing Potential' section below for details of acceptable contraceptive methods).

5.2 Exclusion criteria

- More than 6 months of cumulative iron chelation therapy (such as daily deferasirox (Exjade®) or deferiprone or 5×/week deferoxamine)
  - Intermittent deferoxamine doses in association with blood transfusions are not exclusionary regardless of duration of such treatment
- More than 3 years since patient began receiving regular transfusions (2 units per 8 weeks or 4 units received in a 3 month period)
- Creatinine Clearance <40 ml/min

[redacted]

- Serum creatinine > 1.5 × ULN at screening
  - Serum creatinine will be measured at Screening Visit 1 and Screening Visit 2 (at least 14 days apart) and the mean value will be used for eligibility criteria.
- Significant proteinuria as indicated by a urinary protein/creatinine ratio > 0.5 mg/mg in a non-first void urine sample at Visit 1 or Visit 2 (or alternatively in two of three samples obtained for screening)
- ECOG performance status > 2
- Left ventricular ejection fraction < 50% by echocardiography as per the central reading assessment
- A history of hospitalization for congestive heart failure
- Systemic diseases which would prevent study treatment (e.g. uncontrolled hypertension, cardiovascular, renal, hepatic (including Child-Pugh Class B and C), metabolic, etc.)
- 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)
- History of HIV positive test result (ELISA or Western blot)
- Treatment with systemic investigational drug within 4 weeks or topical investigational drug within 7 days of study start
- ALT or AST > 3.5 × ULN at screening
- Total bilirubin > 1.5 × ULN at screening
- Diagnosis of liver cirrhosis (either established diagnosis or diagnosis by liver biopsy or central ultrasound reading)
- Patients participating in another clinical trial other than an observational registry study
- Patients with a history of another malignancy within the past five years, with the exception of basal skin carcinoma or cervical carcinoma *in situ* or completely resected colonic polyps carcinoma *in situ*.
- History of non-compliance to medical regimens, or patients who are considered potentially unreliable and/or not cooperative
- Presence of a surgical or medical condition which might significantly alter the absorption, distribution, metabolism or excretion of study drug
- Pregnant, or breast-feeding patients, or patients of child-bearing potential not employing an effective method of birth control (see Women of child-bearing potential, below, for further details regarding effective methods of birth control).
- History of drug or alcohol abuse within the 12 months prior to enrollment

[redacted]

Women of child-bearing potential

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must use effective contraception during the study.

Effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Female sterilization (have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Male partner sterilization (at least 6 m prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject.
- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.
- Placement of an intrauterine device (IUD) or intrauterine system (IUS).

The use of hormonal contraceptives (oral or injected) is prohibited in this study due to a decrease in efficacy when used in combination with deferasirox.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms).

Patients who are found to be ineligible after screening procedures will have this documented on the screening log (see Section 6.3 and Section 7.1). These patients will not need to complete the end of study assessments.

6 Treatment

6.1 Investigational and control drugs

The investigational study drug used in the course of this trial is deferasirox (ICL670, Exjade®) provided as 125 mg, 250 mg, and 500 mg dispersible tablets for oral use. As a control medication, placebo matching to each of the strength of active compound will be utilized.

6.1.1 Study drug

Deferasirox (ICL670, Exjade®) and matching placebo will be provided as 125 mg, 250 mg, and 500 mg dispersible tablets packaged in bulk high density polyethylene (HDPE) bottles with induction seals and child resistant closures. Study medications will be blinded, i.e. placebo will be formulated and packaged to be indistinguishable from the 125 mg, 250 mg, and 500 mg tablets of deferasirox.

[redacted]

Bottles of 35 tablets of each strength of deferasirox or corresponding placebo will be prepared, labeled and supplied by Novartis Drug Supply Management (DSM) to the local Country Pharma Organizations (CPOs) for further distribution to the study centers.

Each study site will be supplied by Novartis with study drug in identically-appearing packaging. One component of the packaging has a 2-part label. Each part of this label contains a medication number corresponding to one of the treatment groups. Investigator staff will identify the study drug package to dispense to the patient by contacting the IVRS/IWRS and obtaining the medication number(s). Immediately before dispensing the package to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) containing the patient's unique patient number.

Medication labels will comply with the legal requirements of the countries where the study is implemented and be printed in the local language. They will supply no information about the patient. Only the subject identifier will be entered on the medication label by the investigator or pharmacist before the corresponding medication is handed out to the patient. The storage conditions and the expiration date for study drug will be described on the medication label.

6.1.2 Preparation and storage

6.1.2.1 Study drug

Study medication (deferasirox or placebo) must be taken once daily on an empty stomach at least 30 minutes before food consistently at the same time every day.

The tablets are dispersed by stirring in a glass of water, orange or apple juice (100 ml to 200 ml) until a fine suspension is obtained. Patients should be instructed to rinse any remaining residue from the glass with a small amount of water, orange or apple juice and drink this as well.

Having completed the screening period, patients enrolled and randomized to deferasirox (ICL670, Exjade®) or matching placebo will begin study treatment. The following dosing schedule is to be followed:

- 10 mg/kg/day (once daily) for 2 weeks, followed by 20 mg/kg/day (once daily) (Week 2-End of treatment)
- After 3 months of treatment at the dose of 20mg/kg/day the dose can be adjusted by 5 or 10 mg/kg/day up to 40 mg/kg/day based on serum ferritin response (see Section 6.7.1.2).

The dose of 10 mg/kg/day given for the first 2 weeks of treatment has been implemented in order to reduce the risk of such adverse reactions as diarrhea, nausea, vomiting, and abdominal pain.

Patients will be instructed to take the assigned amount of drug and will be obliged to return all unused study medication at their next visit. Study medication returned by the patient will be counted and unused tablets will be recorded by the investigator/pharmacist involved in the study.

Drug accountability will be noted by the field monitor during site visits and at the completion of the trial.

[redacted]

Table 6-1 Dosing table for 5 mg/kg/d for deferasirox or placebo

Pt Weight in Kg	Closest Dose	125 mg	250 mg	500 mg
35-37	125	1		
38-62	250		1	
63-87	375	3		
88-112	500			1
113-132	625	1		1
> 132	625	1		1

Table 6-2 Dosing table for 10 mg/kg/d for deferasirox or placebo

Pt Weight in Kg	Closest Dose	125 mg	250 mg	500 mg
35-43	375	3		
44-56	500			1
57-68	625	1		1
69-81	750		1	1
82-93	875	3		1
94-106	1000			2
107-118	1125	1		2
119-131	1250		1	2
132	1375	3		2
> 132	1375	3		2

Table 6-3 Dosing table for 15 mg/kg/d for deferasirox or placebo

Pt Weight in Kg	Closest Dose	125 mg	250 mg	500 mg
35-37	500			1
38-45	625	1		1
46-54	750		1	1
55-62	875	3		1
63-70	1000			2
71-79	1125	1		2
80-87	1250		1	2
88-95	1375	3		2
96-104	1500			3
105-112	1625	1		3
113-120	1750		1	3
121-129	1875	3		3
130-132	2000			4
>132	2000			4

[redacted]

Table 6-4 Dosing table for 20 mg/kg/d for deferasirox or placebo

Pt Weight in Kg	Closest Dose	125 mg	250 mg	500 mg
35-40	750		1	1
41-46	875	3		1
47-53	1000			2
54-59	1125	1		2
60-65	1250		1	2
66-71	1375	3		2
72-78	1500			3
79-84	1625	1		3
85-90	1750		1	3
91-96	1875	3		3
97-103	2000			4
104-109	2125	1		4
110-115	2250		1	4
116-121	2375	3		4
122-128	2500			5
129-132	2625	1		5
> 132	2625	1		5

Table 6-5 Dosing table for 25 mg/kg/d for deferasirox or placebo

Pt Weight in Kg	Closest Dose	125 mg	250 mg	500 mg
35-37	875	3		1
38-42	1000			2
43-47	1125	1		2
48-52	1250		1	2
53-57	1375	3		2
58-62	1500			3
63-67	1625	1		3
68-72	1750		1	3
73-77	1875	3		3
78-82	2000			4
83-87	2125	1		4
88-92	2250		1	4
93-97	2375	3		4
98-102	2500			5
103-107	2625	1		5
108-112	2750		1	5
113-117	2875	3		5
118-122	3000			6
123-127	3125	1		6
128-132	3250		1	6
> 132	3375	3		6

[redacted]

Table 6-6 Dosing table for 30 mg/kg/d for deferasirox or placebo

Pt Weight in Kg	Closest Dose	125 mg	250 mg	500 mg
35	1000			2
36-39	1125	1		2
40-43	1250		1	2
44-47	1375	3		2
48-52	1500			3
53-56	1625	1		3
57-60	1750		1	3
61-64	1875	3		3
65-68	2000			4
69-72	2125	1		4
73-77	2250		1	4
78-81	2375	3		4
82-85	2500			5
86-89	2625	1		5
90-93	2750		1	5
94-97	2875	3		5
98-102	3000			6
103-106	3125	1		6
107-110	3250		1	6
111-114	3375	3		6
115-118	3500			7
119-122	3625	1		7
123-127	3750		1	7
128-131	3875	3		7
132	4000			8
> 132	4000			8

[redacted]

Table 6-7 Dosing table for 35 mg/kg/d for deferasirox or placebo

Pt Weight in Kg	Closest Dose	125 mg	250 mg	500 mg
35-37	1250		1	2
38-41	1375	3		2
42-44	1500			3
45-48	1625	1		3
49-51	1750		1	3
52-54	1875	3		3
55-59	2000			4
60-62	2125	1		4
63-66	2250		1	4
67-69	2375	3		4
70-73	2500			5
74-76	2625	1		5
77-80	2750		1	5
81-84	2875	3		5
85-88	3000			6
89-91	3125	1		6
92-94	3250		1	6
95-98	3375	3		6
99-101	3500			7
102-105	3625	1		7
106-108	3750		1	7
109-112	3875	3		7
113-116	4000			8
117-119	4125	1		8
120-123	4250		1	8
124-126	4375	3		8
127-130	4500			9
131-132	4625	1		9
> 132	4625	1		9

[redacted]

Table 6-8 Dosing table for 40 mg/kg/d for deferasirox or placebo

Pt Weight in Kg	Closest Dose	125 mg	250 mg	500 mg
35	1375	3		2
36-39	1500			3
40-42	1625	1		3
43-45	1750		1	3
46-48	1875	3		3
49-51	2000			4
52-54	2125	1		4
55-57	2250		1	4
58-60	2375	3		4
61-64	2500			5
65-67	2625	1		5
68-70	2750		1	5
71-73	2875	3		5
74-76	3000			6
77-79	3125	1		6
80-82	3250		1	6
83-85	3375	3		6
86-89	3500			7
90-92	3625	1		7
93-95	3750		1	7
96-98	3875	3		7
99-101	4000			8
102-104	4125	1		8
105-107	4250		1	8
108-110	4375	3		8
111-114	4500			9
115-117	4625	1		9
118-120	4750		1	9
121-123	4875	3		9
124-126	5000			10
127-129	5125	1		10
130-132	5250		1	10
> 132	5375	3		10

6.2 Treatment arms

Patients will be assigned to one of the two arms in a ratio of 2:1, deferasirox or matching placebo.

6.3 Patient numbering

Each patient in the study is uniquely identified by a 9 digit patient number which is a combination of his/her 4-digit center number and 5-digit subject number. The center number is assigned by Novartis to the investigative site. Upon signing the informed consent form, the patient is assigned a patient number by the investigator. At each site, the first patient is assigned patient number 00001, and subsequent patients are assigned consecutive numbers

[redacted]

(e.g., the second patient is assigned patient number 00002, the third patient is assigned patient number 00003). The investigator or his/her staff will contact the IVRS/IWRS and provide the requested identifying information for the patient to register them into the IVRS. The assigned patient number will be entered into the "Subject ID" field on the EDC data entry screen.

Should a patient screen fail, the patient number must be recorded as a screen failure in the IVRS/IWRS within 2 days of failing entry criteria. In addition, the Screening Log and Demography eCRFs should be completed for these patients. Any serious adverse events which occurred during screening and prior to randomization should be reported. Patient numbers will never be re-issued. A patient may be re-screened at the discretion of the investigator and assigned a new patient number.

6.4 Treatment assignment

At baseline (Day 1, Visit 3), all eligible patients will be randomized via IVRS/IWRS to one of the treatment arms. The investigator or his/her delegate will call or log onto the IVRS/IWRS that will assign a randomization number to the patient once a series of eligibility questions are confirmed by the investigator or his/her delegate. The randomization number will be used to link the patient to a treatment arm and will specify a unique medication number(s) for the first package(s) of study drug to dispense to the patient. The randomization number will not be communicated to the caller.

Randomization will be performed using the following procedure to insure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IVRS provider using a validated system that automates the random assignment of patient numbers to randomization numbers. The patient randomization list will be reviewed and approved by a member of the Biostatistics Quality Assurance Group.

The randomization numbers are linked to the different treatment groups, which in turn are linked to medication numbers. A separate medication randomization list will be produced by or under the responsibility of Novartis DSM using a validated system that automates the random assignment of medication numbers to medication packs containing each of the study drugs.

In the event that a patient is late for a regular scheduled visit, the visit week that should be followed and assessments that need to be recorded on the eCRF may vary. As a rule to follow, the time interval between the current scheduled "late visit" and the next scheduled visit should be divided in half. Should patients present themselves less than mid-way between visits (<15 days), the assessments that should be taken are those for the earlier visit. Should patients present themselves ≥15 days after the scheduled visit, then the previous visit should be skipped and the next scheduled visit should be performed. In any event, future scheduled study visits must be scheduled based on the date of randomization (baseline visit) not based on the date of the previous visit.

[redacted]

6.5 Treatment blinding

Patients, investigator staff, persons performing the assessments, and data analysts will remain blind to the identity of the study treatment from the time of randomization until database lock, using the following methods:

1. Randomization data are kept strictly confidential until the time of final database unblinding, and will not be accessible by anyone else involved in the study with the following exceptions:
   - Independent Data Monitoring Committee (DMC) on special request only.
   - Independent statistician and programmer reporting to the DMC,
   - Investigator and patient once a patient meets a non-fatal event which is confirmed by the Endpoint Adjudication Committee (EAC).
2. The identity of the study treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, and odor.

Unblinding will only occur in the case of patient emergencies (on a per-patient basis), for regulatory reporting, and at the conclusion of the study.

6.6 Treating the patient

6.6.1 Study drug/study treatment/active control administration

The patient will be instructed how to prepare his/her daily dose from the three tablet strengths of ICL670 or placebo available (125 mg, 250 mg, 500 mg). The dose will be assigned based on the patient's weight (detailed in Table 6-1 through Table 6-8). During the scheduled visits the investigator staff will identify the study drug package(s) to dispense to the patient by contacting the IVRS/IWRS and obtaining the medication number(s). The investigator will distribute the appropriate number of study drug bottles containing tablets of 125 mg, 250 mg and/or 500 mg to the patient, including spare medication.

Each time study medication is dispensed to the patient and/or the legal guardian the investigator will provide detailed instructions on how to prepare and administer the study drug properly according to Table 6-1 through Table 6-8.

6.6.1.1 Study drug administration

The study medication packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the treatment arms. Investigator staff will identify the study drug package(s) to dispense to the patient by contacting the IVRS/IWRS and obtaining the medication number(s). Immediately before dispensing the package to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique patient number. All drug kits assigned by the IVRS will be recorded in the IVRS.

ICL670 and matching placebo should be taken daily at least 30 minutes before food, if possible consistently at the same time every morning. The tablets may be dropped into bottled water, tap water, apple juice or orange juice and gently stirred for 1 to 3 minutes until completely dispersed. Tablets should not be dispersed in carbonated liquids. For daily doses

[redacted]

less than 1 g, the tablets should be dispersed in at least 100 ml (3.5 ounces), and for daily doses from 1 g to 3 g, the tablets should be dispersed in at least 200 ml (7 ounces). Following full disintegration of the tablets, the liquid should be consumed promptly. Any residue in the glass and/or on the stirrer should be dispersed in additional liquid and swallowed.

6.6.1.2 Study combination administration

There is no combination therapy in this protocol.

6.6.1.3 Placebo administration

Placebo will be administered in the same fashion as deferasirox.

6.6.1.4 Ancillary treatments

Any additional therapy aimed to treat iron overload during this trial (e.g. therapy with hydroxyurea, butyrate) is not allowed. Except for the study medication, no other iron chelation therapy will be administered while patients are receiving study treatment in this trial.

6.7 Permitted study drug adjustments

For patients who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to keep the patient on study drug. For example, if the patient is unable to tolerate the 10 mg/kg/day dose, the investigator may decrease the dose to 5 mg/kg/day. These changes must be recorded on the Dosage Administration Record (DAR) eCRF and IVRS/IWRS. For safety concerns, the investigator may titrate study drug dose at any time during the trial.

As outlined below, study drug dose adjustments or interruptions will be implemented for specific changes in patient weight, serum ferritin, serum creatinine, ALT/AST and skin rash. In such cases, the change must always be recorded on the DAR eCRF.

The majority of dose adjustments are covered in the Section 6.7.1 below. For cases where an exceptional dose adjustment (i.e., an adjustment not covered in the following sections) is considered necessary, the investigator will send a written request to Novartis. The request must justify the dose change and provide all the supportive clinical and laboratory information for complete evaluation by Novartis. Any exceptional dose adjustment for deferasirox needs to be authorized by Novartis. A written reply will be sent back to the investigator by Novartis within 5 working days.

6.7.1 Dosing modifications

6.7.1.1 Change in patient's weight

The dose of study drug will only be recalculated using Dosing Table 6-1 through Table 6-8 during the study if the change (increase or decrease) in body weight exceeds 10% of the weight compared to the randomization visit.

[redacted]

6.7.1.2 Change in serum ferritin (SF)

Serum ferritin should be monitored monthly, and the dose adjusted every 3 months according to serum ferritin trends. Dose adjustments should be made in steps of 5 or 10 mg/kg/day to achieve the desired rate of reduction or maintenance of iron burden. As patients reach a target serum ferritin level (usually between 500 and 1000 mcg/L) the dose can be reduced by 50% to maintain the serum ferritin within the target range. For most patients, maintenance dose will be between 10-20 mg/kg/day.

If serum ferritin falls to ≤500 mcg/L, the investigator should consider an interruption of study medication until serum ferritin rises above 500 mcg/L according to the transfusion requirement.

Dose may be increased by 5 or 10 mg/kg/day (to a maximum of 40 mg/kg/day) for patients with:

1. Ferritin > 500 mcg/L who have an increasing trend of ferritin after a minimum of 3 months of treatment.
2. Ferritin > 1000 mcg/L who fail to have a decrease in ferritin after a minimum of 3 months of treatment.

Dose must not be increased higher than 40 mg/kg/day.

If after dose reduction, a progressive increase in serum ferritin is observed, study drug may be discontinued if the investigator believes it is in the best interest of the patient. Novartis may be contacted by the investigator to discuss dosing options that fall within the protocol guidelines if the investigator so desires.

6.7.1.3 Elevations in serum creatinine

For patients who develop an increase in serum creatinine ≥33% above their baseline value (the mean value established at screening Visits 1 and 2) resulting in a serum creatinine above the ULN, on two consecutive occasions, a minimum of 7 days apart, the daily dose will be reduced by 10 mg/kg (or 5 mg/kg in patients receiving 10 mg/kg).

If, after a dose reduction, serum creatinine remains above the ULN, a second dose reduction or treatment interruption is recommended. After an interruption, if serum creatinine falls below the age appropriate ULN on two consecutive visits, the investigator may resume therapy at 50% of the last dose and escalate cautiously.

Serum creatinine should be monitored weekly, preferably by local labs, for the first month after study drug initiation or dose modification. Results of these labs need to be entered into the CRF only if they are significantly abnormal, defined as at least a 33% increase over the baseline value.

If after dose reduction, a progressive increase in serum creatinine is observed, study drug may be discontinued if the investigator believes it is in the best interest of the patient. Novartis may be contacted by the investigator to discuss dosing options if the investigator so desires.

Caution should especially be used in patients with creatinine clearance between 40 and less than 60 mL/min, particularly in cases where there are additional risk factors that may impair renal function such as concomitant medications, dehydration, or severe infections.

[redacted]

Study medication should be discontinued in case serum creatinine increases >2 times the age-appropriate upper limit or if creatinine clearance <40 mL/min.

6.7.1.4 Gastrointestinal disturbances

Patients with gastrointestinal symptoms (including abdominal pain, nausea, vomiting, diarrhea) and/or patients who are unable to tolerate once a day study drug dosing, the following can be tried, in the order specified below:

- Change the timing of study drug administration from morning to evening and in addition, try using an anti-diarrheal agent for 2 days in case of diarrhea.
- If the symptoms still continue, try administering the daily dose as a split dose b.i.d.(twice daily). Once symptoms resolve, b.i.d. should be switched back to once daily.

Should the gastrointestinal issues persist, study drug may be discontinued if the investigator believes it is in the best interest of the patient. Novartis may be contacted by the investigator to discuss dosing options if the investigator so desires.

6.7.1.5 Increased proteinuria

For patients who develop proteinuria or a worsening of pre-existing proteinuria (assessed by a dipstick) at any visit, urine samples should be collected and assessed by the central laboratory.

If any other causes of proteinuria have been excluded, the dose should be reduced by 50%.

Should the proteinuria persist, study drug may be discontinued if the investigator believes it is in the best interest of the patient. Novartis may be contacted by the investigator to discuss dosing options if the investigator so desires.

6.7.1.6 Skin rash

6.7.1.6.1 Stevens-Johnson syndrome

Severe skin reactions, including Stevens-Johnson syndrome (SJS), have been reported during Exjade therapy.

If SJS is suspected, study treatment must be immediately discontinued and not be reintroduced.

6.7.1.6.2 Skin Rash (other than SJS)

For skin rash of mild/moderate severity (defined as those causing minimal symptoms which require no or minimal supportive treatment), study drug should be continued without dose adjustment. The skin rash may resolve spontaneously without further intervention.

If the rash persists for >1 week or becomes more severe, hold study drug. After the rash resolves, resume study drug at 50% of the patient's dose level before the skin rash. If the rash does not recur after 2 weeks, increase the dose back to 100%.

For a severe rash (distressing symptoms requiring discontinuation and/or systemic steroids), discontinue treatment until resolution of rash. Once the rash has resolved, resume at 50% of patient's dose. If necessary, a brief course of oral steroids may be given concurrently with

resumption of study drug. If the rash does not recur, increase by 5mg/kg/day increments every 2 weeks until 100% of patient's dose is achieved.

If the rash recurs, study drug may be discontinued if the investigator believes that it is in the best interest of the patient. Novartis may be contacted by the investigator to discuss dosing options if the investigator so desires.

6.7.1.7 Liver function abnormalities

Recommended dose modifications for changes in ALT or AST will be based on the patient's baseline ALT/AST . The baseline ALT/AST value is defined as the mean of the Visit 1 and Visit 2 values.

For patients with a baseline ALT/AST > ULN, study drug will be interrupted if the ALT/AST increases to > 5 × baseline ALT/AST or > 10 x ULN.

For patients with a normal baseline ALT/AST, study drug will be interrupted if the ALT/AST increases to > 5 × ULN.

After drug interruption, the investigator should recheck ALT/AST bi-weekly until ALT/AST return to the values prior to the elevation. The study drug may then be restarted at 50% of the dose used before the ALT/AST elevation.

ALT/AST should be monitored bi-weekly for the first month after restarting the drug. Dose escalation to the original dose may be instituted after 1 month of treatment with 50% of the dose if the re-challenge is not associated with ALT/AST elevations.

Study drug will be interrupted if elevation of serum total bilirubin to > 2.0 mg/dL.

Should a subsequent progressive rise in ALT/AST to greater than 5 × baseline occur, study drug may be discontinued if the investigator believes that it is in the best interest of the patient. Novartis may be contacted by the investigator to discuss dosing options if the investigator so desires.

In patients who develop moderate hepatic impairment (Child-Pugh Class B) during the study, the study medication will be interrupted and patient monitored. If liver disease prognosis improves, study medication can be reintroduced at 10 mg/kg/day or 50% of previous dose, whichever is less. While monitoring continues, dose may be increased by 5 mg/kg/day every 2 weeks to a maximum of 50% of patient's previous dose if the investigator determines that dose increase is in the best interest of the patient. **Study medication must be used with caution in such patients.** In patients who develop severe hepatic impairment (Child-Pugh Class C) during the study, study medication must be discontinued.

6.7.1.8 Dose modification criteria for auditory (decreased hearing) and ocular (lens opacities) disturbances

Auditory (decreased hearing) and ocular (lens opacities) disturbances have been reported with deferasirox treatment. Auditory and ophthalmic testing (see Section 7.5.4) is recommended before the start of deferasirox treatment and at regular intervals thereafter (every 12 months). If disturbances are noted, dose reduction or interruption may be considered and a repeated testing performed as per investigator's judgment.

[redacted]

6.7.1.9 Dose modification criteria for hypersensitivity reactions

Cases of serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been reported in patients receiving deferasirox, with the onset of the reaction occurring in the majority of cases within the first month of treatment. If reactions are severe, deferasirox should be discontinued and appropriate medical intervention instituted.

6.7.1.10 Dose modification criteria for cytopenias

There have been post-marketing reports (both spontaneous and from clinical trials) of cytopenias in patients treated with deferasirox. Most of these patients had pre-existing hematological disorders that are frequently associated with bone marrow failure. The relationship of these episodes to treatment with deferasirox is uncertain. In line with the standard clinical management of such hematological disorders, blood counts should be monitored regularly. Interruption of treatment with deferasirox should be considered in patients who develop unexplained cytopenia. Reintroduction of therapy with deferasirox may be considered (as per investigator decision), once the cause of the cytopenia has been identified.

6.7.2 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an AE or abnormal laboratory value must be followed at least once a week for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilization of the event, whichever comes first. If treatment is permanently discontinued, all patients will continue to be followed for safety and endpoints during the evaluation period at visits occurring 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 every 6 months for iron chelation therapies and overall survival ("Survival Follow-up").

6.7.3 Rescue medication

The use of rescue medication is not permitted during this study.

6.7.4 Other concomitant medications

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug must be listed on the appropriate eCRF page.

The treatment of concomitant medical conditions with non-investigational medications during the study may be continued with the exception of other chelating agents.

The following concomitant medications may be permitted for use while patient is on study and information outlining start date(s) and end date(s) of each medication taken must be recorded on the appropriate eCRF:

[redacted]

- Erythropoietin (growth factor)
- G-CSF (growth factor)
- GM-CSF (growth factor)
- Azacitidine
- Thalidomide
- Arsenic trioxide
- Lenalidomide
- Decitabine
- Cyclosporine A
- Vitamin C supplements (≤ 200 mg/day)

Any investigational drug other than study medication is NOT allowed during the study. After permanent discontinuation of the randomized study medication, the use of commercially available iron chelation therapies is allowed.

6.7.4.1 Concomitant therapy requiring caution and/or action

Caution must be exercised in patients who are taking study drug in combination with the following drugs:

- The concomitant administration of deferasirox and vitamin C has not been formally studied. Doses of vitamin C up to 200 mg/d have not been associated with adverse consequences.
- Aluminum containing antacid therapies should be avoided because they may bind to deferasirox
- Concomitant administration of deferasirox with drugs that have known ulcerogenic potential, such as NSAIDs, corticosteroids, or oral bisphosphonates, and use of deferasirox in patients receiving anticoagulants may increase the risk of gastrointestinal irritation and bleeding
- Deferasirox, as a weak CYP3A4 inducer, may potentially decrease serum levels of substances metabolized through CYP3A4 (e.g. cyclosporin, simvastatin, hormonal contraceptive agents)
- Deferasirox is a moderate inhibitor of CYP2C8 and therefore it may increase serum concentrations of substances metabolised through CYP2C8 (e.g repaglinide, paclitaxel)
- Concomitant administration of deferasirox with CYP1A2 substrates that have a narrow therapeutic index (e.g. theophylline, clozapine, tizanidine), is not recommended. When deferasirox and theophylline are used concomitantly, monitoring of theophylline concentration and theophylline dose reduction should be considered.
- The concomitant use of deferasirox with potent UGT (Uridine 5'-diphospho-glucuronosyltransferase) inducers (e.g. rifampicin, phenytoin, phenobarbital, ritonavir) may result in a decrease in deferasirox efficacy.
- Concomitant use of bile acid sequestrants (e.g., cholestyramine, colesevelan, colestipol) that decrease deferasirox systemic exposure should be avoided.

[redacted]

6.7.5 Study drug discontinuation

Patients who discontinue study drug entirely before completing the study should be scheduled for the End of Treatment visit as soon as possible, at which time all of the assessments listed for Study End of Treatment visit will be performed. This will document the date and reason for stopping randomized study treatment. It must be completed for all patients. Any safety finding that leads to discontinuation of study drug should be captured on the AE eCRF.

All patients who discontinue study drug, including those who refuse to return for a final visit, will be contacted by the investigational site for safety evaluations during the 28 days following the last dose of study drug. All patients must have the 28 Day Follow-Up completed after they discontinue from the study drug.

All iron chelation therapies given to a patient after the last dose of study treatment must be recorded in the 'Chelation therapies given since discontinuation of study drug' eCRF during the 28 day follow up, Evaluation and Survival phases of the study. Patients who discontinue study drug and do not wish to be followed for post-treatment evaluations and survival should be considered withdrawn from the study after the final visit assessments are performed or when it is clear that the patient will not return for these assessments. The End of Treatment eCRF should be completed and the Study Evaluation Completion visit should be performed at this time.

All patients must be followed for AEs and SAEs for 28 days after the last dose of study treatment. Patients lost to follow up should be recorded as such on the Study Evaluation Completion eCRF. If the patient is at the end of treatment, the End of Treatment eCRF must also be completed. For patients who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

The investigator must contact IVRS/IWRS to register discontinued patients.

6.7.5.1 Discontinuation of study treatment after an event contributing to the primary endpoint

The end of study treatment visit may occur if a patient meets any non-fatal component of the composite primary endpoint (confirmed by the EAC). His/her individual randomized study treatment will be unblinded and discontinued at that time via IVRS/IWRS. The unblinded information will only be shared with the investigator and patient. The subsequent iron chelation treatment is subject to the patient's and the investigator's decision. After termination of study treatment, all patients will continue to be followed for safety and non-fatal components of the primary endpoint during the evaluation period at visits occurring 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 every 6 months for iron chelation therapies and overall survival ("Survival Follow-up").

[redacted]

6.7.5.2 Discontinuation of study treatment without an event contributing to the primary endpoint

For patients who do not meet a non-fatal component of the composite primary endpoint, study treatment will continue as long as the patient and treating physician feel it is in the best interest of the patient, or until the study terminates. There is no planned unblinding for patients who terminate study treatment without meeting a non-fatal component of the composite primary endpoint. After termination of study treatment, all patients will continue to be followed for safety and endpoints during the evaluation period at visits occurring 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 every 6 months for iron chelation therapies and overall survival ("Survival Follow-up").

6.7.6 Premature patient withdrawal

Patients may voluntarily withdraw from the study for any reason at any time. Patients may be dropped from the study at the discretion of the investigator at any time. They may be considered withdrawn if they fail to return for visits, or become lost to follow up for any other reason. Patients must be withdrawn from the study if any of the following occur: discovery of not having been randomized, unwillingness to comply with procedures as outlined in the study protocol, female patient pregnancy, or withdrawal of informed consent.

If such withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the Study Evaluation Completion eCRF and notify IVRS.

6.7.6.1 End of Treatment

If study drug is discontinued, IVRS is to be notified and the End of Treatment Page is to be completed with the 'last known date the patient took study drug' and one of the following reasons:

- Adverse Event
- Abnormal laboratory value(s)
- Abnormal test procedure result(s)
- Protocol deviation
- Subject withdrew consent
- Lost to follow-up
- Administrative problems
- Death
- Disease progression
- Pregnancy
- Physician's decision
- Treatment duration completed as per protocol
- Subject / Guardian Decision

[redacted]

- Study terminated by sponsor

6.7.6.2 Study evaluation completion

At the end of the study evaluation period, the Study Evaluation Completion Page is filled out for all patients with the following options:

- Adverse event(s)
- Disease progression
- Pregnancy
- Protocol deviation
- Study terminated by sponsor
- Physician's decision
- Patient withdrew consent
- Lost to follow-up
- Administrative problems
- Death
- Subject / Guardian Decision

For patients who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

6.7.7 Emergency unblinding of treatment assignment

Emergency unblinding should only be undertaken when it is essential for effective treatment of the patient. Most often, study drug discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency code breaks are performed using the IVRS. When the investigator contacts the IVRS/IWRS to unblind a patient, he/she must provide the requested patient identifying information and confirm the necessity to unblind the patient. The investigator will then receive details of the drug treatment for the specified patient and a fax confirming this information. The system will automatically inform the Novartis monitor for the site and the Clinical Trial Head that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IVRS in case of emergency. The investigator will inform the patient how to contact his/her backup in cases of emergency when he/she is unavailable. The protocol number, study drug name if available, patient number and instructions for contacting the local Novartis CPO (or any entity to which it has delegated responsibility for emergency code breaks) will be provided to the patient in case emergency unblinding is required at a time when the investigator and backup are unavailable.

7 Visit schedule and assessments

Following registering in IVRS/IWRS for screening, patient eligibility will be checked once all screening procedures are completed. The eligibility check will be embedded in the IVRS/IWRS system. Detailed guidelines to be followed can be found in the IRT manual.

Table 7-1 lists all of the assessments and indicates with an "X" the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation. Assessments such as laboratory data, ECG, ECHO and assessments by the EAC will be transferred to the database electronically.

[redacted]

Table 7-1 Visit evaluation schedule

	Screening		Randomization	Treatment Period															Week 372[a] End of Treatment	28-day Follow Up[b]	Evaluation[c] Period	Study Evaluation Completion	Survival[d] Follow-Up
Visit	**1**	**2**	**3[e]**	**4[f]**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18-96**	**777**	**501**	**502, 503, etc.**	**778**	**701, 702, etc.**
Week[18]	**-5 to -1**		**Day 1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56--368**	**372**				
Informed consent [g]	X																						
Inclusion/exclusion criteria	X																						
Randomization			X																				
Medical history	X																						
Physical examination[e]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
Weight	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
Height	X																						
Hemoglobin/Transfusion/RBC History[1]	X																						
Bone Marrow[2,3,4]	X		X																				
ECG[5]	X						X			X			X				X	X	X		X	X	
ECHO[5]	X						X			X			X				X	X	X		X	X	
Chest X-ray[6]			X	X																			
Abdominal Ultrasound/liver biopsy[7]	X		X																				
Ocular Exam[8]	X																X	X	X		X	X	

[redacted]

	Screening		Randomization	Treatment Period															Week 372[a] End of Treatment	28-day Follow Up[b]	Evaluation[c] Period	Study Evaluation Completion	Survival[d] Follow-Up
Visit	**1**	**2**	**3[e]**	**4[f]**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18-96**	**777**	**501**	**502, 503, etc.**	**778**	**701, 702, etc.**
Week[18]	**-5 to -1**		**Day 1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56--368**	**372**				
Audiometry[8]	X																X	X	X		X	X	
Hematology	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
BNP[9]			X	X[9]																			
Reticulocyte Count	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
Biochemistry	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
Hepatitis Viral Serology	X																						
Serum Ferritin[10]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
Serum Creatinine[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
Creatinine Clearance [12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
ALT/AST	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
Direct/Indirect/Total Bilirubin	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
TSH/Free T_4 [13]	X																	X	X		X	X	
OGTT[17]	X																	X	X		X	X	
Serum pregnancy test[16]	X																						
Urine dipstick[14]	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
Microscopic urine[14]					X[14]																		
Urine creatinine/ Protein total urine/ urinary protein ratio[14]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
Urine Pregnancy[16]																			X				

[redacted]

	Screening		Randomization	Treatment Period															Week 372[a] End of Treatment	28-day Follow Up[b]	Evaluation[c] Period	Study Evaluation Completion	Survival[d] Follow-Up
Visit	**1**	**2**	**3[e]**	**4[f]**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18-96**	**777**	**501**	**502, 503, etc.**	**778**	**701, 702, etc.**
Week[18]	**-5 to -1**		**Day 1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56--368**	**372**				
Transfusions[15]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
Concomitant medication	X		Continuous →																				
Drug Dispensing			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Overall Survival																					X	X	X[d]
Iron Chelation Therapy																				X	X	X	X
Adverse events																				X			

a. Week 372 End of Treatment: The recruitment period is planned to last until December 2014. The study duration will be up to 3 years after the last patient is enrolled.

b. Follow up must occur 28 days after the last dose of study treatment for adverse event reporting/follow up and chelation therapy reporting

c. Evaluation Period: Patient evaluation required every 3 months after study treatment discontinuation.

d. Survival Follow Up: Patient follow up required every 6 months after study discontinuation.

e. Visit 3.01: At Week 1, Serum Creatinine is drawn and Creatinine Clearance is calculated

f. Visit 4.01: At Week 3, Serum Creatinine is drawn and Creatinine Clearance is calculated

g. Captured in Source Documentation only

1. Hemoglobin/Transfusion History: collect retrospective data for the 6 months prior to study entry
2. Bone marrow for cytogenetics and morphology is not required if the exam has been completed within 6 months of the screening date and the patient has been hematologically stable. Patients with a major hematological response per IWG criteria (Post Text Supplement 4) may undergo an additional bone marrow biopsy or aspiration plus bone marrow examination at the time of response if in the opinion of the investigator the information may be helpful in the management of the patient. Bone marrow examination should also be performed if the patient is suspected to have had an AML progression.
3. Bone marrow aspirate should include cytogenetics and morphology
4. Repeat bone marrow aspiration and cytogenetics, iron stains and biopsy recommended at the time of hematological improvement per IWG criteria (Post Text

[redacted]

	Screening		Randomization	Treatment Period															Week 372[a] End of Treatment	28-day Follow Up[b]	Evaluation[c] Period	Study Evaluation Completion	Survival[d] Follow-Up
Visit	**1**	**2**	**3[e]**	**4[f]**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18-96**	**777**	**501**	**502, 503, etc.**	**778**	**701, 702, etc.**
Week[18]	**-5 to -1**		**Day 1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56--368**	**372**				

Supplement 4). Bone marrow examination should also be performed if the patient is suspected to have experienced disease progression.

5. ECG and ECHO will be performed at screening and approximately every 3 months (Weeks 12, 24, 36, 52, 64, 76, 88, 104, 116, 128, 140, 156, 168,180,192,208 220, 232, 244, 260, 272, 284, 296, 312, 324, 336, 348, 364, 372). Patients in the Evaluation Period will have ECGs, ECHOs performed approximately every 3 months
6. Chest x-ray to be performed at baseline and for any hospitalization related to CHF (pulmonary edema)
7. Liver Ultrasound will be performed at Screening Visit 1 and anytime during the trial if liver function impairment or liver cirrhosis is suspected. Liver biopsy will be performed if abdominal ultrasound results indicated liver damage/failure and there are no contraindications, then liver biopsy is recommended
8. Ocular and Audiometry examinations must be performed at screening, should a patient have evidence at the screening visit that the examination(s) were performed 6 months prior to screening then the examination(s) do not need to be repeated. The examination(s) can be performed at any time at the investigators discretion if symptomatically/clinically indicated, otherwise ocular and audiometry exams should be performed annually. The ocular and audiometry exams should be performed annually during the Evaluation Period.
9. Brain natriuretic peptide (BNP) blood sample should be obtained at baseline and at any time during the study when there is evidence of CHF
10. Serum ferritin: Two samples at screening done at least 14 days apart. If a transfusion is scheduled, draw serum ferritin PRIOR to transfusion or two weeks post-transfusion. The serum ferritin samples should be obtained in the absence of known infection.
11. Serum creatinine will be measured at Screening Visit 1 and Screening Visit 2 and the mean value will be used for eligibility criteria. Serum creatinine will also be measured weekly between the randomization visit and Week 4 visit. For the first month after initiation or modification of dose, labs may be obtained locally until the subject's next scheduled visit. Local labs need only be included on the eCRF in the case of a result that is a 33% increase greater than baseline result.
12. Creatinine clearance will be calculated by the central laboratory at every visit.
13. TSH and Free T4 will be measured at screening, annually and at study treatment discontinuation. TSH and Free T_4 should be performed annually during the Evaluation Period.
14. At screening Visit 1 and 2 a urine sample (at least 15 ml) will be collected and sent to the central laboratory for urinary protein and urinary creatinine to assess the eligibility of the patient. Microscopic analysis will be performed only in case of positive dipstick. Dipsticks will be supplied by the central lab. Proteinuria (urinary protein /creatinine ratio) at Visit 1 and Visit 2 (screening) and then monthly during study.

[redacted]

	Screening		Randomization	Treatment Period															Week 372[a] End of Treatment	28-day Follow Up[b]	Evaluation[c] Period	Study Evaluation Completion	Survival[d] Follow-Up
Visit	**1**	**2**	**3[e]**	**4[f]**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18-96**	**777**	**501**	**502, 503, etc.**	**778**	**701, 702, etc.**
Week[18]	**-5 to -1**		**Day 1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56--368**	**372**				

15. Transfusions may be administered as necessary throughout the study and number and volume (ml) of PRBC and platelets administered are to be recorded in eCRF.
16. Required for Females of child bearing potential only.
17. A 2 hour fasting Glucose Tolerance test will be done at screening and annually (Weeks 52, 104, 156, 208, 260, 312, 364) and at study treatment discontinuation. Patients should fast for at least 5 hours prior to the test being drawn. Should a patient have a documented diagnosis of diabetes requiring treatment with medication, the Glucose Tolerance Test is not mandatory and is up to the Investigator's discretion. The Glucose Tolerance Test should be performed annually during the Evaluation Period.
18. Visit Windows: The following visit windows are permitted: ±3 days Weeks 2 & 4; ±7 days for every monthly visit (Weeks 8, 12, 16, 20 through EOT); ±2 weeks for Evaluation and Survival Follow-Up visits

[redacted]

7.1 Information to be collected on screening failures

A screening log of all patients screened for this study, at each study center, will be kept. This log will include patient number, demographic details, and reason why the patient was a screen failure. Sites should also maintain pre-screening logs capturing all of the reasons why a patient was not eligible for screening. The following information of patients who are screened but fail to be randomized will be collected in the eCRF: demographics, screening log and serious adverse events.

Should a patient screen fail but subsequently become eligible by newly meeting entry criteria resulting from a change in their parameters or due to a protocol amendment, patients may be re-screened. All screening labs outlined in Screening Visit 1 and Screening Visit 2 must be repeated. All other procedures (ECHO, abdominal ultrasound, bone marrow biopsy or aspiration, ocular and audiometery examinations, etc.) do not need to be repeated if they have been performed within 6 months of the original screening visit date.

7.2 Patient demographics/other baseline characteristics

At Visits 1 and/or 2, data will be collected on patient characteristics including demographic information (age, sex, ethnicity, etc.), other background or relevant medical history/current medical condition (6 months) prior to study entry: hemoglobin and transfusion history, disease history, vital signs, previous iron chelation therapies).

Other assessments done for the purpose of determining eligibility for the study include IPSS, history of HIV positive test result (ELISA or Western Blot), active hepatitis B and/or C, urinalysis, ALT/AST, serum creatinine, serum ferritin, serum pregnancy test, other biochemistry studies, echocardiography, bone marrow history/examination.

7.3 Treatments

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

Compliance will be assessed by the investigator and/or study personnel at each visit using tablets/vial counts and information provided by the patient or the caregiver. This information should be captured in the source document at each visit, and also entered on the appropriate eCRF. Concomitant medications/significant non-drug therapies both prior to start of study drug and after start of study drug will be assessed and thus have to be recorded in the eCRF.

Information collected on the Concomitant Medications/Significant Non-drug Therapies eCRF will include concomitant medications/significant non-drug therapy, reason for the medication/therapy, start date, and end date.

The number of tablets of study medication of each strength (125 mg, 250 mg, 500 mg) dispensed will be recorded during the study in the source documents using a drug dispensing log (see [Post-text supplement 2]) and Drug Compliance eCRF. Empty bottles and unused medication will be returned by the patient to the study site. Unused study medication tablets will be counted and recorded by the investigator/pharmacist/study staff involved in the study, according to local legal requirements.

[redacted]

7.4 Efficacy

7.4.1 Composite primary endpoint

The primary objective is to evaluate deferasirox and placebo with regard to event-free survival (including death and non-fatal events related to cardiac and liver function and transformation to AML). The EAC will evaluate the criteria for the composite primary efficacy endpoint on an ongoing basis.

The composite primary endpoint (event-free survival) consists of both death and non-fatal events. Non-fatal events include worsening cardiac function based on echocardiographic evidence, hospitalization for congestive heart failure, liver function impairment reflected by elevated ALT or AST and bilirubin values, confirmed liver cirrhosis, and transformation to AML. Details regarding the components of the composite endpoint are described in Section 7.5.7, Section 7.5.10 and Section 7.5.11.

7.5 Safety

Safety assessments will consist of monitoring and recording all AEs and SAEs, laboratory safety assessments (hematology, blood chemistry and urinalysis) and clinical evaluations (physical examinations, vitals signs, body weight, auditory and ocular tests, ECG) as outlined in Table 7-1.

7.5.1 Adverse events

An adverse event for the purposes of this protocol is the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) occurring after signing the informed consent even if the event is not considered to be related to the study drug(s). However, it must be noted that MDS is not considered an adverse event. MDS is a required condition for study entry and is expected to be reported as Medical History for all patients. Time to disease progression is a secondary efficacy endpoint. Please refer to Section 6.1 for the protocol-specific definitions of study drug and study treatment.

Adverse events (but not serious adverse events) occurring before starting study treatment but after signing the informed consent form are recorded on the Medical History/Current Medical Conditions eCRF. Abnormal laboratory values or test results that induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., any hematological abnormality that requires transfusion or cytokine treatment), or interruption of study medication should be recorded on the Adverse Events eCRF under the signs, symptoms or diagnosis associated with them. Abnormal Laboratory values that do not meet this criteria are not reported as Adverse Events. SAEs occurring after signing the Informed Consent are recorded on the Adverse Event eCRF.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (mild, moderate, severe)
2. Its relationship to deferasirox (suspected/not suspected)

[redacted]

3. Its duration (start and end dates or if continuing at final examination)
4. Action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
5. Whether it is serious, where a serious adverse event (SAE) is defined as one which:
    - Is fatal or life-threatening
    - Results in persistent or significant disability/incapacity
    - Constitutes a congenital anomaly/birth defect
    - Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
        - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
        - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
        - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an SAE given above and not resulting in hospital admission
        - Social reasons and respite care in the absence of any deterioration in the patient's general condition
    - Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 8.1.

All adverse events should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an adverse event is detected, it should be followed until its resolution, an assessment should be made at each visit (or more frequently, if necessary) of any changes in its severity, its suspected relationship to the study drug(s), any of the interventions required to treat it, and its outcome.

Information about common side effects already known about the investigational drug can be found in the [Investigators' Brochure] or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

7.5.2 Physical examination, weight, height

A physical examination will be performed as outlined in Table 7-1. The physical examination at the randomization visit will serve as the baseline physical examination for the entire study. The exam will entail an examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities and nervous system.

[redacted]

Information about the physical examination must be present in the source documentation at the study site. Significant findings that are present prior to the start of the study drug (randomization visit) must be included in the Relevant Medical History/Current Medical Conditions eCRF page. Significant findings made after the start of study drug which meet the definition of an AE must be recorded in the Adverse Event eCRF summary page.

All subjects will have standing height measured at the screening visit(s). This height measurement must be captured in the eCRF. Body weight will be recorded in all patients at screening, then at every clinic visit and captured on the eCRF. Weight should be measured while the patient is wearing ordinary clothing without shoes.

7.5.3 Vital signs

Vital sign determinations are of sitting blood pressure, heart rate, respiratory rate, and body temperature and are taken as outlined in Table 7-1. Systolic and diastolic blood pressure and pulse rate is to be measured after the patient has rested in the sitting position for at least 3 minutes. Blood pressure should be assessed using the same arm at each visit. All measurements will be recorded in metric units when applicable. All vital sign measurements should be recorded on the appropriate eCRF for every visit.

7.5.4 Auditory and ocular examination

Patients will undergo auditory and ocular examinations as outlined in Table 7-1.

If a patient had an auditory or ophthalmologic exam 6 months prior to the screening Visit 1 and the test results are available, then these tests will not need to be re-done at screening.

The auditory examination include the following assessments:

- Comprehensive audiometry threshold examination
- Speech recognition

The ophthalmologic examination include the following assessments:

- Visual acuity test (refraction)
- Tonometry
- Slit lamp exam of anterior segment
- Slit lamp exam of the lens
- A fundoscopic and retinal examination

Information about the audiometry and ocular examinations must be present in the source documentation at study site and will be captured on the eCRF. Significant findings of the audiometry and ocular examinations that meet the definition of an AE must be recorded in the AE summary page of the eCRF. Significant findings at the Screening visit will be reported as Medical History.

7.5.5 Laboratory evaluations

A certified central laboratory will be utilized to process and provide results for the clinical laboratory tests summarized in Table 7-2. The central laboratory chosen for this study will provide instructions regarding the collection, processing and shipment of appropriate samples.

[redacted]

For first month after study drug initiation or dose modification, labs may be obtained locally until the subject's next scheduled visit. Local lab results only need to be entered on the eCRF in the event that the result demonstrates a significant change from baseline. A significant change in serum creatinine is defined as an increase of 33% greater than the baseline result. A significant change for ALT/AST/Total Bilirubin is defined as an increase of 2× the baseline value. For any other laboratory assessment, it is up to the Investigator's opinion if a laboratory result represents a significant abnormality. In the event that a local laboratory is used for assessing patient samples for trial purposes, the site/CRA must complete and submit the Novartis Local Laboratory Normal Ranges (LNR) form to the Data Manager.

7.5.5.1 Hematology

Safety laboratory parameters will be monitored as outlined in Table 7-1.

7.5.5.2 Biochemistry

Blood samples will be sent to the central laboratory as outlined in Table 7-1.

During the first month of treatment, serum creatinine will be measured weekly and preferably via local laboratory assessment. From Week 4 through-End of treatment, serum creatinine levels will be checked at every routine clinic visit. The central laboratory will calculate the creatinine clearance at every visit.

Serum ferritin test will also be performed at screening (Visit 1 and Visit 2) to assess the eligibility of the patient and should be drawn at least 14 days apart. The baseline serum ferritin value is defined as the average of the two measurements obtained during the screening period. Serum ferritin testing will also be performed at every visit starting at week 2 (Visit 4) . Samples should be obtained in the absence of known inflammation or infection. If transfusion is scheduled, blood should be drawn for serum ferritin collection prior to transfusion or two weeks post-transfusion. Results will be provided to the sites within 24 hours after the central laboratory receives the sample.

7.5.5.3 Urinalysis/proteinuria

At screening (Visit 1 and 2) a urine sample (at least 15 ml) will be collected and sent to the central laboratory for urinary protein and urinary creatinine to assess the eligibility of the patient. First morning void samples should not be used for this analysis. Significant proteinuria is indicated by a urinary protein/creatinine ratio > 0.5 mg/mg.

For patients who develop proteinuria or a worsening of pre-existing proteinuria (assessed by a dipstick) at any visit, urine samples should be collected and urine protein assessed by the central laboratory. If any other causes of proteinuria have been excluded, the dose should be reduced by 50%. Should the proteinuria persist, study drug may be discontinued if the investigator believes it is in the best interest of the patient. Novartis may be contacted by the investigator to discuss dosing options if the investigator so desires.

At a frequency outlined in Table 7-1, a midstream, non-first voided urine sample will be obtained. Specific gravity, pH, blood, glucose, protein, bilirubin, ketones, and leukocyte esterase should be assessed. Microscopic analysis will be performed only in case of positive dipstick. Dipsticks will be supplied by the central lab.

7.5.5.4 Transfusion requirements, hematologic counts

Transfusions (i.e. number and volume (ml) of PRBC and platelets administered during the course of the study) will be recorded in the appropriate transfusion eCRF.

For a 6 month period prior to randomization, detailed platelet and PRBC transfusionrecords, and hemoglobin levels associated with these transfusions will be collected. During this time period, complete blood counts (CBCs) must be available. These data will be used to establish baseline transfusion frequency and hematologic counts.

At each visit during the trial beginning at week 2, the number of units of PRBCs administered since the prior study visit will be recorded.

Complete blood counts will be drawn as outlined in Table 7-1.

7.5.5.5 Pregnancy test

All female patients capable of becoming pregnant will have a pregnancy test (serum β-HCG) at screening visit 1. When performed at screening, the results of the test must be available prior to initiating treatment with any study medication. Positive pregnancy tests will exclude a patient from participating in this trial.

Urine pregnancy testing will be performed locally at the End of Treatment visit and if menses are delayed for more than 7 days in a female patient capable of becoming pregnant. See Section 8.2 for procedures to report pregnancy.

Table 7-2 Laboratory evaluations

Evaluation	Sample collection	Analysis	Collection Time-point
Hematology (CBC)	4 mL blood	Hemoglobin, RBC, MCV, hematocrit, WBC count with differential, and platelet count	Screening Visit 1, Weeks 2-Visit 778
Biochemistry	8.5 mL blood	Sodium, potassium, chloride, BUN/Urea, *Creatinine, glucose, calcium, phosphorous, total protein, albumin, total bilirubin, AST, ALT, GGT, Alkaline phosphatase, LDH, CK,CRP, Uric acid, (total bilirubin > 1.5 times ULN will be reported as direct and indirect bilirubin),	Screening Visit 1, Weeks 2-Visit 778, *creatinine will be measured once weekly for 3 weeks following randomization
Iron metabolism	8.5 mL blood	Serum ferritin	Screening V1, V2, Weeks 2-Visit 778
Viral Serology	Same sample as for chemistry	Hepatitis B: HBsAg and anti-HBs Hepatitis C: Anti-HCV, HCV RNA quantification	Screening Visit 1
Serum Pregnancy Test	Same sample as for chemistry	Serum β-HCG for women of child-bearing potential	Screening Visit 1
Urine Pregnancy Test	> 1 mL urine in clean container	Urine HCG for women of child-bearing potential	Visit 777
Urinalysis	30 mL (midstream urine sample)	Specific gravity, pH, semi-quantitative “dipstick” evaluation of glucose, protein, bilirubin, ketones, leukocytes, blood.	Screening Visit 1 and Weeks 2-Visit 778

[redacted]

Evaluation	Sample collection	Analysis	Collection Time-point
Urinary protein / creatinine ratio	10 mL urine (non-first void morning specimen)	Total protein and creatinine	Screening Visits 1 and 2, Weeks 2-Visit 778.
Oral Glucose Tolerance Testing *	2 mL blood, two times	Blood glucose test	Screening Visit 1, then every year
Brain Natriuretic Peptide (BNP)	2 mL blood	BNP	Randomization, then unscheduled visits if CHF is suspected

* Patients should fast for at least 5 hours prior to the test being drawn. Should a patient have a documented diagnosis of diabetes requiring treatment with medication, the glucose tolerance test is not mandatory and is up to the Investigator's discretion.

7.5.6 Electrocardiogram (ECG)

A 12-lead ECG will be performed as outlined in Table 7-1. All ECGs will be read centrally. Details will be outlined in the site manual provided by the central laboratory, and the exam must be performed by the methods described in the manual.

7.5.7 Echocardiogram (ECHO)

Complete two dimensional echocardiograms with two dimensional imaging, color flow, pulsed-wave and continuous Doppler recordings will be performed at screening Visit 1 and approximately every 12 weeks as outlined in Table 7-1.

Congestive heart failure is a clinical syndrome caused by cardiac dysfunction. Left ventricular dysfunction can be asymptomatic or symptomatic and is evaluated by measuring LVEF. All adverse events related to congestive heart failure should be recorded in the appropriate Adverse Event eCRF.

Patients whose left ventricular ejection fraction is < 50% confirmed by the ECHO obtained at Screening, will not be eligible for randomization.

Patients with echographic evidence of worsening cardiac function based on the following criteria will have met a non-fatal component of the primary endpoint event-free survival.

- 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

All events which could potentially fulfill the criteria for one of the components of the composite primary endpoint, will be reported to the Endpoint Adjudication Committee (EAC) for assessment.

For standardization purposes, all echocardiograms must be sent to the central imaging laboratory and will be interpreted by a central reader. Analysis from a central reader will only include endpoints specified in the protocol. Investigators may have images read locally for complete analysis and full report of all other parameters. A detailed manual will be provided

[redacted]

to the sites by the central imaging laboratory and the exam must be performed by the methods described in the manual. The echocardiography reports must be filed with the patient's record and source documentation.

7.5.8 Chest X-ray

A chest x-ray will be performed during the randomization visit (Visit 3) and for any hospitalization related to congestive heart failure. The chest x-ray will be performed and read locally at the study site. The chest x-ray taken at Visit 3 will be used as a baseline reading for any x-rays obtained during the study when an endpoint of congestive heart failure is suspected.

If a patient has been randomized without a chest x-ray, then a chest x-ray should be done at the next scheduled visit.

If a patient had a chest x-ray 6 months prior to the randomization visit and the test results are available, then a chest x-ray will not need to be done at Visit 3.

7.5.9 Bone marrow biopsy or aspirate

If a patient develops laboratory abnormalities suggestive of Disease progression (MDS progression or AML transformation) in the opinion of the investigator, a bone marrow biopsy or aspiration should be conducted in order to confirm the diagnosis. Based upon the most current classification guidelines (Vardiman 2009), AML transformation should be suspected if 20% or more blasts are present in the peripheral blood. A bone marrow biopsy or aspirate with 20% or more blasts seen in the bone marrow would confirm the diagnosis of AML. An unconfirmed diagnosis of AML will not be considered as a "progression to AML" and subsequently will not be considered as an event for the composite primary endpoint. It may, however, meet the criteria for the disease progression (MDS progression) secondary efficacy endpoint (See Section 3.2.1). All bone marrow results must be recorded in the eCRF for utilization in IPSS scoring and subsequent analyses.

Bone marrow biopsy or aspiration and examination must include the following assessments:

- Cellularity
- % Blasts
- Iron Stains (>15% ringed siderblasts, Dysplasia, Myeloid: Erythroid ratio)
- Cytogenetics (isolated 5q deletions, 20q deletions, chromosome 7 abnormalities, absent Y chromosome (males), complex abnormalities (>3 abnormalities)).

7.5.10 Liver abnormalities

Non- fatal events related to liver function are classified by either liver function impairment or liver cirrhosis and should be recorded on the appropriate AE eCRF.

Liver function impairment is 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

Liver cirrhosis confirmed by the presence of at least one of the following symptoms/signs:

[redacted]

- 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)

All events which could potentially fulfill the criteria for one of the components of the composite primary endpoint will be reported to the Endpoint Adjudication Committee (EAC) for assessment.

For standardization purposes, all liver ultrasounds must be sent to the central imaging laboratory and will be interpreted by a central reader. Analysis from a central reader will only include endpoints specified in the protocol. Investigators may have images read locally for complete analysis and full report of all other parameters. A detailed manual will be provided to the sites by the central imaging laboratory and the exam must be performed by the methods described in the manual. The reports must be filed with the patient's record and source documentation.

7.5.11 Cardiac function

Non- fatal events related to congestive heart failure (CHF) requiring hospitalization are defined as meeting the following criteria:

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

[redacted]

- Elevated brain natriuretic peptide (BNP) or pro-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.

All events which could potentially fulfill the criteria for one of the components of the composite primary endpoint will be reported to the Endpoint Adjudication Committee (EAC) for assessment.

7.5.12 Unscheduled safety visits

Unscheduled safety visits will be permitted at any time during the study if deemed clinically necessary by the investigator. Should the patient require an unscheduled safety visit, the study staff will measure vital signs, record AEs, concomitant medications if applicable, and perform those evaluations deemed clinically necessary for the visit.

7.6 Pharmacokinetics

There will be no pharmacokinetics studies completed during this study.

7.7 Exploratory biomarker studies

There will be no exploratory biomarker studies completed during this study.

8 Safety monitoring

8.1 Serious adverse event reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after protocol-specified procedures begin and until 4 weeks after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after this 4 week period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the SAE Report Form. The investigator must assess and record the relationship of each SAE to the study drug, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the local Novartis Drug Safety and Epidemiology (DS&E).

The telephone and fax number of the contact persons in the local department of DS&E, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

[redacted]

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the IB or Package Insert (new occurrence) and is thought to be related to the Novartis study drug, an DS&E associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an IN, to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.2 Pregnancies

To ensure patient safety, each pregnancy in a patient on study drug must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up for 3 months after the termination of the pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology local Novartis Drug Safety and Epidemiology (DS&E) department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study treatment of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Deferasirox is a category B drug. There has not been any evidence of teratogenic effects in animal studies. At the Screening Visit a serum pregnancy test will be performed. Positive results will deem a patient not eligible for participation in the trial.

A urine pregnancy test must be performed locally at the End of Treatment visit and if menses are delayed for more than 7 days in a female patient capable of becoming pregnant.

Each pregnancy must be reported to Novartis as soon as the site becomes aware of it. All pregnancies occurring from the start of study medication administration on Day 1 through End of Treatment for all patients will be reported and followed.

9 Data review and data management

9.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and eCRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol and to

[redacted]

Good Clinical Practice (GCP), the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, ECGs, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

9.2 Data collection

Novartis will supply the investigator site with an Electronic Data Capture (EDC) system that has been fully validated and conforms to 21 CFR Part 11 requirements. Novartis personnel (or designated CRO) will train designated investigator site staff on the EDC system. Investigator site staff will not be given access to the EDC system until they have been trained. Designated investigator staff will enter the data required by the protocol into the Novartis eCRFs using the Novartis-supplied system. Automatic validation programs check for data discrepancies in the eCRFs and, by generating appropriate error messages, allow modification or verification of the entered data by the investigator staff before transfer to Novartis via a secure network. If applicable, the investigator must certify that the data are complete and accurate by signing a memo that will be sent to him by Novartis personnel after the last transfer of the data prior to analysis. After database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

9.3 Database management and quality control

The designated Contract Research Organization (CRO) Data Management group will review the eCRFs entered by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Obvious errors are corrected by the CRO personnel. Queries are sent to the investigational site using an electronic data query.

Designated investigator site staff are required to respond to the query and make any necessary changes to the data.

Concomitant medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and AEs will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

[redacted]

Third-party vendor data (IVRS, central laboratory, ECG, ECHO, liver biopsy) will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization codes and data about all study drug dispensed to the patient and all dosage changes will be tracked using an IVRS. The system will be supplied by a vendor(s), who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

At the conclusion of the study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Novartis. The occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked.

Any changes to the database after that time can only be made by joint written agreement between the Global Head of Biometrics and Data Management and the Global Head of Clinical Development.

9.4 Data Monitoring Committee

An external DMC will meet prior to First Patient First Visit to finalize the DMC charter.

The composition, frequency of the meetings, and roles will be detailed in the DMC charter. The DMC charter will be approved prior to randomization of the first patient. In brief, the DMC will be composed of 5 members including experts in hematology, cardiology, hepatology and biostatistics. All DMC members will be non-Novartis employees and not participating otherwise in the study (detailed description of potential conflicts of interests will be part of the DMC charter).

The independent DMC will monitor patient safety and trial conduct and will receive a blinded summary of serious adverse events on a regular basis (see DMC charter).

The DMC may recommend to the Sponsor:

- To continue the study as planned
- To continue the study with modifications
- To prematurely stop the study for unfavorable safety profile of deferasirox compared to placebo

10 Statistical methods and data analysis

The data will be analyzed by Novartis and/or a designated CRO.

Data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and other assessments. Continuous variables will be summarized by number of patients, mean, standard deviation, minimum, 25^{th}-quantile, median, 75^{th}-quantile and maximum. Categorical variables will be summarized by absolute and relative frequencies. Discrete (count) variables will be summarized by appropriate descriptive statistics depending on the number of observed levels.

Unless otherwise stated the "baseline value" is defined as the last available measurement prior to randomization. Whenever an event is required to have a confirmation at a later assessment, time to event will be calculated from randomization to the initial instance.

Analyses by stratum (i.e., 4 combinations of MDS risk group and region) will be considered as a subgroup analysis. For analyses of parameters describing hematological function subgroups are defined by patients who did/did not receive growth factors or treatment for MDS (see Section 10.5.1.1).

In addition to the statistical methods outlined below, further details and additional, exploratory analyses might be performed and determined in the study's report and analysis plan (RAP).

10.1 Populations for analysis

Full Analysis Set (FAS): the FAS comprises 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.

Per Protocol Analysis Set (PPS): the PPS is a subset of the FAS and comprises all randomized patients:

- Whose first administered study medication was in accordance with the randomized assignment, and
- Without protocol deviations regarding inclusion criteria with respect to underlying disease (e.g., low or intermediate-1 MDS according to IPSS and serum ferritin > 1000 mcg/L at Screening).

Safety analysis set: the safety set 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 recorded in the eCRF.

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

10.2 Patient demographics and other baseline characteristics

Demographic and other BL data (including disease characteristics) will be summarized descriptively for all patients for the FAS.

10.3 Treatments (study drug, concomitant therapies, compliance)

The descriptive analysis listed below will be reported for the safety set. Duration of study drug exposure as well as average and cumulative planned (mg/kg/day) and prescribed doses (mg/day) will be summarized. Frequency tables for dose adjustments and related reason will be provided as well as number and duration of dose interruptions. Any dose adjustments and reasons will be listed.

[redacted]

The prescribed amount of study medication (deferasirox/placebo) versus the amount of medication taken based on dispensed and returned amount of study medication will be described.

Prior and concomitant medications and significant non-drug therapies will be coded according to the WHO Drug Reference List (which employs the Anatomical Therapeutic Chemical classification system). Frequencies will be provided by treatment group.

10.4 Primary objective

The primary efficacy objective is to evaluate event-free survival in low and int-1 risk MDS patients with transfusional iron overload treated with either deferasirox or placebo.

10.4.1 Variable

The composite primary endpoint (event-free survival, a composite including death and non-fatal events related to cardiac, liver and hematological function, see Section 3.1.1) is defined as time from date of randomization to date when death (irrespective of cause) or any of the non-fatal events has been reached (whatever occurred first). Time is measured in days and is defined as date of event minus date of randomization plus 1.

Censoring for patients without information on date of event at the time of a data cut-off (for interim or final analysis) is described in Section 10.4.3.

10.4.2 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.

10.4.2.1 Estimation of survival functions for event-free survival

A graphical estimate of the survival function separately for each treatment group will be obtained 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 95% confidence intervals calculated using the method of (Brookmeyer and Crowley 1982). Additional percentiles might be specified in the RAP.

KM estimates with 95% confidence intervals at days 365, 730, 1095 and 1460 will be provided. The confidence intervals will be constructed using Greenwood's formula (Collett 1994) for the standard error of the Kaplan-Meier estimate.

10.4.2.2 Stratified unadjusted Cox proportional hazards regression model

The stratified unadjusted Cox model and its assumptions are described by

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

with

h (.) 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

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

x_{jk1} randomized study treatment for patient j in stratum k coded as 0 (placebo) or 1 (deferasirox)

β_1 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. The HR point estimate will be based on the partial maximum likelihood function, and a 95% Wald-test-based two-sided confidence interval will be requested by the RISKLIMITS option.

10.4.2.3 Statistical hypotheses (exploratory)

Suppose that $S_D(t)$ and $S_P(t)$ denote the survival functions regarding event-free survival 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_{A1}: $S_D(t) \geq S_P(t)$ 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).

10.4.2.4 Statistical hypothesis test (exploratory)

An exploratory 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: In each of the K strata separately (by using a BY statement), the SAS LIFETEST procedure with a STRATA statement including only the treatment group variable 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:

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

[redacted]

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.

10.4.3 Handling of missing values/censoring/discontinuations

Event-free survival

For the primary analysis of event-free survival,

- 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 were 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 were 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 were available,
  - Hospitalization for congestive heart failure: the last date when the patient had 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 were available,
  - Liver cirrhosis: the last date when the patient had some documented personal contact (visit or phone call) with the investigator,

Progression to AML: the last date when the patient had 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 as described.

For the first main sensitivity analysis described in Section 10.4.4, 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 described in Section 10.4.4, patients with premature discontinuation of randomized study treatment (regardless of whether they were subsequently

[redacted]

treated with marketed iron chelation therapy) will be censored at the date of last administration of randomized study treatment.

The third sensitivity analysis described in Section 10.4.4 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 time 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' are symptom-based, i.e., assessed in unscheduled examinations, missing assessments for them cannot be determined.

Overall survival

For the analysis of overall survival (see Section 10.5.1.1), patients will be censored at the last date when the patient had some documented personal contact (visit or phone call) with the investigator.

Worsening of cardiac function

For the analysis of worsening of cardiac function (as defined in Section 3.1.1), patients who have not experienced a worsening of cardiac function will be censored at the last date when echocardiography results were available.

Hospitalization for congestive heart failure

For the analysis of hospitalization for congestive heart failure (as defined in Section 3.1.1), patients who have not experienced any hospitalization for congestive heart failure will be censored at the last date when the patient had some documented personal contact (visit or phone call) with the investigator.

Liver function impairment

For the analysis of liver function impairment (as defined in Section 3.1.1), patients who have not experienced any liver function impairment will be censored at the last date when laboratory values for ALT, AST and bilirubin were available.

[redacted]

Liver cirrhosis

For the analysis of liver cirrhosis, patients who have not experienced liver cirrhosis will be censored at the last date when the patient had some documented personal contact (visit or phone call) with the investigator.

Progression to AML

For the analysis of progression to AML, patients who have not experienced progression to AML will be censored at the last date when the patient had some documented personal contact (visit or phone call) with the investigator.

Disease progression

For the analysis of time to disease progression (see Section 10.5.1.1), patients who did not experience an MDS progression or progression to AML will be censored at the last date when the patient had some documented personal contact (visit or phone call) with the investigator.

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 (see Section 10.5.1.1), patients who did not experience such an increase in serum ferritin will be censored at the last date when serum ferritin was available.

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 10.5.1.1), respectively, patients who did not experience such an increase will be censored at the last date when LVIDD (or LVISD, respectively) was available.

Study drug discontinuation due to an AE or laboratory abnormality

For the analysis of time from randomization to study drug discontinuation due to an AE or laboratory abnormality (see Section 10.5.2.2), patients who did not discontinue study medication due to an AE or laboratory abnormality will be censored at the date of study drug discontinuation.

10.4.4 Supportive and sensitivity analyses

The two main sensitivity analyses for the primary efficacy analysis (event-free survival) will be based on the two alternative censoring rules described in Section 10.4.3. Otherwise, the same statistical methods will be used as 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 has missing data on some but not all of the components). The censoring rules for this analysis are also described in Section 10.4.3.

[redacted]

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 10.5.1.1);

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 (partly data-driven) demographic or baseline characteristics of clinical interest;
- Statistical analyses based on the PPS instead of the FAS.

10.5 Secondary objectives

10.5.1 Secondary efficacy objectives

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

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

10.5.1.1 Secondary efficacy variables and related analyses

Hematologic improvement

Hematologic improvement in terms of erythroid responses during treatment will be assessed based on 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 increase of ≥ 1.5 g/dL

OR

- Reduction of ≥ 4 RBC transfusions/8 weeks

in comparison to pre-treatment values and lasting at least 8 weeks. According to IWG criteria, HI is measured in patients with pre-treatment hemoglobin levels of less than 11 g/dL or RBC transfusion dependence. Pre-treatment hemoglobin levels must not be influenced by transfusions (no transfusion received for at least one week preceding the hemoglobin measurement). The last hemoglobin value measured prior to randomization will be used as the pre-treatment value. (If 2 pre-treatment 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 value). Similarly, measurements after randomization influenced by preceding transfusions within one week will not contribute to the response criteria. All RBC

transfusions regardless of pre-transfusion hemoglobin level will count in the RBC transfusion response evaluation.

All episodes of HI in the patient will be considered.

The percentage of responders will be reported for the two treatment groups. The equality of proportions in the two groups will be analyzed by an exploratory test. Further details will be described in the RAP.

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 10.4.3. The estimation of survival functions and the Cox model to estimate the HR are defined in analogy to Section 10.4.2.1 and Section 10.4.2.2. An exploratory statistical test will be performed analog to the description in Section 10.4.2.3 and Section 10.4.2.4. In this analysis $S_D(t)$ and $S_P(t)$ denote the survival functions regarding overall survival for deferasirox and placebo, respectively.

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.

TPO antibodies will be measured in patients with elevated TSH levels to determine the status of thyroid autoimmunity.

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.

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 timepoint, i.e. 1, 2, years after randomization. For this classification, fasting and 2-hour post-prandial plasma glucose levels will be measured.

[redacted]

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:

- symptoms of diabetes plus casual plasma glucose concentration ≥ 200 mg/dl (11.1 mmol/L) Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.

  OR

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

  OR

- 2 hour postload glucose ≥ 200 mg/dl (11.1 mmol/L) during an OGTT. The test should be performed as described by WHO, using 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.

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. 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 10.4.2.1 to Section 10.4.2.4. Censoring for patients with neither MDS progression nor progression to AML at the time of a data cut-off is described in Section 10.4.3. Further details will be described in the RAP.

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.

[redacted]

The time-to-event analysis follows the description given in Section 10.4.2.1 to Section 10.4.2.4. Censoring for patients without such a serum ferritin increase at the time of a data cut-off is described in Section 10.4.3.

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 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 10.4.2.1 to Section 10.4.2.4. Censoring for patients without such an increase in LVIDD at the time of a data cut-off is described in Section 10.4.3. If necessary, further details will be described in the RAP.

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 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 10.4.2.1 to Section 10.4.2.4. Censoring for patients without such an increase in LVISD at the time of a data cut-off is described in Section 10.4.3. If necessary, further details will be described in the RAP.

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 selection of 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.)”.
- Contemplable 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 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.

[redacted]

10.5.2 Secondary safety objectives

10.5.2.1 Observation periods for safety

The overall observation 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 day of first dose of study medication to 28 days after last dose of study medication.
3. Post-treatment period: starting at day 29 after last dose of study medication.

Safety summaries (tables and figures) have to include only data from the pre-treatment period (to display "baseline status") and the on-treatment period, i.e. no data from the post-treatment period are to be included. In particular, summary tables for adverse events (AEs) will include only AEs that occurred or worsened during the on-treatment period, the so-called **treatment-emergent** AEs.

However, 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.

10.5.2.2 Secondary safety variables and related analyses

Analyses of safety endpoints related to secondary objectives of the trial will be analyzed for the safety analysis set. Descriptive statistics and two-sided 95% confidence intervals (without adjustment for multiplicity) for evaluation of deferasirox in contrast to placebo will be used as appropriate.

Proportion of patients with significant renal dysfunction

Treatment groups will be evaluated regarding the proportion of patients experiencing a significant renal dysfunction. This is defined as a serum creatinine value ≥ 2 times ULN at two consecutive assessments. The two assessments need to be at least 7 days a part.

Frequency tables by treatment group will be prepared. Results will also be provided for annual time intervals.

Proportion of patients with severe neutropenia or thrombocytopenia

Proportion of patients with newly occurring CTCAE grade 4 neutropenia or thrombocytopenia will be displayed by treatment group. Results will also be provided for annual time intervals.

Proportion of patients with major gastrointestinal bleeding

An evaluation of the proportion of patients with major gastrointestinal bleeding will be performed. Major gastrointestinal bleeding is defined as an AE that may include one of the following MedDRA preferred terms:

[redacted]

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

Frequency tables will be prepared by treatment group. Results will also be provided for annual time intervals.

In addition, a statistical analysis of the multivariate (recurrent) major gastrointestinal bleeding data will be performed.

Time to study drug discontinuation due to an AE or laboratory abnormality

An evaluation of the time from randomization to study drug discontinuation due to an AE or laboratory abnormality will be performed. The variable will be based on the date and reason given on the Study Treatment Completion eCRF page. Only patients for whom the reason for stopping study medication was entered as AE or laboratory abnormality will be considered. The definition of the variable is:

- 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 10.4.2.1 to Section 10.4.2.4. The statistical test will be exploratory. Censoring is described in Section 10.4.3.

10.5.2.3 Adverse events (AE)

Frequency tables for treatment-emergent AEs (see Section 10.5.2.1) will present, 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.

Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by MedDRA preferred term and treatment group.

[redacted]

10.5.2.4 Analysis of laboratory data

For analyzing laboratory data, data from all sources (central and local laboratories) will be combined. Other than for weekly serum creatinine monitoring visits, central laboratory results are the only laboratory results that will be captured in the database.

Grading of laboratory data

For laboratory tests covered by the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 NCI 2006, the study's biometrics team will grade laboratory data accordingly with the exception of grade 5 (death). For laboratory tests covered by CTCAE, a grade 0 will be assigned for all non-missing values not graded as 1 or higher. For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classification based on laboratory normal ranges.

Reporting of laboratory data

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

- Frequency table for newly occurring on-treatment grades 3 or 4.
- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value.
- For laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.

For a specific laboratory test, patients with newly occurring on-treatment grade 3 or 4 are defined as:

- Patients with baseline grade missing, 0, 1 or 2 and worst on-treatment grade 3 or 4 (percentage to be based on all patients with baseline grade missing, 0, 1 or 2).
- Patients with baseline grade missing, 0, 1, 2 or 3 and worst on-treatment grade 4 (percentage to be based on all patients with baseline grade missing, 0, 1, 2 or 3).

The following listings will be generated:

- Listing of laboratory data for patients with newly occurring grade 3 or 4 laboratory toxicities.
- Listing of laboratory data for patients with values outside the laboratory normal ranges with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.
- Listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

10.5.3 Other safety data

Data from other safety tests or assessments will be summarized descriptively and listed, with notable values flagged.

[redacted]

10.5.4 Tolerability

Not applicable.

10.5.5 Pharmacokinetics

Not applicable.

10.5.6 Biomarkers

Not applicable.

10.6 Interim analysis

No interim analysis will be performed.

10.7 Sample size calculation

The foreseen 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.

10.8 Power for analysis of critical secondary variables

Power calculations for secondary variables were not done for the determination of sample size.

11 Administrative procedures

Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the protocol, the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for GCP, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Novartis before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

Informed consent

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH/GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB.

Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC/REB at the study site should be informed within 10 working days.

Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical trial agreement.

Study drug supply and resupply, storage, and tracking/drug accountability

Study drugs must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Upon receipt, the study medication (deferasirox or placebo) should be stored according to the instructions specified on the drug labels. Clinical supplies are to be dispensed only in accordance with the protocol.

[redacted]

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug and the medication number but no information about the patient.

The investigator must maintain an accurate record of the shipment and dispensing of study drug in a drug accountability ledger. Drug accountability will be noted by the field monitor during site visits and at the completion of the trial. Patients will be asked to return all unused study drug and packaging at the end of the study or at the time of study drug discontinuation.

At the conclusion of the study, and, as appropriate during the course of the study, the investigator will return all used and unused study drug, packaging, drug labels, and a copy of the completed drug accountability ledger to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

Steering Committee

A Steering Committee (SC) will be constituted prior to the randomization of the first patient. The composition of the SC will be described in a charter. It will include approximately 4 study investigators and the Novartis Clinical Trial Head, statistician and clinical research physician/clinical program leader.

The responsibilities of the SC will include on-going reviews of trial progress, scientific input into protocol revisions, review of safety reports, advising on dosing modifications, interaction with the DMC, and the writing of all scientific publications. The details will be provided in the SC charter.

Endpoint Adjudication Committee

A Endpoint Adjudication Committee (EAC) will be constituted prior to the randomization of the first patient. The composition of the EAC will be described in the EAC charter. The EAC is responsible for ensuring whether pre-specified endpoint criteria were met for all non-fatal events. The role of the EAC is to ensure that all events that have been reported by the sites are judged uniformly using the same criteria. The EAC is blinded to study treatment allocation.

In the event that a patient experiences a suspected non-fatal event, the appropriate Site Reported Endpoint eCRF must be completed. The investigative sites will be responsible for reporting all suspected non-fatal event cases in the eCRF for EAC review. Further details are available in the EAC site guide. The EAC will determine in a blinded fashion if the event submitted satisfied the pre-specified endpoint criteria and rule if the case is an endpoint. This information will be communicated to the investigative site by the Sponsor. Refer to protocol Section 6.7.5 for study drug discontinuation details.

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the trial to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the Clinical Study Report.

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