# 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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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...

| | |
|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Will not start |
| **Health condition type** | Haematological disorders NEC |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON38011

**Source**
ToetsingOnline

**Brief title**
TELESTO

### Condition

- Haematological disorders NEC

**Synonym**
iron overload

**Research involving**

Human

## Sponsors and support

**Primary sponsor:** Novartis
**Source(s) of monetary or material Support:** Novartis

## Intervention

**Keyword:** Deferasirox, iron overload, MDS, myelodysplastic syndromes

## Outcome measures

**Primary outcome**

Time from date of randomization to date when death or any of the nonfatalevents

defined below has been reached (event-free survival):

* Death

* Non-fatal event:

1. Echocardiographic evidence of worsening cardiac function based on the

following criteria:

at least > 15% absolute decrease in left ventricular ejection fraction (LVEF)

from screening value at two consecutive assessments at least two weeks apart OR

LVEF below institutional limits of normal and at least > 10% absolute decrease

from LVEF screening value at two consecutive assessments at least two weeks

apart

2. Hospitalization for congestive heart failure defined as follows:

Overnight stay (i.e., change in calendar day) due to congestive heart failure

confirmed by the presence of the following:

a) At least one of the following symptoms:

* Paroxysmal nocturnal dyspnea

* Orthopnea

* Dyspnea on exertion

AND

b) Two or more of the following signs consistent with heart failure:

* Pulmonary edema by radiography

* Rales

* Enlarged heart by radiography

* Peripheral edema

* S3 gallop

* Hepatojugular reflux

* Neck vein distention

* Rapid weight gain

* Elevated brain natriuretic peptide (BNP)

AND

c) Treatment with either intravenous diuretics, intravenous vasodilators, intravenous inotropes, mechanical fluid removal (e.g., ultrafiltration or dialysis), or insertion of an intra-aortic balloon pump for hemodynamic compromise. Initiation of oral diuretics or intensification (doubling) of the maintenance diuretic dose will also qualify.

3. Liver function impairment reflected by:

* ALT or AST > 2 times the baseline value and > 3.5 times ULN

AND

* Total bilirubin > 2 mg/dL at two consecutive visits

4. Liver cirrhosis confirmed by:

* The presence of at least one of the following symptoms/signs:

cirrhosis-related ascites, spontaneous bacterial peritonitis, hepatic

encephalopathy, variceal bleeding due to portal hypertension

OR

* Abdominal ultrasonography (if clinically indicated)

OR

* Liver biopsy (if clinically indicated)

5. Progression to Acute Myeloid Leukemia (confirmed by bone marrow biopsy)

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 outcome**

Efficacy:

* Overall survival (key secondary)

*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 either hematological 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.

* Hematological function expressed in frequency/total amount of blood

transfusions

* 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

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 description

**Background summary**

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 *-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 hemaglobinopathies, primarily *-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.

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 *-thalassemia (Cappellini 2006), but has not been well described in a prospective study until now.

**Study objective**

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 demonstrate in low/int-1 risk MDS patients, treated as per standard practice, the clinical superiority of deferasirox to placebo, while rigorously monitoring relevant clinical parameters (cardiac and liver function and transformation to Acute Leukemia AML)) potentially affected by iron overload complications.

**Study design**

This is a prospective, randomized, double-blind, placebo-controlled, parallel group design study with a maximum of two interim analyses for efficacy and safety. The recruitment period is planned to last 24 months. 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 end of study is expected to occur 5 years after first patient first visit (FPFV) when 244 events for the composite primary endpoint have been observed. 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 an event (e.g., for an adverse event) will continue to be evaluated at specified time intervals. 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. Interim analyses for safety and efficacy are planned when approximately 50% and 75% of the required number of events (244) will have been observed.

**Intervention**

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 oftreatment at thedose 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

**Study burden and risks**

Joining this study requires quite a lot of the patient. The patient will need to come to the hopsital at regular intervals for a period of 5 years for monitoring and testing. Most tests would also happen if the patient did not participate in the study, although the timing and number might be different.

The study medication should be taken every day at about the same time and 30 minutes before the meal on an empty stomach.

The patient must come to the hospital for a maximum of 5 years once a month (every 4 weeks). Each visit will last approximately 1 hour or less.

The researcher performs a complete physical exam and checks weight and vital signs. There will also be a chest X-ray taken, except if one was made in the last 6 months and results are available. During 3 weeks after randomization, the patient will visit the study doctor once a week. The patient undergoes a simple blood test to check the kidneys, each time approximately 8.5 ml of blood will be taken. After four weeks of treatment, the patient will come to the hospital once a month (approximately every 4 weeks). During the visits, the study doctor will ask health questions and do tests. At each visit, vital signs

and weight will be checked. Each visit approximately 17 ml of blood will be taken and a urine sample of 40 ml will be collected. Every three months, the patient undergoes an ECG and an ultrasound to monitor the heart function. Once a year, the patient will need to have an ophthalmic examination and hearing tests.

It is possible that in the course of the study additional tests will need to be performed if the patient has certain heart or liver problems. The study doctor will decide which tests are necessary. This may include an X-ray of the chest, a bone marrow examination, an ultrasound of abdomen, a liver biopsy, but also an additional blood test.

Blood tests may hurt or cause a hematoma. In rare cases, a liver biops may cause a hemorrhage in the liver, internal bleeding, puncture of the gallbladder, an infection, an abscess or puncture of a lung. It is also possible that the blood pressure cuff or inconvenience caused a contusion of the upper arm.

## Contacts

**Public**
Novartis

Lichtstrasse 35
Basel CH-4056
CH
**Scientific**
Novartis

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## Trial sites

### Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## 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

## 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.
- 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, 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, intending-to-become pregnant, or breast-feeding patients
-History of drug or alcohol abuse within the 12 months prior to enrollment.

# Study design

## Design

| | |
|---|---|
| Study phase: | 3 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Placebo |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Will not start |
| Enrollment: | 10 |
| Type: | Anticipated |

## Medical products/devices used

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | Exjade |
| Generic name: | Deferasirox |
| Registration: | Yes - NL intended use |

## Ethics review

| | |
|---|---|
| Approved WMO Date: | 25-02-2011 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 09-06-2011 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 11-07-2012 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 13-08-2012 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 19-12-2012 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |

## Study registrations

### Followed up by the following (possibly more current) registration

No registrations found.

### Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2009-012418-38-NL |
| CCMO | NL35105.029.11 |