Phase II clinical evaluation of deferasirox, a once-daily oral chelating agent, in pediatric patients with β-thalassemia major

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Background and Objectives. Deferasirox (ICL670) is a novel once-daily oral iron chelator developed for the treatment of chronic iron overload from blood transfusions. This study evaluated the safety and tolerability of deferasirox in pediatric patients with transfusion-dependent β-thalassemia major. Efficacy and pharmacokinetic assessments were secondary objectives.

Design and Methods. Forty patients equally stratified into two age groups – children (2 to <12 years) and adolescents (12–17 years) – were treated with deferasirox for 48 weeks. All received once-daily deferasirox 10 mg/kg/day with modifications allowed after 12 weeks' treatment. Safety, liver iron concentration (LIC), serum ferritin and pharmacokinetic assessments were assessed.

Results. Thirty-nine patients completed the study. One withdrew due to a skin rash. Adverse events were typical of this population, but only four were considered related to the study drug: mild nausea (two adolescents) and moderate skin rash (two children). There were no serious adverse events related to the study drug. Five patients briefly interrupted treatment due to elevated transaminases with no recurrences when treatment resumed. The mean deferasirox dose was 11.3 mg/kg/day. Overall LIC increased gradually from week 12 as mean daily iron intake was higher than excretion. Steady-state plasma levels of deferasirox and its iron complex, Fe-[deferasirox]⁺, were comparable between children and adolescents.

Interpretation and Conclusions. Deferasirox was well tolerated by this pediatric population. Toxicities known to be associated with other commercially available iron chelators were not observed. The dose employed was too low to induce a net negative iron balance in this regularly transfused population. Pharmacokinetic data support a once-daily dosing regimen based on body weight.

Key words: iron chelation, deferasirox, ICL670, thalassemia, pediatric, Exjade.

Haematologica 2006; 91:1343-1351
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Regular blood transfusions are essential support therapy for patients with transfusion-dependent anemias such as thalassemia and sickle cell disease. However, since humans lack a mechanism for the active excretion of excess iron, these patients invariably develop iron overload acquired from chronic blood transfusions.¹² Since each milliliter of packed red blood cells (RBCs) processed for transfusion contains approximately 1 milligram of elemental iron, iron overload can present as early as 2 years of age in pediatric patients who are frequently transfused from infancy. The excess iron is deposited as ferritin and as insoluble hemosiderin in tissues of the body, mainly the liver, heart, spleen and endocrine organs. At the cellular level, accumulated toxic quantities of iron cause damage to membranes, proteins and intracellular organelles which ultimately produces tissue and organ dysfunction.² Diverse manifestations of iron overload are commonly seen in regularly transfused children and adolescents with β-thalassemia. These may include growth impairment and delayed sexual maturation due to impaired pituitary function, diabetes mellitus due to damage to pancreatic islet cells, and cardiac complications later in life.¹³ Iron overload can be effectively managed by adequate chelation therapy as documented by experience with deferoxamine (Desferal®), which has been in clinical use for more than 40 years and is the current reference standard chelating agent.⁴ However, many patients' long-term outcome is negatively affected by poor compliance with deferoxamine treatment due to the demanding regimen of parenteral infusions over an 8–12-hour period, 5–7 times a week.⁵ Poor compliance to deferoxamine therapy is even more pronounced among adolescents.³ There is, therefore, a clear requirement for an effective, well-tolerated iron chelator with a less demanding mode of administration to ensure patient compliance to life-long chelation therapy in transfusion-dependent anemia. Deferasirox (Exjade®, ICL670), an N-substituted bis-hydroxyphenyl-triazole⁶ was selected from more than 700 compounds as part of a rational drug development program. Deferasirox represents a new class of tridentate iron chelators with a high specificity for iron.⁷ Selective and efficient mobilization of tissue iron has been demonstrated in animal models, with greater efficiency than with deferoxam-
Phase I trials with deferasirox confirmed that the compound is well tolerated at single oral doses of up to 80 mg/kg. Iron excretion occurs almost entirely in the feces and is dose-dependent, averaging 0.13, 0.34 and 0.56 mg/kg/day at deferasirox doses of 10, 20 and 40 mg/kg/day, respectively. The plasma half-life of 11-19 hours supports a once-daily oral dosing regimen that has been used in subsequent clinical trials. A phase II randomized trial (deferoxamine versus deferasirox) found a dose of 20 mg/kg/day deferasirox to have similar efficacy as 40 mg/kg/day deferoxamine and to be well tolerated in adult β-thalassemia patients over 48 weeks. This current study was primarily aimed at evaluating the safety and tolerability of deferasirox chelation therapy in pediatric patients with transfusion-dependent β-thalassemia major. Efficacy, as measured by liver iron concentration (LIC) and ferritin trends, and pharmacokinetic assessments were secondary objectives.

Design and Methods

This open-label, non-comparative phase II trial with deferasirox in pediatric patients with transfusion-dependent β-thalassemia major was carried out in three centers in Italy and one center in France. The trial was conducted in accordance with Good Clinical Practice, as outlined in the International Conference on Harmonization guidelines. Ethics Committee approval was obtained at each participating institution and written informed consent was obtained from all patients or guardians prior to participation in any study procedures. A Study Monitoring Committee, comprised of the four principal investigators, supervised the trial conduct and made decisions regarding dose adjustment for individual patients on a case-by-case basis. An independent Program Safety Board confidentially reviewed clinical and laboratory data on several occasions during this trial in order to ensure patient safety.

Patients

Male and female patients aged 2–17 years with transfusion-dependent β-thalassemia major were enrolled and stratified by age into two groups: children aged 2 to <12 years, and adolescents aged 12–17 years. Enrollment of children began only when ten adolescents had completed 4 weeks of deferasirox treatment with no safety concerns. All patients had been previously treated with deferoxamine at a mean dose of 20–60 mg/kg/day for ≥4 weeks prior to screening, and had serum ferritin ≥1000 ng/mL confirmed by ≥2 measurements during the previous year or LIC ≥2.5 mg Fe/g dry weight (dw) measured during the previous year. Patients with active hepatitis B and C were excluded from participating in this study. The serology markers HBeAg, HBsAg or HBbc-IgM in the absence of HBsAb were utilized to rule out active hepatitis. For hepatitis C, patients with a serology marker HCVAb+ and hepatitis C viral RNA+ were excluded. Furthermore, any patients found at screening to have transaminase levels >5 times the upper limit of normal or serum ferritin above the upper limit of normal were also excluded from participating in this study.

Study design

After a 9-day screening period, eligible patients discontinued routine chelation therapy with deferoxamine and entered a 5-day washout period prior to commencing the 48-week study treatment period. All patients, regardless of their baseline LIC, commenced deferasirox at a dose of 10 mg/kg/day, the lowest dose of the therapeutic range found in previous deferasirox studies. This conservative dosing regimen and the open-label, non-comparative study design were considered appropriate for this initial pediatric study, which included children as young as 2 years of age. Dose adjustments (range of 5 mg/kg/day up to 30 mg/kg/day), which were possible only after 12 weeks of study treatment, were decided on a case-by-case basis by the Study Monitoring Committee and were based on repeated LIC determinations, repeated measurements of serum ferritin and/or other surrogate markers, and/or regularly measured laboratory safety parameters. Deferasirox was administered once daily, 30 minutes before breakfast, and doses were prepared using 250 mg quadri-divisible tablets dispersed in a glass of non-carbonated bottled water, stirred and ingested immediately.

Safety, efficacy and pharmacokinetic assessments

Study visits and assessments were scheduled every 2 weeks during the 48-week treatment period (Figure 1). All laboratory assessments were performed by a central laboratory, EXACTA Clinical Trials Services, Verona, Italy. Safety assessments included monitoring and recording adverse events (AEs) at each study visit. The severity of each AE was graded as mild, moderate or severe. Serious adverse events (SAEs) were defined as a medically significant event that was either fatal or life-threatening, required surgical intervention, prolonged hospitalization or resulted in persistent disability. All AEs and SAEs were assessed by the investigator for a possible relationship to the study drug. Laboratory abnormalities were only recorded as an AE if they induced clinical signs or symptoms considered clinically significant or if they required therapy. Other safety evaluations included regular evaluation of renal function by assessing serum creatinine and total urinary protein. An increase in serum creatinine of >33% from baseline (at two consecutive measurements) was considered a notable finding. Urinary protein to creatinine ratio was also computed, and compared against the notable and extended ranges (urinary protein/creatinine ratio: <0.2; 0.2 to <0.4; 0.4 to <0.6; and ≥0.6). The creatinine clearance was calculated using the Schwartz formula. In addition, liver function tests, liver ultrasound, electrocardiograms (ECG), audiometry, ophthalmology, and sexual and physical development were assessed at regular intervals during the study. Sexual...
and physical development were evaluated by assessing standing and sitting height, growth velocity, bone age, weight and pubertal stage with reference to Tanner’s standard charts.\textsuperscript{15,16}

The efficacy of iron chelation with deferasirox was evaluated by determining changes in LIC, which is a reliable indicator of total body iron.\textsuperscript{17} To avoid the need for invasive liver biopsy, LIC was measured non-invasively by magnetic susceptometry using SQUID (superconducting quantum interference device);\textsuperscript{18} LIC was expressed as mg Fe/g dw. A wet-to-dry weight factor of 3.3 was used to translate the direct measure.\textsuperscript{19,20} Studies have shown SQUID to be a reliable method for repeated measurements in the same individual.\textsuperscript{18,21} All SQUID evaluations were performed using the same device at the Department of Pediatric Hematology, University of Turin, Italy. LIC was determined at screening and then every 12 weeks during treatment and at the end of the study. Responders to chelation were defined as those patients whose LIC fell by >10% of the baseline value by the end of study.

During the study, markers of iron metabolism (serum ferritin, serum iron, serum transferrin and transferrin saturation) were analyzed by a central laboratory. Transferrin saturation was calculated from serum iron (Fe) and transferrin concentrations according to the formula:

\[ \text{Fe (µg/dL) / transferrin (µg/dL) • 1.25.} \]

Net iron balance (total body iron excretion) was calculated based on the amount of RBCs transfused (iron intake in mg=Kin) and on the changes in total body iron from baseline to study end:

\[ \text{Net body iron balance = (Kin + [Us(t0)-Us(t)]/(t-t0)} \]

Iron intake (mg of iron) was calculated as \( Kin = \) (total amount of RBCs transfused) x 1.08. The total amount of RBCs transfused was calculated as the total amount of blood (mL) multiplied by the hematocrit of each unit (%) divided by 100. Complete datasets (volume and hematocrit) were available for all transfusions in three-quarters of the patients. If an individual hematocrit was missing, the average hematocrit of the blood given as transfusions at the respective center was used, and if this was not available the value was assumed to be 65%. If the amount of blood transfused was given only as units, instead of in mL, with the hematocrit, the volume of RBC was assumed to be 185 mL and thus 200 mg of iron was assumed to be given per unit. \( Us(t) \) is the total body iron extrapolated from the LIC (in mg Fe/g dw) at time \( t (t=0, \) for baseline measurement):

\[ Us(t)=10.6\times \text{LIC}\times \text{(body weight in kg)} \]

Both the iron intake \( Kin \) and the changes in total body iron \( Us(t0)-Us(t) \) are expressed in mg of iron, therefore the net body iron balance is expressed in mg iron/day.

Plasma deferasirox trough levels were measured in all patients using blood samples collected approximately 24 hours post-dose at weeks 2, 4, 8, 12, 24, 36 and 48. Plasma pharmacokinetic profiles of deferasirox were determined in a subpopulation of ten adolescents and ten children using blood samples collected pre-dose and at 0.5, 1, 2, 4, 8 and 24 hours post-dose, on day 1 after the first dose and then on days 14 and 28. The plasma concentrations of deferasirox and its iron complex, Fe-[deferasirox]\( \text{2} \), were determined by a liquid chromatography-mass spectrometry/mass spectrometry technique. Lower limits of quantification were 0.670 µmol/L for deferasirox and 0.314 µmol/L for Fe-[deferasirox]\( \text{2} \). Standard non-compartmental pharmacokinetic parameters (AUC, C\text{max}, t\text{max} and half-life) were derived from the plasma concentrations of deferasirox and Fe-[deferasirox].

**Statistical analysis**

The primary objective of the study was to evaluate the safety and tolerability profile of deferasirox (at a starting dose of 10 mg/kg/day with potential adjustments) in pediatric patients with \( \beta \)-thalassemia stratified into two age groups (children aged 2 to <12 years, and adolescents aged...
mg/kg/day (median 10.3, range 9.1–17.7) with little difference between the two age groups. The mean duration of exposure to deferasirox was 47.1 weeks (SD±11.4) in children and 51.2 weeks (SD±2.3) in adolescents.

**Safety and tolerability**

All patients experienced at least one AE during the study regardless of the relationship to study medication (Table 2), and the pattern of AEs was comparable between children and adolescents. As expected for a pediatric population, infections (mainly rhinitis and pharyngitis) and gastrointestinal complaints (mainly vomiting and diarrhea) were the most common AEs. The majority of AEs were mild or moderate in intensity, and not considered related to the study drug. Of the AEs observed, only four were considered to be treatment-related: mild nausea in two adolescents and moderate skin rash in two children. It was a skin rash that led to the single discontinuation from the study of an 11-year old female after 11 days of treatment with deferasirox 10 mg/kg/day. There were no deaths during the study. Four patients experienced a total of seven SAEs (pancreatitis, cholelithiasis, gastroenteritis, head injury, transfusion reaction, cholecystectomy and tonsillitis), all of which were typical complications of thalassemia or...
incidental medical problems. None of the SAEs were considered to be treatment-related and none led to discontinuation from the study. Elevated transaminase levels (>5 x the upper limit of normal at ≥2 post-baseline visits) resulted in treatment interruptions lasting 7–15 days in one child and four adolescents. While a relationship to study drug treatment was suspected in each case, treatment was resumed at the prior dose without recurrence of transaminase elevation. There was no evidence of progressive elevation of transaminases in any of the patients.

One adolescent patient had a serum creatinine value above the upper limit of normal at two consecutive visits, which normalized at the next visit without treatment interruption or dose adjustment of deferasirox. Neither of the serum creatinine values was >33% greater than the average of the two baseline samples. Post-baseline urinary protein/creatinine ratios of ≥0.2 were detected in at least one sample in more than half the patients. However, the changes were not considered clinically significant as increases were generally mild and transient and no patient showed a progressive increase of proteinuria. No patient had a urinary protein/creatinine ratio of ≥1. Overall changes in serum creatinine levels across the study period, which were mild and non-progressive, are presented in Figure 2. In this study, clinically significant neutropenia was defined as an absolute neutrophil count (ANC) of <1.5 x 10^9/L in two or more consecutive post-baseline samples taken at least 7 days apart. Three patients (one child and two adolescents) met this criterion (nadir values of 1.12, 1.23 and 1.27 x 10^9/L, respectively). However, two of these patients exhibited borderline ANC (2.0 x 10^9/L) at baseline, and in all three patients there was a subsequent spontaneous increase in ANC without treatment interruption or dose adjustment of deferasirox. As such, all these events were considered to be unrelated to the study drug. No patient in either age group had baseline platelet counts <150 x 10^9/L, the lower limit of normal. In addition, no patient developed post-baseline platelet counts of <100 x 10^9/L, which was defined as a clinically significant level of thrombocytopenia for this study.

As for trace elements, 14 patients (35.0%) had low levels of serum copper at study entry and a further nine patients (22.5%) exhibited low levels at some point during the study. However, the levels fluctuated and the changes were not progressive. No patient had serum zinc concentrations below the lower limit of normal. There was a single episode of asymptomatic prolongation of the QTc interval (from 392 ms on 29 July 2003, to 490 ms on 23 October 2003) in a 6-year old girl. This occurred approximately 4 weeks after deferasirox dose had been increased from 10 to 20 mg/kg/day. After a brief interruption (8 days) in therapy, the QTc normalized and treatment with deferasirox was resumed at the same dose. Repeat ECG performed at weekly intervals over 4 weeks did not reveal any recurrent abnormalities. No clinically significant abnormalities were detected in visual or auditory function and no abnormalities considered to be study-drug related were found by liver ultrasound. Changes in patients’ height, weight and body mass index were within the normal parameters (Table 3). Mean standing height increased normally during 48 weeks’ deferasirox treatment in children (6.8±1.8 cm; n=17) and adolescents (3.4±2.1 cm; n=20). Bone age increased by up to 3 years in some patients, but did not change in others. Two children and three adolescents had abnormal metaphyseal findings at baseline (four were mild and one was moderately abnormal). These abnormalities had normalized by the end of the study in two patients and remained stable in three others. Assessments of sexual development indicated that the patients’ growth progressed normally during the study. In the female patients, two adolescents progressed to the next Tanner stage of breast development and five patients progressed to the next Tanner stage of pubic hair development (one child and four adolescents). One adolescent patient exhibited progression of sexual maturity by two pubic hair stages. In the male patients, seven progressed to the next stage of pubic hair development (one child and six adolescents). The change from baseline in left and right testicular volume was 0.5±0.5 cm³ in children (n=8) and 3.6±1.1 cm³ in adolescents (n=9).

Efficacy

In both age groups, the majority of patients had a baseline LIC ranging from 2 to <7 mg Fe/g dw, a third of the patients from 7 to <10 and only two patients (one in each

![Figure 2. Serum creatinine levels over 48 weeks of treatment with deferasirox.](image)

<table>
<thead>
<tr>
<th></th>
<th>Children</th>
<th>Adolescents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean standing height ± SD</td>
<td>6.8±1.8</td>
<td>3.4±1.1</td>
</tr>
<tr>
<td>Mean sitting height ± SD</td>
<td>4.8±2.2</td>
<td>2.1±2.1</td>
</tr>
<tr>
<td>Mean weight ± SD, kg</td>
<td>2.6±1.0</td>
<td>2.6±3.2</td>
</tr>
<tr>
<td>Mean BMI ± SD</td>
<td>0.0±0.5</td>
<td>0.2±1.1</td>
</tr>
<tr>
<td>Mean bone age ± SD, years</td>
<td>1.0±0.7</td>
<td>1.0±1.0</td>
</tr>
</tbody>
</table>

BMI: body mass index.
age group) had a LIC ≥10 mg Fe/g dw. Overall, mean LIC remained relatively stable during the first 12 weeks of study treatment. However, subsequently there was a slight, gradual increase in LIC as measured by SQUID, which was more evident in children than in adolescents (Figure 3). The change in LIC was shown to be directly dependent on transfusional iron intake: 0.2±1.5 mg Fe/g dw with low intake (<0.4 mg/kg/day); 0.7±1.5 mg Fe/g dw with intermediate intake (0.4-0.5 mg/kg/day); and 2.2±4 mg Fe/g dw with high intake (≥0.5 mg/kg/day). Response to chelation, defined as a >10% fall in LIC at the end of study in comparison to baseline, was shown to be primarily dependent on transfusional iron intake rate, ie patients with lower intake had a greater chance of experiencing a decrease in LIC. The number of responders also tended to be higher in adolescents than in children and responders were mainly in the category of patients who had a baseline LIC within 2 to <7 mg Fe/g dw. Serum ferritin levels increased over the duration of the study (Figure 4). Estimated iron intake arising from blood transfusions was greater than the calculated iron excretion. The iron intake/excretion ratio was less in children than in adolescents (Table 4). There were no consistent changes in the levels of other markers of iron homeostasis (serum iron, transferrin and transferrin saturation).

**Pharmacokinetics**

One child was excluded from the pharmacokinetic analysis because no samples were taken at any visit.

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**Table 4. Calculated iron intake and excretion.**

<table>
<thead>
<tr>
<th>Mean±SD</th>
<th>Children (n=20)</th>
<th>Adolescents (n=20)</th>
<th>All patients (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of transfusions</td>
<td>14.8±4.54</td>
<td>16.4±2.21</td>
<td>15.6±3.61</td>
</tr>
<tr>
<td>Calculated iron intake, mg/kg/day</td>
<td>0.48±0.13</td>
<td>0.44±0.09</td>
<td>0.46±0.11</td>
</tr>
<tr>
<td>Calculated iron excretion, mg/kg/day</td>
<td>0.43±0.08</td>
<td>0.47±0.09</td>
<td>0.46±0.08</td>
</tr>
<tr>
<td>Iron excretion/intake ratio</td>
<td>0.85±0.09</td>
<td>0.94±0.10</td>
<td>0.90±0.10</td>
</tr>
</tbody>
</table>
Overall, similar deferasirox pharmacokinetics were observed in children and adolescents. As shown in Figure 5, the mean plasma concentrations of deferasirox increased following a single 10 mg/kg dose with median tmax of 2 hours (range 1-8 hours) in both age groups. After 2 and 4 weeks of receiving 10 mg/kg/day deferasirox, the median tmax at steady state was 2 hours at week 2, and 4 hours at week 4 (range 1-9 hours) in both age groups (Figure 5).

Table 5 summarizes the main pharmacokinetic parameters. Steady-state deferasirox Cmax, AUC0–24 and half-life were similar in the two age groups. From the statistical analysis, adjusting for the total daily dose across the two age groups, AUC0–24 was 60% greater after 2 weeks of treatment than at day 1 (90% CI for the ratio: 1.30–4.11). Overall, the adolescents had a 53% higher Fe-[deferasirox]; AUC0–24 than the children (90% CI for the ratio: 0.48–4.85). Nevertheless the 90% confidence interval included 1, showing that this increase is not statistically significant. The steady-state exposure to deferasirox and to Fe-[deferasirox]; were comparable in children and adolescents. Trough plasma levels of deferasirox and iron complex showed no accumulation after multiple dosing during 48 weeks of treatment. Overall trough concentrations of deferasirox and iron complex were stable in both age groups and there was no occurrence of particularly high exposure to deferasirox.

### Discussion

The primary objective of this study was to evaluate the safety and tolerability of once-daily oral deferasirox therapy over 48 weeks in pediatric patients with transfusion-dependent β-thalassemia major. The safety evaluation was particularly focused on toxicities that have been reported with other iron chelators. The evaluation included assessments of bone marrow, liver and kidney function, trace metal homeostasis, and screening for the development of lens opacities and high-frequency sensorineural hearing loss. In addition, the physical and sexual development of these pediatric patients was monitored throughout the study.

In this study that recruited patients as young as 2 years of age, once-daily deferasirox administered over a period of 48 weeks was well tolerated in both children and adolescents. The majority of AEs were as expected for this population with no differences between children and adolescents. The only AEs considered related to study drug were mild nausea and moderate skin rash, the latter being the reason for the single discontinuation of a child from the study. There were no deaths during the study. Three patients (one child and two adolescents) exhibited clinically significant neutropenia (ANC <1.5 ×10⁹/L) at baseline, and in all three patients there was a subsequent spontaneous increase in ANC without treatment interruption or dose adjustment of deferasirox, indicating that the low ANC counts were unrelated to the
study drug. No patient had a platelet count of <100×10^9/L. No patient developed falling levels in serum zinc or copper indicating that deferasirox treatment did not cause depletion of these trace elements. No patient developed progressive increases in serum creatinine or consecutive measurements above the upper limit of normal during the 48-week study. Elevated transaminase levels led to brief treatment interruptions in five patients, though treatment was resumed at the prior dose with no recurrences of transaminase elevations. Moreover, there was no evidence of progressive elevation of transaminases in any patient. It is likely that these episodes reflected liver damage due to iron overload or underlying chronic viral hepatitis. The physical and sexual development of the patients received treatment with deferasirox over 48 weeks appeared normal. The patients continued to grow, as indicated by overall increases in standing and sitting height. Body mass index remained stable, with only a small number of patients losing weight during the study. Overall, mean bone age increased by 1 year, as expected. Sexual development also progressed within normal parameters during the 48 weeks of treatment with deferasirox. Given that patients continue to be treated with deferasirox and are being followed in an extension study for up to 3 years, further insights about physical and sexual development during treatment with deferasirox will likely emerge.

The efficacy of deferasirox at removing excess iron was assessed as a secondary objective in this study. LIC was measured non-invasively by SQUID, which allows the measurement of the paramagnetic susceptibility of the iron stored in the liver as hemosiderin and ferritin. Although the results of SQUID measurements of hepatic non-heme iron have been reported to be quantitatively equivalent to those obtained by conventional analysis of liver biopsy, recent data from other trials indicate that variability may be important and that the wet-to-dry weight ratio widely used gives an underestimation of SQUID results.\(^{22,23}\) The results showed that during the 48-week treatment period, there was a gradual increase in LIC from week 12 onwards in both age groups (Figure 3). Response to chelation (defined as a >10% fall in LIC as evaluated by SQUID at the end-of-study in comparison to baseline) was primarily dependent on transfusional iron intake and tended to be higher in adolescents than in children. Overall, increases in serum ferritin concentration during the study were largely in tandem with the LIC trends (Figure 4).

As this was the first clinical study in adolescents and children, a conservative starting dose of 10 mg/kg/day was used irrespective of the degree of iron overload at baseline. Although dose adjustments were permitted after 12 weeks of treatment, the fact that these were performed relatively late in the study (median 39 weeks, range 29-41) meant that the average dose of deferasirox at 11.3 mg/kg/day remained close to the starting dose. Moreover, the average number of transfusions given over the 48 weeks of the study indicates that this population was regularly transfused and receiving a considerable mean daily iron intake of 0.46±0.11 mg/kg/day. Therefore the conservative dosing regimen combined with the fact that dose increases occurred relatively late, most likely accounts for the gradual increase in LIC seen in both age groups in this regularly transfused population. The amount of iron removed by deferasirox at the dose employed was too low to counterbalance iron intake as demonstrated by the mean iron excretion/intake ratio of 0.90. On average, dose increases were performed later in children than in the adolescents, and children had a higher iron intake from blood transfusions. It is interesting that these results contrast with the net reduction in mean iron concentration (mean iron excretion/intake ratio >1) observed with a planned dose of 10 mg/kg/day deferasirox in a phase II, 48-week study in adults with \(\beta\)-thalassemia.\(^{19}\) The difference is likely to be due, in part, to the high mean iron intake in this pediatric study (0.46 mg/kg/day), which is close to the upper limit of standard transfusion regimens in thalassemia, in contrast to 0.36 mg/kg/day in the adult study.\(^{11}\) The results of the current study (in which the primary endpoint was to evaluate the safety and tolerability of once-daily oral deferasirox therapy over 48 weeks) are, however, consistent with the reported efficacy results from a large, randomized phase III study of deferasirox.\(^{24}\) In that study, Cappellini et al demonstrated that doses of 10 mg/kg/day were inadequate in regularly transfused patients (both pediatric and adult), likely due to the high rate of iron intake in the study population. These results highlight the variation in iron load arising from different transfusion regimens and underline the importance of adapting the deferasirox dose to the individual patient’s needs as dictated by the transfusion regimen and treatment goal, defined as either maintenance or reduction of iron burden. Accurate monitoring of iron input is easily done by recording the net weight and hematocrit of transfused blood, while regular serum ferritin assessment can guide adjustments of the deferasirox dose in a given individual patient, which has important clinical implications for general iron chelation therapy. To our knowledge, this is the first prospective study in which both the transfusional iron load and LIC have been accurately assessed.

The pharmacokinetic characteristics of deferasirox were similar in children and adolescents. The steady-state exposure to deferasirox in children and adolescents observed in this study was ~20-30% lower than that seen in a previous phase I study of adult patients with transfusion-dependent \(\beta\)-thalassemia.\(^{12}\) Likewise, steady-state exposure to the complex Fe-[deferasirox] was ~41-77% lower than that seen in adults. Trough plasma levels of deferasirox and iron complex showed no evidence of accumulation after multiple dosing during 48 weeks of treatment. Overall trough concentrations of deferasirox and iron complex were stable in both age groups and there was no occurrence of particularly high exposure to deferasirox. Based on the similarity in pharmacokinetic exposure between adolescents and...
children, dosing in mg/kg/day was shown to be a valid approach. This was confirmed by the absence of a relationship between deferasirox and Fe-[deferasirox]. AUC, ICL670, a once-daily, orally-administered iron chelator, was investigated in a phase II study of children with transfusion-dependent β-thalassemia. No drug-related neutropenia, agranulocytosis, arthralgia, growth/bone impairment or other toxicities known to be associated with other commercially available iron chelators were observed in this study. Only four patients experienced AEs attributable to the study medication, these being mild nausea and moderate skin rash. Five patients briefly interrupted treatment due to elevated transaminases, with no recurrences when treatment was resumed. Recently published data indicate that some AEs observed with deferasirox may be dose-related. Although the safety data presented here may not reflect the safety profile at the recommended doses of 20–30 mg/kg/day, the dose was increased from 10 mg/kg/day in 21 patients, generally late in the study. The limited dose escalation results from this study and data from the recently published phase III study demonstrate that deferasirox is generally well tolerated at doses of 20-30 mg/kg/day. The conservative dosing regimen employed was not optimal for inducing or maintaining a negative iron balance in this regularly transfused population. The pharmacokinetic data support a once-daily deferasirox dosing for children based on body weight. The patients have now been enrolled into an extension study which is planned to continue for up to 3 years, and will be treated with deferasirox at doses that take account of the iron intake from transfusion regimens in addition to the LIC and serum ferritin trends. This extension study will provide long-term safety data on the use of once-daily oral deferasirox in the pediatric population.

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