REGULAR ARTICLE

blood advances

Deferiprone for transfusional iron overload in sickle cell disease and other anemias: open-label study of up to 3 years

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Key Points

- Long-term deferiprone therapy was not associated with new safety concerns in patients with SCD or other anemias.
- Long-term deferiprone therapy led to continued and progressive reduction in iron load in patients with SCD or other anemias.

Long-term safety and efficacy data on the iron chelator deferiprone in sickle cell disease (SCD) and other anemias are limited. FIRST-EXT was a 2-year extension study of FIRST (Ferriprox in Patients With Iron Overload in Sickle Cell Disease Trial), a 1-year, randomized noninferiority study of deferiprone vs deferoxamine in these populations. Patients who entered FIRST-EXT continued to receive, or were switched to, deferiprone. Altogether, 134 patients were enrolled in FIRST-EXT (mean age: 16.2 years), with mean (SD) exposure to deferiprone of 2.1 (0.8) years over the 2 studies. The primary end point was safety. Secondary end points were change in liver iron concentration (LIC), cardiac T2*, serum ferritin (SF), and the proportion of responders (≥20% improvement in efficacy measure). The most common adverse events considered at least possibly related to deferiprone were neutropenia (9.0%) and abdominal pain (7.5%). LIC (mg/g dry weight) decreased over time, with mean (SD) changes from baseline at each time point (year 1, −2.64 [4.64]; year 2, −3.91 [6.38]; year 3, −6.64 [7.72], all $P < .0001$). Mean SF levels (μg/L) decreased significantly after year 2 (−771, $P = .0008$) and year 3 (−1016, $P = .0420$). Responder rates for LIC and SF increased each year (LIC: year 1, 46.5%; year 2, 57.1%; year 3, 66.1%; SF: year 1, 35.2%; year 2, 55.2%; year 3, 70.9%). Cardiac T2* remained normal in all patients. In conclusion, long-term therapy with deferiprone was not associated with new safety concerns and led to continued and progressive reduction in iron load in individuals with SCD or other anemias. The trial was registered at www.clinicaltrials.gov as #NCT02443545.

Introduction

People with sickle cell disease (SCD) or other anemias often require regular lifelong blood transfusions. Each unit of transfused blood contains ~200 to 250 mg of iron,[1] and the body has no natural mechanism to eliminate excess iron. Therefore, in absence of chelation therapy, free iron accumulates in

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tissues, causing iron overload.[2] Free iron is highly reactive and catalyzes the formation of free radicals, which can result in organ damage including liver fibrosis, cardiomyopathy, and endocrine complications.[2-6] If left untreated, iron overload can lead to organ failure and death.[2-6]

The orally administered iron chelator deferiprone (Ferriprox, Chiesi USA, Cary, NC) is approved in the United States for the treatment of transfusional iron overload in adult and pediatric patients (aged ≥3 years) with thalassemia syndromes and was recently approved for the treatment of SCD and other transfusion-dependent anemias.[7,8] Long-term safety and efficacy of deferiprone for thalassemia syndromes is well established[3,9,10]; however, long-term safety and efficacy data in people with SCD or other transfusion-dependent anemias are limited. Ferriprox in Patients With Iron Overload in Sickle Cell Disease Trial (FIRST) was a noninferiority study performed upon request of the US Food and Drug Administration to compare the safety and efficacy of deferiprone with that of deferoxamine (DFO) in iron-overloaded patients with SCD or other anemias (NCT02041299).[11] In the FIRST study, patients were randomly assigned (2:1) to treatment with either deferiprone or DFO for 12 months. The FIRST study showed noninferiority of deferiprone to DFO with respect to the change in liver iron concentration (LIC) from baseline to 12 months (the primary efficacy end point) as well as similar rates of adverse events (AEs) between the 2 treatment groups.

Patients who completed FIRST were eligible for enrollment in a 2-year extension study, FIRST-EXT, in which all patients were treated with deferiprone. The objective of FIRST-EXT was to evaluate the long-term safety, tolerability, and efficacy of deferiprone when used for up to 3 years to treat iron overload in people with SCD or other anemias (NCT02443545).

Methods

Study design

FIRST-EXT was a prospective 2-year, multicenter, single-arm, open-label extension study of FIRST. Permitted doses of deferiprone ranged from 75 to 99 mg/kg per day depending on transfusional iron input and severity of iron overload. Patients treated with deferiprone in the FIRST study continued to receive deferiprone in FIRST-EXT at the same dose, so their total time on deferiprone treatment could be up to 3 years. Patients treated with DFO in the FIRST study were switched to deferiprone, so their total time on deferiprone treatment could be up to 2 years. Patients switching from DFO had their dose escalated over 3 to 4 weeks to a final dose.

At the start of the FIRST-EXT study, patients who had already received deferiprone for 12 months had monthly monitoring of complete blood counts, including absolute neutrophil count (ANC). Patients who switched from DFO to deferiprone initially underwent weekly monitoring for the first 6 months, biweekly for the next 6 months, and then monthly thereafter.

Both the FIRST and FIRST-EXT studies were terminated before their planned completion based on recommendation of the Data Safety Monitoring Board on the basis that sufficient data had been obtained and that existing methods of surveillance for deferiprone safety were adequately informative.

Study population

To be eligible for the FIRST study, patients had to be ≥2 years of age, have a baseline LIC exceeding 7 mg/g dry weight (dw), have a diagnosis of SCD (including hemoglobin SS or SC disease, and hemoglobin SB^0 or SB^+ thalassemia) or other anemias with iron overload from repeated blood transfusions (≥20 transfusions overall with ≥1 per year in the 2 years before enrollment in FIRST), and be expected to have a continuing requirement for transfusions during the duration of the trial.[11] Patients with thalassemia, myelodysplastic syndrome, myelofibrosis, and Diamond-Blackfan syndrome were excluded.[11] For FIRST-EXT, the main inclusion criterion was completion of FIRST, and exclusion criteria included pregnancy, breastfeeding, and participation in another clinical trial. There were no restrictions on LIC for enrolling into the FIRST-EXT study. Full eligibility criteria are listed in supplemental Table 1.

Benign ethnic neutropenia (ANC $<1.8 \times 10^9$/L in the absence of other causes[12]) was not captured in the study and it was not an explicit exclusion criterion, but patients with a history of recurrent neutropenia or an episode of agranulocytosis were excluded from treatment.

The study sites and number of patients enrolled at each site are listed in supplemental Table 2.

End points

The primary end point was safety, assessed by AEs including the frequency, severity, time to onset, duration, relatedness to study product, and number of discontinuations owing to AEs. Frequency, time to onset, and duration of serious AEs (SAEs; such as neutropenia and agranulocytosis) were also calculated, and relatedness to the study product was assessed.

Neutropenia and agranulocytosis were confirmed if ANC was within the specified range on 2 consecutive measurements, a maximum of 3 days apart. Neutropenia was defined as an ANC of $\geq 0.5 \times 10^9$/L and $<1.5 \times 10^9$/L, and agranulocytosis was defined as ANC $<0.5 \times 10^9$/L. In contrast, decreased neutrophil count was defined as a single occurrence of ANC $<1.5 \times 10^9$/L, with a second value captured within 3 days above this threshold, and was considered not clinically significant. Patients who developed moderate neutropenia (0.5×10^9/L $<$ ANC $< 1.0 \times 10^9$/L) or agranulocytosis were required to discontinue treatment, whereas patients with milder neutropenia were allowed to continue therapy. In the case of SAEs, causal relationship to deferiprone was based on the more conservative assessments of the investigators and the company.

Secondary end points were efficacy measures (assessed by change in LIC by R2* magnetic resonance imaging [MRI]), cardiac T2* MRI, and serum ferritin (SF) level, all measured from baseline to year 1 (all patients), year 2 (all patients), and year 3 (patients treated with deferiprone in FIRST). In addition, the proportion of responders were determined, defined as patients with a decline of ≥20% from baseline in LIC or SF or an increase of ≥20% from baseline in cardiac T2* MRI (for those with baseline T2* <20 ms). LIC, cardiac iron, and responder rates were assessed annually, whereas SF levels were assessed quarterly. SF was measured by blood and through a centralized laboratory.

MRI systems were required to have 1.5-Tesla magnets. The Philips MRI systems had to be on Release 2.5 or higher, General Electric

MRI systems had to be operating at v15.0 or higher, and Siemens MRI systems had to be using operating system VB15/VA25 or higher. All MRI scan results were transmitted to a central laboratory for independent iron content assessment. Liver and cardiac scans were sent to different central assessment centers.

Statistical analyses

All enrolled patients who received ≥1 dose of deferiprone were included in the safety population (the primary analysis population for all safety assessments). All patients who received ≥1 dose of deferiprone and had ≥1 postbaseline efficacy assessment were included in the intent-to-treat (ITT) population (the primary analysis population for all efficacy end points). Patient demographic characteristics were summarized by descriptive statistics for continuous variables and by frequency for discrete variables. Incidences of AEs and SAEs were tabulated, and AEs were summarized by severity and by relationship to study medication.

LIC, cardiac T2* MRI, and SF levels at baseline were summarized with descriptive statistics (mean, standard deviation [SD], minimum and maximum values). Baseline was defined as start of deferiprone treatment. For patients receiving deferiprone in the FIRST study, baseline was the start of FIRST. For those receiving DFO in the FIRST study, baseline was the start of FIRST-EXT. Changes in LIC, cardiac T2* MRI, and SF levels from baseline to year 1, year 2, and year 3 of deferiprone therapy were summarized with descriptive statistics and were analyzed using a one-sample *t* test.

Ethics approval statement

This study was approved by independent ethics committees and institutional review boards and conducted in accordance with the accepted version of the Declaration of Helsinki and all relevant federal regulations, and in compliance with ICH E6 Good Clinical Practice guidelines.

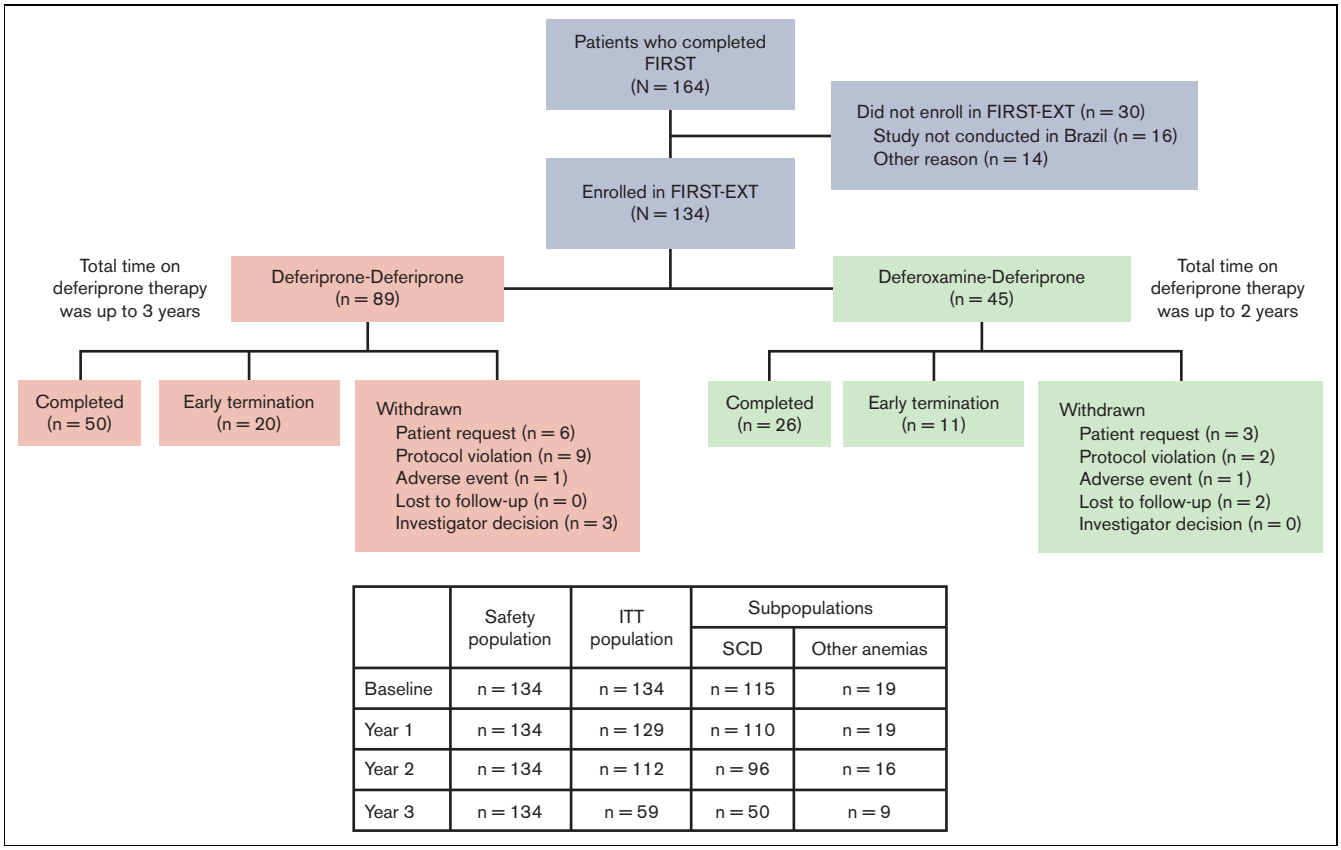
Patient consent statement

Before the conduct of any study procedures, adult patients provided written informed consent, whereas for minors (<16 years of age in the United Kingdom and ≤17 years of age elsewhere), parent/guardian consent and, where applicable, child assent, were obtained.

Results

Study population

Of 164 patients who completed the FIRST study, 134 enrolled in FIRST-EXT (89 who had received deferiprone and 45 who had received DFO in FIRST) (Figure 1). Most patients who did not enroll in FIRST-EXT did so owing to patient request. In addition, 16 patients were excluded because FIRST-EXT was not conducted in Brazil. The mean age of patients at the start of the study was 16.2 years (SD, 8.6; range, 4-47 years), and 39.6% were female (Table 1). As their primary diagnosis, 115 patients (85.8%) had a diagnosis of SCD, and 19 patients (14.2%) had a diagnosis of another red blood cell disorder managed with blood transfusions (Table 1). Most patients (81.3%) were enrolled at study sites in Egypt (supplemental Table 2).



	Safety population	ITT population	Subpopulations	
			SCD	Other anemias
Baseline	n = 134	n = 134	n = 115	n = 19
Year 1	n = 134	n = 129	n = 110	n = 19
Year 2	n = 134	n = 112	n = 96	n = 16
Year 3	n = 134	n = 59	n = 50	n = 9

Figure 1. Participant flow. FIRST, Ferriprox in Patients with Iron Overload in Sickle Cell Disease Trial; ITT, intent-to-treat; SCD, sickle cell disease.

Table 1. Demographics (safety population) and baseline iron burden (ITT population) of patients in the FIRST-EXT study

	Deferiprone (N = 134)
Age, y	
Mean (SD)	16.2 (8.6)
Median (P25, P75) [min-max]	14.0 (10, 20) [4-47]
Sex, n (%)	
Female	53 (39.6)
Male	81 (60.4)
Race, n (%)	
White	114 (85.1)
Black	20 (14.9)
Primary diagnosis, n (%)	
Sickle cell disease	115 (85.8)
Sickle cell anemia	73 (54.5)
Hemoglobin S-beta-thalassemia	40 (29.9)
Sickle cell with hemoglobin C disease	2 (1.5)
Other anemias	19 (14.2)
Hereditary spherocytosis	8 (6.0)
Congenital dyserythropoietic anemia	4 (3.0)
Spherocytic anemia*	4 (3.0)
Hemoglobinopathy†	1 (0.7)
Chronic nonspherocytic hemolytic anemia	1 (0.7)
Autoimmune hemolytic anemia	1 (0.7)
Baseline iron burden, mean (SD) [min-max]‡	
LIC, mg/g dw	14.93 (7.61) [2.33-36.84]
Cardiac T2* MRI, ms	32.69 (17.66) [20.70-48.20]
SF, μg/L	3894 (2591) [134-12397]
Concomitant hydroxyurea, n (%)	22 (16.4)

dw, dry weight; ITT, intent-to-treat; LIC, liver iron concentration; max, maximum; min, minimum; MRI, magetic resonance imaging; ms, milliseconds; P25, twenty-fifth percentile; P75, seventy-fifth percentile; SD, standard deviation; SF, serum ferritin.

*Hereditary status was not captured.

†Hemoglobinopathy other than beta-thalassemia.

‡Baseline was defined as the start of deferiprone treatment. Baseline LIC and cardiac T2* MRI values were missing for 1 patient and 3 patients, respectively.

In the FIRST study, 121 patients received a total of 939 blood transfusions (mean [SD], 7.76 [4.75]), and during the FIRST-EXT study, 97 patients received a total of 714 blood transfusions (mean [SD], 7.36 [4.64]). The mean iron input was significantly higher in the FIRST study than in the FIRST-EXT study. Mean (SD) iron input for those who received deferiprone initially was 0.19 (0.11) and 0.14 (0.10) mg/kg per day in FIRST and FIRST-EXT, respectively ($P = .0001$); for those who initially received DFO in the FIRST study, iron input was 0.18 (0.10) and 0.15 (0.09) mg/kg per day in FIRST and FIRST-EXT, respectively ($P = .0014$).

In total, 76 patients (56.7%) had completed FIRST-EXT at time of study termination, with similar completion rates for patients who had received deferiprone in FIRST (n = 50 of 89 [56.2%]) and those who had received DFO in FIRST (n = 26 of 45 [57.8%]) (Figure 1). The most common reason for not completing the study was early study termination as recommended by the Data Safety Monitoring Board, with 31 patients (23.1%) being withdrawn at that time. Other reasons for study withdrawal included patient request (n = 9 [6.7%]), protocol deviation (n = 11 [8.2%]), investigator decision (n = 3 [2.2%]), AEs (n = 2 [1.5%]), and loss to follow-up (n = 2 [1.5%]). Most withdrawals due to patient request were inability to attend weekly assessments or follow the study protocol (n = 5). One death occurred during the study, which was assessed as unlikely to be related to the use of deferiprone.

Safety outcomes

All 134 patients received ≥1 dose of deferiprone during FIRST-EXT. Over the duration of both the FIRST and FIRST-EXT studies, total exposure to deferiprone was 285.5 person-years, and mean (SD) exposure was 2.1 (0.8) years. Most patients (91.0%) received deferiprone for ≥1 year, 51.5% received it for ≥2 years, and 41.8% received it for ≥2.5 years.

Table 2 provides an overall summary of AEs, SAEs seen in >1 patient, and AEs in ≥5% of patients during the FIRST-EXT study

Table 2. Summary of AEs during years 2 and 3 of deferiprone treatment in the FIRST-EXT study (safety population)

	Deferiprone (N = 134), n (%)
Overall summary of AEs	
AEs	104 (77.6)
Severe AEs	19 (14.2)
SAEs	35 (26.1)
AEs at least possibly related to study treatment*	41 (30.6)
SAEs at least possibly related to study treatment*	13 (9.7)
AEs leading to withdrawal†	2 (1.5)
SAEs by preferred term seen in >1 patient*	
Sickle cell crisis	19 (14.2)
Neutropenia‡,§	12 (9.0)
Pyrexia	5 (3.7)
Cholecystectomy	3 (2.2)
Agranulocytosis‡,§	2 (1.5)
Pneumonia	2 (1.5)
Arthralgia	2 (1.5)
Splenectomy	2 (1.5)
Hypotension	2 (1.5)
Treatment-related AEs by preferred term seen in ≥5% of patients‖	
Neutropenia§	12 (9.0)
Neutrophil count decreased§	12 (9.0)
Abdominal pain¶	10 (7.5)

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SAE, serious adverse event.

*The causal relationship of an AE to study drug was assessed according to the World Health Organization criteria[13] and defined as not related, possibly related, probably related, and definitely related. SAEs were classified by the principal investigator and represent the data as collected.

†Of the 2 patients (1.5%) who withdrew from the study owing to AEs, 1 experienced AEs of thrombocytopenia and neutropenia, and 1 was hospitalized for generalized edema.

‡Neutropenia and agranulocytosis were serious AEs that were deemed to be at least possibly related to study treatment.

§Neutropenia and agranulocytosis were confirmed if the ANC was within the specified range on 2 consecutive measurements a maximum of 3 days apart, whereby neutropenia was an ANC ≥ 0.5×10^9/L and < 1.5×10^9/L and agranulocytosis was an ANC < 0.5×10^9/L. Decreased neutrophil count was defined as a single occurrence of ANC < 1.5×10^9/L with no confirmatory second value below this threshold within 3 days.

‖AEs at least possibly related to deferiprone.

¶Includes the preferred terms of abdominal pain and abdominal pain (upper).

considered at least possibly related to deferiprone. Most patients (77.6%) had ≥1 AE, 14.2% had AEs of severe intensity, and 26.1% had ≥1 SAE.

Two patients (1.5%), both with SCD, withdrew from the study because of an AE. One of these patients experienced transient AEs of thrombocytopenia (platelet count, 13×10^{-3}/L) and decreased neutrophil count (single reading of ANC = 0.37×10^9/L), both of which were considered at least possibly related to deferiprone. The patient was taking concomitant medications including hydroxyurea (HU), amoxicillin/clavulanate potassium for anal fissure, and mefenamic acid for an unknown indication. Treatment with deferiprone was permanently discontinued, and neutropenia and thrombocytopenia resolved in 14 and 13 days, respectively, without additional treatment. The other patient who withdrew was hospitalized for generalized edema. The patient had been on deferoxamine therapy in the FIRST study and had underlying risk factors including hepatitis C infection, mild mesangial glomerulonephritis, elevated direct bilirubin levels, and elevated aspartate aminotransferase (AST) levels before starting deferiprone in FIRST-EXT. The patient withdrew from the study 9 days after the onset of generalized edema and died ~4 weeks after the event. The death was suspected to have been caused by hepatic encephalopathy and unlikely related to the use of deferiprone but instead related to the patient's underlying risk factors.

Of the 836 AEs reported over the 2 years during FIRST-EXT, most (n = 567 [67.8%]) were of mild intensity. The most common AEs were pyrexia (n = 35 [26.1%]; 5 serious and 3 severe), bone pain (n = 35 [26.1%]), abdominal pain (n = 26 [19.4%]), and sickle cell crisis (n = 25 [18.7%]). Most AEs (n = 727 [87.0%]) were not considered to be related to deferiprone. The most common AEs considered at least possibly related to deferiprone in FIRST-EXT were neutropenia occurring in 12 patients (9.0%) and abdominal pain occurring in 10 patients (7.5%) (Table 2). Two patients experienced sickle cell crisis considered related to deferiprone during FIRST-EXT, one of mild intensity and the other of moderate intensity.

All patients had ANC values at baseline in the normal range. ANCs were monitored throughout the study and indicated that deferiprone use was not associated with any trends in declining ANCs (supplemental Figure 1).

At baseline, mean alanine aminotransferase (ALT) and AST levels were within normal range, and 6% of patients had hepatitis C. A significant increase in ALT of 32.0 (67.8) U/L ($P = .0000$) from baseline was seen at month 1; thereafter, the mean value declined progressively and after month 6, the mean values returned to baseline. Six patients (4.5%) experienced transient increased ALT and/or AST levels: 3 (2.2%) of these patients had both increased ALT and AST levels, 2 (1.5%) had increased ALT only, and 1 (0.7%) had increased AST only. Three patients (2.2%) each had a single episode of ALT >5 times the upper limit of normal (5 × ULN), 2 patients (1.5%) each had a single episode of AST > 5 × ULN, and 2 patients (1.5%) had episodes of elevated AST and ALT >5 × ULN. Four cases (3.0%) of increased ALT levels and 4 cases (3.0%) of increased AST levels were considered at least possibly related to deferiprone. Two patients had treatment interruptions because of elevated ALT levels. No patient had ALT > 5 × ULN at 2 or more consecutive visits; therefore, no patient discontinued deferiprone or was withdrawn from the study because of hepatic transaminitis.

Thirty-five patients (26.1%) experienced a total of 106 SAEs during FIRST-EXT (Table 2). The most frequent SAE was sickle cell crisis, which was observed in 19 patients (14.2%), deemed unrelated to deferiprone treatment. Thirteen patients (9.7%) experienced SAEs that were deemed to be at least possibly related to study treatment. Two patients (1.5%) reported agranulocytosis (ANC < 0.5×10^9/L) that was considered possibly related to deferiprone. The 2 cases of agranulocytosis occurred after 2.0 and 2.6 years of deferiprone therapy and lasted 93 and 21 days, respectively. One of these events occurred in a patient with SCD who had a normal ANC at baseline (2.54×10^9/L) and was not reported to be on concomitant HU but experienced multiple episodes of decreased ANC during the study ranging from 0.3×10^9/L to 1.3×10^9/L; deferiprone treatment was interrupted, and the agranulocytosis was resolved. In the second case, a patient with hereditary spherocytosis had 2 episodes of decreased ANC and an episode of neutropenia; treatment was interrupted for the neutropenia. Upon diagnosis of agranulocytosis, the patient was instructed to stop deferiprone therapy; however, the patient had already interrupted therapy (for reasons unknown) a day before onset. The agranulocytosis resolved 3 weeks after onset.

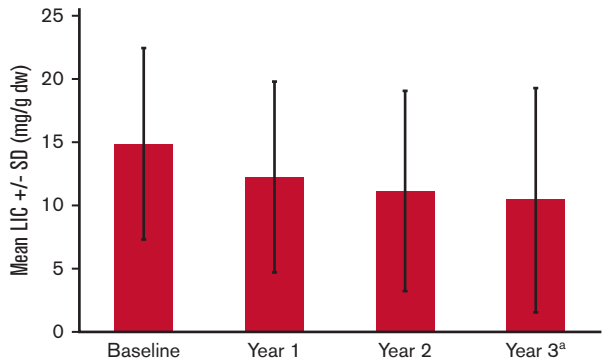
In the FIRST-EXT study, 22 patients with SCD received concomitant HU at some point. Among patients who received HU during the FIRST study, 1 event of leukopenia (6.21 of 100 patient-years) and 22 events of sickle cell anemia with crisis (136.56 of 100 patient-years) occurred. In the FIRST-EXT study, there were 5 events of decreased neutrophil count (n = 3; 18.49 of 100 patient-years), 6 events of neutropenia (n = 4; 22.19 of 100 patient-years), and 24 events of sickle cell anemia with crisis (n = 9; 88.76 of 100 patient-years) among those receiving HU. Overall, rates of neutropenia were not higher in patients receiving concomitant HU than in the remainder of the study population.

Efficacy outcomes

LIC. All patients had above-normal LIC values at baseline, with a mean (SD) of 14.93 (7.61) mg/g dw (range 2.33–36.84 mg/g dw) (Table 1). LIC decreased significantly over time compared with baseline (year 1: −2.64, year 2: −3.91, year 3: −6.64; all $P < .0001$) (Figure 2). Furthermore, reductions in LIC were maintained in patients who were switched from DFO (mean [SD] difference from baseline of FIRST-EXT to last visit: −0.96 [4.59]). There was a consistent increase in the proportion of responders for LIC at each time point compared with baseline, from 46.5% (60 of 129) at year 1, 57.1% (64 of 112) at year 2, and 66.1% (39 of 59) at year 3 of deferiprone therapy (supplemental Table 3).

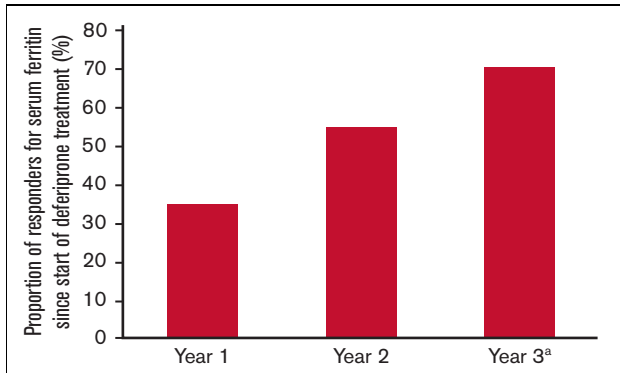
Decreases in LIC were seen over time in both the SCD subpopulation and the subpopulation of patients with other anemias (supplemental Tables 4 and 5). The proportions of responders within the 2 subpopulations were similar to the proportion of responders in the overall study population, except that the responder rate decreased from year 2 to year 3 of deferiprone therapy for patients with other anemias.

Cardiac T2* MRI. All patients had normal cardiac T2* MRI values at baseline, with a mean (SD) value of 32.69 (17.66) ms (range: 20.70–48.20 ms) (Table 1). Overall, cardiac iron level was unchanged and remained normal for the duration of FIRST-EXT, with mean T2* MRI in the range of 32.04 to 32.90 ms, and the



Time period	n	Change in LIC (mg/g dw), mean (SD) [min, max]	*P* value[b]
Baseline to year 1	129	−2.64 (4.64) [−17.50, 8.72]	<.0001
Baseline to year 2	112	−3.91 (6.38) [−22.11, 12.28]	<.0001
Baseline to year 3[a]	59	−6.64 (7.72) [−22.81, 12.58]	<.0001

Figure 2. LIC since the start of deferiprone treatment (ITT population). [a]Only patients who received deferiprone in FIRST and continued deferiprone in FIRST-EXT. [b]One-sample *t* test. dw, dry weight; ITT, intent-to-treat; LIC, liver iron concentration; max, maximum; min, minimum; SD, standard deviation.



Time period	n	Change in serum ferritin (μg/L), mean (SD) [min, max]	*P* value[b]
Baseline to year 1	125	−1 (1986) [−6123, 6697]	.9952
Baseline to year 2	96	−771 (2171) [−7498, 5569]	.0008
Baseline to year 3[a]	55	−1016 (3617) [−7188, 20058]	.0420

Figure 3. Proportion of responders and change in SF since the start of deferiprone treatment (ITT population). A responder was defined as a patient who showed a ≥20% decline from baseline in SF. Mean (SD) SF at baseline was 3894 (2591) μg/L. [a]Only patients who received deferiprone in FIRST and continued deferiprone in FIRST-EXT. [b]One-sample *t* test. max, maximum; min, minimum; ITT, intent-to-treat; SF, serum ferritin; SD, standard deviation.

geometric mean at each year of deferiprone therapy was almost identical to the baseline value (ratio was ~1.00, $P > .05$).

Serum Ferritin. All but 1 patient had above-normal SF levels at baseline, with a mean (SD) of 3894 (2591) μg/L (range, 134–12397 μg/L) (Table 1). The mean (SD) SF was 3914 (3102) μg/L (range, 76–3102 μg/L) at year 1, 3048 (2820) μg/L (range, 19–13981 μg/L) at year 2, and 2818 (4172) μg/L (range, 51–27 768 μg/L) at year 3. There were 17 patients with long-term SF levels of <500 μg/L, which were maintained with therapy. Mean values did not change significantly from baseline over the first year of therapy ($P = .9952$) but decreased significantly thereafter (year 2 compared with baseline, $P = .0008$; year 3 compared with baseline, $P = .0420$), with a consistent increase in the proportion of responders at each time point compared with baseline (Figure 3; supplemental Table 3). Although SF levels increased slightly in patients who were switched from DFO (mean [SD] difference from baseline of FIRST-EXT to last visit: 81.54 [2261.6], $P = .8121$), the increase was not statistically significant.

The changes in SF and the responder rates for the SCD subpopulation were similar to those observed for the overall study population (supplemental Table 4). For the subpopulation of patients with other anemias, SF decreased at each time point and the responder rate remained constant (supplemental Table 5).

Discussion

This report provides results from the FIRST and FIRST-EXT studies, in which patients with SCD and other transfusion-dependent anemias were treated with deferiprone for up to 3 years, and presents safety and efficacy data from one of the longest and largest studies of this chelator in these patient populations. Deferiprone treatment effectively decreased transfusional iron overload and maintained reductions in SF achieved with DFO for 2 years after patients switched therapy from DFO to deferiprone. The safety profile of deferiprone was acceptable and consistent with that previously seen in patients with thalassemia major.[3,14] AEs that occurred during the FIRST-EXT were similar in type and frequency to those seen during FIRST.[11] Most AEs were of mild intensity, and no new safety concerns were observed.

Two patients (1.5%) discontinued the study: one owing to the AEs of decreased neutrophil count and thrombocytopenia, and the other owing to generalized edema, unlikely to be related to deferiprone. The patient who experienced thrombocytopenia and decreased neutrophil count was taking a number of concomitant medications that are associated with increased risk of leukopenia and thrombocytopenia.[15-17] The rate of discontinuation due to AEs in FIRST-EXT was lower than that reported in a study investigating long-term safety of deferasirox (DFX) in patients with SCD.[18] The rate of discontinuation in FIRST-EXT was also less than that reported in other studies using nonchelating treatments for patients with SCD. In the HOPE trial, 84% of patients received voxelotor (OXBRYTA, Global Blood Therapeutics) for at least 24 weeks, a percentage that declined to 74% by 48 weeks,[19] and in another trial, 73% of patients were exposed to L-glutamine (ENDARI, Emmaus Medical, Inc) for 6 months, which declined to 58% by 1 year.[20]

The rate of agranulocytosis was 1.5% in this study and was similar to the rate reported in prior clinical studies.[21] In the authors' opinion, the incidence of agranulocytosis was manageable with adequate monitoring especially during the first 6 months of onset of therapy. A previous study concluded that less frequent ANC monitoring and continuation of deferiprone therapy during neutropenia are not associated with prolonged neutropenia or with progression to agranulocytosis.[22] In a separate study, it was found that not all cases of neutropenia during deferiprone therapy develop into agranulocytosis, suggesting that many cases of agranulocytosis may not be caused by deferiprone.[23] Transient declines in ANC to levels defined as neutropenic are common even

in healthy individuals, particularly children, and it could be that the frequent monitoring of ANC mandated during deferiprone therapy may reveal cases of transient neutropenia that would otherwise have gone undetected and resolved on their own without clinical consequences. In the FIRST-EXT study, the onset of 2 cases of agranulocytosis occurred at a later time point than previously observed in patients enrolled in clinical trials and reported in postmarketing experience, whereby most cases of agranulocytosis occur within the first year of deferiprone therapy.[4,21,24] Both cases of agranulocytosis in this study resolved despite continuation of deferiprone therapy in 1 case. Data from other studies suggest that agranulocytosis is separate and distinct from episodes of milder neutropenia during deferiprone use. The development of mild to moderate neutropenia is likely unrelated to deferiprone,[21] as shown by the similar incidence of decreased neutrophil count during treatment with other chelators.[11,25] HU is a known myelosuppressive agent.[26,27] In this study, 22 patients took concomitant HU, and none of these patients experienced agranulocytosis. Further study is needed to evaluate the consequences of concomitant HU use on patients with anemia taking deferiprone.

Transient elevations in ALT and AST levels were reported for some patients, which was not unexpected based on data from previous clinical trials.[28,29] ALT is an important marker of liver abnormalities, whereas AST levels can be elevated in this population owing to hemolysis.[30]

In this study, there were no confirmed ALT values $> 5 \times$ ULN, and therefore, no drug discontinuations were due to increased ALT values. The ALT findings from this study are consistent with what has been observed with the use of deferiprone for the treatment of patients with thalassemia syndromes.

Findings from the FIRST-EXT study provide evidence of the long-term efficacy of deferiprone in controlling transfusional iron load in patients with SCD and other anemias. In contrast with thalassemia, cardiac iron overload is not frequently observed in patients with SCD. In this study, the mean baseline cardiac MRI T2* was ~30 ms, demonstrating that patients had no cardiac iron overload at baseline and that T2* MRI remained stable throughout the study, which can be considered a favorable outcome.

LIC is the major indicator of total body iron load.[31] LIC changes in transfusion-dependent patients are the product of the balance between transfusional iron input and chelator-induced iron excretion. Mean iron input was significantly lower in the FIRST-EXT study compared with the FIRST study both for patients who received DFO and deferiprone.[11] In the FIRST-EXT study, mean LIC values decreased consistently and significantly over time compared with baseline while the proportion of responders increased steadily. The lower mean iron input in FIRST-EXT may have had a positive effect on the greater proportion of LIC responders in the FIRST-EXT study than the FIRST study.

Deferiprone use is frequently associated with a transient increase in SF levels at initiation of therapy despite a decrease in liver and cardiac iron load.[32] SF levels were increased slightly and transiently in patients who were switched from DFO to deferiprone, but the increase was not statistically significant, indicating that the reduction in SF achieved with DFO was maintained after the patients switched therapy. Unlike DFO, deferiprone works intracellularly in cells and organs to chelate intracellular free/labile iron for excretion; therefore, SF may not decline immediately.[33] There was no significant change in SF from baseline after 1 year of deferiprone treatment, but decreases in SF were seen at 2 years and 3 years of treatment for the ITT population, and the proportion of responders with improvement in SF also increased over time. For the SCD subgroup, a decrease in SF was seen after 2 years of treatment. SF levels are a less reliable assessment of iron burden in the SCD population because they may be elevated with inflammation characteristic of this disorder.[34]

Seventeen patients maintained long-term SF levels of <500 μg/L while receiving deferiprone, indicating that deferiprone may be used in individuals with SCD and other anemias without increased risk of toxicity, as previously shown in patients with neurodegeneration and brain iron accumulation.[35] In addition to LIC, SF levels are generally a good surrogate measure of total body iron load,[36] and as such, the overall reductions in LIC and SF levels observed in FIRST-EXT indicate that deferiprone effectively reduced total body iron load. Over the course of the study, LIC and SF levels improved, and cardiac iron was stable and within the normal range. Responses were similar between the overall study population and the SCD and other anemias subpopulations, except that SF levels were further improved in the other anemias subpopulation compared with the SCD subpopulation. Future studies evaluating the effects of chelation therapy on LIC are needed.

DFX is generally effective at reducing body iron load, is well tolerated, and may be used long term.[18,37-39] This study did not evaluate DFX or DFO efficacy or safety. In DEEP-2, treatment with DFX was compared with deferiprone in 435 pediatric patients (of whom 90% had β-thalassemia, 7% had SCD, and 3% had other hemoglobinopathies) and showed noninferiority of deferiprone to DFX in both efficacy and safety.[40] Future studies comparing deferiprone with DFX treatment on unglycosylated SF and LIC in patients with SCD and other anemias would be informative.

Full adherence to chelation therapy is essential to optimize long-term patient outcomes.[41,42] In this study, the use of deferiprone 3 times daily was evaluated. Clinical trial data show adherence rates with deferiprone 3 times daily ranging from 79% to 98%,[43,44] but real-world adherence is generally lower than that in clinical trials owing to the inconvenient midday dose.[45-47] The US Food and Drug Administration recently approved a twice-daily modified-release formulation of deferiprone for the treatment of patients with transfusional iron overload due to thalassemia syndromes, SCD, or other anemias. In a recent clinical trial, treatment adherence with the twice-daily formulation in patients with thalassemia was 99%.[48] In FIRST-EXT, 36 patients (26.9%) were nonadherent to therapy, defined as taking <80% of the prescribed dosage. The use of deferiprone twice-daily may further improve real-world patient adherence and subsequently improve efficacy outcomes for patients with SCD prescribed deferiprone.

In conclusion, across the FIRST and FIRST-EXT studies, deferiprone progressively decreased body iron load for up to 3 years of treatment in patients with SCD and other transfusion-dependent anemias. There were no new safety concerns, and the long-term safety profile of deferiprone was consistent with that seen in other patient populations. Deferiprone offers an additional oral iron chelation option for long-term use in patients with SCD and other anemias.

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Authorship

Contribution: C.F., A.R., N.T.T., D.L., and F.T. contributed to design of the study; M.S.E., M.H., A.E., F.S.E.E., M.B., J.K., B.I., A.A.M.A., S.W., Y.K., and J.L.K. contributed to the conduct of the study; D.L. performed the statistical analyses; and all authors contributed to the interpretation of the data, reviewed and critically revised the manuscript for important intellectual content, and approved the final version for submission.

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