Deferasirox significantly reduces iron overload in non-transfusion-dependent thalassemia: 1-year results from a prospective, randomized, double-blind, placebo-controlled study

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Short title for running head: Reducing iron overload in NTDT with deferasirox
Scientific category: Red Cells, Iron and Erythropoiesis
Abstract

Non-transfusion-dependent thalassemia (NTDT) patients may develop iron overload and associated complications, despite occasional/no transfusions. The 1-year, randomized, double-blind, placebo-controlled THALASSA trial assessed efficacy and safety of deferasirox in iron-overloaded NTDT patients. 166 patients were randomized in a 2:1:2:1 ratio to starting doses 5 mg/kg/day deferasirox/placebo, or 10 mg/kg/day deferasirox/placebo. Mean±SD actual deferasirox dose received over the study in the 5 and 10 mg/kg/day starting dose cohorts was 5.7±1.4 and 11.5±2.9 mg/kg/day, respectively. At 1 year, LIC significantly decreased versus placebo (least-squares mean [LSM]±SE): –2.33±.7 (P = .001) and –4.18±.69 mg Fe/g dw (P < .001) for deferasirox 5 and 10 mg/kg/day groups, respectively (baseline values [mean±SD]: 13.11±7.29 and 14.56±7.92 mg Fe/g dw). Similarly, serum ferritin significantly decreased versus placebo by LSM –235 and –337 ng/mL for deferasirox 5 and 10 mg/kg/day groups, respectively (P < .001). In placebo patients, LIC and serum ferritin increased from baseline by .38 mg Fe/g dw and 115 ng/mL (LSM), respectively. Most common drug-related AEs were nausea (n = 11, 6.6%), rash (n = 8, 4.8%) and diarrhea (n = 6, 3.6%). This is the first randomized study to show iron chelation with deferasirox significantly reduces iron overload in NTDT patients, with a similar frequency of overall AEs as placebo.

Keywords: Clinical Iron Overload, Iron Chelation; Non-transfusion-dependent Thalassemia
Introduction

Unlike transfusion-dependent β-thalassemia major,¹ patients with clinically milder forms of thalassemia, including β-thalassemia intermedia, α-thalassemia (mainly HbH disease), and HbE/β-thalassemia require occasional or no blood transfusions. Despite limited transfusion needs, non-transfusion-dependent thalassemia (NTDT) patients may develop clinically relevant iron overload with serious sequelae, including liver and endocrine dysfunction.² Furthermore, elevated liver iron concentration (LIC) has been associated with increased morbidity in patients with β-thalassemia intermedia.² Iron overload in NTDT primarily results from increased intestinal iron absorption caused by ineffective erythropoiesis,³ and may develop as early as 5 years of age.⁴ It usually becomes clinically relevant after 10 years,⁵ making iron loads in NTDT patients in their 30s–40s comparable with transfusion-dependent β-thalassemia patients.³ For example, in a previous study of β-thalassemia major patients (mean age, 17 years), LIC was 11.1 mg Fe/g dw, although this may reflect prior suboptimal chelation therapy.⁶ For the NTDT patients examined here, (mean age, 32 years), LIC is 12.1 mg Fe/g dw,⁷ despite few patients having received previous iron chelation therapy. Therefore, effective monitoring and control of iron burden is important, although often underappreciated.

Iron chelation therapy is the only option for decreasing iron burden, as clinical anemia contraindicates phlebotomy. Data on iron chelation in NTDT patients are currently restricted to small uncontrolled studies and case reports.⁴,⁸-¹⁴ Deferasirox (Novartis Pharmaceuticals, East Hanover, NJ, USA) is a once-daily oral iron chelator with demonstrated efficacy and a well-characterized safety profile in patients with various chronically transfused anemias.¹⁵-²⁰ Given the different pathophysiology of iron metabolism and slower iron loading rate in NTDT compared with transfusion-dependent β-thalassemia, it is important to establish the efficacy, safety and optimal doses of deferasirox in this population. Here we report 1-year data from a Phase II, prospective, randomized, double-blind, placebo-controlled trial (THALASSA [assessment of Exjade in non-transfusion-dependent THALASSemiA patients] assessing the efficacy and safety of deferasirox in NTDT patients with iron overload.
This is the first randomized, placebo-controlled study evaluating iron chelation in NTDT.
Materials and Methods

Key inclusion and exclusion criteria

Male or female patients (aged ≥10 years) with NTDT and iron overload (R2 MRI-measured LIC ≥5 mg Fe/g dry weight [dw]) and serum ferritin >300 ng/mL at screening [based on two consecutive values ≥14 days apart]) were eligible. Additionally, patients were required to have not received transfusions within 6 months or chelation therapy within 1 month prior to study entry. Patients with previous exposure to deferasirox or with anticipated regular transfusions were excluded; unplanned transfusions during the study were allowed. Exclusion criteria also included: HbS variants of thalassemia syndromes, active hepatitis B (positive hepatitis B surface antigen with negative hepatitis B surface antibody) or C (positive hepatitis C virus antibody and detectable hepatitis C virus RNA with alanine aminotransferase [ALT] above the normal range), cirrhosis, levels of ALT >5 x the upper limit of normal (ULN), serum creatinine >ULN or creatinine clearance ≤60 mL/min on two measurements, or significant proteinuria (urine protein/urine creatinine ratio >1·0 mg/mg) on two measurements. Patients (or parents/guardians) provided written, informed consent prior to enrolment.

Study Design

THALASSA was a multi-national, prospective, randomized, double-blind, placebo-controlled Phase II study (ClinicalTrials.gov number NCT00873041). Patients were randomized in a 2:1:2:1 ratio to the following four treatment groups: 1) 5 mg/kg/day deferasirox, 2) 5 mg/kg/day matching placebo, 3) 10 mg/kg/day deferasirox, 4) 10 mg/kg/day matching placebo, for a 52-week treatment period. Doses were doubled at 24 weeks for patients with LIC >7 mg Fe/g dw and LIC reduction <15% from baseline. Dose adjustment recommendations were also provided based on continuous safety assessments. If serum ferritin was <100 ng/mL or LIC <3 mg Fe/g dw at any visit, treatment was to be suspended until LIC increased to ≥5 mg Fe/g dw and serum ferritin to >300 ng/mL. The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. The study was approved by local ethics committees of all participating study sites. An independent
data monitoring committee reviewed safety data and advised on study continuation and/or changes to protocol.

Randomization and masking

Following a 4-week screening phase, patients were block randomized using an interactive voice response system (IVRS). After confirming the patient fulfilled the inclusion/exclusion criteria, the investigator contacted the IVRS to obtain a randomization number linking the patient to a treatment arm. As blinding of dose was not possible, blinding was only applied to the treatment received. All persons were blinded to the treatment from the time of randomization until database lock.

Assessments

The primary efficacy endpoint was the absolute change from baseline in LIC at 52 weeks. Supportive analyses of the primary endpoint included assessment of the number and proportion of patients with a LIC decrease of $\geq 3$ mg Fe/g dw, those with $\geq 30\%$ reduction in LIC and those with LIC $\leq 7$, $\leq 5$ and $\leq 3$ mg Fe/g dw at 1 year. Secondary endpoints included the change from baseline in LIC at 24 weeks; change from baseline in serum ferritin at 52 weeks; and correlation of serum ferritin and LIC. Results are presented by starting dose group.

LIC was assessed at screening, Week 24 and at Week 52, or when serum ferritin stopping target was achieved, or at discontinuation for other reasons. LIC was measured using a validated R2 MRI technique (FerriScan), assuming reproducibility over the range of clinical conditions studied. Serum ferritin was measured during screening and 4-weekly thereafter. Baseline serum ferritin was calculated as the average of all screening measurements on, or before, the day of randomization. Both LIC and serum ferritin were analyzed at a central laboratory. Patients attended the study site at all visits to perform the scheduled assessments.

Safety was evaluated through continuous monitoring and recording of adverse events (AEs) and serious AEs (SAEs), laboratory testing and clinical evaluations. Compliance was estimated based on the cumulative dose taken, based on
dispensed and returned amount of study medication or patient diary, versus the cumulative planned dose.

**Statistical methods**

Power calculations indicated a total sample size of 52 patients for each deferasirox group and 26 patients for each placebo group (156 patients in total) were required to achieve a study power of 90% to demonstrate superiority of at least one deferasirox group compared with placebo for the primary endpoint. This was based on the assumption of a mean decrease of 3 mg Fe/g dw in deferasirox patients compared with placebo and a common standard deviation of 4 mg Fe/g dw.

The primary efficacy variable was the absolute change in LIC from baseline to Week 52. If no LIC measurement was available at Week 52, the last available post-baseline LIC measurement before Week 52 was used. Analysis of covariance (ANCOVA) was performed including the treatment as factor and baseline LIC as covariate. As a result, the primary efficacy results were presented adjusted for baseline. Multiplicity was addressed by controlling the one-sided family-wise type I error rate to .025 with Dunnett’s method and presenting two-sided simultaneous 95% confidence intervals. Absolute change from baseline LIC at Week 24 was analyzed in the same way as the primary efficacy variable.

For serum ferritin quarterly change from baseline, a mixed effect model was fitted on the Full Analysis Set with fixed factors treatment, quarter and treatment-by-quarter interaction. When the results were missing for a quarter, the results from the last available quarter were used for that patient. For the fourth quarter, each deferasirox group was compared to placebo using Dunnett’s adjustment for multiple comparisons to the placebo control group (family-wise type I error rate .025). The two deferasirox groups were compared with two-sided significance level of 5%.

The correlation of LIC versus serum ferritin at baseline was assessed as well as the correlation of relative change in LIC versus relative change in serum ferritin at Week 24 and Week 52.
The effect of dose increase was evaluated by summarizing the last LIC value after the Week 24 LIC assessment and the last value before or at the Week 24 LIC assessment with descriptive statistics by treatment group and separately for patients with and without increase. Patient subgroup analyses were also performed.

Efficacy was assessed for the Full Analysis Set (all randomized patients). Placebo groups were pooled and shown as one group for efficacy analyses. If there was no LIC measurement available at Week 52, the last available post-baseline LIC measurement was carried forward. Absolute change in LIC at Week 52 with last observation carried forward (LOCF) were analyzed using analysis of covariance with treatment as factor and baseline LIC as covariate. Differences between deferasirox and placebo were compared using Dunnett’s adjustment,22 one-sided significance level of .025 to establish that the mean decrease with deferasirox was greater than with placebo. In the event that both deferasirox arms were statistically superior to placebo, the two deferasirox groups were compared at 2-sided significance level of .05. Correlation of baseline LIC and serum ferritin was assessed.

All patients who received at least one dose of study medication were included in the safety population. Safety data for the two placebo groups were analyzed separately to allow for potential effects of different excipient quantities in deferasirox formulations.

**Role of funding source**

The study was sponsored by Novartis Pharma AG and designed by the sponsor in close collaboration with the Study Steering Committee composed of expert hematologists in the field of thalassemia. The sponsor conducted the statistical analysis. Authors had full access to the data and actively participated in data interpretation and drafting and critical review of the article, with the assistance of a medical writer funded by the sponsor. The corresponding author had final responsibility for the manuscript content and decision to submit for publication.
Results

Patient disposition

The study was conducted between 24 November 2008 and 22 June 2011. A total of 339 patients were screened and 166 were randomized to receive treatment (Figure 1). Overall, 89.2% of patients (n = 148) completed 1 year.

Baseline demographics and clinical characteristics

Baseline demographics and clinical characteristics were similar across groups (Table 1). The baseline LIC was slightly higher in the placebo group than in the deferasirox 5 mg/kg/day and 10 mg/kg/day starting dose cohorts.

Exposure to treatment and compliance

Mean ± SD actual deferasirox dose received over the study (taking into consideration dose adjustments permitted from Week 24), in the 5 and 10 mg/kg/day starting dose cohorts was 5.7 ± 1.4 and 11.5 ± 2.9 mg/kg/day, respectively. The median duration of treatment was 12.2 (range 0–15) and 12.1 (range 2–14) months, respectively. Dose was increased at Week 24 in 81 (48.4%) patients overall. These dose increases occurred in 26 (47.3%) patients receiving deferasirox 5 mg/kg/day, and 25 (45.5%) patients receiving deferasirox 10 mg/kg/day as starting doses. Fifteen (56.3%) patients in each of the placebo 5 and 10 mg/kg/day groups also had dose increases. Doses were interrupted at least once in 36 (65.5%), 42 (76.4%), and 36 (64.3%) patients in the deferasirox 5, 10 mg/kg/day and placebo groups, respectively. Dose was reduced in 12 (21.8%), 11 (20.0%), and eight (14.3%) patients in the deferasirox 5, 10 mg/kg/day and placebo groups, respectively. Among the patients with dose reductions, these reductions were due to AEs in 12/12 patients treated with deferasirox 5 mg/kg/day, 9/11 patients treated with deferasirox 10 mg/kg/day and 7/8 placebo patients. Other reasons for dose reductions were dosing error, increased serum creatinine and low LIC (n = 1 for each) in the deferasirox 10 mg/kg/day group, and laboratory test abnormality (n = 1) in the placebo group. Medication compliance was high with 94.8% of deferasirox and 95.7% of placebo-treated patients taking the planned study dose.
Twenty-one patients required at least one blood transfusion during the study. These included seven (12.7%) patients receiving deferasirox 5 mg/kg/day, eight (14.5%) patients receiving deferasirox 10 mg/kg/day and six (10.7%) patients receiving placebo. Of these 21 patients, 10 received one transfusion, seven received two transfusions, two received three transfusions and two received four transfusions.

**Effect of deferasirox on LIC**

LIC significantly decreased from baseline to Week 52 by a least-squares mean (LSM) ± SE of –1.95 ± .50 mg Fe/g dw (95% CI, −2.94, −.96) in the deferasirox 5 mg/kg/day starting dose cohort, and by –3.80 ± .48 mg Fe/g dw (95% CI, −4.76, –2.85) in the deferasirox 10 mg/kg/day starting dose cohort (Figure 2A). There was a significantly greater decrease in LSM ± SE LIC of –1.85 ± .70 mg Fe/g dw in the deferasirox 10 versus 5 mg/kg/day cohort (95% CI, –3.22, −.48; \( P = .009 \)). Decreases in LIC were significantly greater with deferasirox compared with placebo in deferasirox 5 mg/kg/day (−2.33 ± .70 mg Fe/g dw; \( P = .001 \)) and deferasirox 10 mg/kg/day cohorts (−4.18 ± .69 mg Fe/g dw; \( P < .001 \)). In placebo patients, LIC increased from baseline by .38 ± .49 mg Fe/g dw (95% CI, −.59, 1.34). Reduction in LIC with both doses of deferasirox was observed from Week 24 (Figure 2A; Table 2). Mean ± SD LIC at Week 24 in patients receiving dose increases in the deferasirox 5 and 10 mg/kg/day starting dose cohorts was 16.2 ± 8.9 and 18.0 ± 9.6 mg Fe/g dw, respectively. Mean ± SD actual deferasirox dose over the 52-week treatment period in patients receiving dose increases was 6.8 ± 1.0 and 14.1 ± 2.0 mg/kg, respectively. There was a trend for greater reduction in LIC in patients with higher baseline LIC. A decrease in LIC of ≥3 mg Fe/g dw at last assessment was observed in 18 (32.7%) patients in the deferasirox 5 mg/kg/day cohort, 31 (56.4%) patients in the 10 mg/kg/day cohort and six (10.7%) patients in the placebo group. A ≥30% reduction in LIC at last assessment was observed in 14 (25.5%) patients in the deferasirox 5 mg group, 27 (49.1%) patients in the 10 mg/kg/day deferasirox group and one (1.8%) patient in the placebo group (Table 2). A shift table for LIC category change is presented in Supplementary Table S1. Overall, a greater proportion of patients moved to a lower iron burden range by Week 52 in the deferasirox 10 mg/kg/day
group (n=26; 47.3%) compared with the deferasirox 5 mg/kg/day group (n=20; 36.4%) or the placebo group (n=7; 12.5%). Of these patients, 13 (23.6%) achieved LIC <5 mg Fe/g dw in the deferasirox 10 mg/kg/day group compared with only eight (14.5%) in the 5 mg/kg/day group and two (3.6%) in the placebo group.

Effect of deferasirox on serum ferritin

At Week 52, serum ferritin significantly decreased from baseline by a LSM of –121 ng/mL (95% CI, –203, –38; median –99 ng/mL) in the deferasirox 5 mg/kg/day group and by –222 ng/mL (95% CI, –304, 140; median –190 ng/mL) in the deferasirox 10 mg/kg/day group (Figure 2B). Serum ferritin levels increased by 115 ng/mL (median 78 ng/mL) in the placebo group. Decreases in serum ferritin were significantly greater with deferasirox compared with placebo; –235 ng/mL (P < .001) and –337 ng/mL (P < .001) in the deferasirox 5 and 10 mg/kg/day groups, respectively. At Week 24, serum ferritin levels were reduced from baseline for both deferasirox cohorts (Figure 2B; Table 2). The correlation (R) between baseline LIC and serum ferritin was .639 (Figure 2C).

Safety

Overall AEs were reported in 130 (78.3%) patients, including 42 (76.4%) receiving deferasirox 5 mg/kg/day, 43 (78.2%) receiving deferasirox 10 mg/kg/day and 45 (80.4%) receiving placebo. Investigator-assessed drug-related AEs were reported in 40 (24.1%) patients, most of which were of mild-to-moderate severity and resolved without discontinuing treatment. The most common drug-related AEs were nausea, rash and diarrhea (Table 3).

Six investigator-assessed drug-related serious AEs (SAEs) were reported in four patients receiving deferasirox (abdominal pain, pyrexia, hepatotoxicity [not confirmed by central laboratory], cellulitis, pruritus, and rash; n = 1 each). No drug-related SAEs were reported with placebo. No deaths occurred during the study in any group. Eight patients experienced AEs resulting in study discontinuation. These included three patients in the deferasirox 5 mg/kg/day cohort (fractured pelvis; anemia; increased urine protein level); three patients in the deferasirox 10 mg/kg/day cohort.
(pregnancy \([n = 2]\), rash, and pruritus \([n = 1]\)), and two patients in the placebo 10 mg/kg/day (optic neuritis and severe anemia).

A cataract was recorded in a male patient (aged 46) randomized to deferasirox 5 mg/kg/day. This patient entered the study with a cataract and therefore it was unlikely to have been related to study drug. One incidence of neurosensory deafness was reported in a patient receiving placebo 10 mg/kg/day and proteinuria was reported in one patient receiving deferasirox 5 mg/kg/day. The overall number of AEs and SAEs reported before and after dose increases was comparable within each treatment group.

Three (5.5%) patients in the deferasirox 10 mg/kg/day cohort had two consecutive serum creatinine increases of >33% above baseline and above ULN, occurring in the second half of the study. Serum creatinine returned to normal without dose interruption or reduction in one patient (receiving 20 mg/kg/day when the event occurred) who achieved LIC of 1.3 mg Fe/g dw at end of study. In the remaining two patients, serum creatinine returned to normal after drug interruption (one patient receiving 20 mg/kg/day and one receiving 10 mg/kg/day); both patients achieved reduction in LIC and serum ferritin levels. Of these three patients, one also experienced two consecutive creatinine clearances <60 mL/min during the study in addition to one other patient receiving deferasirox 5 mg/kg/day.

No patients receiving deferasirox demonstrated an increase in ALT >5 x ULN and >2 x baseline, although there was one incidence in a patient receiving placebo 10 mg/kg/day. There were no progressive changes in mean serum creatinine, creatinine clearance, ALT or urinary protein/creatinine ratio (Supplementary Figure 1).

**Discussion**

This is the first randomized, placebo-controlled trial evaluating iron chelation in NTDT patients with iron overload mainly due to increased intestinal iron absorption. These data provide the largest set of efficacy and safety data for iron chelation therapy in NTDT patients to date, confirming preliminary findings in small studies and
case reports. Despite no or only sporadic transfusions in these NTDT patients, high baseline LIC and serum ferritin levels confirm significant iron burden, requiring iron chelation. Of interest, in patients receiving placebo treatment, LIC and serum ferritin increased by .38 mg Fe/g dw (95% CI, –.59, 1.34) and 115 ng/mL, respectively over 1 year; only six (10.7%) patients required transfusions in this group during this time. This is equivalent to a body iron increase of .011 mg/kg/day based on the formula published by Angelucci et al.

Compared with placebo, deferasirox at starting doses of 5 and 10 mg/kg/day with dose escalations up to 20 mg/kg/day in patients with high levels of iron overload significantly reduced LIC and serum ferritin levels. Experience with deferoxamine has demonstrated that to minimize drug toxicity, lower doses should be used when body iron levels are low. This principle was built into the design of our study as considerably lower doses were used compared with those used in transfusion-dependent β-thalassemia patients (20–40 mg/kg/day). Use of 20 mg/kg/day in this study is limited; further data will be obtained from the extension study. Reductions in LIC and serum ferritin were greater in patients receiving starting doses of deferasirox 10 versus 5 mg/kg/day. A LIC decrease ≥3 mg Fe/g dw was one of the success criteria used in the Phase III study of deferasirox vs deferoxamine and a 30% decrease in 1 year was agreed to be clinically relevant by the Study Steering Committee. After 1 year, over half (56.4%) of patients receiving deferasirox 10 mg/kg/day and almost a third (32.7%) of patients receiving deferasirox 5 mg/kg/day achieved reductions in LIC of ≥3 mg Fe/g dw. The apparent response observed in a small number of placebo patients may be attributed to variability in MRI assessments. A greater proportion of patients achieved LIC <7, LIC <5, and LIC <3 mg Fe/g dw in the deferasirox 10 mg/kg/day compared to the 5 mg/kg/day group or placebo. As patients started with significantly elevated LIC, it is expected that more patients would achieve therapeutic targets with continued treatment in the extension. Dose was increased in 46.4% of deferasirox-treated patients after 24 weeks, highlighting the importance of dose adjustments for achieving therapeutic goals.

Despite increased knowledge of iron metabolism in NTDT patients, and the known association between LIC and morbidity, clinical guidelines on managing iron
overload are lacking. For patients with β-thalassemia intermedia, it has been suggested that iron chelation should be initiated if LIC exceeds 7 mg Fe/g dw\textsuperscript{26,27,28-30}. However, recent data in patients with β-thalassemia intermedia indicates that LIC ≥7 and ≥6 mg Fe/g dw are associated with an increased risk of vascular and endocrine/bone morbidity, respectively.\textsuperscript{2} Our data indicate that chelation in NTDT patients may be initiated earlier, when LIC exceeds 5 mg Fe/g dw, without evidence of tolerability issues with a treatment goal of preventing the accumulation of iron to toxic levels.

This is the first study to report the safety of deferasirox compared with placebo. AEs were manageable, even when some patients achieved LIC <5 mg Fe/g dw towards the end of study, with overall AE incidence comparable between deferasirox and placebo. The incidence of ALT abnormalities was low and renal abnormalities were reversible, which is consistent with previous experience with deferasirox. Investigator-assessed drug-related AEs were mainly gastrointestinal, as has been demonstrated in deferasirox-treated patients with transfusion-dependent anemias;\textsuperscript{15} however, the incidence was similar in the deferasirox and placebo-treated groups. Although the majority of dose reductions were as a result of AEs, the incidence of drug-related AEs was approximately half that reported over 1 year in patients with transfusion-dependent anemias.\textsuperscript{15} Interestingly, the incidences of nausea and headache that were attributed to study drug by the investigators were higher in the placebo 10 mg/kg/day group compared with the placebo 5 mg/kg/day group, perhaps suggesting an effect of excipients in the formulation. These differences warrant further investigation.

Approximately one-third of screened patients were excluded because of not meeting the iron overload inclusion criteria (LIC at baseline ≥5 mg Fe/g dw). These criteria were agreed by the steering committee to take into account the risks of overchelation and safety issues observed in transfusion-dependent β-thalassemia patients. The outcome of this study shows that NTDT patients may be chelated at starting doses of 5 and 10 mg/kg/day to low LICs without increasing the risk of renal problems.
In conclusion, many NTDT patients may have high iron burdens that require iron chelation therapy. Compared with placebo, deferasirox at starting doses of 5 and 10 mg/kg/day with dose escalations up to 20 mg/kg/day in patients with higher levels of iron overload significantly reduced iron overload in NTDT patients, along with a similar frequency of overall AEs.
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Authorship contributions
A Taher, J Porter, V Viprakasit, A Kattamis, S Chuncharunee, P Sutcharitchan, N Siritanaratkul, R Galanello, Z Karakas, and MD Cappellini served as investigators on this trial, enrolling patients. They contributed to data interpretation, reviewed and provided their comments on this manuscript. A Taher, J Porter, V Viprakasit, A Kattamis, and MD Cappellini served as Study Steering Committee members overseeing the conduct of the trial, from study design to analysis plan and data interpretation. T Lawniczek, D Habr, and J Ros assisted in developing the trial protocol, coordinated the execution of the trial and contributed to the analysis, interpretation, and reporting of the trial data. Y Zhang served as the trial statistician. All authors approved the final manuscript. As a contributor, R Helson PhD provided medical editorial assistance in developing the manuscript, under the guidance of all authors, and assisted in distribution of drafts and final version to all authors.

Conflicts of interest
A Taher reports receiving research funding and honoraria from Novartis Pharmaceuticals; J Porter received research funding from Novartis Pharmaceuticals, being a member of an advisory committee and participating in a Novartis speaker’s bureau; V Viprakasit received research grant support and lecture fees from Novartis Pharmaceuticals and research grant support from GPO-L-ONE, Thailand, FerroKin Biosciences and National Research University (NRU), Thailand; A Kattamis received honoraria and research funding from Novartis Pharmaceuticals and participating in a speaker’s bureau; S Chuncharunee, P Sutcharitchan, and N Siritanaratkul received research funding from Novartis Pharmaceuticals; R Galanello received research grants and speaker’s honoraria from Novartis Pharmaceuticals; Z Karakas received research grants and speaker’s honoraria from Novartis Pharmaceuticals; T Lawniczek, J Ros, Y Zhang, and D Habr are full-time employees of Novartis
Pharmaceuticals; MD Cappellini reports participating in a Novartis Pharmaceuticals speaker’s bureau.

**Appendix**

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References


### Table 1. Demographic, disease and baseline patient characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Deferasirox 5 mg/kg/day</th>
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<td>n = 55</td>
<td>n = 55</td>
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<td>Disease, n (%)</td>
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<td>30 (54.5)</td>
<td>33 (58.9)</td>
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<td>α-thalassemia*</td>
<td>5 (9.1)</td>
<td>9 (16.4)</td>
<td>8 (14.3)</td>
</tr>
<tr>
<td>HbE/β-thalassemia</td>
<td>18 (32.7)</td>
<td>16 (29.1)</td>
<td>15 (26.8)</td>
</tr>
<tr>
<td>Mean age ± SD, years</td>
<td>33.1 ± 12.3</td>
<td>31.7 ± 11.7</td>
<td>31.4 ± 12.2</td>
</tr>
<tr>
<td>Median age (range)</td>
<td>33 (10–60)</td>
<td>31 (12–69)</td>
<td>32 (10–59)</td>
</tr>
<tr>
<td>Pediatric patients, † n (%)</td>
<td>6 (10.9)</td>
<td>7 (12.7)</td>
<td>8 (14.3)</td>
</tr>
<tr>
<td>Male:female, n</td>
<td>29:26</td>
<td>29:26</td>
<td>31:25</td>
</tr>
<tr>
<td>Splenectomy, n (%)</td>
<td>29 (52.7)</td>
<td>31 (56.4)</td>
<td>28 (50.0)</td>
</tr>
<tr>
<td>Prior transfusions received‡, n (%)</td>
<td>49 (89.1)</td>
<td>50 (90.9)</td>
<td>46 (82.1)</td>
</tr>
<tr>
<td>Previous chelation, n (%)</td>
<td>8 (14.5)</td>
<td>16 (29.1)</td>
<td>20 (35.7)</td>
</tr>
<tr>
<td>Deferoxamine</td>
<td>7 (12.7)</td>
<td>15 (27.3)</td>
<td>17 (30.4)</td>
</tr>
<tr>
<td>Deferiprone</td>
<td>–</td>
<td>1 (1.8)</td>
<td>3 (5.4)</td>
</tr>
<tr>
<td>Deferoxamine + Deferiprone</td>
<td>1 (1.8)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Mean LIC ± SD (mg Fe/g dw)§</td>
<td>13.11 ± 7.29</td>
<td>14.56 ± 7.92</td>
<td>15.94 ± 10.85</td>
</tr>
<tr>
<td>Median LIC (range)</td>
<td>11.7 (2.6–38.6)</td>
<td>11.7 (5.0–32.8)</td>
<td>13.0 (5.0–49.1)</td>
</tr>
<tr>
<td>LIC category,** n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7 mg Fe/g dw</td>
<td>10 (18.2)</td>
<td>8 (14.5)</td>
<td>13 (23.2)</td>
</tr>
<tr>
<td>7–15 mg Fe/g dw</td>
<td>31 (56.4)</td>
<td>26 (47.3)</td>
<td>20 (35.7)</td>
</tr>
<tr>
<td>&gt;15 mg Fe/g dw</td>
<td>14 (25.5)</td>
<td>21 (38.2)</td>
<td>22 (39.3)</td>
</tr>
<tr>
<td>Mean serum ferritin ± SD (ng/mL)</td>
<td>1141 ± 805</td>
<td>1174 ± 684</td>
<td>1305 ± 1017</td>
</tr>
<tr>
<td>Median serum ferritin, ng/mL (range)</td>
<td>988 (370–5609)</td>
<td>1015 (342–4224)</td>
<td>994 (304–6419)</td>
</tr>
<tr>
<td>Serum ferritin category, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;500 ng/mL</td>
<td>5 (9.1)</td>
<td>4 (7.3)</td>
<td>8 (14.3)</td>
</tr>
<tr>
<td>500–1000 ng/mL</td>
<td>24 (43.6)</td>
<td>23 (41.8)</td>
<td>20 (35.7)</td>
</tr>
<tr>
<td>1000–2500 ng/mL</td>
<td>23 (41.8)</td>
<td>26 (47.3)</td>
<td>23 (41.1)</td>
</tr>
<tr>
<td>&gt;2500 ng/mL</td>
<td>3 (5.5)</td>
<td>2 (3.6)</td>
<td>5 (8.9)</td>
</tr>
</tbody>
</table>

†HbH [n = 8], HbH Constant Spring [n = 6], genotype not determined [n = 6], CSEA Bart’s [n = 1], Hb Agrino [n = 1].

‡Pediatric subjects were aged <18 years.

§Patients did not receive any transfusion in the 6 months prior to study entry.

§95% upper limit of normal (ULN) for LIC is <1.8 mg Fe/g dw."
**One patient missing from the placebo group.

Abbreviations: SD=standard deviation; LIC=liver iron concentration; dw=dry weight
### Table 2. LIC and serum ferritin responses over 1 year with deferasirox versus placebo

<table>
<thead>
<tr>
<th></th>
<th>Deferasirox 5 mg/kg/day (n = 55)</th>
<th>Deferasirox 10 mg/kg/day (n = 55)</th>
<th>Placebo (n = 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSM change from baseline in LIC ± SE (95% CI)*, mg Fe/g dw</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 weeks</td>
<td>–.87 ± .45 (–1.76, .01)</td>
<td>–1.95 ± .50 (–2.94, –.96)</td>
<td>–.24 ± .44 (–1.10, .63)</td>
</tr>
<tr>
<td>52 weeks</td>
<td>–1.95 ± .50 (–2.94, –.96)</td>
<td>–3.80 ± .48 (–4.76, –2.85)</td>
<td>.38 ± .49 (–.59, 1.34)</td>
</tr>
<tr>
<td>Median change from baseline in serum ferritin ng/mL (min, max)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 weeks</td>
<td>33 (–531, 688)</td>
<td>–9 (–290, 759)</td>
<td>27 (–296, 1250)</td>
</tr>
<tr>
<td>24 weeks</td>
<td>–21 (–520, 1056)</td>
<td>–64 (–833, 1562)</td>
<td>33 (–620, 1415)</td>
</tr>
<tr>
<td>36 weeks</td>
<td>–54 (–671, 592)</td>
<td>–103 (–1041, 883)</td>
<td>87 (–233, 1050)</td>
</tr>
<tr>
<td>52 weeks</td>
<td>–102 (–839, 376)</td>
<td>–202 (–1407, 988)</td>
<td>81 (–344, 835)</td>
</tr>
<tr>
<td>Number (%) with decrease of ≥3 mg Fe/g dw between baseline and Week 52 (LOCF)</td>
<td>18 (32.7)</td>
<td>31 (56.4)</td>
<td>6 (10.7)</td>
</tr>
<tr>
<td>Comparison with placebo†</td>
<td>Estimated odds ratio‡</td>
<td>6.7</td>
<td>16.3</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>2.1, 21.1</td>
<td>5.2, 50.8</td>
</tr>
<tr>
<td>Number (%) with a reduction of ≥30% in LIC between baseline and Week 52 (LOCF)</td>
<td>14 (25.5)</td>
<td>27 (49.1)</td>
<td>1 (1.8)</td>
</tr>
</tbody>
</table>

---

*Derived from an analysis of covariance model with treatment as factor and baseline LIC as covariate; †Estimates were obtained from a logistic regression model with treatment regimen and baseline LIC as explanatory variables; ‡Ratios greater than one favor deferasirox.

Abbreviations: SE=standard error; LIC=liver iron concentration; LSM=least-squares mean; dw=dry weight; LOCF=last observation carried forward
Table 3. Most common (≥3 patients overall) investigator-assessed drug-related adverse events

<table>
<thead>
<tr>
<th>Adverse events, n (%)</th>
<th>Deferasirox 5 mg/kg/day n = 55</th>
<th>Placebo 5 mg/kg/day n = 28</th>
<th>Deferasirox 10 mg/kg/day n = 55</th>
<th>Placebo 10 mg/kg/day n = 28</th>
<th>Total n = 166</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>3 (5.5)</td>
<td>1 (3.6)</td>
<td>4 (7.3)</td>
<td>3 (10.7)</td>
<td>11 (6.6)</td>
</tr>
<tr>
<td>Skin rash</td>
<td>2 (3.6)</td>
<td>0</td>
<td>5 (9.1)</td>
<td>1 (3.6)</td>
<td>8 (4.8)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>0</td>
<td>5 (9.1)</td>
<td>1 (3.6)</td>
<td>6 (3.6)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (3.6)</td>
<td>0</td>
<td>1 (1.8)</td>
<td>2 (7.1)</td>
<td>5 (3.0)</td>
</tr>
<tr>
<td>Upper abdominal pain</td>
<td>2 (3.6)</td>
<td>0</td>
<td>1 (1.8)</td>
<td>0</td>
<td>3 (1.8)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1 (1.8)</td>
<td>1 (3.6)</td>
<td>1 (1.8)</td>
<td>0</td>
<td>3 (1.8)</td>
</tr>
</tbody>
</table>
Figure legends

Figure 1. Patient disposition

Figure 2. A. Absolute change ± SE in LIC over time; B. Absolute change ± SE in serum ferritin over time; C. Relationship between LIC and serum ferritin at baseline

*Adjusted P-value with Dunnett’s method

Abbreviations: SE= standard error; LIC=liver iron concentration; LSM=least-squares mean; dw=dry weight. For serum ferritin, quarterly average was used and the last available quarter was carried forward.
Figure 1

Screened, n = 339

Excluded, n = 173
- LIC < 5 mg Fe/g dw or SF < 300 ng/mL, n = 95
- Abnormal proteinuria/protein-creatinine ratio, n = 22
- Patient withdrew consent, n = 19
- Transfusions < 6 months of study start, n = 16
- Unable/unwilling to comply with screening timelines/protocol, n = 8
- Refused /unsuitable for MRI, n = 4
- Other, n = 9*

Randomized, n = 166

Deferasirox 5 mg/kg/day
n = 55

- Discontinued, n = 7
  - Adverse event, n = 2
  - Consent withdrawn, n = 2
  - Lost to follow-up, n = 3
  - Protocol deviation, n = 1

- Completed week 52
  n = 48

Placebo 5 mg/kg/day
n = 28

- Discontinued, n = 3
  - Consent withdrawn, n = 2
  - Protocol deviation, n = 1

- Completed week 52
  n = 25

Deferasirox 10 mg/kg/day
n = 55

- Discontinued, n = 6
  - Adverse event, n = 3
  - Consent withdrawn, n = 2
  - Lost to follow-up, n = 1

- Completed week 52
  n = 49

Placebo 10 mg/kg/day
n = 28

- Discontinued, n = 2
  - Adverse event, n = 1
  - Abnormal lab value, n = 1

- Completed week 52
  n = 26

*Other: (n = 2) > 20 transfusions/lifetime (note: patients were excluded before the protocol was amended to remove this criterion); (all n = 1): (i) Iron chelation therapy < 6 months of study start (note: the protocol was amended to exclude patients with iron chelation therapy < 1 month of study start; however, this patient was excluded before this protocol amendment); (ii) concomitant HU; (iii) concomitant autoimmune hemolytic anemia with severe anemia; (iv) ALT > 3x ULN (note: the protocol was amended to exclude patients with ALT > 5xULN; however, this patient was excluded before this protocol amendment); (v) invalid creatinine results; (vi) safety concern; and (vii) rescreened by mistake.
Figure 2A

Absolute change from baseline in LIC, LSM ± SE (mg Fe/g dw)

- Deferasirox 5 mg/kg/day (n = 55)
- Deferasirox 10 mg/kg/day (n = 55)
- Placebo (n = 56)

P = .009  P < .001*  P = .001*
Figure 2B

Absolute change from baseline in SF, LSM ± SE (mg Fe/g dw)

- Deferasirox 5 mg/kg/day (n = 55)
- Deferasirox 10 mg/kg/day (n = 55)
- Placebo (n = 56)

Time (weeks)

24

52

P = 0.088  P < 0.001*

P < 0.001*
Figure 2C

Correlation $r = 0.639$

$r^2 = 0.408$

$n = 165$
Deferasirox significantly reduces iron overload in non-transfusion-dependent thalassemia: 1-year results from a prospective, randomized, double-blind, placebo-controlled study

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