Long-term safety and efficacy of deferasirox in young pediatric patients with transfusional hemosiderosis: Results from a 5-year observational study (ENTRUST)

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Abstract
Background: Children with red blood cell disorders may receive regular transfusions from an early age and consequently accumulate iron. Adequate iron chelation therapy can prevent organ damage and delayed growth/development. Deferasirox is indicated for treatment of pediatric patients with chronic iron overload due to transfusional hemosiderosis; however, fewer than 10% of patients in the registration studies were aged 2 to less than 6 years.

Procedure: Deferasirox, a once-daily oral iron chelator, was evaluated in young pediatric patients with transfusional hemosiderosis during the observational 5-year ENTRUST study. Patients aged 2 to less than 6 years at enrollment received deferasirox according to local prescribing information, with the primary objective of evaluating safety, specifically renal and hepatic function. Serum ferritin was observed as a surrogate efficacy parameter.

Results: In total, 267 patients (mean age 3.2 years) predominantly with β-thalassemia (n = 176, 65.9%) were enrolled. Mean ± standard deviation deferasirox dose was 25.8 ± 6.5 mg/kg per day over a median of 59.9 months. A total of 145 patients (54.3%) completed 5 years’ treatment. The proportion of patients with two or more consecutive postbaseline measurements (≥7 days apart) of serum creatinine higher than age-adjusted upper limit of normal (ULN) and alanine aminotransferase more than five times the ULN was 4.4% (95% confidence interval [CI]: 2.1–7.9) and 4.0% (95% CI: 1.8–7.4), respectively. Median serum ferritin decreased from 1,702 ng/ml at baseline to 1,127 ng/ml at 5 years. There were no new safety signals.

Conclusions: Safety and efficacy of deferasirox in young pediatric patients in this long-term, observational study in everyday clinical practice were consistent with the known deferasirox profile.

KEYWORDS
deferamorx, hemosiderosis, iron chelation, iron overload, pediatric, real world

1 INTRODUCTION

Children with inherited red blood cell disorders, such as β-thalassemia, sickle-cell disease (SCD), and Diamond–Blackfan anemia (DBA), may receive regular transfusions from an early age as supportive therapy. Iron overload is an expected consequence of regular red blood cell transfusion therapy, resulting in complications, including organ damage and delayed growth/development if left untreated. Therefore, optimal management of iron loading is required.

The oral, once-daily iron chelator deferasirox (Exjade®) is indicated for the treatment of adult and pediatric patients with chronic iron overload. The registration program for deferasirox enrolled

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; CrCl, creatinine clearance; DBA, Diamond–Blackfan anemia; FAS, full analysis set; FDA, US Food and Drug Administration; SAE, serious adverse event; SCD, sickle cell disease; Scr, serum creatinine; SD, standard deviation; ULN, upper limit of normal
patients with a range of underlying transfusion-dependent conditions, including \( \beta \)-thalassemia, SCD, and DBA.\(^6\) With appropriate dosing based on iron intake, efficacy, and safety parameters, deferasirox reduced the total body iron burden for up to 5 years.\(^{10,11}\) Deferasirox had a manageable safety profile with respect to laboratory parameters and adverse events (AEs). The most frequently reported AEs over 5 years were transient, mild-to-moderate gastrointestinal disturbances, skin rash, and increases in serum creatinine (Scr), the incidence of which decreased over time. Events rarely required drug discontinuation and most resolved spontaneously. Deferasirox has a mild effect on renal hemodynamics.\(^{12}\) Increases in Scr, a renal function marker, are generally dose related and can be resolved with dose reductions or interruptions.\(^4,5,12\) However, cases of deferasirox-induced renal tubular acidosis have occurred.\(^{13,14}\) Monitoring alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin is also recommended to assess hepatic function. While hepatic dysfunction may occur, most increases in aminotransferase levels are not drug related and correlate with iron load.\(^{5,10,15}\) Deferasirox treatment has been associated with liver fibrosis reversal or stabilization in most iron-overloaded patients with thalassemia.\(^{15}\) However, abnormal liver function tests have been more frequently reported in children receiving deferasirox,\(^{16}\) highlighting the necessity for close monitoring, particularly pediatric patients. Of the 1,005 patients enrolled in the registration studies, only 83 (8.3%) were 2 to less than 6 years old; therefore, further collection of efficacy and safety data in young patients was deemed necessary. In addition, for patients who cannot be cured with hematopoietic stem cell transplantation, requirements for transfusions with chelation therapy may be lifelong. Furthermore, intensive chelation therapy with parenteral deferoxamine in young patients (<3 years old) has been associated with growth retardation.\(^{17}\) As such, continual assessment of outcomes of supportive therapy are valuable, supplementing data from the deferasirox registration studies and extensions in patients with \( \beta \)-thalassemia\(^{10}\) and SCD.\(^{11}\) The 5-year ENTRUST study assessed long-term safety of deferasirox in young pediatric patients with transfusional hemosiderosis in everyday clinical practice as part of the active postapproval deferasirox surveillance program.

2 | METHODS

2.1 | Study design and patient population

Male and female patients aged 2 to less than 6 years with transfusional hemosiderosis, eligible for deferasirox treatment according to local prescribing information, were enrolled and followed prospectively for 5 years in this observational study (ENTRUST; ClinicalTrials.gov identifier: NCT00466063). Retrospective data were collected for patients who started on deferasirox less than or 12 months prior to enrollment (i.e., data were collected from the start of deferasirox treatment for 5 years). Patients were excluded if they were involved in other iron chelator trials.

The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki and was approved by independent ethics committees at participating sites. Patients’ parents/guardians provided written, informed consent prior to enrollment.

2.2 | Deferasirox dosing and iron intake

Patients were treated with deferasirox and monitored in accordance with local (country-specific) deferasirox prescribing information. As such, there was no therapy protocol, diagnostic or therapeutic intervention outlined, or strict visit schedule. In summary, initial deferasirox dose was \( 10–30\) mg/kg body weight based on country-specific prescribing information, with recommendations to adjust dose according to serum ferritin levels, therapeutic goals, tolerability, and patient weight changes. Total and average amount of blood transfused and average iron intake during the observation period were recorded. Compliance was assessed at retrospective interviews.

2.3 | Assessments

The co-primary endpoints were as follows: the proportion of patients (within a maximum of 5 years’ observation) with Scr over the age-adjusted upper limit of normal (ULN) and more than 33% from baseline on two or more consecutive postbaseline measurements taken 7 or more days apart; and the proportion of patients with ALT levels higher than five times the ULN in two or more consecutive postbaseline measurements taken 7 or more days apart. Secondary endpoints included monthly serum ferritin levels (surrogate marker for body iron levels) to assess long-term deferasirox effectiveness.

Safety was evaluated by regular monitoring and recording of AEs and serious AEs (SAEs), laboratory testing, and clinical evaluations. Particular attention was given to collection of Scr, creatinine clearance (CrCl; calculated), urea, liver aminotransferases, bilirubin, alkaline phosphatase, and proteinuria data; blood pressure; auditory and ophthalmological assessments; and growth and sexual development.

2.4 | Sample size and statistical analysis

Assuming a 20% dropout rate, a 200-patient sample size at registry end was proposed so that a two-sided 95% confidence interval (CI) would extend 0.03 from the observed proportion for a true probability of 0.05. Safety was evaluated in all patients who received one or more deferasirox dose during the study, with one or more postbaseline safety assessment (safety set). The full analysis set (FAS) consisted of all patients who received one or more deferasirox dose during the study and was used for efficacy analyses. The primary endpoints were estimated together with two-sided 95% CIs. Descriptive statistics were used for continuous variables and frequency was used for categorical variables.
TABLE 1  Patient demographics at the start of deferasirox treatment

| Demographic                           | Patients (N = 267) |
|---------------------------------------|--------------------|
| Underlying disease, n (%)             |                    |
| β-Thalassemia major                   | 176 (65.9)         |
| SCD                                   | 52 (19.5)          |
| DBA                                   | 12 (4.5)           |
| Othera                                | 27 (10.1)          |
| Mean age, years (range)               | 3.2 (1.0–6.0)      |
| Age group, n (%)                      |                    |
| <2 yearsb                             | 4 (1.5)            |
| ≥2 to <4 years                        | 160 (59.9)         |
| ≥4 to <6 years                        | 100 (37.5)         |
| ≥6 yearsb                             | 3 (1.1)            |
| Male:female, n                        | 139:128            |
| Race, n (%)                           |                    |
| Caucasian                             | 113 (42.3)         |
| Black                                 | 46 (17.2)          |
| Asian                                 | 63 (23.6)          |
| Other                                 | 44 (16.5)          |
| Unknown                               | 1 (0.4)            |
| Median serum ferritin (range), ng/ml  | 1,702 (334–9,577)  |
| Serum ferritin, n (%)                 |                    |
| ≤1,000 ng/ml                          | 16 (6.0)           |
| >1,000–2,500 ng/ml                   | 182 (68.2)         |
| >2,500–4,000 ng/ml                   | 36 (13.5)          |
| ≥4,000 ng/ml                          | 9 (3.4)            |
| Missing                               | 24 (9.0)           |
| Mean SCr, μmol/l (range)              | 30.9 (8.8–64.5)    |
| Mean ALT, U/l (range)                 | 41.6 (7.0–353.0)   |

*a*Hb E/β-thalassemia (n = 7), *α*-thalassemia (n = 6), hereditary spherocytosis (n = 5), congenital dyserythropoietic anemia (n = 2), hemolytic anemia (n = 1), hemoglobin Hakkari (n = 1), hereditary erythroidlastic multinuclearity with positive acidified serum lysis test (n = 1), myelodysplasia (n = 1), Shwachman–Diamond syndrome (n = 1), X-linked sideroblastic anemia (n = 1), pyruvate kinase deficiency (n = 1).

*b*Patients outside of the age range for enrollment per protocol.

3.2 | Deferasirox dosing and exposure

During the study, patients received a mean ± standard deviation (SD) dose of 25.8 ± 6.5 mg/kg per day. Deferasirox dose increased from a planned starting dose of 26.2 ± 5.9 mg/kg per day to a final actual dose of 28.6 ± 7.7 mg/kg per day. The number of patients receiving dose adjustments (including increases or reductions) each year was 158 (60.5%), 125 (47.9%), 105 (40.2%), 96 (36.8%), and 84 (32.2%), respectively. Yearly dose adjustments according to weight changes were reported in 37 (14.2%), 26 (10.0%), 33 (12.6%), 29 (11.1%), and 32 (12.3%) patients. In total, 34 patients (12.7%) did not receive any dose adjustments over the 5-year period, despite the requirement to take into account weight changes of pediatric patients over time when calculating the daily dose. Although average actual dose was generally aligned with weight, initial deferasirox doses received were suboptimal to manage iron intake and dose adjustments based on weight gain were delayed. Median deferasirox treatment duration was 59.9 months (range 1.2–65.6). Most patients took deferasirox as instructed, with the mean ± SD number of doses missed being 15.5 ± 10.1 during the observation period (n = 154; 96 patients missed 1 to less than or equal to 15 doses, 53 missed 16 to less than or equal to 30 doses, and 5 missed 31 to less than or equal to 45 doses). Multiple reasons were provided for missing a dose; most commonly running out of medication (n = 72, 46.8%) and forgetting to take medication (n = 55, 35.7%).

3.3 | Average iron intake

Most patients experienced frequent blood transfusions, with 172 patients (64.4%) receiving at least 7 ml/kg per month. Average iron intake was recorded in 229 patients (85.8%): less than 0.3 mg/kg per day in 93 patients (34.8%), 0.3–0.5 mg/kg per day in 115 patients (43.1%), and more than 0.5 mg/kg per day in 21 patients (7.9%).

3.4 | Long-term safety of deferasirox

3.4.1 | Laboratory parameters

Mean SCr levels increased as expected in a pediatric patient population from 28 μmol/l at baseline to 39.4 μmol/l at the end of study (EOS; Fig. 1A). The proportion of patients with SCr greater than the age-adjusted ULN on two or more consecutive postbaseline measurements, 7 or more days apart, was 4.4% (95% CI: 2.1–7.9). Two consecutive SCr increases to greater than the age-adjusted ULN and more than 33% compared with baseline occurred in eight patients (3.1%). In two of these patients, deferasirox dose was decreased, SCr levels normalized, and the patients completed the study. In the other six patients, deferasirox dose was not adjusted; four patients completed the study...
and two patients discontinued because of stem cell transplantation and upper gastrointestinal bleed (n = 1 each). No patient discontinued because of SCR increases. CrCl remained stable throughout the study. Among evaluable patients during the 5-year observation period, CrCl was consistently 90 ml/min or higher in 185 patients (70.9%). Thirteen patients (5.0%) had confirmed CrCl 60 to less than 90 ml/min at least once during the study. No patient had confirmed CrCl less than 60 ml/min.

Mean ALT levels showed a slight increase within the first 6 months, followed by a steady decline over time (Fig. 1B). The proportion of patients with ALT more than five times the ULN on two or more consecutive postbaseline measurements, 7 or more days apart, was 4.0% (n = 9; 95% CI: 1.8–7.4). In total, 74 patients (28.4%) entered the study with ALT levels higher than the ULN, 43 (58.1%) of whom achieved ALT levels less than or equal to the ULN by EOS. In all, 31 patients (11.9%) received deferasirox dose adjustments or interruptions because of elevated ALT and seven (2.7%) discontinued treatment because of ALT increases. Overall, 11 patients (4.2%) had two consecutive ALT increases more than five or more than 10 times the ULN, three of whom received dose interruptions accordingly. Although simultaneously increased ALT or AST levels more than three times the ULN and total bilirubin levels more than two times the ULN were occasionally observed, there were no cases that fulfilled the criteria of Hy’s law.18
Table 2  Most common investigator-assessed drug-related AEs (occurring in four more patients) by preferred term overall and by annual incidence

| AE                              | All patients (safety set; a N = 261) | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---------------------------------|--------------------------------------|--------|--------|--------|--------|--------|
| Patients with any drug-related AE, n (%) | 102 (39.1)                          | 61 (23.4) | 37 (14.2) | 21 (8.0) | 15 (5.7) | 21 (8.0) |
| AE by preferred term, n (%)     |                                      |        |        |        |        |        |
| Investigations                  |                                      |        |        |        |        |        |
| ALT increased                  | 55 (21.1)                            | 32 (12.3) | 20 (7.7) | 10 (3.8) | 3 (1.1)  | 4 (1.5)  |
| AST increased                  | 31 (11.9)                            | 24 (9.2)  | 9 (3.4)  | 3 (1.1)  | 2 (0.8)  | 3 (1.1)  |
| Blood creatinine increased     | 10 (3.8)                             | 4 (1.5)  | 5 (1.9)  | 5 (1.9)  | 2 (0.8)  | 3 (1.1)  |
| Blood bilirubin increased      | 4 (1.5)                              | 3 (1.1)  | –       | 1 (0.4)  | –       | –       |
| Gastrointestinal disorders     |                                      |        |        |        |        |        |
| Vomiting                       | 14 (5.4)                             | 8 (3.1)  | 6 (2.3)  | 3 (1.1)  | 1 (0.4)  | 1 (0.4)  |
| Abdominal pain                 | 8 (3.1)                              | 3 (1.1)  | 3 (1.1)  | 1 (0.4)  | 1 (0.4)  | 2 (0.8)  |
| Diarrhea                       | 5 (1.9)                              | 3 (1.1)  | –       | 1 (0.4)  | –       | 1 (0.4)  |
| Skin and subcutaneous tissue disorders |                                  |        |        |        |        |        |
| Rash                           | 13 (5.0)                             | 10 (3.8) | –       | –       | 3 (1.1)  | –       |
| Hepatobiliary disorders        |                                      |        |        |        |        |        |
| Hepatocellular injury          | 4 (1.5)                              | 3 (1.1)  | 1 (0.4)  | 1 (0.4)  | –       | –       |
| Infections and infestations    |                                      |        |        |        |        |        |
| Gastroenteritis                | 4 (1.5)                              | –       | 1 (0.4)  | 1 (0.4)  | 2 (0.8)  | –       |
| Renal and urinary disorders    |                                      |        |        |        |        |        |
| Proteinuria                    | 4 (1.5)                              | –       | 1 (0.4)  | 2 (0.8)  | 1 (0.4)  | 1 (0.4)  |

aAll patients who received ≥1 dose of deferasirox over the analyzed period and ≥1 post-baseline safety assessment.

3.4.2  Adverse events

In the safety set, AEs regardless of relationship to deferasirox were reported in 217 patients (83.1%) during the 5-year observation period. There was a gradual decrease in the number of patients experiencing AEs over time, from 148 (56%) in Year 1 to 124 (47.5%) in Year 2, 114 (43.7%) in Year 3, 102 (39.1%) in Year 4, and 97 (37.2%) in Year 5. AEs with a suspected relationship to deferasirox were reported in 102 patients (39.1%) and were predominantly related to abnormal liver enzyme levels (Table 2). Of the 55 patients with reported increases in ALT levels suspected to be deferasirox related, 20 entered the study with ALT levels more than 40 U/l and two had a history of gallstones.

Nine patients (3.4%) were reported with SAEs suspected to be deferasirox related: increased liver aminotransferases (n = 3), hepatocellular injury (n = 2), vomiting/abdominal pain (n = 1), renal tubular disorder (n = 1), upper gastrointestinal bleed (n = 1), and hematuria/gastroenteritis (n = 1). Of these, six patients discontinued the study because of AEs. No patient had a fatal outcome while under observation.

3.4.3  Auditory and ophthalmological assessments

Of 153 patients with postbaseline auditory reports, 15 (9.8%) reported an AE related to ear and labyrinth disorders (most commonly, conductive deafness [n = 8, 5.2%] and ear pain [n = 3, 2.0%]). These were transitory and usually associated with upper respiratory or middle ear infections. There were 21 patients (13.7%) with evidence of hearing impairment in at least one ear, none of which were suspected to have any relationship to deferasirox. There was one case of mild neurosensory deafness with a suspected relationship to deferasirox. The patient was lost to follow-up and the event was ongoing at EOS.

Of 168 patients with postbaseline ophthalmological reports, 12 (7.1%) had an AE related to eye disorders, although none were considered study drug related. Two patients had an abnormal ophthalmological examination. One case of mild ocular icterus occurred, not suspected to be deferasirox related. The patient did not receive dose alterations and discontinued the study because of low serum ferritin levels. A subcapsular cataract was reported with suspected relationship to deferasirox, although the patient did not have a baseline ocular examination or any relevant ocular medical history recorded. Deferasirox dose was not adjusted and the patient completed the study.

3.4.4  Growth velocity, height, and weight assessments

Mean growth velocity was 4.9–6.0 cm per year in male and 5.4–6.1 cm per year in female patients (Supplementary Table S1), as observed across all geographical regions. Mean weight also increased steadily over time (Supplementary Table S1), in line with mean growth velocity. One patient with β-thalassemia major experienced an AE of below normal height that was not suspected to be drug related.

3.4.5  Long-term efficacy of deferasirox

Mean serum ferritin levels decreased from 1,702 ng/ml (range 334–9,577) at baseline (n = 243) to 1,127 ng/ml (range 38–6,428) at 5 years (n = 84), although there were slight increases at the start and toward the end of the observation period (Fig. 2). These observations
FIGURE 2  Distribution of median serum ferritin levels over time in the observed patient population. Boxes indicate median ± 25th/75th percentile. Connected dots indicate the mean value. Number of patients with data available indicated for each time point. IQR, interquartile range

may be explained by inadequate dosing during the early stages of the study and the presence of outliers attributed to patients with SCD. Excluding patients with SCD (because serum ferritin levels can be affected by factors such as inflammation), median serum ferritin levels decreased from 1,686 ng/ml (range 509–9,577) at baseline (n = 200) to 1,076 ng/ml (range 132–4,721) at 5 years (n = 69). Overall, two patients discontinued the study per protocol because of serum ferritin levels falling below 500 ng/ml.

4 | DISCUSSION

This study reports the safety profile of deferasirox over 5 years in young children aged 2 to less than 6 years at enrollment, with chronic iron overload related to blood transfusions. These long-term findings in the largest formal study of deferasirox therapy in young pediatric patients support previously reported 1-year safety and efficacy data,6–9 as well as longer term trials showing a decreasing annual AE incidence.10,11 Importantly, no new or unexpected safety findings were observed with regard to AEs or laboratory abnormalities, with a limited number of patient discontinuations as a direct result of AEs. Although direct comparison between trials is precluded by differences in study design and patient demographics, the discontinuation rate was in line with that previously reported in thalassemia patients receiving deferasirox in a controlled clinical trial.10 Furthermore, analyses from the present study indicate a decreasing trend in the number of patient discontinuations over time, reflecting successful patient management and treatment acceptance in clinical practice.

As patients in this observational study were treated in accordance with local prescribing information, pre-existing renal impairment represents a contraindication for deferasirox treatment. In this study, the renal safety profile was consistent with the known deferasirox safety profile. No patients exited the study because of renal dysfunction, and there was no evidence of irreversible renal damage. Renal abnormalities may occur in children treated with deferasirox. However, transfusion-dependent thalassemia patients may also develop renal dysfunction independent of deferasirox therapy.19 Both iron overload and anemia likely contribute to renal dysfunction.20,21 In this study, the proportion of patients experiencing clinically relevant changes in renal hemodynamics during the 5-year observation period was low (4.4%), with few patients experiencing reduced renal function, consistent with previous studies.10 Observed absolute SCr values showed a slight linear increase over time, without exceeding the age-adjusted ULN. This is consistent with the normal proportional increase in SCr and muscle mass22 expected during continued growth for a pediatric population. Importantly, these results show no indication of progressive worsening of renal function over time, which conforms with a Phase I study showing deferasirox to have only a mild, generally reversible hemodynamic effect.12

The proportion of patients experiencing clinically relevant changes in hepatic function was also low (4.0%). Notably, almost a third of patients (27.6%) entered the study with ALT higher than the ULN, and many patients were iron overloaded at baseline according to serum ferritin levels; over half of these patients achieved ALT levels less than or equal to the ULN by the EOS. There was an initial increase in ALT levels followed by a downward trend over time, which was also observed in a previous 5-year analysis of deferasirox in adult and pediatric patients with β-thalassemia.10 Patients were managed according to the perceived risk by the investigator for deferasirox contributing to liver cell injury, with 12% of the patients receiving dose adjustments accordingly. Most patients who experienced ALT and/or AST increases continued deferasirox treatment at the same or reduced dose. The most frequently reported AE with suspected relationship to
deferasirox was increased ALT alongside increased AST. In this observational study, the overall drug-related gastrointestinal disorders were less frequently reported than in previous studies, although it has been recently incorporated into the deferasirox label that children aged 2–5 years are at higher risk of experiencing diarrhea compared with the overall patient population. Therefore, further analyses of the current dataset are warranted and are ongoing.

Previous long-term studies of deferasirox in pediatric patients with β-thalassemia and SCD have indicated that growth and sexual development are not impaired and progress normally. Owing to the young age of patients enrolled in this study, long-term effects of deferasirox therapy on sexual development could not be definitively assessed. However, annual growth velocity was as expected in this prepubertal patient population and was in line with public growth curves for children aged 2 to less than or equal to 11 years. Therefore, adequate deferasirox therapy does not appear to have an adverse effect on growth, confirming previous findings.

The observed reduction in serum ferritin further supports deferasirox effectiveness in controlling and decreasing body iron, when used at an appropriate dose for the degree of iron overload and ongoing iron intake rate. The increase in total deferasirox dose from baseline to EOS was as expected for a growing population. However, failure to adjust the deferasirox dose in some cases, despite substantial weight gain, likely affected the magnitude of change in serum ferritin over the 5-year period. These data highlight the need to adjust deferasirox dose based on increases in patient weight in order to provide optimal therapy.

Assessment of efficacy was limited to serum ferritin analysis in this study. Serum ferritin levels can be influenced by inflammatory processes, which are often exacerbated in patients with SCD because of vaso-occlusive crises, hemolysis, and infection. Serum ferritin levels in patients with SCD have shown varying degrees of correlation with liver iron concentration, a more direct measure of iron overload recommended for monitoring iron, particularly in SCD patients and β-thalassemia patients, when available. Approximately 20% of the observed patients in this study had SCD, which likely confounded the efficacy outcomes based on serum ferritin assessments alone. Indeed, the slight increase in median serum ferritin levels at EOS was attributable to patients with SCD.

This study has several limitations. The study was limited by its observational nature, as well as the lack of a predefined therapy protocol, diagnostic/therapeutic interventions, and visit schedule. Therefore, this study did not determine if more aggressive therapy could result in a higher incidence of AEs.

Identifying an effective and tolerable chelator for young children, who may require treatment for the rest of their lives, is critically important to prevent the risk of iron overload, which can lead to organ failure, growth retardation, and premature death. Deferasirox is the most commonly used iron chelator in the United States and long-term information concerning safety and efficacy in young children is important. The results of this observational study provide real-world evidence that supports the manageable safety profile and sustained efficacy of long-term deferasirox therapy in pediatric patients aged 2 to less than 6 years at enrollment with transfusional hemosiderosis. Most patients with increased SCr or ALT continued therapy at the same or a reduced dose. In this prepubertal population, overall growth and development was normal. Furthermore, over half the patients completed the 5-year observation, with limited discontinuations due to AEs. As such, with regular monitoring and dose adjustments, effective long-term chelation therapy with deferasirox is manageable in most pediatric patients in clinical practice. Optimal treatment efficacy and safety require close monitoring of each patient. Individual dose titration according to serum ferritin trends, periodic quantitative iron imaging, and analysis of safety markers are essential.

While the deferasirox safety profile in young children more than 2 years old appears similar to that in older children and adults, long-term effects on puberty, cataract formation, auditory, renal, and liver function after decades of drug exposure starting in early childhood have not been evaluated. Life-threatening, drug-related events are rare in more than 5,000 patients treated with deferasirox in clinical trials and many more in postmarketing monitoring.

Three iron chelators are available, with different routes of administration and potential side effects. Deferoxamine requires parenteral infusions over 8 hr per day and is associated with visual, auditory, and renal dysfunction. Two oral iron chelators, deferoxamine and deferasirox, are approved by the US Food and Drug Administration (FDA). Deferoxamine requires administration three times a day, and relatively common side effects include hepatic enzyme elevation, gastrointestinal discomfort, and arthralgias; agranulocytosis is an uncommon but potentially life-threatening side effect that resulted in a FDA black box warning and routine weekly white cell count monitoring. Deferasirox, administered once daily with a safety profile outlined herein, has a FDA black box warning for rare, life-threatening complications including renal failure, liver failure, and gastrointestinal hemorrhage; patients at most risk have comorbidities including advanced age, myelodysplastic syndromes, and preexisting renal and liver impairment. While young children appear to be at lower risk of these life-threatening events, long-term follow-up studies are needed to determine their cumulative risk. All patients require close monitoring based on efficacy and safety guidelines.

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CONFLICTS OF INTEREST

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AUTHORSHIP CONTRIBUTIONS

EV, AE-B, AA, AK, SK, TC, and ME served as investigators in this study, enrolling patients. They also served as study steering committee members, overseeing the conduct of the trial from study design to analysis planning and data interpretation. AB and GG contributed to the analysis, interpretation, and reporting of the trial data. JH served as the trial statistician. All authors contributed to data interpretation, reviewed and provided their comments on this manuscript, and approved the final version.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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