RESEARCH ARTICLE

Sustained improvements in myocardial T2* over 2 years in severely iron-overloaded patients with beta thalassemia major treated with deferasirox or deferoxamine

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Long-term controlled studies are needed to inform on the clinical benefit of chelation therapy for myocardial iron removal in transfusion-dependent beta thalassemia patients. In a 1-year nonrandomized extension to the CORDELIA study, data collected from patients with myocardial siderosis provided additional information on deferasirox or deferoxamine (DFO) efficacy and safety. Myocardial (m)T2* increased from baseline 11.6 to 15.9 ms in patients receiving deferasirox for 24 months (n = 74; geometric mean [G_{mean}] ratio of month 24/baseline 1.38 [95% confidence interval 1.28, 1.49]) and from 10.8 to 14.2 ms in those receiving DFO (n = 29; G_{mean} ratio 1.33 [1.13, 1.55]; P = 0.93 between groups). Improved mT2* with deferasirox was evident across all subgroups evaluated irrespective of baseline myocardial (mT2* < 10 vs. ≥ 10 ms) or liver (LIC <15 vs. ≥15 mg Fe/g dw) iron burden. Mean LVEF was stable and remained within normal limits with deferasirox or DFO. Liver iron concentration decreased from high baseline values of 30.6 ± 18.0 to 14.4 ± 16.6 mg Fe/g dw at month 24 in deferasirox patients and from 36.8 ± 15.6 to 11.0 ± 12.1 mg Fe/g dw in DFO patients. The long-term safety profile of deferasirox or DFO was consistent with previous reports; serious drug-related AEs were reported in 6.8% of deferasirox and 6.9% of DFO patients. Continued treatment of severely iron-overloaded beta thalassemia patients with deferasirox or DFO led to sustained improvements in myocardial iron irrespective of high or low baseline myocardial or liver iron burden, in parallel with substantial improvements in liver iron (Clinicaltrials.gov identifier: NCT00600938).
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Introduction

Myocardial siderosis resulting in heart failure is a major cause of death in transfusion-dependent beta thalassemia major patients [1,2]. The heart is one of the most sensitive organs to iron toxicity [3] and the clinical consequences of iron overload including symptoms of cardiac dysfunction have been observed from an early age, even in children aged less than 10 years [4]. Considerable variation has been observed in the kinetics of iron loading in the heart and liver, which is not completely understood [5]. Iron clears more slowly from the heart than the liver and as such, patients with myocardial siderosis may require a longer duration of iron chelation therapy to achieve a low-risk myocardial iron status (cardiovascular magnetic resonance [CMR]-measured T2* >20 ms) [6,7].

The controlled studies evaluating the available iron chelators, deferoxamine (DFO; Desferal®), deferiprone (Ferriprox®), and deferasirox (Exjade®) have all demonstrated efficacy in the removal of myocardial iron with acceptable safety profiles [7–13]; however, many of these clinical trials were limited to 1 year. Longer-term single-arm studies with deferasirox for myocardial iron removal have shown a continuous decrease in

Additional Supporting Information may be found in the online version of this article.

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TABLE I. Characteristics at Core Baseline for Patients Who Continued into the Extension

Variable	Deferasirox (n = 74)	DFO (n = 29)
Beta-thalassemia major, *n* (%)	74 (100.0)	29 (100.0)
Mean age (years)	20.1 (6.9)	17.0 (5.4)
Male, *n* (%)	44 (59.5)	17 (58.6)
Race, *n* (%)		
Caucasian	43 (58.1)	12 (41.4)
Asian	31 (41.9)	17 (58.6)
Hepatitis status, *n* (%)		
Hepatitis B	0	1 (3.4)
Hepatitis C	18 (24.3)	6 (20.7)
Hepatitis B and C	0	1 (3.4)
No hepatitis	56 (75.7)	23 (79.3)
Geometric mean myocardial T2* (CV) (ms)	11.6 (30.9)	10.8 (29.8)
Myocardial T2* categories, *n* (%)		
6 to <10 ms	22 (29.7)	11 (37.9)
10 to ≤20 ms	52 (70.3)	18 (62.1)
Mean LVEF ± SD (%)	67.1 ± 5.4	67.7 ± 5.5
LVEF categories, *n* (%)		
<LLN by Westwood[a]	7 (9.5)	2 (6.9)
≥LLN by Westwood[a]	67 (90.5)	27 (93.1)
Mean LIC ± SD, mg Fe/g dw	30.6 ± 18.0	36.8 ± 15.6
LIC categories, *n* (%)		
<7 mg Fe/g dw	8 (10.8)	2 (6.9)
7 to <15 mg Fe/g dw	11 (14.9)	1 (3.4)
≥15 mg Fe/g dw	55 (74.3)	26 (89.7)
Median serum ferritin (range), ng/mL	4902 (613–13,104)	5896 (2368–9898)

CV, coefficient of variation; LIC, liver iron concentration; LLN, lower limit of normal; LVEF, left ventricular ejection fraction; SD, standard deviation.
[a] Westwood criteria: low, normal, and high for males: <59, ≥59 to ≤83, and >83; for females: <63, ≥63 to ≤87, and >87, respectively.

myocardial iron with up to 3 years of treatment with a clinically manageable safety profile [7,14,15]. CORDELIA was a large, prospective randomized study comparing deferasirox with DFO in patients with beta thalassemia major who demonstrated, at the end of 1 year, the noninferiority of deferasirox versus DFO for myocardial iron removal, with a trend for superiority (P = 0.057) [8]. A 1-year extension to CORDELIA was planned to collect additional long-term controlled data on the efficacy and safety of deferasirox or DFO in patients with myocardial siderosis when treated for up to 2 years.

Methods

Patients. Detailed patient inclusion and exclusion criteria have been reported previously [8]. Briefly, patients eligible for enrollment at baseline were male or female, aged ≥10 years with beta thalassemia major, sideroblastic anemia, myelodysplastic dysplastic syndromes (low/intermediate-1) or Diamond-Blackfan anemia; however, only patients with beta thalassemia major fulfilled all inclusion criteria and were enrolled. Patients were required to have CMR-measured myocardial T2* between 6 and 20 ms and R2-magnetic resonance imaging (MRI)-measured liver iron concentration (LIC) ≥3 mg Fe/g dry weight (dw). Patients provided written consent for participating in the extension study having completed 12 months of study treatment as described in the core protocol. Patients must also have been deemed to be benefiting from study treatment by the investigator.

Study design. The CORDELIA study (NCT00600938) was a 1-year prospective, multinational, randomized, open-label, parallel-group, Phase II study conducted in 22 centers across 11 countries as previously reported [8]. Patients completing first year could decide to continue on deferasirox or DFO as assigned, or switch treatment upon entering a 1-year extension, if the treatment was judged by the investigator to be of therapeutic benefit. Results for patients continuing on the same therapy in the extension (deferasirox or DFO) are reported here. Target doses were either an intensified DFO regimen of between 50 and 60 mg/(kg day) administered subcutaneously for 8 to 12 hrs, 5–7 days/week, or once-daily oral deferasirox at 40 mg/(kg day). Study medication was dispensed at each visit, and all medications returned by the patient were recorded to assess compliance. The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. An independent data monitoring committee reviewed the safety data and advised on study continuation and/or any changes to the protocol.

Assessments and statistical methods. CMR assessments for myocardial iron (T2*) and cardiac function, and liver R2-MRI were performed after completing 6 and 12 months of the extension study. Serum ferritin was assessed on blood samples drawn monthly during the extension. Efficacy was assessed using the full analysis set, including all patients enrolled in the extension. Efficacy data were analyzed as changes from core baseline to month 24. The change in myocardial T2* was assessed as the ratio of the geometric mean (G_{mean}) T2* at month 24 divided by that at baseline ($G_{mean\ month24}/G_{mean\ baseline}$), in patients with data available at both baseline and month 24. Safety was assessed in all patients enrolled in the extension who received at least one dose of study drug and had at least one safety assessment in the extension period. Safety was evaluated through continuous monitoring and recording of adverse events (AEs), serious AEs (SAEs), laboratory testing, and clinical evaluations. All data were analyzed descriptively and graphically. An analysis of covariance model adjusting for baseline LIC was used to compare the T2* ratio at month 24 ($G_{mean\ month24}/G_{mean\ baseline}$) between treatment groups. Ad hoc analysis of mean absolute change in myocardial iron concentration (MIC) was conducted. The MIC was derived from myocardial T2* values based on the formula described by Carpenter et al. [16]. Briefly, $[Fe] = 45 \cdot (T2^*)^{-1.22}$, where [Fe] is measured in mg/g dw and T2* is measured in milliseconds.

Results

Patient disposition

Overall, 160/197 patients completed the core 1-year study, and 146 patients entered the extension. In total, 74/82 (90.2%) patients who completed 1 year continued to receive deferasirox in the extension, and 65/74 (87.8%) patients completed 2 years; discontinuations during the extension were due to unsatisfactory therapeutic effect (n = 4), withdrawal of consent (n = 2), AEs (increased transaminases and hepatic neoplasm, n = 1), lost to follow-up (n = 1), and death (n = 1; not considered to be drug related). For DFO therapy, 29/78 (37.2%) patients continued to receive DFO in the extension, and 24/29 (82.8%) patients completed 2 years; discontinuations were due to consent withdrawals (n = 2), abnormal test procedure result (n = 1), unsatisfactory therapeutic effect (n = 1), and lost to follow-up (n = 1). Of patients entering the extension phase, 42 (28.8%) switched from DFO to deferasirox, and only one patient switched from deferasirox to DFO.

Baseline demographics and clinical characteristics

Since patients entering the extension were no longer randomized, there were some small differences across baseline demographics and

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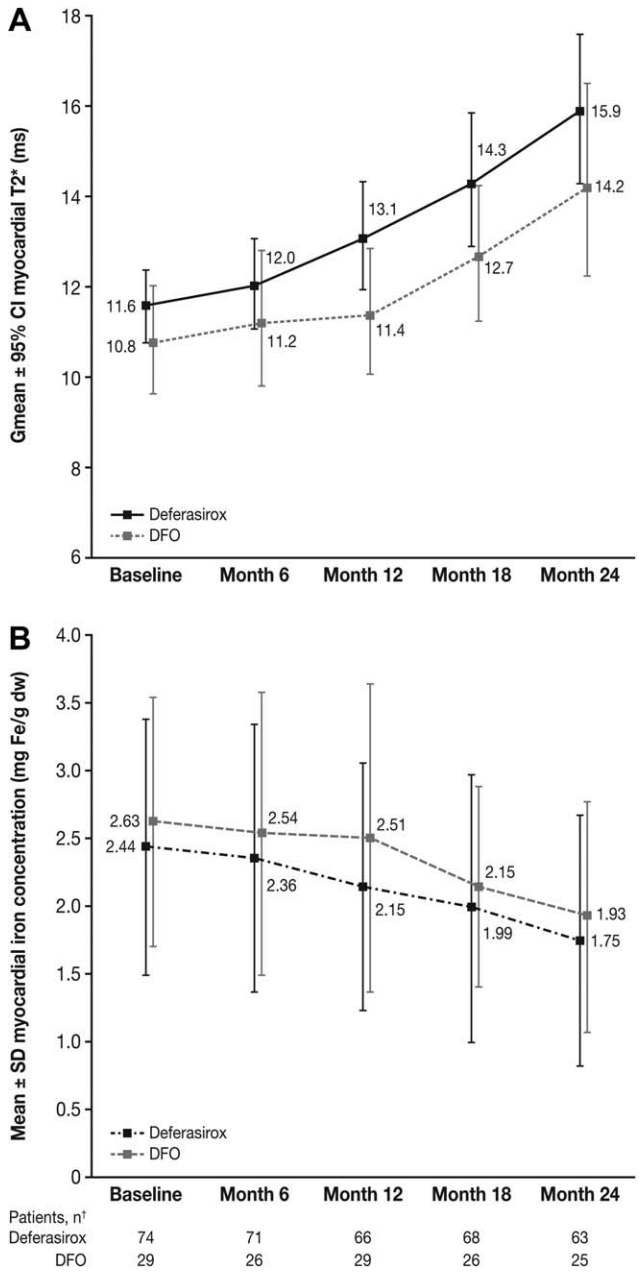


Figure 1. (A) Myocardial T2* and (B) MIC in patients with beta thalassemia major treated with deferasirox or DFO for 2 years. Asterisk *n* refers to the last available value for each time point. CI, confidence interval; G_{mean}, geometric mean; SD, standard deviation.

characteristics between the deferasirox and DFO groups (Table I). Of note, patients continuing to receive DFO had higher baseline LIC and serum ferritin levels. Nevertheless, at the core study baseline, all patients included in this analysis exhibited heavy iron overload. Among deferasirox patients, G_{mean} myocardial T2* was 11.6 ms (coefficient of variation [CV] 30.9) and 29.7% of patients had severe myocardial iron overload (myocardial T2* <10 ms). Among DFO patients, G_{mean} myocardial T2* was 10.8 ms (CV 29.8) and 37.9% of patients had severe myocardial iron overload. In addition to myocardial iron overload, mean LIC ± standard deviation (SD) was also elevated at 30.6 ± 18.0 and 36.8 ± 15.6 mg Fe/g dw in deferasirox and DFO patients, respectively.

Exposure to treatment and compliance

Mean ± SD actual dose over 2 years was 35.5 ± 6.3 mg/(kg day) deferasirox [36.9 ± 4.2 mg/(kg day) in the core and 34.2 ± 8.8 mg/(kg day) in the extension phase] and 57.0 ± 13.3 mg/(kg day) DFO for 5 days/week [40.7 ± 9.5 mg/(kg day) when normalized to a 7-day regimen; 60.7 ± 15.4 mg/(kg day) in the core and 53.7 ± 15.0 mg/(kg day) in the extension phase for 5 days/week]. In total, seven (9.6%) and 24 (32.9%) patients received deferasirox doses ≥40 mg/(kg day) in the core and extension phase, respectively. For DFO, 23 (79.3%) and 19 (65.5%) patients received doses ≥50 mg/(kg day) for 5 days/week in the core and extension phase, respectively. Overall, patients received study drug for a median (range) duration of 720 (377–762) and 719 (358–738) days in deferasirox and DFO groups; 99.1 and 98.1% of the planned deferasirox and DFO doses were taken, respectively.

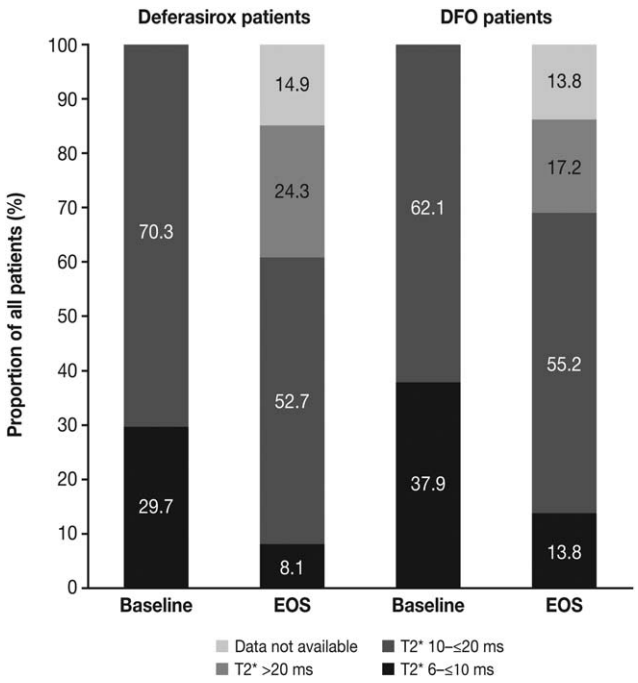


Figure 2. Shift in the proportion of patients with severe, mild-to-moderate and normalized myocardial T2* at baseline and end of study (EOS).

Iron intake

Average iron intake was <0.3 mg/(kg day) in 56.8% of deferasirox patients and 65.5% of DFO patients, 0.3–0.5 mg/(kg day) in 36.5% of deferasirox patients and 34.5% of DFO patients, and >0.5 mg/(kg day) in 6.8% of deferasirox patients.

Efficacy of deferasirox and DFO

Myocardial T2.* At month 24, G_{mean} myocardial T2* (CV) had increased from 11.6 (30.9) ms at baseline to 15.9 ms (43.4) in deferasirox patients ($G_{mean\ ratio}$ of month 24/baseline 1.38 [95% confidence interval (CI) 1.28, 1.49]) and from 10.8 (29.8) to 14.2 ms (37.3) in DFO patients ($G_{mean\ ratio}$ 1.33 [1.13, 1.55]), indicating a 38 and 33% improvement, respectively (following improvements of 17 and 6% after 12 months; Fig. 1A). A comparison of T2* ratios (month 24/baseline), adjusting for baseline LIC, revealed no difference between groups ($P = 0.93$).

After 2 years, 18 (24.3%) patients continuing to receive deferasirox and five (17.2%) continuing on DFO normalized their myocardial T2* (value >20 ms; Fig. 2). Furthermore, 16 (72.7%) patients receiving deferasirox, and six (54.5%) patients receiving DFO improved from severe baseline myocardial iron overload to a lower risk status (from myocardial T2* 6 to <10 ms to 10 to ≤20 ms). However, 3 (5.8%) deferasirox and 2 (11.1%) DFO patients worsened from baseline myocardial T2* of between 10 and ≤20 ms to <10 ms after 2 years.

TABLE II. Summary of Deferasirox and DFO Efficacy by Iron Overload Status at Core Baseline

Variable	Baseline myocardial T2* ≥10 ms (n = 52)	Baseline myocardial T2* <10 ms (n = 22)	Baseline LIC <15 mg Fe/g dw (n = 19)	Baseline LIC ≥15 mg Fe/g dw (n = 55)
Deferasirox				
Mean age (years)	20.2 (6.8)	19.6 (7.2)	22.3 (6.4)	19.3 (6.9)
Geometric mean myocardial T2* at baseline (CV) (ms)	13.6 (18.7)	7.9 (14.0)	13.0 (28.7)	11.1 (30.8)
Geometric mean myocardial T2* at month 24 (CV) (ms)	18.0 (40.5)	12.1 (34.3)	20.0 (40.4)	14.5 (40.8)
$G_{mean\ ratio}$ of month 24/baseline (95% CI)	1.32 (1.20, 1.44)	1.52 (1.31, 1.75)	1.54 (1.40, 1.68)	1.32 (1.19, 1.46)
Mean baseline LIC ± SD (mg Fe/g dw)	29.8 ± 18.5	32.6 ± 17.1	7.7 ± 3.0	38.5 ± 13.6
Mean month 24 LIC ± SD (mg Fe/g dw)	15.7 ± 17.8	11.6 ± 13.7	3.0 ± 1.9	19.3 ± 17.8
Mean LIC ± SD absolute change from baseline (95% CI) (mg Fe/g dw)	−13.7 ± 15.6 (−18.6, −8.8)	−20.2 ± 13.7 (−26.8, −13.6)	−4.9 ± 3.5 (−6.7, −3.2)	−20.4 ± 16.0 (−25.3, −15.4)
Mean ± SD actual deferasirox dose [mg/(kg day)]	35.6 ± 6.7	35.2 ± 5.1	28.9 ± 7.9	37.8 ± 3.3
Variable	Baseline myocardial T2* ≥10 ms (n = 18)	Baseline myocardial T2* <10 ms (n = 11)	Baseline LIC <15 mg Fe/g dw (n = 3)	Baseline LIC ≥15 mg Fe/g dw (n = 26)
DFO				
Mean age(years)	16.9 (5.2)	17.2 (5.9)	21.7 (3.1)	16.5 (5.4)
Geometric mean myocardial T2* at baseline (CV) (ms)	12.9 (20.3)	8.1 (14.9)	10.3 (10.8)	10.9 (31.4)
Geometric mean myocardial T2* at month 24 (CV) (ms)	14.9 (35.8)	13.3 (40.2)	11.6 (22.2)	14.5 (38.1)
G_{mean} ratio of month 24/baseline (95% CI)	1.17 (0.96, 1.44)	1.60 (1.25, 2.04)	1.19 (0.08, 17.46)	1.34 (1.13, 1.59)
Mean baseline LIC ± SD (mg Fe/g dw)	37.3 ± 15.5	36.0 ± 16.5	7.6 ± 3.4	40.2 ± 12.5
Mean month 24 LIC ± SD (mg Fe/g dw)	14.2 ± 13.8	5.6 ± 5.9	4.1 ± 0.8	11.6 ± 12.5
Mean LIC ± SD absolute change from baseline (95% CI) (mg Fe/g dw)	−26.0 ± 15.7 (−34.7, −17.4)	−26.0 ± 14.4 (−37.1, −15.0)	−4.0 ± 5.5 (−53.6, 45.6)	−28.0 ± 13.8 (−34.1, −21.9)
Mean ± SD actual DFO dose [mg/(kg day)]	61.3 ± 10.5	50.1 ± 15.0	59.8 ± 10.2	56.7 ± 13.7

CV, coefficient of variation; DFO, deferoxamine; dw, dry weight; LIC, liver iron concentration, SD, standard deviation.

Cardiac function. Mean ± SD left ventricular ejection fraction (LVEF) remained stable and within the normal range after 2 years of treatment with deferasirox (baseline: 67.1 ± 5.4%; month 24: 67.7 ± 5.7%; absolute change +0.6 ± 4.7%), and DFO (baseline: 67.7 ± 5.5%; month 24: 67.5 ± 4.6%; absolute change –0.6 ± 5.0%). Among patients who remained on the study, no patient developed clinical heart failure during the extension phase.

Other iron parameters. Estimation of MIC showed decreases during 2 years of treatment in both patient groups (Fig. 1B). For deferasirox, mean ± SD MIC decreased from 2.44 ± 0.94 at baseline to 2.15 ± 0.91 mg Fe/g dw at month 12 (mean ± SD absolute change from baseline −0.38 ± 0.67 mg Fe/g dw [95% CI −0.55, –0.21], a 13.9% reduction), and 1.75 ± 0.93 at month 24 (−0.70 ± 0.83 mg Fe/g dw [95% CI −0.91, −0.49]; a 27.4% reduction). For DFO, values decreased from 2.63 ± 0.92 at baseline to 2.51 ± 1.13 mg Fe/g dw at month 12 (−0.12 ± 0.70 mg Fe/g dw [95% CI −0.38, 0.15]; a 3.2% reduction), and 1.93 ± 0.85 at month 24 (−0.69 ± 0.99 mg Fe/g dw [95% CI −1.10, −0.28]; a 21.9% reduction). Mean LIC reduced by 39.3 and 53.3% in deferasirox and DFO patients, respectively, after 12 months and by 54.7 and 68.8% after 24 months. LIC at month 24 reduced to 14.4 ± 16.6 mg Fe/g dw in deferasirox patients (−15.7 ± 15.2 mg Fe/g dw [95% CI −19.7, −11.8]) and 11.0 ± 12.1 mg Fe/g dw in DFO patients (−26.0 ± 14.9 mg Fe/g dw [95% CI −32.3, −19.7]). At month 24, the association between the change from baseline in LIC and the change from baseline in MIC was weak in both the deferasirox (n = 59, r = 0.191) and DFO cohorts (n = 24, r = 0.294). Treatment with deferasirox for 2 years also led to median absolute reductions in serum ferritin of −2163 ng/mL (−10,600 to 939) to a median (range) of 1899 ng/mL (308 to 10,474) at month 24 in deferasirox patients, and −2907 ng/mL (−8180 to 4223) to 1979 ng/mL (533 to 10,630) at month 24 in DFO patients.

Efficacy of deferasirox and DFO by iron overload status at core baseline

Change in myocardial T2* and LIC in patients with baseline T2* ≥10 and <10 ms as well as patients with baseline LIC <15 or ≥15 mg Fe/g dw are summarized in Table II. In patients with baseline myocardial T2* ≥10 ms receiving deferasirox (n = 52), myocardial T2* (CV) increased from 13.6 ms (18.7) to 18.0 ms (40.5) by month 24 (G_{mean} ratio 1.32 [1.20, 1.44]), and from 7.9 ms (14.0) to 12.1 ms (34.3) in patients with T2* <10 ms (n = 22) at baseline ($G_{mean\ ratio}$ 1.52 [1.31, 1.75]; Table II). With DFO, myocardial T2* increased from 12.9 ms (20.3) to 14.9 ms (35.8; G_{mean} ratio 1.17 [0.96, 1.44]) and from 8.1 ms (14.9) to 13.3 ms (40.2; $G_{mean\ ratio}$ 1.60 [1.25, 2.04]) in patients with T2* ≥10 ms (n = 18) and <10 ms (n = 11) at baseline (Table II).

For patients with baseline LIC <15 (n = 19) or ≥15 (n = 55) mg Fe/g dw, myocardial T2* (CV) increased from 13.0 ms (28.7) at baseline to 20.0 (40.4) at month 24 ($G_{mean\ ratio}$ 1.54 [1.40, 1.68]) and from 11.1 ms (30.8) at baseline to 14.5 ms (40.8) at month 24 ($G_{mean\ ratio}$ 1.32 [1.19, 1.46]), respectively in patients receiving deferasirox (Table II). Patient numbers in the LIC <15 mg Fe/g dw DFO arm were too

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low for meaningful interpretation of differences. For patients with baseline LIC ≥15 mg Fe/g dw (n = 26), myocardial T2* increased from 10.9 ms (31.4) at baseline to 14.5 ms (38.1) at month 24 ($G_{mean\ ratio}$ 1.34 [1.13, 1.59]; Table II). Data by serum ferritin subgroups <2500 and ≥2500 ng/mL are included in the Appendix, Supporting Information Table 1.

Safety

Adverse events. The most common AEs (>5%) suspected by the investigator to be related to study drug over 2 years of treatment are shown in Supporting Information Table II. Overall, five (6.8%) deferasirox patients and two (6.9%) DFO patients experienced a drug-related SAE (Supporting Information Table II). One deferasirox patient discontinued due to AEs; increased transaminases, with a suspected relationship to study drug, and hepatic neoplasm, not suspected to be related to study medication. One patient who was receiving deferasirox in the core study entered the extension, but died 3 days later before receiving any study drug (planned deferasirox); therefore, this patient was not included in safety assessments. The patient died as a result of cardiac arrest, which was not considered related to study drug; LVEF had improved from 63 to 66% and the patient was responding to chelation therapy (myocardial T2* increased from 14.2 to 15.1 ms and LIC decreased from 17.5 to 4.2 mg Fe/g dw). Although not at high cardiac risk, the patient had previously been diagnosed with a pulmonary artery stenosis.

Laboratory parameters. Two deferasirox patients (2.7%) and one (3.4%) DFO patient had two consecutive (≥7 days apart) serum creatinine increases of >33% above baseline and above the upper limit of normal (ULN), which occurred during the core phase. Increases were transient and resolved with dose reduction/interruption. Urinary protein/creatinine ratio >1 mg/mg on two consecutive occasions developed in 4 (5.5%) deferasirox patients (2 during the core, 1 during the extension, and 1 during both the core and extension phases), all of whom continued deferasirox treatment at a planned dose of 40 mg/(kg day). Urinary protein/creatinine ratio spontaneously reduced to <1 mg/mg in three patients, but remained high in one patient who had levels >1 mg/mg at the last visit on record. The one DFO patient with serum creatinine increases described above also had a urinary protein/creatinine ratio >1 mg/mg at the same time during the core phase and was resolved with dose reduction/interruption. Mean ± SD alanine aminotransferase (ALT) improved from elevated values at baseline in both deferasirox (baseline: 63.4 ± 43.2 U/L; month 24: 35.4 ± 32.2 U/L; absolute change: −28.5 ± 40.8 U/L) and DFO (baseline: 60.7 ± 31.4 U/L; month 24: 37.7 ± 50.5 U/L; absolute change: −20.8 ± 43.1 U/L) patients. At month 24, 41 (56.2%) and 18 (62.1%) deferasirox and DFO patients, respectively, had ALT values within the normal range compared with 25 (34.2%) and 5 (17.2%) at baseline. ALT increases >5× ULN and 2× baseline at two consecutive measurements were reported in three (4.1%) deferasirox patients and two (6.9%) DFO patients. Increases mainly occurred during the core phase, with only one patient experiencing an increase in both the core and extension phase. ALT increases were transient and resolved with dose reduction/interruption (4 patients), but remained high in one patient receiving deferasirox at the last visit on record.

Discussion

Since the removal of accumulated iron from the heart of transfusion-dependent beta thalassemia major patients is a slow process [5,7], additional long-term controlled studies are needed to strengthen the evidence demonstrating clinical benefits of iron chelation regimens. The 1-year extension to the CORDELIA study generated long-term data on the efficacy and safety of deferasirox or DFO in patients with myocardial siderosis when treated for up to 2 years, adding to the body of evidence supporting a consensus statement on the use of these chelators in the treatment of myocardial siderosis in patients without cardiac decompensation [17]. Deferiprone monotherapy is also recommended in patients with myocardial siderosis; however, prospective data beyond 1 year of treatment are limited.

Continued treatment of beta thalassemia major patients with severe iron overload (myocardial T2* between 6 and 20 ms without cardiac decompensation [LVEF ≥ 56%]) with either deferasirox or DFO for 2 years led to sustained improvements in myocardial T2*. The extension period of the study was not designed to detect differences between the chelation regimens since patients were no longer randomized. The relative improvement in myocardial T2* from baseline in deferasirox patients was consistent with previous 2-year data from the single-armed EPIC cardiac substudy [18] and also indicated a greater improvement in myocardial T2* in the second year compared with the first. Variation in the rate of improvement between CORDELIA and trials based on other chelation strategies, including DFO and/or deferiprone, should be interpreted with caution as a result of differences in study design and patient populations [9,10,12,19]. Notably, the patients included in the present study had substantially higher iron overload at baseline. Consideration of the rate of myocardial iron removal is important, since the implications and subsequent treatment of patients with myocardial T2* values of 10 to 20 ms differ from those with values <10 ms, who are at a greater risk of heart failure. Even so, the present study demonstrated that patients could normalize their myocardial T2* to >20 ms; achieved by a greater proportion of patients at 24 months than at 12 months in both deferasirox (24.3 versus 17.6%) and DFO patients (17.2 versus 6.2%) [8]. Importantly, 72.7% of patients treated with deferasirox and 54.5% of patients treated with DFO improved from severe (T2* <10 ms) to mild-to-moderate (T2* 10–20 ms) myocardial iron overload after 24 months—a clinically important increase since the relative risk of heart failure in patients with myocardial T2* <10 ms compared with T2* >10 ms has been shown to be significantly higher (relative risk 160 [95% CI 39–653]) [20]. This study did not evaluate chelation in patients with the most severe levels of myocardial iron overload (T2* <6 ms), where therapy based on a combination of DFO and deferiprone is advised [17].

Notably, improvements in myocardial T2* were evident across all baseline subgroups evaluated irrespective of baseline iron burden for deferasirox (myocardial T2* <10 vs. ≥10 ms and LIC <15 vs. ≥15 mg Fe/g dw; Table II), highlighting the efficacy of an intensive deferasirox dosing regimen for myocardial iron removal across low and high iron burdens; close monitoring is advised, particularly in patients with low myocardial T2*. There was a steady reduction in mT2* in patients with baseline LIC ≥15 mg Fe/g dw, consistent with other deferasirox studies over 2 years [15,18]. Patient numbers in the LIC <15 mg Fe/g dw DFO arm were too low for meaningful interpretation of differences, but in patients with G_{mean} myocardial T2* <10 ms at baseline, G_{mean} levels improved to above the clinically relevant threshold of 10 ms at month 24 for both treatment groups. In addition to improvements in myocardial T2*, clear improvements in MIC were also notable, consistent with previous data from the EPIC cardiac substudy in deferasirox-treated patients [7]. In addition to improvement in myocardial and liver iron, deferasirox or DFO treatment over 2 years was associated with an increasing number of patients normalizing ALT levels (an indicator of hepatocellular damage), with mean values within the normal range (0–45 U/L) by end of study. These results further support data showing that considerable reduction of liver iron during chelation therapy may reduce iron toxicity in the liver [21].

Continued improvements in myocardial iron levels were also complemented by continued decreases from high baseline levels of total

body iron burden as measured by serum ferritin and LIC in both deferasirox and DFO patients. Median serum ferritin levels in both patient groups at month 24 were lower than the threshold of 2500 ng/mL, which is associated with increased morbidity and mortality [22,23]. In parallel, mean LIC was reduced to below the threshold of 15 mg Fe/g dw by month 24, indicating a substantial reduction in iron burden (from baseline values above 30 mg Fe/g dw; considerably higher than in other monotherapy and combination therapy studies [9,10]) and a reduced risk of progressive organ damage and early death [24,25]. Despite substantial total body iron overload at baseline, the majority of patients enrolled in this study had a relatively low level of transfusional iron intake [<0.3 mg/(kg day) in 56% of patients] during the study, although iron intake varied from 0.1 to 0.7 mg/(kg day).

Overall improvements in LVEF have been demonstrated following treatment with deferiprone monotherapy or in combination with DFO [9,10]. Consistent with the 1-year data from CORDELIA [8] and other prospective clinical trials with deferasirox [7,13,18,26], mean LVEF remained stable in both cohorts of patients treated for up to 2 years. It is notable that no patients treated with either deferasirox or DFO experienced clinical heart failure in the extension; patients were, however, closely monitored by CMR every 6 months, a resource that may not be readily available in countries with limited access to equipment.

The frequency of AEs was similar between treatment arms. The long-term safety profile of deferasirox was consistent with previous reports [7,27], with the most common drug-related AEs being increased laboratory parameters. Although patients received intensified dosing regimens for deferasirox and DFO, there was no impact on the AE profile, supporting the positive risk–benefit ratio of high-dose therapy for patients with high myocardial and/or hepatic iron burden, as recommended in the Thalassaemia International Federation guidelines [28]. Patient-reported adherence to treatment in both arms continued to be very good in the extension period.

In conclusion, the 1-year extension to the CORDELIA study demonstrated continued reduction of myocardial iron over 2 years with either deferasirox or DFO treatment in beta thalassemia major patients. Notably, clinically relevant improvements in myocardial iron were paralleled by substantial improvements in LIC and serum ferritin levels, irrespective of high or low body iron burden at baseline. These findings add to the increasing body of evidence demonstrating the long-term effects of iron chelation therapy on myocardial iron removal and the use of intensified dosing regimens in heavily iron-overloaded patients, informing and guiding physicians in their treatment decisions. The comparability of deferasirox to DFO in terms of myocardial iron efficacy is important given that long-term DFO therapy has been shown to improve survival in beta thalassemia major patients, mainly driven by a reduction in myocardial iron-related complications [1]. While the efficacy of DFO has been established in patients who are compliant with therapy, long-term adherence with the subcutaneous infusion treatment regimen is challenging for many patients and, as such, treatment with deferasirox, which has demonstrated comparable efficacy, may be preferred.

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