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Iron chelation with deferasirox in adult and pediatric patients with thalassemia major: Efficacy and safety during 5 years' follow-up

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Abstract

Patients with β-thalassemia require lifelong iron chelation therapy from early childhood to prevent complications associated with transfusional iron overload. To evaluate long-term efficacy and safety of once-daily, oral iron chelation with deferasirox, patients aged ≥2 years who completed a 1-year, Phase III, randomized trial entered a 4-year extension study, either continuing on deferasirox (deferasirox cohort) or switching from deferoxamine to deferasirox (crossover cohort). Of 555 patients who received ≥1 deferasirox dose, 66.8% completed the study; 43 patients (7.7%) discontinued because of adverse events (AEs). In patients with ≥4 years' deferasirox exposure who had liver biopsy, mean liver iron concentration significantly decreased by 7.8±11.2 (n=103;*P*<0.001) and 3.1±7.9 (n=68;*P*<0.001) mg Fe/g dw in the deferasirox and crossover cohorts, respectively. Median serum ferritin significantly decreased by 706 (n=196;*P*<0.001) and 371 (n=147;*P*<0.001) ng/mL, respectively, after ≥4 years exposure. Investigator-assessed, drug-related AEs, including increased blood creatinine (11.2%), abdominal pain (9.0%) and nausea (7.4%), were generally mild-to-moderate, transient and reduced in frequency over time. There was no adverse effect on pediatric growth or adolescent sexual development. This first prospective study of long-term deferasirox use in pediatric and adult β-thalassemia patients suggests treatment for up to 5 years is generally well tolerated and effectively reduces iron burden. This study is registered at clinicaltrials.gov as NCT0017210.

Introduction

Iron overload is a leading cause of morbidity and mortality in transfusion-dependent patients with β-thalassemia major; related complications include liver cirrhosis and cardiac disease.[1-3] The introduction of iron chelation therapy has led to a significant improvement in the survival of patients with β-thalassemia,[4] but long-term management of iron overload is suboptimal in many patients, in part because of compliance issues associated with the parenteral administration regimen of iron chelation therapy with deferoxamine (DFO).[5] Iron overload may also contribute to retardation of growth and sexual development during adolescence in patients with β-thalassemia,[6-8] which can be further exacerbated by the toxic effects of intensive iron chelation therapy with DFO on bone structure.[9-11] Therefore, in addition to exploring long-term efficacy and safety in patients with β-thalassemia, it is important to address the shortage of data from long-term trials on oral iron chelation and pediatric growth and development.

Deferasirox is a once-daily oral iron chelator that has proven effective in reducing liver iron concentration (LIC) and serum ferritin levels over 1 year in patients with various transfusion-dependent anemias.[12-15] As the requirements for transfusion therapy, and therefore iron chelation therapy, are lifelong in patients with β-thalassemia, there is a need to assess the long-term safety and efficacy of deferasirox in both adult and pediatric patients. This Phase III study initially randomized patients with β-thalassemia aged ≥2 years to receive deferasirox or DFO for 1 year.[12] Patients who completed the 1-year core study were eligible to enter a 4-year extension, either continuing to receive deferasirox, or switching from DFO to deferasirox. Efficacy and safety data for patients treated with deferasirox for up to 5 years are now available. These data represent the first analysis of long-term treatment with deferasirox in pediatric and adult patients with β-thalassemia, including the effects on pediatric growth and development.

Methods

Patients, study design and dosing

The study was reviewed and approved by the Independent Ethics Committee or Institutional Review Board for all participating centers. Patients with β-thalassemia and transfusional iron overload who completed the 1-year randomized core study (inclusion/exclusion criteria for which have been described previously[12]) were eligible to enter the 4-year extension study. During the extension study, patients either continued to receive deferasirox (deferasirox cohort) or switched from DFO to deferasirox (crossover cohort). Deferasirox dose was initially assigned according to LIC at the start of deferasirox treatment, where patients with LIC values of 2–3, >3–7, >7–14 and >14 mg Fe/g dry weight (dw) were assigned deferasirox doses of 5, 10, 20 or 30 mg/kg/day, respectively. One patient in the crossover cohort was assigned a deferasirox starting dose of 15 mg/kg/day (summarized in the ≤10 mg/kg/day planned starting dose category in the following analyses) and a further three patients in the crossover cohort were assigned a starting dose of 40 mg/kg/day. Subsequent dose increases or decreases of 5–10 mg/kg/day could be made every 3 months based on trends in serum ferritin levels and safety markers. Dose adjustments could also be based on transfusion requirements at the investigator's discretion.

Efficacy assessments

LIC was assessed at the start of deferasirox treatment and at end of study (EOS) by liver biopsy or superconducting quantum interference device (SQUID) methodology, as described for the core study.[12] Calibration issues noted during the core study meant that LIC values determined by SQUID were approximately half those determined by biopsy; as this observation was made after the study was initiated, a correction factor was not applied to the SQUID data.[12] Serum ferritin levels were evaluated every 4 weeks.

Safety assessments

Safety was assessed by monitoring adverse events (AEs) and laboratory parameters, including serum creatinine and liver transaminase levels. In adults, creatinine clearance was estimated based on serum creatinine levels and body mass, according to the Cockcroft–Gault formula.[16] In pediatric patients, height

was also used to estimate creatinine clearance, using the Schwartz formula.[17] Additional specific assessments for pediatric patients included height, body mass and sexual development. Height was measured every 3 months after the start of deferasirox with an approximation of ± 0.1 cm using a Harpenden stadiometer. Yearly height assessments of individual patients were plotted against the 5%, 50% and 95% percentiles of the US Clinical Growth Charts for a non-thalassemia population, available at http://www.cdc.gov/growthcharts.[18] Body mass was assessed every 3 months, always using the same scale with an approximation of ± 0.1 kg, with patients clothed in a light-weight suit. Sexual development was assessed annually by physical examination with reference to Tanner stages.[19,20] Pediatric growth was evaluated by monitoring changes in height and body mass index (BMI), expressed as height- and BMI-standard deviation scores (h-SDS and BMI-SDS, respectively). SDS are standardized normal-distributed scores with mean 0 and standard deviation 1 of an age- and gender-specific normal population.

Statistical methods

Data are reported for all patients who received at least one dose of deferasirox during the core or extension studies. LIC and serum ferritin levels were further analyzed for patients who were treated with deferasirox for at least 4 years. Patients were assigned to planned starting dose categories according to the planned dose at the start of deferasirox treatment. *P*-values for change in LIC in this population were based on one-sided Student's *t*-tests. *P*-values for change in serum ferritin levels were based on a two-sided sign test.

h-SDS was calculated using the formula h-SDS = ([(X / M)**L] – 1) / (L * S), where X is the patient's standing height measurement (cm) and L, M and S are the parameters for the Box–Cox transformation (as provided in the US Clinical Growth Charts[18] at http://www.cdc.gov/growthcharts). L is the Box–Cox parameter used to normalize the data (exponent), M is the median height corresponding to age and S is the measure of the spread of the data (generalized coefficient of variation). BMI-SDS was calculated as for h-SDS, where X is the patient's BMI (kg/m^2) and M is the median BMI corresponding to age.

Results

Patient characteristics

In total, 555 patients received at least one dose of deferasirox in the core or extension studies between 13 February 2003 (first patient, first visit in core study) and 28 November 2008 (last patient, last visit in extension study): 296 patients in the deferasirox cohort and 259 patients in the crossover cohort. Pediatric patients aged 2–<16 years accounted for 49.2% of patients (n=273) overall. Table 1 details the patient demographics at the start of deferasirox treatment, which corresponds to the start of the core study for the deferasirox cohort and the start of the extension study for the crossover cohort. The majority of patients who entered the core study (97.4%) had a history of prior iron chelation therapy.[12] However, at the start of deferasirox treatment, serum ferritin levels and LIC were generally lower in the crossover cohort where patients had received 1 year of DFO treatment in the core study, compared with the deferasirox cohort where patients had started deferasirox upon entry to the study. LIC assessments by SQUID were lower than LIC assessments by biopsy (Table 1). As assessment by biopsy was optional for pediatric patients, SQUID methodology was more likely to be used in this group. Overall, 91 of 555 patients (16.4%) had LIC assessments by SQUID at baseline.

Deferasirox dosing

The mean deferasirox dose was 21.6 ± 6.4 mg/kg/day in the deferasirox cohort and 23.2 ± 5.9 mg/kg/day in the crossover cohort. Over the course of the study, the percentage of patients receiving <15 mg/kg/day showed a marked decrease, as the majority of all patients received final doses of ≥25 mg/kg/day (Table 2).

Patient discontinuations

Of the 555 patients included, 181 (61.1%) patients in the deferasirox cohort and 190 (73.4%) in the crossover cohort completed the 5-year study (Table 3). Thirty-two of 296 patients (10.8%) from the deferasirox cohort chose not to enter the extension phase and one patient left the study at the end of extension year 3, before a protocol amendment increased the extension study length to 4 years. The most common reasons for discontinuation were withdrawal of consent and AEs. The reasons for discontinuation were relatively consistent throughout the

study (Online Supplementary Table S1), with the exception that discontinuation because of an unsatisfactory therapeutic effect was more likely in the later stages of the trial. Of the AEs that led to discontinuation, the most common (in four or more patients overall) were increased alanine aminotransferase (ALT; n=5, 0.9%), increased transaminases (n=4, 0.7%) and glycosuria (n=4, 0.7%) (Online Supplementary Table S2). Five patients died while receiving deferasirox, one during the core study[12] and four during the extension. One patient died in the crossover cohort following a road traffic accident. The three other deaths during the extension (two in the deferasirox cohort and one in the crossover cohort) were due to cardiac disorders (congestive cardiac failure, myocardial dysfunction and cardio-respiratory arrest, respectively). These three patients received their last deferasirox dose 14, 12 and 9 days prior to death, respectively. Deferasirox was discontinued as a result of atrial flutter in the patient who died of congestive cardiac failure and DFO was subsequently administered for iron chelation for 10 days prior to death. In two of the patients who died as a result of cardiac disorders, including the patient who switched to DFO, their last available serum ferritin assessments were elevated above levels at the start of deferasirox treatment. No deaths reported during the extension were attributed to deferasirox toxicity.

Efficacy

There were no clinically relevant differences in the transfusion requirements of the deferasirox and crossover cohorts. Overall blood intake after the start of deferasirox was <7 mL/kg/month in 69 (12.4%) patients, 7–14 mL/kg/month in 454 (81.8%) patients and >14 mL/kg/month in 32 (5.8%) patients. Mean iron intake was 0.37 ± 0.1 and 0.38 ± 0.1 mg/kg/day in the deferasirox and crossover cohort, respectively, and was similar irrespective of planned starting dose.

In 103 patients in the deferasirox cohort who had liver biopsies at the start of deferasirox and after at least 4 years of deferasirox exposure, mean LIC significantly decreased from 17.4 ± 10.5 to 9.6 ± 8.0 mg Fe/g dw (one-sided $P<0.001$). Deferasirox treatment for at least 4 years had a dose-dependent effect on LIC (Figure 1[a]), with the largest reduction in LIC observed in patients assigned a planned starting dose of 30 mg/kg/day (Online Supplementary Table S3). Reductions in LIC were similarly dose dependent in the crossover cohort

(Figure 1[b]); Online Supplementary Table S3). Overall, the mean LIC of 68 patients in the crossover cohort who had liver biopsies at the start of deferasirox and after at least 4 years of deferasirox exposure significantly decreased from 12.5 ± 6.8 to 9.3 ± 6.4 mg Fe/g dw (one-sided $P<0.001$). An additional 28 patients in the deferasirox cohort and 19 patients in the crossover cohort had LIC measurements via SQUID assessment at start of deferasirox and after at least 4 years of deferasirox treatment. In the deferasirox cohort, SQUID-assessed mean LIC significantly reduced from 5.6 ± 2.7 to 4.0 ± 4.0 mg Fe/g dw (one-sided $P=0.024$). In the crossover cohort, the mean SQUID-assessed LIC was similar at start of deferasirox and after at least 4 years' deferasirox (5.2 ± 2.8 versus 5.1 ± 4.5 mg Fe/g dw). Patient numbers in the crossover cohort were too low to determine statistical significance.

In 393 patients with LIC assessed using the same method at both start of deferasirox and EOS (last observation carried forward), over 40% had LIC <7 mg Fe/g dw at EOS, irrespective of iron intake. The mean deferasirox dose during the study generally reflected iron intake; in the <0.3 mg/kg/day iron intake category, 15 (18.1%) patients received mean doses of 5–<15 mg/kg/day and 23 (27.7%) patients received mean doses of 25–<35 mg/kg/day, whereas in the >0.5 mg/kg/day iron intake category, two (4.5%) patients received mean doses of 5–<15 mg/kg/day and 19 (43.2%) patients received mean doses of 25–<35 mg/kg/day. This trend was further reinforced in the final dose received; the majority of patients in the >0.5 mg/kg/day iron intake category received final doses ≥25 mg/kg/day with a corresponding decrease in the proportion receiving 15–<25 mg/kg/day (Table 4).

Median serum ferritin levels generally decreased over the study duration in both the deferasirox (Figure 1[a]) and crossover (Figure 1[b]) cohorts, with decreases in serum ferritin levels becoming more pronounced when the average actual dose increased to above 20 mg/kg/day. In the deferasirox cohort, for 196 patients who had serum ferritin levels assessed at start of deferasirox and after at least 4 years of deferasirox exposure, median serum ferritin levels decreased significantly from 2117 to 1124 ng/mL ($P<0.001$). A total of 100 (51.0%) patients achieved serum ferritin levels of ≤1000 ng/mL (considered a target of iron chelation therapy[21]) after at least 4 years of deferasirox, of whom 13, 58, 16 and 13 had serum ferritin

levels of ≤1000, >1000–2500, >2500–4000 and ≥4000 ng/mL, respectively, at the start of treatment. A total of 167 (85.2%) patients attained serum ferritin levels ≤2500 ng/mL (a threshold associated with a decreased risk of cardiac failure and death[22]) after at least 4 years of deferasirox treatment. Median serum ferritin levels also significantly decreased in 147 patients in the crossover cohort with assessments at start of deferasirox and after at least 4 years of deferasirox treatment, from 1731 to 1047 ng/mL (*P*<0.001). Sixty-four (42.4%) patients achieved serum ferritin levels ≤1000 ng/mL after at least 4 years' exposure, of whom 17, 37, eight and two had serum ferritin levels of ≤1000, >1000–2500, >2500–4000 and ≥4000 ng/mL, respectively, at the start of deferasirox treatment. A total of 121 (80.1%) patients in the crossover cohort had serum ferritin levels of ≤2500 ng/mL after at least 4 years of deferasirox exposure. As observed for LIC, deferasirox had a dose-dependent effect on serum ferritin levels in both the deferasirox and crossover cohorts (Figure 1); the median absolute change in serum ferritin levels was greatest in patients assigned a planned starting dose of 30 mg/kg/day (Online Supplementary Table S4).

The median serum ferritin levels of pediatric patients in the deferasirox cohort who received 5 years of exposure to deferasirox decreased significantly from 2409 ng/mL at the start of deferasirox treatment to 1208 ng/mL (n=107; *P*<0.001). After 4 years of exposure to deferasirox, the serum ferritin levels of pediatric patients in the crossover cohort also significantly decreased from 1922 ng/mL at the start of deferasirox to 1047 ng/mL (n=83; *P*<0.001).

Safety and tolerability

Adverse events

The most common (≥5% overall) investigator-assessed deferasirox-related AEs were increased blood creatinine levels (n=62, 11.2%), abdominal pain (including upper abdominal pain; n=50, 9.0%), nausea (n=41, 7.4%), rash (n=36, 6.5%), vomiting (n=35, 6.3%) and diarrhea (n=28, 5.0%). Gastrointestinal disorders with a suspected relationship to deferasirox treatment were observed more frequently in patients aged ≥16 years (n=82, 29.1%) than <16 years (n=43, 15.8%). AEs were predominantly transient and mild-to-moderate in nature. Their incidence generally decreased after the first year of deferasirox treatment in both cohorts (Figure 2). Overall, the frequency of AEs with a suspected relationship to

deferasirox was higher in patients receiving doses of 25–<35 mg/kg/day (n=136, 39.4%) compared with those receiving 15–<25 mg/kg/day (n=118, 31.1%) or <15 mg/kg/day (n=101, 29.4%), but there was no marked increase in AE frequency in 66 patients treated with doses ≥35 mg/kg/day (n=13, 19.7%). Serious AEs, irrespective of relationship to deferasirox treatment, were reported in 163 (29.4%) patients overall; 102 (34.5%) patients in the deferasirox cohort and 61 (23.6%) patients in the crossover cohort. The most common (≥2% overall) were pyrexia (n=16, 2.9%), hypersplenism (n=14, 2.5%), cholelithiasis (n=13, 2.3%) and abdominal pain (n=13, 2.3%). Serious AEs considered by investigators to be related to deferasirox treatment were reported in 26 (4.7%) patients overall. Full details are provided in Online Supplementary Table S5.

Laboratory parameters

Median serum creatinine levels remained in the normal range during the study in both the deferasirox and crossover cohorts; observed increases in serum creatinine were generally mild and non-progressive. Two consecutive serum creatinine level increases >33% above the value at the start of deferasirox and greater than the upper limit of normal (ULN) were reported in 26 (8.8%) patients in the deferasirox cohort and 11 (4.2%) patients in the crossover cohort. All patients had serum creatinine levels ≤ULN at the start of deferasirox treatment. Such increases in serum creatinine were observed throughout the study, most frequently in patients receiving 25–<35 mg/kg/day (Online Supplementary Table S6). Following two consecutive increases in serum creatinine levels >33% above the value at the start of deferasirox and >ULN, three patients in the deferasirox cohort and one patient in the crossover cohort had dose adjustments, while four patients in the deferasirox cohort had temporary dose interruptions. No patients discontinued the study as a result of such serum creatinine level increases. Median creatinine clearance decreased slightly during the first 6 months of deferasirox treatment in both cohorts then remained stable for the remainder of the study (Figure 3).

Mean ALT levels were slightly increased during the first 2 years of deferasirox treatment before showing a downward trend for the remainder of the study in both cohorts. Two consecutive increases in ALT levels >10 x ULN were reported in three (1.0%) patients in the deferasirox cohort and two (0.8%) patients in the

crossover cohort. ALT levels were <ULN in one patient in the deferasirox cohort at the start of deferasirox treatment. The other four patients had elevated ALT levels >ULN to ≤5 x ULN. In the deferasirox cohort, one patient discontinued deferasirox and another had a temporary dose interruption following two consecutive increases in ALT levels ≥10 x ULN. There was no apparent relationship between these ALT increases and the deferasirox dose at time of onset. Progressive increases in ALT were reported in one patient in the crossover cohort; ALT levels increased to 265 U/L, which was considered by investigators to be a serious AE related to deferasirox, and treatment was permanently discontinued. No patients had increases in aspartate aminotransferase levels >10 x ULN at two consecutive visits.

Pediatric growth and development

For the 273 pediatric patients included in this study, individual growth curves demonstrated continuous growth in male and female pediatric patients from both cohorts during deferasirox treatment, although growth trends tended to lie within the lower percentiles of US Clinical Growth Charts (Online Supplementary Figure S1). Absolute change for h-SDS from start of deferasirox to EOS for patients aged 2–<6 and 6–<12 years also suggested slightly reduced growth compared to a non-thalassemic North American control population, with evidence of growth normalization in parallel with pubertal development in patients aged 12–<16 years (Figure 4).

BMI-SDS was stable during deferasirox treatment; the mean change from the start of deferasirox treatment to EOS in pediatric patients aged 2–<6, 6–<12 and 12–<16 years, respectively, was –0.42 ± 0.9, –0.13 ± 0.8 and –0.05 ± 0.7 in the deferasirox cohort, and 0.28 ± 1.1, 0.2 ± 0.7 and –0.07 ± 0.6 in the crossover cohort. Values were similar for male and female patients.

During the study, the observed transition through Tanner stages for female breast development, male testes volume and both male and female pubic hair, was as expected for patients aged 12–<16 at the start of deferasirox treatment (Online Supplementary Figure S2). The proportion of patients at Tanner stage 5 for female breast development increased from 8.8% and 18.1% at start of deferasirox to 51.5% and 72.7% at EOS in the deferasirox and crossover cohorts,

respectively, and the proportion of female patients at Tanner stage 5 for pubic hair increased from 8.8% and 27.2% to 51.5% and 77.2% in the deferasirox and crossover cohorts, respectively. No male patients aged 12–<16 were at Tanner stage 5 for testicular volume at the start of deferasirox treatment; at EOS, 27.2% and 28.5% were at stage 5 in the deferasirox and crossover cohorts, respectively. Similarly, none of the male patients aged 12–<16 were at Tanner stage 5 for pubic hair at the start of deferasirox treatment. At EOS, 18.1% in the deferasirox cohort and 28.5% in the crossover cohort were at stage 5 for pubic hair.

Discussion

Iron chelation therapy is a lifelong requirement for transfusion-dependent patients with β-thalassemia, but to date, long-term efficacy and safety data from prospective clinical trials in pediatric and adult patients are limited. This is the first prospective study to report long-term monitoring of the efficacy and safety of iron chelation with deferasirox in both pediatric and adult patients with β-thalassemia. It also represents the first report of observed long-term effects on pediatric growth and adolescent sexual development for any oral iron chelation therapy.

Overall, two-thirds of patients completed the 5-year study. Deferasirox became commercially available during the trial; therefore, the patients who discontinued as a result of consent withdrawal or loss to follow-up may include subjects who left the study but continued to take deferasirox. The completion rate is similar to that observed in a 5-year prospective study of deferiprone–DFO combination therapy versus deferiprone monotherapy[23] and higher than a 4-year prospective analysis of long-term deferiprone (in which dose-adjustments were not permitted by the study protocol), where less than half of the enrolled patients completed the study.[24]

Long-term deferasirox treatment led to a sustained reduction in the iron burden of the patients enrolled in the study. The limited efficacy of the 10 mg/kg/day dose was noted during the core phase[12] and patients with relatively low LIC who were planned doses of 10 mg/kg/day were dose escalated during the extension; the final actual doses of over half the patients studied were ≥25 mg/kg/day. Significant decreases in both LIC and serum ferritin levels were observed in patients who received at least 4 years of exposure to deferasirox, irrespective of whether patients had switched from DFO. Changes in LIC generally reflected changes in serum ferritin levels, despite fewer patients having EOS liver biopsy versus serum ferritin assessments. The effects of deferasirox on cardiac iron were not examined in this study, but other long-term trials are ongoing to investigate this.[25,26] Overall, 83.0% of patients attained serum ferritin levels of ≤2500 ng/mL. Serum ferritin levels above this threshold are associated with decreased survival and increased risks of cardiac disease and impaired puberty in patients with β-thalassemia.[22,27] Of 347 patients who received deferasirox for at

least 4 years, 30 patients (8.6%) had serum ferritin levels of ≤1000 ng/mL at the start of deferasirox treatment compared with 164 patients (47.3%) after 4 years. Of these 164 patients, almost a quarter (23.8%) had serum ferritin levels of >2500 ng/mL at the start of deferasirox treatment. The largest decreases in LIC and serum ferritin were reported in patients assigned planned deferasirox doses of 30 mg/kg/day. As the initial deferasirox dose was assigned based on LIC at start of deferasirox treatment, this observation agrees with reports that deferasirox doses of ≥30 mg/kg/day may be required in some patients to reduce iron burden to clinically acceptable levels.[28] Furthermore, while over 40% of patients had LIC <7 mg Fe/g dw at EOS, patients with higher mean iron intake appeared more likely to require doses in the 25–<35 mg/kg/day range to reach this threshold. In clinical practice, the need for doses ≥30 mg/kg/day may be particularly associated with higher transfusion requirements. It should be noted, however, that changes in iron burden were subject to inter-patient variability even at higher doses. There is some evidence that variable gastrointestinal absorption may contribute to a decreased response in some patients, which should be considered when evaluating dose adjustments and timing.[29]

The invasive nature of performing a liver biopsy resulted in many patients or investigators electing not to repeat the procedure at EOS, meaning the number of patients included in the EOS LIC analysis was markedly reduced compared to the actual number of patients who completed the study. This issue was confounded by the identification during the core trial and other studies[12,15] of differences in the calibration of SQUID and biopsy LIC values, whereby SQUID values were approximately one half of those obtained by biopsy and subsequently reported separately from LIC values. Since the initiation of this study, magnetic resonance imaging (MRI) technology has now emerged as a robust, non-invasive technique for determining LIC,[30,31] meaning that such calibration and patient uptake issues are likely to be less problematic in future iron chelation studies.

Deferasirox was generally well tolerated over the long term in both pediatric and adult patients. Overall, 72 patients (14.2%) discontinued the long-term study as a result of AEs, abnormal laboratory values, abnormal test procedure results or unsatisfactory therapeutic effects. The most common AEs with a suspected

relationship to deferasirox during the extension study were similar to those reported for the core study,[12] being predominantly gastrointestinal, transient and mild-to-moderate in nature. Of note, gastrointestinal AEs with a suspected relationship to deferasirox treatment were more likely to be reported by adult than pediatric patients. Deferasirox tolerance appeared to improve over the long term, as the proportions of patients presenting with the most common drug-related AEs decreased considerably after the first year of deferasirox treatment.

Renal and liver function was closely monitored. No progressive increases in serum creatinine or liver transaminase levels were observed during long-term deferasirox treatment and creatinine clearance remained stable. Fanconi-like syndrome in the kidney during deferasirox treatment has been reported very rarely[32-34] but was not observed in this study. Patients with two consecutive increases in serum creatinine >33% above the start of deferasirox and >ULN were most frequently in higher average actual dose categories, but such increases were manageable and did not lead to permanent discontinuation of deferasirox. There was no apparent relationship between deferasirox dose and liver transaminase increases. A relatively high cut-off for elevated liver transaminases of 10 x ULN was used in this study because iron overload itself is known to increase liver enzyme levels, in particular in patients with high LIC.[35] While changes in renal and liver parameters were manageable in this trial, it should be noted that the study enrollment criteria excluded patients with clinically significant kidney and liver dysfunction and the tolerability of deferasirox in such patients cannot therefore be deduced from these observations. Ongoing monitoring of renal and liver function during deferasirox treatment in clinical practice remains a requirement.

Deferasirox dosing strategy was the same for adult and pediatric patients. As transfusion therapy to manage β-thalassemia is initiated in early childhood and continues for life, it is important to evaluate the long-term effects of iron chelation therapy in pediatric patients. Growth of pediatric patients and sexual development of adolescent patients with β-thalassemia is of particular relevance, since multiple factors, including iron toxicity, can lead to reduced stature and delayed puberty in this population.[6-8] Although the prevalence has decreased since iron chelation therapy has become available,[4] many patients continue to suffer complications of

growth and sexual development, which are often associated with poor compliance to DFO.[4,6,36] In this 5-year study, pediatric patients showed continued growth and development during deferasirox treatment. The observed growth assessments suggested that patients aged <12 years had slightly reduced growth compared with a control population, although it should be noted that the control data have some limitations for use in an international thalassemia study, being derived from a healthy population in the USA. h-SDS appeared to improve during adolescence, most likely with the onset of puberty. Sexual development was observed to progress through the Tanner stages as expected in patients aged 12–<16 years. It is therefore unlikely that growth problems such as those encountered in early DFO studies[9-11] are an issue with deferasirox at the doses used in this study. It is possible that deferasirox activity in removing iron from the endocrine organs contributes to growth progression observed during the study; however, in the absence of a satisfactory control cohort (ie, untreated patients with β-thalassemia major), it is difficult to draw more definitive conclusions.

This is the first study to demonstrate significant reduction of liver and total body iron overload with long-term deferasirox treatment in both adult and pediatric patients with β-thalassemia and the data presented are supportive of published shorter-term clinical trials of 1-year duration.[13,37] Many patients achieved maintenance serum ferritin levels of approximately 1000 ng/mL and treatment for up to 5 years was well tolerated. Deferasirox did not show an adverse effect on pediatric growth or adolescent sexual development in pediatric patients who are prone to growth retardation as a result of iron overload. Appropriate dose adjustments led to clinically relevant decreases in LIC and serum ferritin, highlighting the necessity for dose titration to achieve negative iron balance. Deferasirox, with dosing tailored to individual patient requirements, is therefore an effective long-term treatment for transfusional iron overload in adult and pediatric patients with β-thalassemia.

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Author contributions and disclosure of conflicts of interest

MDC, MB, LA, DC, MC, AC, GD, ME, SF, AK, YK, SP, AP, JBP and YA served as investigators on this trial, enrolling patients. The manuscript was drafted by MDC with contribution from YA on the pediatrics section. All other authors reviewed and contributed their comments on each draft of this manuscript and approved the final version. MDC, AC, AP and AK also served as Study Monitoring Committee members overseeing the conduct of the trial. LG and VD provided clinical insight, assisted in the interpretation of the trial data and contributed their comments on this manuscript. JC served as the trial statistician and contributed comments on the manuscript.

MDC is a member of the Novartis Speakers Bureau. AC has received research funding from Novartis Pharmaceuticals and reimbursement from ApoPharma for travel expenses for an annual meeting of the Safety Committee. AK has received honoraria and research funding from Novartis Pharmaceuticals and reports membership of the Novartis Speakers Bureau. SP has received research funding from Novartis Pharmaceuticals. AP has received honoraria and research funding from Novartis Pharmaceuticals. JBP has received research funding from Novartis Pharmaceuticals and reports membership of Novartis advisory boards and Speakers Bureau. LG, VD and JC are employed by a company (Novartis Pharmaceuticals) whose product was studied in the present work. YA has received honoraria and research funding from Novartis Pharmaceuticals and reports membership of Novartis advisory boards. MB, LA, DC, MC, GD, ME, SF and YK have no relevant conflicts of interest to disclose.

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Tables

Table 1. Demographics and patient characteristics at the start of deferasirox treatment

Characteristic	Deferasirox cohort (n=296)	Crossover cohort (n=259)	All patients (n=555)
Mean age (range), years	17.1 (2–49)	18.3 (3–54)	17.7 (2–54)
Age group, n (%)			
2–<16 years	153 (51.7)	120 (46.3)	273 (49.2)
≥16 years	143 (48.3)	139 (53.7)	282 (50.8)
Male:female, n	140:156	134:125	274:281
Race (Caucasian:Oriental:other), n	263:9:24	225:10:24	488:19:48
Mean LIC ± SD, mg Fe/g dw			
Biopsy	15.5 ± 9.9	11.5 ± 7.8	13.3 ± 9.2
SQUID	6.1 ± 2.8	5.2 ± 2.9	5.7 ± 2.8
LIC category, n (%)*			
<7 mg Fe/g dw (biopsy)	60 (20.3)	64 (24.7)	124 (22.3)
<7 mg Fe/g dw (SQUID)	33 (11.1)	35 (13.5)	68 (12.3)
7–14 mg Fe/g dw (biopsy)	68 (23.0)	93 (35.9)	161 (29.0)
7–14 mg Fe/g dw (SQUID)	15 (5.1)	6 (2.3)	21 (3.8)
≥14 mg Fe/g dw (biopsy)	120 (40.5)	58 (22.4)	178 (32.1)
≥14 mg Fe/g dw (SQUID)	0	2 (0.8)	2 (0.4)
Median serum ferritin (range), ng/mL	2211 (321–12646)	1758 (273–8529)	2007 (273–12646)
Serum ferritin category, n (%)			
≤1000 ng/mL	21 (7.1)	48 (18.5)	69 (12.4)
>1000–2500 ng/mL	155 (52.4)	140 (54.1)	295 (53.2)
>2500–4000 ng/mL	64 (21.6)	50 (19.3)	114 (20.5)
>4000 ng/mL	56 (18.9)	21 (8.1)	77 (13.9)

*****LIC at start of deferasirox was not available for one patient in the crossover cohort

dw, dry weight; SD, standard deviation

Table 2. Deferasirox dosing

	Deferasirox cohort (n=296)	Crossover cohort (n=259)	All patients (n=555)
Patients in planned dose groups at start of deferasirox, n (%)			
<15 mg/kg/day	92 (31.1)	104 (40.2)	196 (35.3)
15–<25 mg/kg/day	85 (28.7)	94 (36.3)	179 (32.3)
25–<35 mg/kg/day	119 (40.2)	58 (22.4)	177 (31.9)
≥35 mg/kg/day	0	3 (1.16)	3 (0.54)
Patients in final actual dose groups, n (%)			
<15 mg/kg/day	43 (14.5)	13 (5.0)	56 (10.1)
15–<25 mg/kg/day	113 (38.2)	100 (38.6)	213 (38.4)
25–<35 mg/kg/day	108 (36.5)	101 (39.0)	209 (37.7)
≥35 mg/kg/day	32 (10.8)	45 (17.4)	77 (13.9)

Table 3. Adult and pediatric patient disposition

	Deferasirox cohort		Crossover cohort		All
Disposition, n (%)	**Adults (n=143)**	**Pediatrics (n=153)**	**Adults (n=139)**	**Pediatrics (n=120)**	**patients (n=555)**
Completed	74 (51.7)	107 (69.9)	88 (63.3)	102 (85.0)	371 (66.8)
Discontinued	69 (48.3)	46 (30.1)	51 (36.7)	18 (15.0)	184 (33.2)
Adverse events	14 (9.8)	13 (8.5)	10 (7.2)	6 (5.0)	43 (7.7)
Abnormal laboratory value	1 (0.7)	2 (1.3)	4 (2.9)	2 (1.7)	9 (1.6)
Abnormal test procedure result	1 (0.7)	–	–	–	1 (0.2)
Unsatisfactory therapeutic effect	11 (7.7)	4 (2.6)	7 (5.0)	4 (3.3)	26 (4.7)
Protocol violation	1 (0.7)	1 (0.7)	–	–	2 (0.4)
Withdrawal of consent*	24 (16.8)	6 (3.9)	26 (18.7)	6 (5.0)	62 (11.2)
Lost to follow-up	–	–	1 (0.7)	–	1 (0.2)
Administrative problems	1 (0.7)	–	1 (0.7)	–	2 (0.4)
Death	2 (1.4)	1 (0.7)	2 (1.4)	–	5 (0.9)
Stopped at end of core	13 (9.1)	19 (12.4)	–	–	32 (5.8)
Stopped at end of extension year 3	1 (0.7)	–	–	–	1 (0.2)

*May include patients who left the study when deferasirox became commercially available

Table 4. Proportion of patients with LIC <7, 7–14 or >14 mg Fe/g dw at EOS (last observation carried forward) and mean actual dose categories by iron intake

	Iron intake during study (mg/kg/day)		
	<0.3 (n=83)	**0.3–0.5 (n=266)**	**>0.5 (n=44)**
LIC category at EOS, n (%)			
<7 mg Fe/g dw	36 (43.4)	120 (45.1)	20 (45.5)
7–14 mg Fe/g dw	30 (36.1)	77 (28.9)	13 (29.5)
>14 mg Fe/g dw	17 (20.5)	69 (25.9)	11 (25.0)
Mean actual dose during study, n (%)			
5–<15 mg/kg/day	15 (18.1)	29 (10.9)	2 (4.5)
15–<25 mg/kg/day	45 (54.2)	145 (54.5)	23 (52.3)
25–<35 mg/kg/day	23 (27.7)	89 (33.5)	19 (43.2)
≥35 mg/kg/day	0	3 (1.1)	0
Final actual dose during study, n (%)			
5–<15 mg/kg/day	16 (19.3)	20 (7.5)	2 (4.5)
15–<25 mg/kg/day	32 (38.6)	115 (43.2)	11 (25.0)
25–<35 mg/kg/day	28 (33.7)	93 (35.0)	26 (59.1)
≥35 mg/kg/day	7 (8.4)	38 (14.3)	5 (11.4)

NOTE: Only patients with a LIC value at both start of deferasirox and EOS evaluated with the same method (either SQUID or biopsy) are included. EOS values represent the last observation carried forward after starting deferasirox, irrespective of length of deferasirox exposure.

Figure legends

Figure 1. Median serum ferritin ± range, mean LIC ± SD (biopsy) and mean actual dose ± SD in (a) the deferasirox cohort and (b) the crossover cohort for patients with at least 4 years of deferasirox exposure by planned starting dose category ≤10, 20 or 30 mg/kg/day

Only patients with at least 4 years of exposure to deferasirox are included. LIC values are for patients assessed by biopsy at start of deferasirox and at EOS, where EOS represents the last available biopsy assessment occurring after at least 4 years of exposure to deferasirox. Patients with LIC assessments by SQUID are not included in this figure. One crossover cohort patient included in the ≤10 mg/kg/day category had a planned starting dose of 15 mg/kg/day. Error bars indicate the minimum and maximum values for the serum ferritin plot and the SD for both the LIC and dose plots.
SD, standard deviation

Figure 2. Annual frequency of the most common (≥5% overall) investigator-assessed drug-related AEs during deferasirox treatment in the (a) deferasirox and (b) crossover cohorts

*Reports of abdominal pain and abdominal pain (upper) are combined and presented as abdominal pain

Figure 3. Creatinine clearance over time after start of deferasirox

Creatinine clearance in patients aged 2–<16 years was adjusted to a typical adult size of 1.7 m^2. Length of the box represents the interquartile range; whiskers extend to 10^{th} and 90^{th} percentiles. The median values are connected.

Figure 4. Change in h-SDS from start of deferasirox treatment to EOS in (a) male and (b) female pediatric patients receiving deferasirox for up to 5 years

Age groups refer to age at start of deferasirox treatment. EOS value corresponds to last available value after start of deferasirox for patients aged 2–<16 years at the start of deferasirox treatment. Height data for patients aged 2–<16 years at the start of deferasirox are included for as long as they remain in the study. Length of the box represents the inter-quartile range; whiskers extend to minimum and maximum values.

Figure 1a

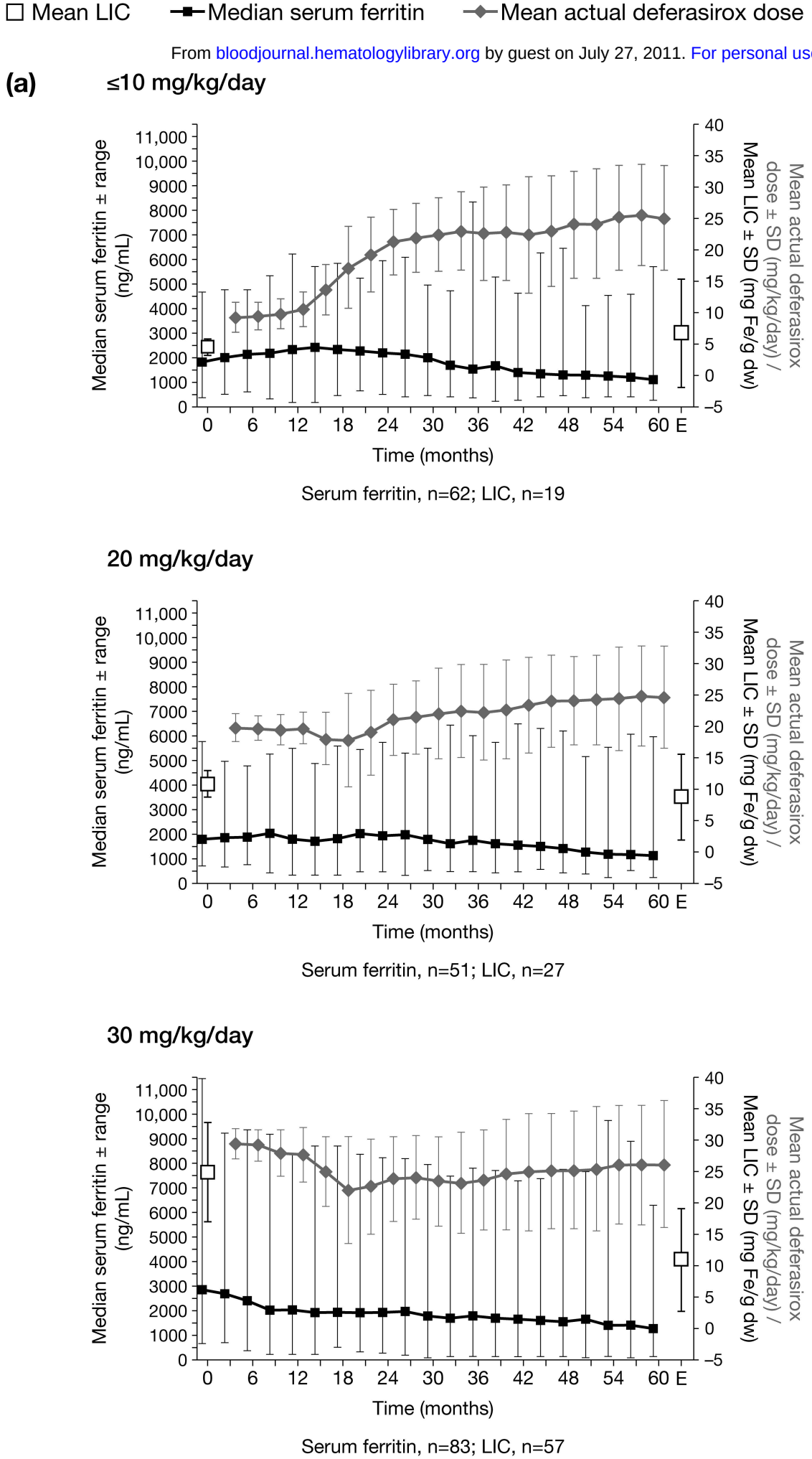


Figure 1b

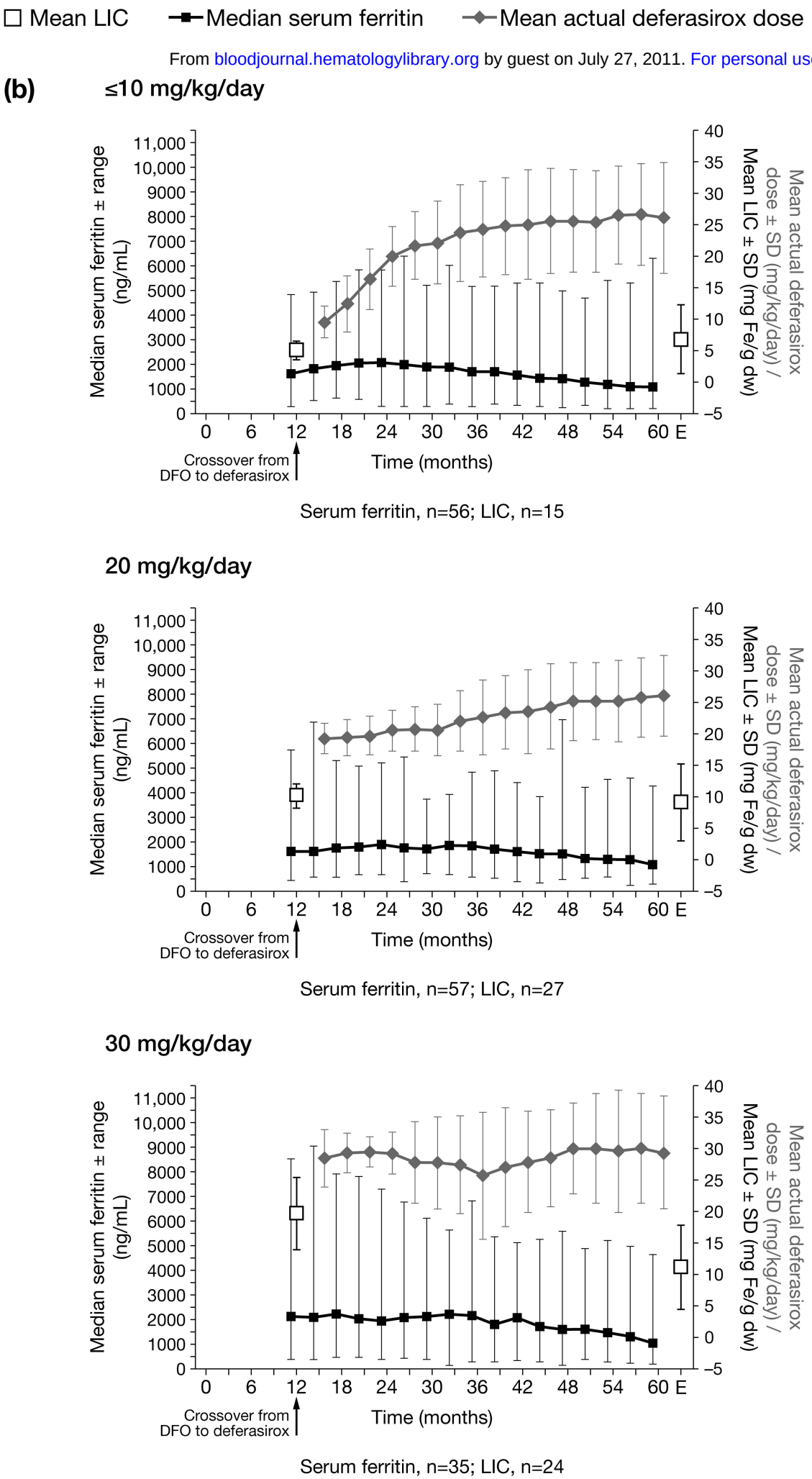
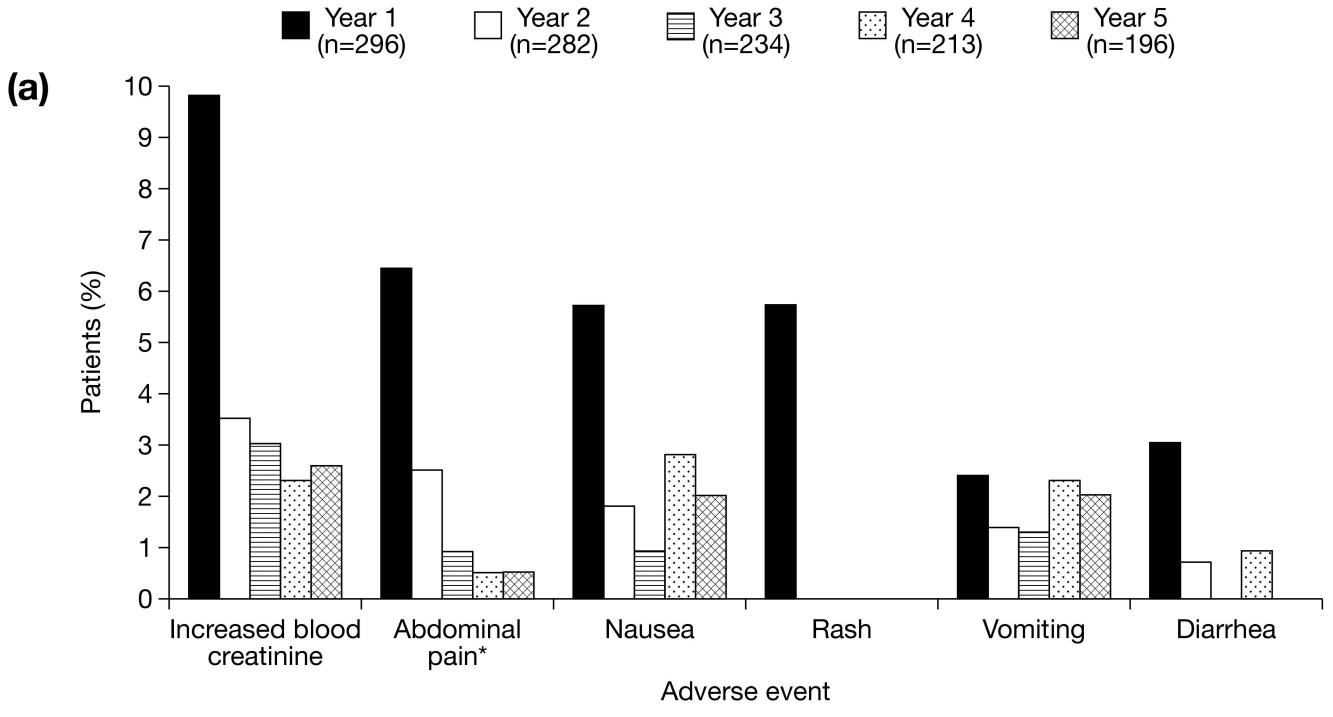

Mean LIC
Median serum ferritin
Mean actual deferasirox dose
From bloodjournal.hematologylibrary.org by guest on July 27, 2011. For personal use only
(b)
≤10 mg/kg/day
Median serum ferritin ± range (ng/mL)
Mean actual deferasirox dose ± SD (mg/kg/day) / Mean LIC ± SD (mg Fe/g dw)
Crossover from DFO to deferasirox
Time (months)
Serum ferritin, n=56; LIC, n=15
20 mg/kg/day
Serum ferritin, n=57; LIC, n=27
30 mg/kg/day
Serum ferritin, n=35; LIC, n=24

Figure 2


(a)
Year 1 (n=296)
Year 2 (n=282)
Year 3 (n=234)
Year 4 (n=213)
Year 5 (n=196)
Patients (%)
0
1
2
3
4
5
6
7
8
9
10
Increased blood creatinine
Abdominal pain*
Nausea
Rash
Vomiting
Diarrhea
Adverse event

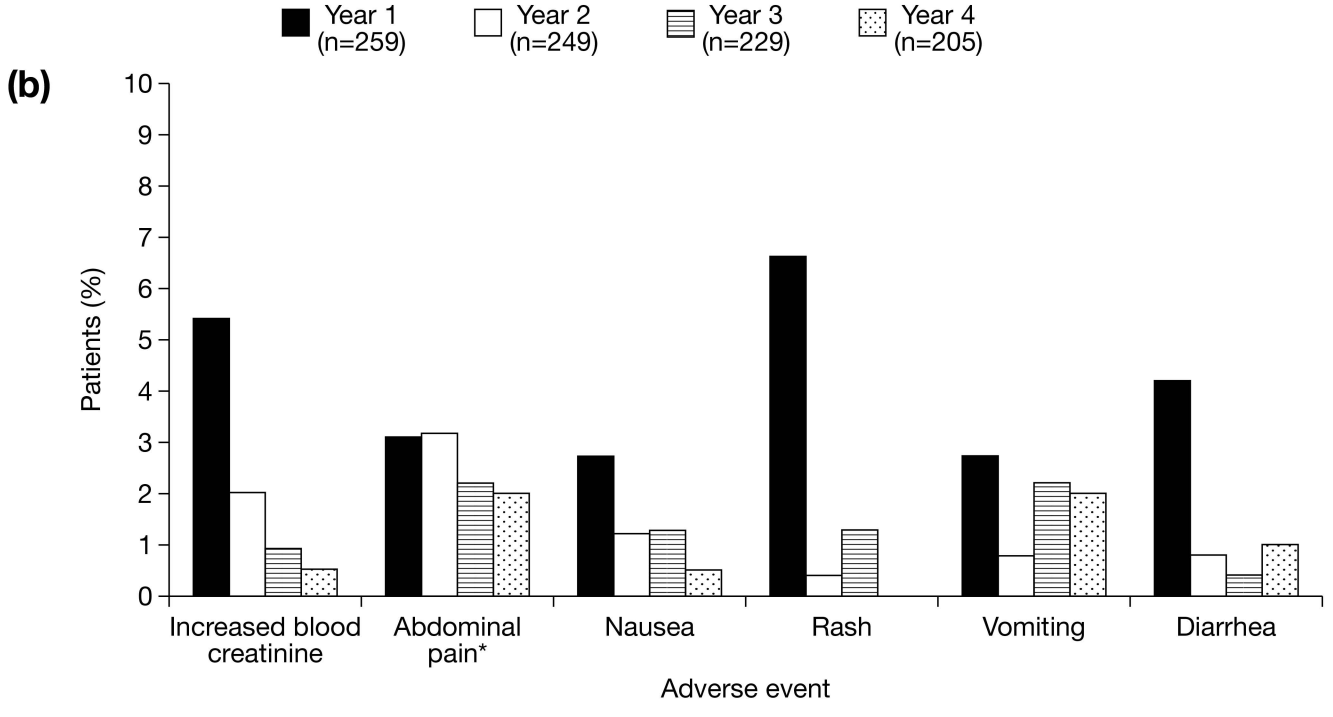

(b)
Year 1 (n=259)
Year 2 (n=249)
Year 3 (n=229)
Year 4 (n=205)
Patients (%)
0
1
2
3
4
5
6
7
8
9
10
Increased blood creatinine
Abdominal pain*
Nausea
Rash
Vomiting
Diarrhea
Adverse event

Figure 3

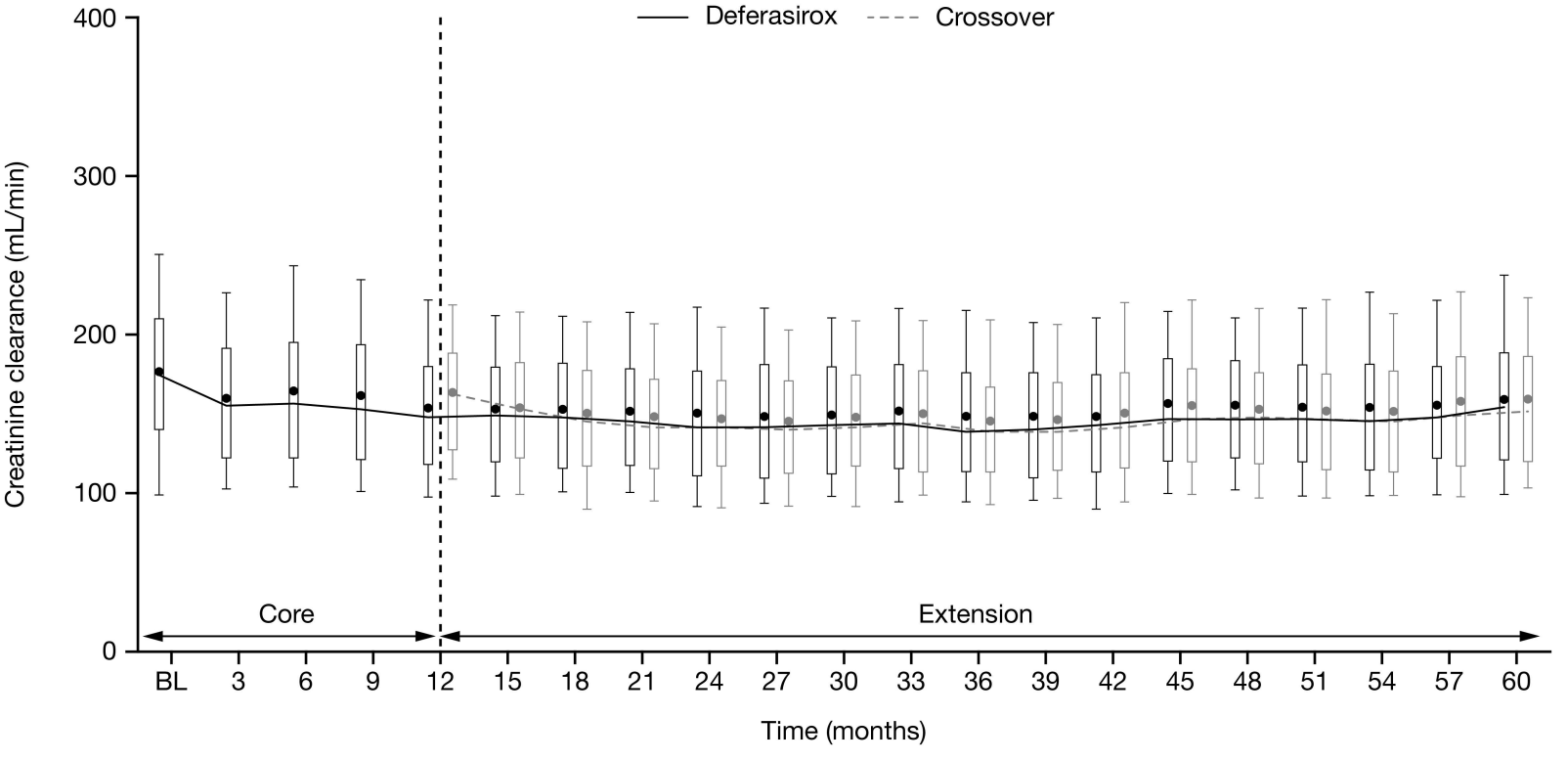
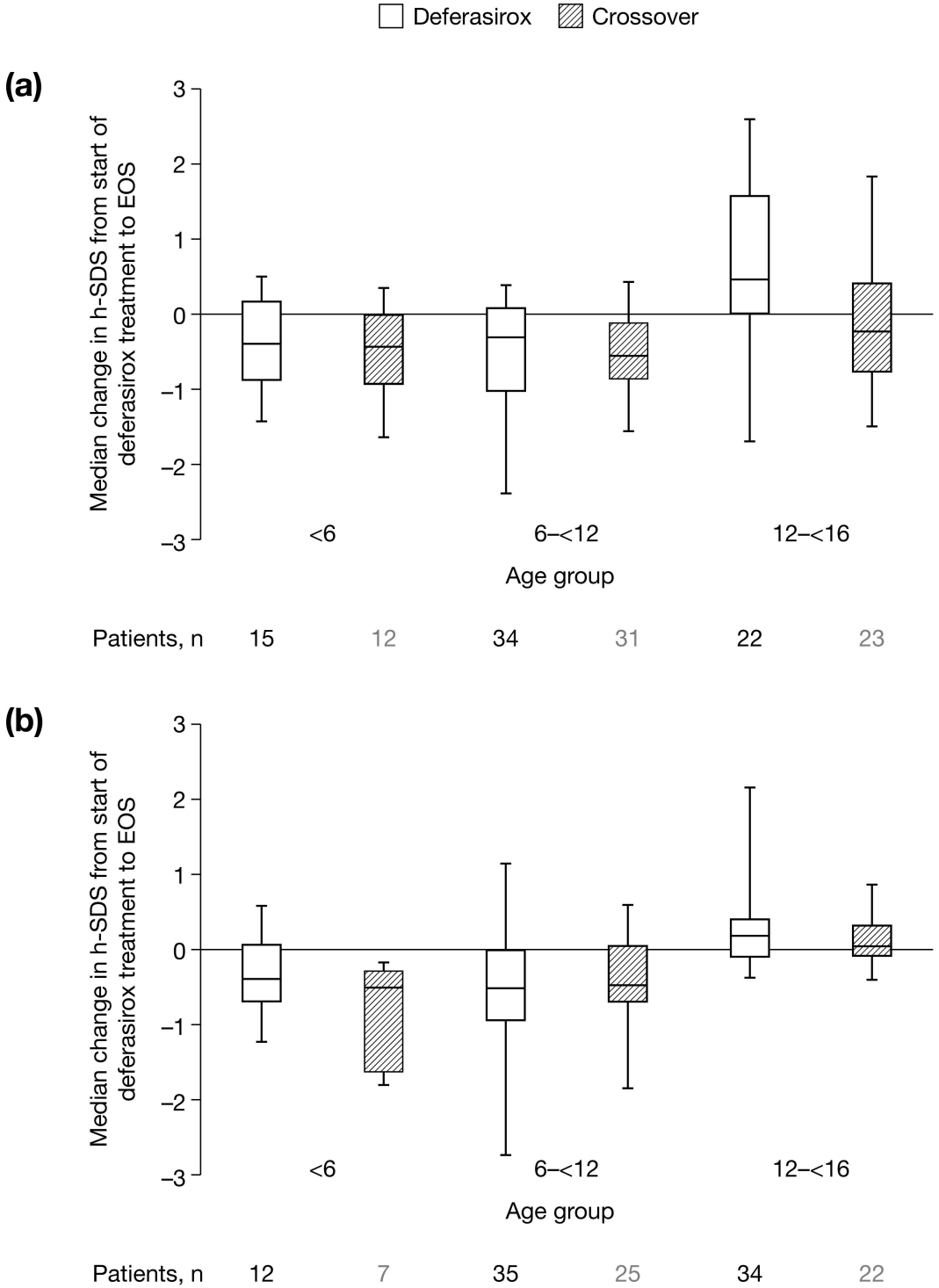

Deferasirox
Crossover
Creatinine clearance (mL/min)
400
300
200
100
0
Core
Extension
BL
3
6
9
12
15
18
21
24
27
30
33
36
39
42
45
48
51
54
57
60
Time (months)

Figure 4


Deferasirox
Crossover
(a)
Median change in h-SDS from start of deferasirox treatment to EOS
3
2
1
0
−1
−2
−3
<6
6–<12
12–<16
Age group
Patients, n
15
12
34
31
22
23
(b)
Median change in h-SDS from start of deferasirox treatment to EOS
3
2
1
0
−1
−2
−3
<6
6–<12
12–<16
Age group
Patients, n
12
7
35
25
34
22