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CORRESPONDENCE

An open-label, multicenter, efficacy, and safety study of deferasirox in iron-overloaded patients with non-transfusion-dependent thalassemia (THETIS): 5-year results

To the Editor:

Non-transfusion-dependent thalassemia (NTDT)—a group of genetic disorders affecting hemoglobin (Hb) chain synthesis—does not generally require regular blood transfusions for survival. NTDT includes beta-thalassemia intermedia, alpha-thalassemia intermedia (HbH disease), and Hb E/beta-thalassemia.[1,2] Patients with NTDT are at risk of iron overload because of increased iron uptake from the gastrointestinal tract. Iron overload is associated with the development of serious morbidities, including liver dysfunction and vascular, bone, and endocrine complications. Thus, monitoring the iron overload and its management with iron chelation therapy is necessary.[3,4] Deferasirox (ICL670, Exjade) has been approved for the treatment of chronic iron overload in both adult and pediatric patients with transfusion-dependent thalassemia and NTDT.[2] THETIS was an open-label, single-arm, multicenter, 5-year study (with a 1-year primary analysis) conducted to assess the long-term efficacy and safety of deferasirox in iron-overloaded patients with NTDT (NCT01709838).

Patients with NTDT aged ≥10 years with liver iron concentration (LIC) ≥5 mg Fe/g dw and serum ferritin (SF) ≥300 ng/mL at screening were included in the study. The primary endpoint was a change in LIC from baseline after 52 weeks of treatment.[5] Secondary endpoints included the proportion of patients with baseline LIC >15 mg Fe/g dw achieving LIC <5 mg Fe/g dw and the time taken for the same; time from target LIC 3 mg Fe/g dw to the first LIC ≥5 mg Fe/g dw in the follow-up period; change in LIC from baseline over time; change in LIC from baseline to week 52 by the underlying disease; SF versus LIC at baseline and end of the study; quality of life (QOL); and safety and change in the endocrine function from baseline during the treatment period.

A total of 134 patients were enrolled (median age, 27 years; 56.7% male); except one patient (0.7%) who had congenital dyserythropoietic anemia, all other patients had NTDT (69 [51.5%] with beta-thalassemia intermedia, 24 [17.9%] with Hb E/beta-thalassemia, and 40 [29.9%] with alpha-thalassemia intermedia). Overall, 57.5% of patients had a splenectomy and 47.8% received prior chelation therapy, including deferasirox (21.6%), deferoxamine (13.4%), and deferiprone (12.7%). The mean (standard deviation [SD]) baseline values of LIC and SF were 15.13 mg Fe/g dw (10.718) and 1426.7 ng/mL (1117.7), respectively.

All patients initiated deferasirox (dispersible tablet) at a starting dose of 10 mg/kg/day for 4 weeks after which the dose was escalated based on the iron burden at baseline; if the baseline LIC was >15 mg Fe/g dw, the dose was escalated to 20 mg/kg/day and if it was >7 to ≤15 mg Fe/g dw, the dose was escalated to 15 mg/kg/day. No dose escalation was needed for patients with LIC ≥5 and ≤7 mg Fe/g dw. At week 24 and every 6 months thereafter, further dose adjustments were made according to the LIC at that visit. If LIC was >15 mg Fe/g dw, the dose was increased by 5–10 mg/kg/day (up to a maximum of 30 mg/kg/day), and if LIC was >7 and ≤15 mg Fe/g dw, the dose was increased by 5 mg/kg/day (up to a maximum of 20 mg/kg/day). Treatment was to be interrupted when LIC was <3 mg Fe/g dw or SF <300 ng/mL and restarted at a dose of 10 mg/kg/day upon reaching LIC ≥5 mg Fe/g dw and SF ≥300 ng/mL. Overall, the maximum permitted deferasirox dose was 30 mg/kg/day. Of the 134 patients treated, 112 (83.6%) completed 1 year of treatment,[5] and 67 (50%) completed 5 years of treatment. The reasons that led to 50% of patients discontinuing the study included consent withdrawal (15.7%), loss to follow-up (11.9%), and pregnancy (7.5%); no clear pattern was observed regarding the reasons for early discontinuation. The median duration of treatment exposure was 35.7 months (range, 0.7–63.2 months).

As previously reported,[5] the THETIS study met its primary endpoint (1-year analysis results), with the mean LIC decreasing significantly from baseline to week 52 (absolute change from baseline, −6.68 [7.02] mg Fe/g dw; P <.0001). In this correspondence, we report additional analyses of change in LIC from baseline to 52 weeks of treatment (stratified by age and underlying disease), along with the long-term (5 years) efficacy and safety data from the study.

When stratified by age, the mean (SD) absolute decrease in LIC (mg Fe/g dw) from baseline to week 52 was −4.16 (4.368) in patients aged <18 years and −7.30 (7.414) in those aged ≥18 years. The mean (SD) absolute decrease in LIC (mg Fe/g dw) was −6.11 (6.481), −6.18 (7.572), and −7.97 (7.652) in patients with beta-thalassemia intermedia, Hb E/beta-thalassemia, and alpha-thalassemia intermedia, respectively. Overall, the efficacy of deferasirox at 52 weeks was observed both in pediatric and adult patients, regardless of the underlying disease.

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The reduction in LIC observed at week 52[5] was maintained up to 5 years (week 260), as observed in this longer follow-up analysis (Table 1). The mean (SD) absolute change in LIC from baseline to week 260 was −10.57 (10.366) mg Fe/g dw. Of the 49 patients with baseline LIC >15 mg Fe/g dw, 51.0% achieved the first LIC <5 mg Fe/g dw in a median time of 28.55 months (range, 10.18–54.08 months). Target LIC of <3 mg Fe/g dw was achieved by 61 of 134 patients (45.5%); the long-term efficacy of deferasirox is evidenced by the fact that only 24 of these 61 patients (39.3%) reached the first LIC ≥5 mg Fe/g dw in a median time of 13.91 months (range, 3.88–29.54 months).

The median decrease in SF from baseline to week 52 was −304.20 ng/mL (range, −5306.7 to 1669.0), as reported in the primary analysis.[5] This trend in SF decrease was maintained during the 5-year follow-up, with a median decrease of −434.00 ng/mL (range, −3289.2 to 955.5) at week 260 (Figure S1). The correlation analysis for absolute changes in LIC and SF over time showed a moderate and consistent correlation from week 52 onward, with a correlation coefficient of 0.740 at week 208, indicating a reduction in both LIC and SF in the majority of the patients during long-term treatment with deferasirox. A similar correlation between LIC and SF decrease was also observed in the THALASSA study.[6] When there is limited access to MRI technology and expertise to measure LIC, the replication of this relationship suggests the practicality of using SF to predict LIC ≥5 mg Fe/g dw.

Long-term treatment with deferasirox had minimal effect on the endocrine function. Most of the endocrine function parameters were within the normal range at both baseline and post-treatment. Furthermore, although the number of patients in the subgroups by age was relatively small and results should be taken with caution, there was no indication of a detrimental effect of long-term treatment with deferasirox on adult or pediatric health-related QOL.

No new safety concerns emerged in this study. Of the 134 patients, 82.1% experienced adverse events (AEs). The incidence of study drug-related AEs remained similar to that observed in the 1-year primary analysis (37.3% vs. 31.3%)[5] and included diarrhea

TABLE 1 Summary of LIC values over time

Summary of LIC values and absolute change from baseline in LIC over time		
Time point	**All patients $N = 134$**	
	Mean LIC value (SD), mg Fe/g dw	**Absolute mean (SD) change in LIC from baseline, mg Fe/g dw**
Baseline ($n = 134$)	15.13 (10.718)	n/a
Week 24 ($n = 126$)	11.47 (8.816)	−3.67 (3.778)
Week 52[a] ($n = 118$)	8.08 (6.202)	−7.02 (7.132)
Week 76 ($n = 107$)	6.94 (5.216)	−8.93 (8.922)
Week 104 ($n = 100$)	5.96 (4.680)	−9.63 (9.474)
Week 128 ($n = 95$)	5.39 (3.339)	−10.03 (9.445)
Week 156 ($n = 92$)	5.15 (3.077)	−10.20 (9.746)
Week 180 ($n = 86$)	4.92 (3.271)	−9.94 (9.838)
Week 208 ($n = 81$)	4.85 (2.731)	−10.04 (10.010)
Week 232 ($n = 66$)	5.02 (3.319)	−10.58 (10.045)
Week 260 ($n = 66$)	4.87 (2.707)	−10.57 (10.366)
Summary of time to first LIC <5 mg Fe/g dw in patients with baseline LIC >15 mg Fe/g dw ($n = 49$)		
Patients achieving first LIC <5 mg Fe/g dw, *n* (%)		25 (51.0)
Median (range) time to first LIC <5 Fe/g dw, months		28.55 (10.18 to 54.08)
% Event probability estimate to the first LIC <5 mg Fe/g dw at 5 years (95% CI)[b]		73.5 (56.22, 88.19)
Long-term efficacy of treatment in patients achieving target LIC of <3 mg Fe/g dw ($n = 61$)		
Patients achieving first LIC ≥5 mg Fe/g dw, *n* (%)		24 (39.3)
Median (range) time to first LIC ≥5 Fe/g dw, months		13.91 (3.88 to 29.54)
% Event probability estimate to the first LIC ≥5 within 3 years (95% CI)[b]		54.9 (40.31, 70.69)

Abbreviations: CI, confidence interval; dw, dry weight; Fe, iron; LIC, liver iron concentration; n/a, not applicable; SD, standard deviation.

[a]For primary analysis, the last available post-baseline LIC was carried forward if no LIC value was available at week 52, which was not the case for analyzing change in LIC over time; this is the reason for the difference in mean LIC changes reported in Taher et al.[5] ($n = 127$) versus value reported in Table 1 ($n = 118$).

[b]Percentage of event probability estimate is the estimated probability that a patient will have an event prior to the specified time point (year). Percentages of event probability estimates are obtained from the Kaplan–Meier (KM) survival estimates for all the treatment groups; Greenwood formula is used for CIs of KM estimates.

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(6.0%), nausea (5.2%), and abdominal discomfort, abdominal pain, abdominal pain upper, and increased urine protein/creatinine ratio (4.5% each), which is consistent with the known safety profile of deferasirox. Only three patients experienced severe study drug-related AEs such as cataract in the right eye, increased creatinine, increased urine protein/creatinine ratio with leg edema, and progressive liver disease. Serious AEs (SAEs) were reported in 33.6% of patients, with pneumonia (5.2%) being the most common; five patients (3.7%) permanently discontinued the treatment due to SAEs. Three patients died during the study due to cardiac failure, pneumonia, and autoimmune hemolytic anemia, all unrelated to the study treatment.

In conclusion, long-term treatment with deferasirox is an effective and well-tolerated oral iron chelator in pediatric and adult patients with NTDT, regardless of the underlying disease subtype. Initiating treatment with 10 mg/kg/day followed by a dose adjustment at week 4 based on the baseline LIC and further dose adjustments every 6 months by LIC was efficacious in the long term (5 years) and did not incur an increased safety risk.

AUTHOR CONTRIBUTIONS

Maria Domenica Cappellini, Yesim Aydinok, John Porter, and Ali Taher contributed to the conceptualization and design of the study. Yong-Rong Lai, Maria Domenica Cappellini, Yesim Aydinok, John Porter, Zeynep Karakas, Vip Viprakasit, Noppadol Siritanaratkul, Antonis Kattamis, Rongrong Liu, and Ali Taher contributed to patient accrual, clinical care, and data collection. Maria Domenica Cappellini, Yesim Aydinok, John Porter, Antonis Kattamis, and Ali Taher contributed to data interpretation. All authors (Yong-Rong Lai, Maria Domenica Cappellini, Yesim Aydinok, John Porter, Zeynep Karakas, Vip Viprakasit, Noppadol Siritanaratkul, Antonis Kattamis, Rongrong Liu, Miguel Izquierdo, Janet Lasher, Sameera Govindaraju, Ali Taher) were involved in drafting, revision, final review, and approval of the correspondence.

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CONFLICT OF INTEREST

Yong-Rong Lai has nothing to disclose. Maria Domenica Cappellini is a member of the advisory board at Novartis, Sanofi-Genzyme, Celgene-BMS, CRISPR-Vertex, Vifor, Novo-Nordisk, and Ionis. Yesim Aydinok is a member of the advisory board at BMS; has provided consultancy to CRISPR-Vertex Therapeutics and Silence Therapeutics; and received research funding from BMS, Novartis, Ionis Pharmaceuticals, Resonance Health, and Imara. John Porter, Zeynep Karakas, and Vip Viprakasit have nothing to disclose. Noppadol Siritanaratkul has received research grants from Novartis, Roche, and Janssen. Antonis Kattamis has provided consultancy to Agios Pharmaceuticals, Amgen, Bristol Myers Squibb/Celgene, Chiesi, Crispr/Vertex, Ionis Pharmaceuticals, Novartis, and Vifor, and received research funding from Bristol Myers Squibb/Celgene and Novartis. Rongrong Liu has nothing to disclose. Miguel Izquierdo, Janet Lasher, and Sameera Govindaraju are employees of Novartis. Ali Taher has provided consultancy to BMS, Ionis Pharmaceuticals, Novartis, Silence Therapeutics, and Vifor Pharma, and received research funding from BMS, Novartis, Ionis Pharmaceuticals, and Vifor Pharma.

PATIENT CONSENT STATEMENT

Patients provided written informed consent before any study procedures and in accordance with the local laws and regulations.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. Novartis is committed to sharing with qualified external researchers, access to patient-level data, and supporting the clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. The availability of this trial data is according to the criteria and process described on www.clinicalstudydatarequest.com.

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