A 1-Year Randomized Controlled Trial of Deferasirox versus Deferoxamine for Myocardial Iron Removal in Beta-Thalassemia Major (CORDELIA)

Dudley J Pennell, MD¹ John B Porter, MD² Antonio Piga, MD³ Yongrong Lai, MD⁴ Amal El-Beshlawy, MD⁵ Khawla M Belhouli, MD⁶ Mohsen Elalfy, MD⁷ Akif Yesilipek, MD⁸ Yurdanur Kilinç, MD⁹ Tomasz Lawniczek, MD¹⁰ Dany Habr, MD¹¹ Marianne Weisskopf, PhD¹⁰ Yiyun Zhang, PhD¹¹ Yesim Aydinok, MD¹² on behalf of CORDELIA study investigators

¹Royal Brompton Hospital, London, UK; ²University College London, London, UK; ³Università di Torino, Turin, Italy; ⁴The First Affiliated Hospital of Guangxi Medical University, Nanning, China; ⁵Cairo University, Cairo, Egypt; ⁶Thalassemia Centre, Latifa Hospital, Dubai, UAE; ⁷Ain Shams University, Cairo, Egypt; ⁸Akdeniz University, Antalya, Turkey; ⁹Cukurova University Medical Facility, Adana, Turkey; ¹⁰Novartis Pharma AG, Basel, Switzerland; ¹¹Novartis Pharmaceuticals, East Hanover, NJ, USA; ¹²Ege University Hospital, Izmir, Turkey

Corresponding author: Dudley J Pennell, NIHR Cardiovascular Biomedical Research Unit, Royal Brompton Hospital, Sydney Street, London, SW3 6NP, UK
Tel: +44 20 7351 8810; Fax: +44 20 7351 8816; Email: d.pennell@ic.ac.uk

Running head: Deferasirox vs DFO for cardiac iron removal

Primary scientific category: Clinical trials and observations
Secondary scientific category: Red cells, iron and erythropoiesis
Key points

- In transfused beta-thalassemia major patients with severe iron burden, deferasirox was non-inferior to DFO for myocardial iron removal
- Liver iron burden may have an impact on the rate of myocardial iron removal during deferasirox treatment

Abstract

Transfusion-dependent patients are at risk of myocardial iron deposition. Randomized comparison data on the efficacy and safety of deferasirox for myocardial iron removal are lacking. CORDELIA was a prospective, randomized comparison of deferasirox (target dose 40mg/kg/day) vs subcutaneous deferoxamine (50–60mg/kg/day for 5–7 days/week) for myocardial iron removal in 197 beta-thalassemia major patients with myocardial siderosis (T2* 6–20ms) and no signs of cardiac dysfunction (mean age 19.8 years). The primary objective was to demonstrate non-inferiority of deferasirox for myocardial iron removal, assessed by changes in myocardial T2* after 1 year using a per protocol analysis. The geometric mean (Gmean) myocardial T2* improved with deferasirox from 11.2ms at baseline to 12.6ms at 1 year (Gmeans ratio 1.12) and with deferoxamine (11.6ms to 12.3ms; Gmeans ratio 1.07). The between-arm Gmeans ratio was 1.056 (95% confidence intervals [CI] 0.998, 1.133). The lower 95% CI boundary was greater than the pre-specified margin of 0.9, establishing non-inferiority of deferasirox vs deferoxamine (P=0.057 for superiority of deferasirox). LVEF remained stable in both arms. Frequency of drug-related adverse events was comparable between deferasirox (35.4%) and deferoxamine (30.8%). CORDELIA met its primary endpoint of demonstrating non-inferiority of deferasirox compared with deferoxamine for myocardial iron removal.

Clinical Trial Registration: ClinicalTrials.gov number NCT00600938

Key Words: thalassemia; iron chelation; magnetic resonance imaging; cardiac
Introduction

Without effective iron chelation therapy, patients with transfusional iron overload are at risk of iron deposition in vital organs such as the liver and heart. The heart is more sensitive to iron overload than the liver, whereby lower levels of iron are sufficient to cause iron-related heart failure and death, relative to the larger iron load that can be tolerated by the liver before hepatic dysfunction occurs.\(^1\) Significant variation has been observed between heart and liver iron loading,\(^2\) which is incompletely understood. Iron may load earlier in the liver and only later in the myocardium, with differential kinetics of iron chelators between organs playing a role.\(^3\) In beta-thalassemia major patients treated with deferoxamine evidence of myocardial iron deposition only becomes apparent towards the end of the first decade of life.\(^4\)

Although a decrease in cardiac-related mortality has recently become apparent,\(^5\) heart failure due to iron-induced cardiomyopathy remains a key cause of death in patients with beta-thalassemia major.\(^6-9\) The decrease in cardiac-related mortality is due in part to the introduction of T2* cardiovascular magnetic resonance (CMR) for the estimation of myocardial iron, which has contributed to improved management of cardiac siderosis.\(^10-15\) T2* CMR is now widely used, is highly reproducible,\(^16-18\) and is calibrated in animal\(^19\) and human hearts.\(^1\) Myocardial T2* >20ms is considered normal\(^2\) and iron accumulation causes a reduction in T2*, with values <10ms being associated with increased risk of heart failure.\(^15\)

Iron chelation therapy aims to prevent iron accumulation, or to remove iron deposition when it has already occurred. The available iron chelators deferoxamine (DFO), deferiprone and deferasirox can all remove myocardial iron with acceptable safety profiles.\(^14,20-25\) However, there are limited data from randomized controlled trials comparing iron chelation therapies for removal of myocardial iron,\(^14,22,25\) and none for deferasirox. Efficacy and safety of deferasirox in myocardial iron removal has only been reported in uncontrolled single-arm trials.\(^20,26-28\) Here, we describe the first prospective, randomized comparison of changes in myocardial T2* with deferasirox or DFO in beta-thalassemia major patients with myocardial siderosis. The primary objective was to demonstrate non-inferiority of deferasirox when compared with DFO in myocardial iron removal, as assessed by changes in myocardial T2* after 1 year.
Methods

Patients
CORDELIA was conducted between April 10, 2008 and March 1, 2012. Patients with beta-thalassemia major, Diamond–Blackfan anemia, Low/Int-1 myelodysplastic syndromes (MDS) or sideroblastic anemia, aged ≥10 years with myocardial T2* 6–20ms without clinical symptoms of cardiac dysfunction (shortness of breath at rest or exertion, orthopnea, exercise intolerance, lower extremity edema, arrhythmias) were eligible for recruitment into the study. Other inclusion criteria included left ventricular ejection fraction (LVEF) ≥56%; R2-magnetic resonance imaging (MRI) liver iron concentration (LIC) ≥3mg Fe/g dw; with lifetime history of ≥50 units of red blood cell (RBC) transfusions, and receiving ≥10 units/year of RBC transfusions.

Patients with serum creatinine above the upper limit of normal (ULN), or significant proteinuria (urinary protein/creatinine ratio ≥1.0mg/mg in a non-first void urine sample at baseline) were excluded. In order to avoid excluding patients with increased alanine aminotransferase (ALT) levels due to liver iron overload, the ALT exclusion criterion was modified to exclude patients with ALT >5 times ULN only if their LIC was <10mg Fe/g dw. Other exclusion criteria included: considerable impaired gastrointestinal (GI) function or GI disease, history of clinically relevant ocular and/or auditory toxicity related to iron chelation therapy and history of HIV seropositivity or malignancy within the past 5 years.

Study design
CORDELIA was a prospective, multinational, randomized, open-label, parallel-group, Phase II study conducted in 22 centers across 11 countries. Following a 35-day screening phase, patients were randomized in a 1:1 ratio to receive deferasirox (Exjade®, Novartis) or DFO (Desferal®, Novartis) for 1 year. Randomization was based on permuted blocks; stratification by center was not conducted. The once-daily deferasirox starting dose was 20mg/kg/day for 2 weeks, followed by 30mg/kg/day for 1 week, then continued with 40mg/kg/day. An intensified dosing regimen of DFO was administered, at 50 to 60mg/kg/day via subcutaneous infusion over 8 to 12 hours, 5 to 7 days a week, in accordance with Thalassaemia International Federation guidelines.29 Dose adjustment recommendations were provided based on continuous assessment of efficacy and safety.
markers. Study medication was dispensed during regular study visits, and all medication returned by the patient was counted and recorded to assess compliance. Patients were instructed to contact the investigator if unable to take the study drug as prescribed.

The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki, and was approved by institutional ethics committees at all participating sites. All patients or parents/guardians gave informed consent. An independent data monitoring committee reviewed the safety data and advised on study continuation and/or any changes to protocol.

Endpoints
Change in myocardial T2* was assessed as the ratio of the geometric mean (Gmean) T2* at end of study (EOS) divided by that at baseline (Gmean_{EOS}/ Gmean_{baseline}). The primary efficacy endpoint was the ratio of Gmean myocardial T2* after 1 year of treatment with deferasirox divided by the ratio of Gmean for DFO.

A key secondary endpoint was to compare the two treatment groups for changes in LVEF after 1 year of treatment, assessed by absolute change from baseline CMR. Other endpoints included absolute change from baseline in LIC and serum ferritin after 1-year treatment with deferasirox and DFO.
Assessments

Efficacy was assessed using the per-protocol analysis set including all randomized patients treated for at least 6 months and with no major protocol violations. If Month 12 myocardial T2* value was not available, the last value obtained at ≥150 days was used. Patients without any T2* value after ≥150 days were excluded. Myocardial T2* and LVEF were measured with CMR at baseline, Month 6 and EOS. A standardized CMR protocol for T2* acquisition technique was used and images were assessed by a central CMR core laboratory. LIC was measured using a validated R2 MRI technique at baseline and then after 6 and 12 months of study treatment. Core laboratories were blinded to treatment allocation. Serum ferritin levels were assessed on blood samples drawn monthly from baseline to EOS. Monthly mean iron intake in mg/kg/day was determined based on the formula of average blood intake x 1.08/30 days.

The safety set consisted of all randomized patients who received at least one dose of study drug and had at least one post-baseline safety assessment. Patients were analyzed according to treatment received (first study drug administered). Safety was evaluated through continuous monitoring and recording of adverse events (AEs), serious AEs, laboratory testing and clinical evaluations. Patients enrolled with a baseline myocardial T2* <10ms underwent additional 3-monthly monitoring for cardiac function and myocardial iron.

Myocardial iron concentration was derived from myocardial T2* values based on the formula described by Carpenter et al. Briefly, [Fe] = 45·(T2*)^{-1.22}, where [Fe] is measured in mg/g dw and T2* is measured in milliseconds. Ad hoc analysis of mean absolute change in myocardial iron concentration was thus conducted.

Statistical methods

Study sample size was determined for the primary endpoint of testing the non-inferiority of deferasirox compared with DFO for ratio of T2* Gmeans with two-sided 0.05 alpha-level, 85% power and a non-inferiority margin of 90%. Sample size accounted for an interim assessment using O'Brien–Fleming boundaries and for a potential 30% patient drop out before Month 6. The analysis plan for the primary endpoint pre-specified the per-protocol study population for testing of non-inferiority, as per European Medicines Agency and International Conference on Harmonisation guidelines. A sensitivity analysis of the
intention-to-treat population was planned. In order to eliminate potential unrecognized biases, the core clinical trial team was blinded to the treatment assignment prior to the database lock for the primary analysis.

For the primary efficacy variable, the two-sided repeated 95% confidence interval (CI) for the ratio of T2* Gmeans of deferasirox over DFO was calculated. A non-inferiority margin of 0.9 (90%) was applied since a loss of 10% efficacy relative to DFO was considered not clinically relevant. Non-inferiority was therefore pre-defined if the lower limit of the repeated 95% CI for ratio of two Gmeans was >0.9. If non-inferiority was established, a superiority test would be performed by comparing the lower limit of the repeated CI with 1. If the lower limit was >1, deferasirox would be declared superior to DFO; otherwise deferasirox would not be declared superior. A two-sided adjusted $P$-value based on the Tsiatis, Rosner and Mehta stage-wise ordering was calculated, testing superiority of deferasirox over DFO. Demographic and baseline characteristics and safety variables were summarized by frequency tables or summary statistics for continuous distributions.
Results

Patient disposition
Overall, 925 patients were screened and 197 randomized (Figure 1). The majority of patients screened were beta-thalassemia major patients (902/925; 99.1%). Other patients who were screened and for whom underlying anemia was captured had Low/Int-risk MDS (n=4), Diamond–Blackfan anemia, beta-thalassemia intermedia, congenital dyserythropoietic anemia and paroxysmal nocturnal hemoglobinuria (all n=1). Only beta-thalassemia major patients fulfilled the inclusion criteria and were enrolled in the study. 81.2% of patients (n=160) completed 1 year of treatment (Figure 1). Three patients in each group discontinued as a result of worsening of myocardial T2*.

Baseline demographics and clinical characteristics
Baseline demographics and clinical characteristics across deferasirox and DFO groups were similar (Table 1). Mean ±standard deviation (SD) age of patients was 19.8±6.4 years. In patients randomized to deferasirox, Gmean (coefficient of variance [CV]) myocardial T2* at baseline was 11.2 (32.6), and 11.6 (30.7) in DFO patients. Patients were heavily iron overloaded, with baseline LIC of 30.0 ±17.7mg Fe/g dw and median (range) serum ferritin levels of 4878 (613–15,331)ng/mL.

Exposure to treatment and compliance
Mean actual dose over 1-year treatment was 36.7±4.2mg/kg/day deferasirox (range: 19.7–43.3mg/kg/day). Mean actual dose of DFO was 41.5±8.7 (13.2–60.2) mg/kg/day, when normalized to a 7-day regimen. The maximum dose used at any time during the study was 49.9mg/kg/day deferasirox and 62.5mg/kg DFO. As a result of rounding to the nearest whole tablet strength, eight patients received deferasirox doses >40mg/kg/day.

Patients received study drug for a median duration of 355.5 days (range 3.0–418.0) and 355.0 days (range 86.0–394.0) in the deferasirox and DFO cohort, respectively. Total exposure was 87.8 patient-years for deferasirox patients and 81.5 patient-years for DFO patients. Overall, deferasirox patients took 99.0±3.5% of the planned dose, and DFO patients took 100.4±10.9%. Dose was interrupted at least once in 18.8% of deferasirox patients and in 17.6% of DFO patients. The main reason for interruption was an AE (n=21
[21.9%] vs n=19 [20.9%, respectively). Dose was reduced at least once in 15.6 and 19.8% of patients, respectively; the main reason was also an AE (n=24 [25.0%] vs n=21 [23.1%]).

**Average iron intake**

Average iron intake throughout the study was <0.3mg/kg/day in 55.2% patients (deferasirox, 53.8%; DFO 56.8%), 0.3 to 0.5mg/kg/day in 36.6% patients (deferasirox, 38.5%; DFO 34.6%), and >0.5mg/kg/day in 8.1% patients (deferasirox, 7.7%; DFO 8.6%) and was similar between groups.

**Efficacy of deferasirox compared with DFO**

Myocardial T2* improved after 1 year of treatment (Table 2). In the per-protocol population, Gmean (CV) myocardial T2* improved after 1 year of treatment with deferasirox by 12% (11.2 [32.6]ms at baseline to 12.6 [42.6]ms at EOS); and by 7% for DFO (11.6 [30.7]ms to 12.3 [34.7]ms; Figure 2A). The ratio of the Gmeans of deferasirox over DFO was 1.056 (repeated 95% CI 0.998, 1.133). Since the lower bound of the 95% CI was greater than pre-specified margin of 0.9, non-inferiority of deferasirox compared with DFO for myocardial iron removal was demonstrated. A trend for superiority of deferasirox compared with DFO was observed, although this did not reach statistical significance (P=0.057). An analysis of the intention-to-treat population showed similar results to the per-protocol population (Table 2).

Myocardial T2* improved with deferasirox and DFO treatment in patients who had T2* below or above 10ms at baseline (Figures 2B and C). In patients with baseline LIC <7mg Fe/g dw, increase from baseline in myocardial T2* was 30% (n=11) for deferasirox and 10% for DFO (n=8), and for patients with baseline LIC ≥15mg Fe/g dw, increase was 9% (n=66) and 5% (n=59), respectively (Figures 2D–F).

After 1 year, 16 (17.6%) patients treated with deferasirox normalized their myocardial T2*, and 11 (35.5%) patients improved from a baseline myocardial T2* of 6 to <10ms to 10 to ≤20ms at EOS (Figure 3A). In comparison, five (6.2%) DFO patients overall normalized their myocardial T2*, and five (20.0%) patients treated with DFO improved from a baseline myocardial T2* of 6 to <10ms to 10 to ≤20ms at EOS (Figure 3B). Overall, four (6.7%) and three (5.4%) patients treated with deferasirox and DFO worsened to 6 to <10ms from a baseline of 10 to ≤20ms. These results are based on the per-protocol analysis population
and do not take into account patients discontinuing as a result of worsening of cardiac T2* prior to Month 6.

**Effect of deferasirox compared with DFO on cardiac function**

Mean LVEF remained stable and within the normal range after 1 year of treatment with deferasirox (66.9±5.6% at baseline to 66.3±5.8% at EOS) and DFO (66.4±5.2% to 66.4±5.8%). Change in mean LVEF after 1 year was not different between the two treatments ($P=0.54$). Of patients with abnormal LVEF at baseline, six (54.5%) deferasirox patients and five (50.0%) DFO patients had improved LVEF to within the normal range. Overall, seven (8.8%) deferasirox patients and nine (12.7%) DFO patients who had LVEF in the normal range at baseline had decreased LVEF to below lower limit of normal (LLN) by EOS.$^{34}$

**Other Iron parameters**

*Myocardial iron concentration*

After 1 year of treatment with deferasirox, myocardial iron concentration decreased from a baseline of 2.6±1.0mg Fe/g dw to 2.3±1.2mg Fe/g dw (absolute change from baseline −0.24±0.7mg Fe/g dw; 95% CI −0.1, −0.4). In patients treated with DFO, myocardial iron decreased from 2.4±0.9mg Fe/g dw at baseline to 2.3±0.9mg Fe/g dw at EOS (absolute change from baseline −0.15±0.5mg Fe/g dw; 95% CI −0.03, 0.3). Decreases in myocardial iron were observed in all subgroups examined (Supplementary Table 1).

*Liver iron concentration*

After 1 year of treatment with deferasirox, LIC decreased from 29.8±17.5mg Fe/g dw at baseline to 20.1±17.5mg Fe/g dw at EOS (absolute change from baseline, −8.9±11.4mg Fe/g dw, 95% CI −11.5, −6.4). LIC decreased from a baseline of 30.3±17.9 to 17.7±14.4mg Fe/g dw in DFO patients (change from baseline, −12.7±11.4mg Fe/g dw, 95% CI −15.3, −10.1).

*Serum ferritin level*

Treatment with deferasirox for 1 year reduced serum ferritin levels from a baseline of 5062 (613–15,331)ng/mL to 3375 (346–31,942)ng/mL at EOS (absolute change from baseline, −1044 [−5561 to 18,838]ng/mL). In DFO patients, serum ferritin levels reduced from 4684
(677–13,342)ng/mL at baseline to 3129 (470–9487)ng/mL after 1 year (change from baseline, −1277 [−7577 to 2810]ng/mL).

**Safety parameters**

**Adverse events**

Investigator reported AEs, regardless of causality, were reported in 65 (67.7%) deferasirox patients and 69 (75.8%) DFO patients (Supplementary Table 2). AEs suspected to be related to study drug occurred in 35.4% of deferasirox patients and 30.8% of DFO patients; the most common (≥5%) were increased blood creatinine (8.3% vs 2.2%, respectively), proteinuria (7.3% vs 3.3%), increased ALT (6.3% vs 1.1%), increased aspartate aminotransferase (6.3% vs 1.1%) and diarrhea (6.3% vs 1.1%) (Supplementary Table 3).

Serious AEs (SAEs), irrespective of causality, were reported in 10 (10.4%) deferasirox patients and 10 (11.0%) DFO patients (Supplementary Table 2). Of these, two SAEs in one patient (vomiting and upper abdominal pain) were suspected to be related to deferasirox and two SAEs (GI infection and meningitis) were suspected to be related to DFO.

One deferasirox patient experienced an AE (arrhythmia) leading to study drug discontinuation, which was not suspected to be related to study drug. Three DFO patients had AEs that led to study drug discontinuation: meningitis and neurosensory deafness suspected to be related to treatment, and myocardial T2* <6ms not suspected related to DFO. Two deaths occurred during the study; both following AEs leading to discontinuation. One death in the deferasirox arm was due to arrhythmia, and was not suspected to be related to study drug. The other death in a DFO patient was due to meningitis, and was suspected by the investigator to be related to study drug with splenectomy and progression of diabetes considered possible contributory factors.

**Laboratory parameters**

Overall, three (3.1%) patients in the deferasirox cohort and one (1.1%) in the DFO cohort had two consecutive serum creatinine increases of >33% above baseline values and above the ULN. Increases were transient and managed with dose reduction and/or interruption. Increased blood creatinine was also reported as an AE in all four patients. After 1-year of
treatment, mean ±SD creatinine clearance had decreased in both deferasirox (–37.0±42.9mL/min) and DFO patients (–23.1±36.6mL/min), although on average no progressive decreases were observed.

Mean ±SD baseline ALT was elevated in both deferasirox (71.6±84.0U/L) and DFO (58.7±44.5U/L) treatment arms. Among patients with abnormal baseline ALT, levels had improved to within the normal range in 20 (31.7%) and 22 (39.3%) patients after 1 year of treatment with deferasirox or DFO, respectively. Overall, mean ALT levels decreased during treatment with deferasirox (Month 12: 54.2±83.9U/L; change from baseline, –3.5±80.4U/L) and with DFO (46.3±42.2U/L; 18.9±35.5U/L). During the study, six (3.2%) patients had two consecutive ALT increases >5x ULN and 2x baseline; including four (4.2%) deferasirox patients and two (2.2%) DFO patients. ALT increases in deferasirox patients were transient and resolved with dose interruption (in two patients) or without intervention (in one patient). In the remaining deferasirox patient, this was noted at the last visit on record and no follow-up information was available. In DFO patients, ALT levels returned to baseline after dose interruption in one patient, and without intervention in the second patient.
Discussion

Myocardial siderosis remains a common cause of death in patients with beta-thalassemia major, and there is therefore a need to optimize chelation regimens specifically for myocardial iron removal.\textsuperscript{6–9} CORDELIA was the first randomized controlled trial comparing deferasirox with an intensified DFO regimen for myocardial iron removal in patients with beta-thalassemia major. The study met its primary endpoint in demonstrating non-inferiority of deferasirox compared with DFO. After 1 year of treatment, myocardial T2* improved by 12% from baseline with deferasirox, and by 7% in patients treated with DFO. There was a trend towards superiority for deferasirox, which failed to meet conventional significance (\(P=0.057\)). The importance of deferasirox as a non-inferior alternative treatment for cardiac siderosis to DFO lies in its oral preparation which is preferable to injected DFO, which may have substantial long-term compliance problems.

There are few randomized controlled trials assessing the efficacy and safety of iron chelation therapy in beta-thalassemia major patients with myocardial iron overload.\textsuperscript{14,22,25} While CORDELIA adds to this body of data, additional well-designed randomized comparisons would still be valuable. A comparison of deferiprone and DFO in 61 patients by Pennell \textit{et al.} showed that improvement in myocardial T2* was significantly greater for deferiprone than DFO (27% vs 13%; \(P=0.023\)) over 1 year.\textsuperscript{14} Patients treated with deferiprone (\(n=29\)) had baseline myocardial T2* of 13.0ms, and patients treated with DFO (\(n=32\)) had T2* of 13.3ms. A study by Tanner \textit{et al.} reports that in 65 patients, myocardial T2* improved by 50% in patients receiving deferiprone and DFO combination therapy and by 24% in patients receiving DFO alone.\textsuperscript{22} In all treatment arms, including DFO, improvements in myocardial T2* in these two studies were greater than observed in CORDELIA. However, differences observed between the CORDELIA study and prior studies also need to be interpreted in the light of baseline patient demographics in the respective studies and differences in treatment doses of DFO. It is notable, for example, that baseline LIC in both the Pennell \textit{et al.} and Tanner \textit{et al.} studies was significantly lower than in the CORDELIA study, which may impact cardiac T2* response. In the Pennell \textit{et al.} study, for example, patients randomized to deferiprone and DFO had LIC reported as 6.2±6.0mg Fe/g dw and 6.3±5.8mg Fe/g dw respectively.\textsuperscript{14} Even when taking into account underestimation (around 50%)\textsuperscript{35} by superconducting quantum interference device
measurements used in this previous study, the baseline LIC levels observed in CORDELIA patients (30.0±17.7mg Fe/g dw) remain higher. This is also confirmed by differences in serum ferritin levels (mean of 1791 ng/mL in deferiprone patients and 2795 ng/mL in DFO patients,\textsuperscript{14} versus a median of 4878 ng/mL in CORDELIA patients). Serum ferritin levels were also lower in the Tanner et al. study (1574 and 1379ng/mL for combined deferiprone and DFO vs DFO alone, respectively)\textsuperscript{22}, compared with CORDELIA. Wood et al. have reported that baseline LIC and serum ferritin levels are clinically relevant predictors of cardiac response to deferasirox therapy.\textsuperscript{23} This is consistent with results from CORDELIA, in which patients with LIC <7mg Fe/g dw treated with deferasirox showed a trend towards greater improvement in myocardial T2* compared with patients with higher baseline LIC.

Further differences between the CORDELIA study and other randomized comparisons included patient demographics, study design and dose of DFO. Pennell et al. reported a DFO dose equivalent to 35mg/kg/day for 7 days/week,\textsuperscript{14} Tanner et al. reported 31.0mg/kg/day for 7 days/week,\textsuperscript{22} while the dose in CORDELIA was higher at 41.5mg/kg/day for 7 days/week. Lower DFO dosing might have favored deferiprone (or deferiprone plus DFO combination). Patient compliance can be a concern with DFO treatment, however, patient-reported adherence to study drug regimen was very good in CORDELIA. DFO compliance as assessed by the percentage of completed infusions in the two studies by Pennell et al. and the Tanner et al. was also >90%\textsuperscript{14,22}

Longitudinal studies of up to 3 years of treatment with deferasirox have shown improvements in myocardial T2* over time.\textsuperscript{20,23,26} Since heart iron clearance is slower than that of the liver,\textsuperscript{10} normalization of myocardial T2* may take several years. To that end, a 1-year extension for CORDELIA is currently ongoing. Nevertheless, over a period of 1 year, we observed normalization of myocardial T2* in 17.6% of deferasirox patients, compared with 6.2% of DFO patients overall. Importantly, 35.5% of deferasirox patients and 20.0% of DFO patients with severe myocardial siderosis improved to the mild-to-moderate category after 1-year treatment. Three patients in each treatment group discontinued the study as a result of worsening of myocardial T2*.

Improvements in LVEF have been shown after treatment with either deferiprone monotherapy or in combination with DFO.\textsuperscript{14,22} In CORDELIA, LVEF remained stable during
the study period. Other prospective clinical trials with deferasirox in patients with myocardial siderosis have also shown no change in LVEF for treatment periods up to 3 years.\textsuperscript{20,23,26,28} In contrast, recent results from a small study of 13 patients with T2\textsuperscript{*} from 10 to 20ms treated with deferasirox for 32±7 months showed improvement in LVEF, albeit from lower baseline values of 59.8\%.\textsuperscript{36} In CORDELIA, approximately half of both the deferasirox and DFO patients who had low LVEF at baseline improved to within the normal range\textsuperscript{34} by EOS. This may be important since even small improvements in LVEF can reduce the risk of heart failure, even in beta-thalassemia patients with LVEF in the normal range.\textsuperscript{37} However, 8.8\% of deferasirox patients and 12.7\% of DFO patients decreased LVEF to below LLN.

Rates of dose reduction and/or interruption were similar between treatment groups, and frequency of AEs was also similar. The safety profile of deferasirox was comparable to previous reports; with the most common drug-related AEs being increased laboratory parameters and diarrhea.\textsuperscript{20,23,26} Two deaths occurred during the study. The death of the patient treated with deferasirox was due to arrhythmia and was not considered related to study drug. The DFO patient who died as a result of meningitis was suspected by the investigator to be related to DFO, with splenectomy and progression of diabetes identified as possible contributory factors.

In conclusion, the randomized controlled trial CORDELIA met its primary endpoint, demonstrating non-inferiority of once-daily oral treatment with deferasirox compared with DFO for the removal of myocardial iron, with a trend towards superiority for deferasirox. These data add to the body of knowledge allowing physicians to make best informed choices for their patients.
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Authorship contributions

JBP, YL, AE-B, KMB, ME, AY, YK and YA served as investigators on this trial, enrolling patients. They contributed to data interpretation, reviewed and provided their comments on this manuscript. DJP, JBP, AP and YA served as Study Steering Committee members overseeing the conduct of the trial, from study design to analysis plan and data interpretation. TL, DH and MW assisted in developing the trial protocol, coordinating the execution of the trial and contributing to the analysis, interpretation and reporting of the trial data. YZ served as the trial statistician. All authors approved the final manuscript.

Disclosures

DJP reports consultancy and receiving research grant funding and honoraria from Novartis Pharmaceuticals and AMAG; lecture fees from Novartis Pharmaceuticals; consultancy and honoraria from ApoPharma Inc and from Shire; and is a director and equity holder in Cardiovascular Imaging Solutions. YA reports participation in advisory boards and speaker’s bureau, and receiving honoraria and research grant funding from Novartis Pharmaceuticals; and participation in advisory boards and receiving research grant funding from Shire. JBP reports consultancy, receiving research grant funding and honoraria from Novartis Pharmaceuticals; consultancy and receiving research grant funding from Shire;
and consultancy for Celgene. AP reports participation in advisory boards and receiving research grant funding from Novartis Pharmaceuticals. DH and YZ are employees of Novartis Pharmaceuticals, and TL and MW are employees of Novartis Pharma AG. KMB, AE-B, AY, YK, ME and YL have no relevant conflicts of interest to disclose.
References


### Table 1. Baseline patient characteristics (mean ±SD unless otherwise stated)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Deferasirox (N=98)</th>
<th>DFO (N=99)</th>
<th>All patients (N=197)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta-thalassemia major, n (%)</strong></td>
<td>98 (100)</td>
<td>99 (100)</td>
<td>197 (100)</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td>19.9±6.5</td>
<td>19.7±6.3</td>
<td>19.8±6.4</td>
</tr>
<tr>
<td><strong>Age range, years</strong></td>
<td>10.0–39.0</td>
<td>10.0–40.0</td>
<td>10.0–40.0</td>
</tr>
<tr>
<td><strong>Male:female, n</strong></td>
<td>58:40</td>
<td>57:42</td>
<td>115:82</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>59 (60.2)</td>
<td>59 (59.6)</td>
<td>118 (59.9)</td>
</tr>
<tr>
<td>Black</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Asian</td>
<td>38 (38.8)</td>
<td>40 (40.4)</td>
<td>78 (39.6)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1.0)</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td><strong>Hepatitis status, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>1 (1.0)</td>
<td>2 (2.0)</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>22 (22.4)</td>
<td>19 (19.2)</td>
<td>41 (20.8)</td>
</tr>
<tr>
<td>Hepatitis B and C</td>
<td>0 (0.0)</td>
<td>2 (2.0)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>No hepatitis</td>
<td>75 (76.5)</td>
<td>80 (80.8)</td>
<td>155 (78.7)</td>
</tr>
<tr>
<td><strong>Time since start of blood transfusions, years</strong></td>
<td>19.3±6.4</td>
<td>18.4±6.2</td>
<td>18.8±6.3</td>
</tr>
<tr>
<td><strong>Total number of blood transfusions received</strong></td>
<td>315.6</td>
<td>294.8</td>
<td>305.3</td>
</tr>
<tr>
<td><strong>Previous chelation therapy, n (%)</strong></td>
<td>96 (100)</td>
<td>91 (100)</td>
<td>187 (100)</td>
</tr>
<tr>
<td>DFO</td>
<td>41 (42.7)</td>
<td>39 (42.9)</td>
<td>80 (42.8)</td>
</tr>
<tr>
<td>Deferiprone</td>
<td>9 (9.4)</td>
<td>5 (5.5)</td>
<td>14 (7.5)</td>
</tr>
<tr>
<td>DFO + deferiprone</td>
<td>21 (21.9)</td>
<td>21 (23.1)</td>
<td>42 (22.5)</td>
</tr>
<tr>
<td>Deferasirox</td>
<td>18 (18.8)</td>
<td>23 (25.3)</td>
<td>41 (21.9)</td>
</tr>
<tr>
<td>Other†</td>
<td>7 (7.3)</td>
<td>3 (3.3)</td>
<td>10 (5.3)</td>
</tr>
<tr>
<td><strong>Time since start of first chelation therapy, years</strong></td>
<td>14.0±7.0</td>
<td>14.3±7.2</td>
<td>14.2±7.1</td>
</tr>
<tr>
<td><strong>Myocardial T2+ categories, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 to &lt;10ms</td>
<td>33 (33.7)</td>
<td>32 (32.3)</td>
<td>65 (33.0)</td>
</tr>
<tr>
<td>10 to ≤20ms</td>
<td>65 (66.3)</td>
<td>67 (67.7)</td>
<td>132 (67.0)</td>
</tr>
<tr>
<td><strong>LVEF, n (%)†</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;LLN by Westwood†</td>
<td>11 (12.1)</td>
<td>10 (12.3)</td>
<td>21 (12.2)</td>
</tr>
<tr>
<td>LIC categories, n (%)</td>
<td>≥LLN by Westwood&lt;sup&gt;a&lt;/sup&gt;</td>
<td>LIC, mg Fe/g dw&lt;sup&gt;b&lt;/sup&gt;</td>
<td>LIC categories, n (%)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>----------------------</td>
<td>-----------------------------</td>
<td>-----------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>LIC &lt;7 mg Fe/g dw</td>
<td>11 (12.1)</td>
<td>8 (9.9)</td>
<td>19 (11.0)</td>
</tr>
<tr>
<td>LIC 7–&lt;15 mg Fe/g dw</td>
<td>14 (15.4)</td>
<td>14 (17.3)</td>
<td>28 (16.3)</td>
</tr>
<tr>
<td>LIC ≥15 mg Fe/g dw</td>
<td>66 (72.5)</td>
<td>59 (72.8)</td>
<td>125 (72.7)</td>
</tr>
<tr>
<td>Median serum ferritin (range), ng/mL&lt;sup&gt;d&lt;/sup&gt;</td>
<td>5062</td>
<td>4684</td>
<td>4878</td>
</tr>
</tbody>
</table>

<sup>a</sup>Unknown, or patients received irregular deferiprone and/or deferoxamine therapy.  
<sup>b</sup>Westwood criteria: lower limit of normal (LLN) for males: <59, and for females: <63.  
<sup>c</sup>Based on the per-protocol population.  
<sup>d</sup>Based on the per-protocol population.
Table 2. Comparison of myocardial T2* change from baseline in patients treated with deferasirox or DFO for 1 year

<table>
<thead>
<tr>
<th></th>
<th>Deferasirox</th>
<th>DFO</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=91)</td>
<td>(N=81)</td>
<td>(N=172)</td>
</tr>
<tr>
<td><strong>Per-protocol population</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gmean T2* (CV) at baseline</td>
<td>11.2 (32.6)</td>
<td>11.6 (30.7)</td>
<td>11.4 (31.7)</td>
</tr>
<tr>
<td>Gmean T2* (CV) at end of study‡</td>
<td>12.6 (42.6)</td>
<td>12.3 (34.7)</td>
<td>12.5 (38.9)</td>
</tr>
<tr>
<td>Gmean ratio of Month 12/Baseline (95% CI)</td>
<td>1.12 (1.07, 1.18)</td>
<td>1.07 (1.02, 1.11)</td>
<td>1.10 (1.06, 1.13)</td>
</tr>
<tr>
<td>Ratio of Gmean ratios of deferasirox vs DFO</td>
<td>–</td>
<td>–</td>
<td>1.056</td>
</tr>
<tr>
<td>Repeated 95% CI of the ratio of Gmean ratios</td>
<td>–</td>
<td>–</td>
<td>(0.998, 1.133)</td>
</tr>
<tr>
<td>P-value for superiority‡</td>
<td>–</td>
<td>–</td>
<td>0.057</td>
</tr>
<tr>
<td><strong>Intention to treat population</strong></td>
<td>(N=92)</td>
<td>(N=88)</td>
<td>(N=180)</td>
</tr>
<tr>
<td>Gmean T2* (CV) at baseline</td>
<td>11.2 (31.9)</td>
<td>11.6 (32.9)</td>
<td>11.4 (32.4)</td>
</tr>
<tr>
<td>Gmean T2* (CV) at end of study‡</td>
<td>12.5 (43.0)</td>
<td>12.0 (36.3)</td>
<td>12.2 (39.7)</td>
</tr>
<tr>
<td>Gmean ratio of Month 12/Baseline (95% CI)</td>
<td>1.12 (1.07, 1.18)</td>
<td>1.06 (1.02, 1.11)</td>
<td>1.09 (1.06, 1.13)</td>
</tr>
<tr>
<td>Ratio of Gmean ratios of deferasirox vs DFO</td>
<td>–</td>
<td>–</td>
<td>1.055</td>
</tr>
<tr>
<td>Repeated 95% CI of the ratio of Gmean ratios</td>
<td>–</td>
<td>–</td>
<td>(0.999, 1.129)</td>
</tr>
<tr>
<td>P-value for superiority‡</td>
<td>–</td>
<td>–</td>
<td>0.054</td>
</tr>
</tbody>
</table>

‡Last available value at least 150 days after randomization;
§Two-sided adjusted P-value based on the Tsiatis, Rosner and Mehta stage-wise ordering.
Figures

Figure 1. Patient disposition

<table>
<thead>
<tr>
<th>Screened, n=925</th>
<th>Excluded, † n=728</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unacceptable test procedure result, n=588</td>
</tr>
<tr>
<td></td>
<td>Unacceptable laboratory value, n=99</td>
</tr>
<tr>
<td></td>
<td>Subject withdrew consent, n=40</td>
</tr>
<tr>
<td></td>
<td>Other, n=30</td>
</tr>
<tr>
<td></td>
<td>Unacceptable medical history/concomitant diagnosis, n=4</td>
</tr>
<tr>
<td></td>
<td>Did not meet diagnostic/severity criteria, n=1</td>
</tr>
<tr>
<td></td>
<td>Unknown, n=1</td>
</tr>
</tbody>
</table>

Randomized, n=197

Deferasirox, n=98

Discontinued, n=2
- Consent withdrawn, n=1
- Protocol deviation, n=1

Received study drug, ‡ n=96

Analyzed for efficacy, § n=91
- Excluded from analysis, † n=7
- Did not receive ≥6 months study drug, n=5
- No T2* value after ≥150 days, n=7

Discontinued, n=14
- Un satisfactory therapeutic effect, n=1
- Consent withdrawn, n=6
- Lost to follow-up, n=3
- Abnormal test procedure result, n=3

Completed 12 months, n=82

DFO, n=99

Discontinued, n=8
- Consent withdrawn, n=7
- Protocol deviation, n=1

Received study drug, ‡ n=91

Analyzed for efficacy, § n=81
- Excluded from analysis, † n=18
- Did not receive ≥6 months study drug, n=12
- No T2* value after ≥150 days, n=15
- >20% days without dose, n=4

Discontinued, n=13
- Death, n=1
- Unsatisfactory therapeutic effect, n=2
- Consent withdrawn, n=5
- Lost to follow-up, n=2
- Abnormal test procedure result, n=2
- Protocol deviation, n=1

Completed 12 months, n=78

† A patient could have multiple reasons for screening failure or exclusion from efficacy analysis. ‡ These patients comprised the safety set. § Efficacy was assessed using the per-protocol analysis set. † Because of worsening of cardiac T2* in three deferasirox patients and three DFO patients; LVEF decreased <50% in a DFO patient and cardiomegaly in a deferasirox patient.
Figure 2. Gmean myocardial T2* in patients treated with deferasirox or DFO for 1 year, in (A) all patients, or patients with (B) baseline myocardial T2* <10ms (C) baseline myocardial T2* ≥10ms (D) baseline LIC <7mg Fe/g dw (E) baseline LIC 7–<15mg Fe/g dw or (F) baseline LIC ≥15mg Fe/g dw†

†Based on the per-protocol population.
Figure 3. Shift in proportion of patients with severe, mild-to-moderate and normalized cardiac T2* values at baseline and EOS in patients treated with (A) deferasirox or (B) DFO for 1 year†

A

B

†Based on the per-protocol population.
A 1-year randomized controlled trial of deferasirox versus deferoxamine for myocardial iron removal in beta-thalassemia major (CORDELIA)


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