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Optimising iron chelation therapy with deferasirox for non-transfusion-dependent thalassaemia patients: 1-year results from the THETIS study

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ABSTRACT

Efficacy and safety of iron chelation therapy with deferasirox in iron-overloaded non-transfusion-dependent thalassaemia (NTDT) patients were established in the THALASSA study. THETIS, an open-label, single-arm, multicentre, Phase IV study, added to this evidence by investigating earlier dose escalation by baseline liver iron concentration (LIC) (week 4: escalation according to baseline LIC; week 24: adjustment according to LIC response, maximum 30 mg/kg/day). The primary efficacy endpoint was absolute change in LIC from baseline to week 52. 134 iron-overloaded non-transfusion-dependent anaemia patients were enrolled and received deferasirox starting at 10 mg/kg/day. Mean actual dose ± SD over 1 year was 14.70 ± 5.48 mg/kg/day. At week 52, mean LIC ± SD decreased significantly from 15.13 ± 10.72 mg Fe/g dw at baseline to 8.46 ± 6.25 mg Fe/g dw (absolute change from baseline, −6.68 ± 7.02 mg Fe/g dw [95% CI: −7.91, −5.45]; $P < 0.0001$). Most common drug-related adverse events were gastrointestinal: abdominal discomfort, diarrhoea and nausea (n = 6 each). There was one death (pneumonia, not considered drug related). With significant and clinically relevant reductions in iron burden alongside a safety profile similar to that in THALASSA, these data support earlier escalation with higher deferasirox doses in iron-overloaded non-transfusion-dependent anaemia patients.

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1. Introduction

Non-transfusion-dependent thalassaemia (NTDT) describes a group of inherited genetic disorders that affect haemoglobin (Hb) chain synthesis, leading to ineffective erythropoiesis and anaemia [1–4]. NTDT comprises several thalassaemia syndromes that do not require regular blood transfusions for survival (transfusions may be required in some instances, such as pregnancy, infection or growth failure), most commonly including β thalassaemia intermedia, Hb H disease and Hb E/β thalassaemia [5]. Despite infrequent blood transfusions, patients with NTDT are at risk of iron overload mainly because of increased iron uptake from the gastrointestinal tract [6,7], as a result of ineffective erythropoiesis, accompanied by anaemia and hypoxia [8]. While the

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; ANC, absolute neutrophil count; CI, confidence interval; CrCl, creatinine clearance; dw, dry weight; Hb, haemoglobin; LIC, liver iron concentration; LOCF, last observation carried forward; MRI, magnetic resonance imaging; NTDT, non-transfusion-dependent thalassaemia; SAE, serious AE; SCr, serum creatinine; SD, standard deviation; SE, standard error; TDT, transfusion-dependent thalassaemia; ULN, upper limit of normal; UPCR, urine protein/urine creatinine ratio.

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phenotypic spectrum in NTDT varies widely, the clinical sequelae of iron overload and elevated liver iron concentration (LIC) in NTDT is similar to patients with transfusion-dependent thalassaemia (TDT), including abnormal liver function, fibrosis and cirrhosis, as well as endocrine disorders [9–12].

Clinical studies have provided evidence for the efficacy and safety of iron chelation therapy in NTDT patients with iron overload [13–19]. The THALASSA study was the first randomised, placebo-controlled study demonstrating the efficacy and safety of deferasirox (Exjade®, Novartis Pharmaceuticals) in a large cohort of NTDT patients [19–22]. In the 1-year THALASSA study, deferasirox was initiated at doses of 5 and 10 mg/kg/day and increased to 10 and 20 mg/kg/day at month 6. Deferasirox 10 mg/kg/day demonstrated significantly improved efficacy over the 5 mg/kg/day regimen in reducing LIC, and nearly half of all patients required dose escalations up to 20 mg/kg/day. These findings indicated that a higher chelation dose may be required and should be initiated earlier in the course of treatment to achieve a more rapid reduction in iron burden. Both deferasirox starting doses and placebo groups had a similar safety profile and incidence of adverse events (AEs) [19]. Based on these outcomes, the Thalassaemia International Federation guidelines recommend iron chelation therapy with deferasirox in NTDT patients ≥10 years of age when LIC reaches ≥5 mg Fe/g dw (or serum ferritin ≥800 ng/mL), starting at 10 mg/kg/day. After 6 months of treatment, the dose may be escalated to 20 mg/kg/day in patients with LIC >7 mg Fe/g dw (or serum ferritin levels 1500–2000 ng/mL if LIC measurement is unavailable) and <15% reduction in baseline values [23].

Here we report 1-year data from the THETIS study, a Phase IV, open-label, multicentre efficacy and safety study of deferasirox in iron-overloaded patients with NTDT. This study adds to existing knowledge by assessing a broader patient population through allowing inclusion of patients with non-transfusion-dependent congenital or chronic anaemias in addition to the non-transfusion-dependent thalassaemias also studied in THALASSA (β thalassaemia intermedia, Hb E/β thalassaemia or α thalassaemia intermedia [Hb H] disease), concomitant medications commonly used in the treatment of NTDT syndromes, and by investigating earlier dose escalation according to baseline LIC and every 6 months according to LIC.

2. Methods

2.1. Key inclusion/exclusion criteria

Patients ≥10 years of age with non-transfusion-dependent congenital or chronic anaemias and iron overload (LIC measured by R2 magnetic resonance imaging [MRI] ≥5 mg Fe/g dw) and serum ferritin ≥300 ng/mL at screening were recruited. Ancillary treatments for NTDT, such as hydroxyurea, were allowed. Exclusion criteria included: blood transfusions within 6 months of study enrolment or anticipated regular transfusions (unplanned transfusions were allowed), Hb S variants of thalassaemia, active hepatitis B or C, cirrhosis, history of clinically relevant ocular and/or auditory toxicity related to iron chelation therapy, or on two consecutive measurements: alanine aminotransferase (ALT) > 5× the upper limit of normal (ULN), serum creatinine (SCr) > ULN, creatinine clearance (CrCl) ≤ 40 mL/min, or urine protein/urine creatinine ratio (UPCR) > 1.0 mg/mg. Paediatric patients had to weigh at least 20 kg. Patients (or parents/guardians) provided written, informed consent prior to enrolment.

2.2. Study design

THETIS is an open-label, single-arm, multicentre, Phase IV, 5-year study with the primary endpoint after 52 weeks of treatment. The starting deferasirox dose was 10 mg/kg/day, with dose increases permitted at week 4 (maximum dose of 20 mg/kg/day) and week 24 (maximum dose of 30 mg/kg/day; Fig. 1), selected based on the results from the THALASSA study. Dose decreases according to safety assessments were performed in increments of 5 mg/kg/day to a minimum of 5 mg/kg/day. If repeated serum ferritin levels were <300 ng/mL or LIC < 3 mg Fe/g dry weight (dw) at any visit, treatment was suspended, then restarted at the previous effective dose (maximum 10 mg/kg/day) when serum ferritin increased to ≥300 ng/mL and LIC to ≥5 mg Fe/g dw. The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki and was approved by independent ethics committees at participating sites.

2.3. Assessments

The primary endpoint was the absolute change in LIC (mg Fe/g dw) from baseline to 52 weeks, supported by analyses of the proportion of patients with an absolute LIC reduction of at least 3 mg Fe/g dw or relative reduction of ≥30%. Secondary endpoints included mean absolute change in LIC from baseline to 24 weeks, change in serum ferritin from baseline to 52 weeks, and correlation of LIC with serum ferritin at baseline and week 52.

LIC was assessed at screening, week 24 and week 52 using validated R2 MRI (FerriScan®) [24]. Serum ferritin was measured at screening, on day 1 and every 4 weeks thereafter. LIC and serum ferritin were analysed at a central laboratory.

Safety was evaluated by regular monitoring and recording of AEs and serious AEs (SAEs), laboratory testing and clinical evaluations. Compliance was estimated based on the prescribed versus dose taken, calculated using the dose administration record.

2.4. Statistical evaluations

Assuming a standard deviation of 6 mg Fe/g dw and drop-out rate of 20%, a sample size of 117 patients was calculated to obtain 90% power to detect an absolute change in LIC of ≥2 mg Fe/g dw from baseline to week 52, using a two-sided paired t-test with 5% significance level. The primary efficacy analysis utilised the full analysis set (all patients assigned study drug). If no LIC measurement was available at week 52, the last available post-baseline LIC measurement before week 52 was used (last observation carried forward [LOCF]). The null hypothesis (change from baseline to week 52 equal to 0) was tested against the alternative hypothesis. LIC change from baseline to week 24 and serum ferritin change from baseline to week 52 were analysed as secondary objectives. Correlation analyses were performed for paired LIC and serum ferritin values.

3. Results

3.1. Patient demographics and clinical characteristics

A total of 134 patients enrolled between 6 December 2012 and 22 November 2013; 112 (83.6%) completed 1 year of treatment. Patients discontinued treatment because of withdrawal of consent (n = 10, noted as personal or logistical reasons), loss to follow-up (n = 4), pregnancy (n = 4) and other reasons (death, AE, protocol deviation and patient decision, n = 1 each). The majority of patients received prior intermittent transfusion therapy (85.8%) and had elevated baseline mean LIC ± standard deviation (SD) and median serum ferritin levels; 47.8% of patients received prior chelation therapy (Table 1).

3.2. Exposure to treatment and compliance

The mean actual deferasirox dose ± SD received during the 1-year study (considering dose adjustments) was 14.70 ± 5.48 mg/kg/day over a mean duration of 11.57 ± 2.68 months. Over 1 year, 124 (92.5%) patients received dose adjustments according to the protocol, including restarts (n = 53, 39.6%), to achieve LIC < 3 mg Fe/g dw (n = 15, 11.2%) and serum ferritin < 300 ng/mL (n = 10, 7.5%). AEs

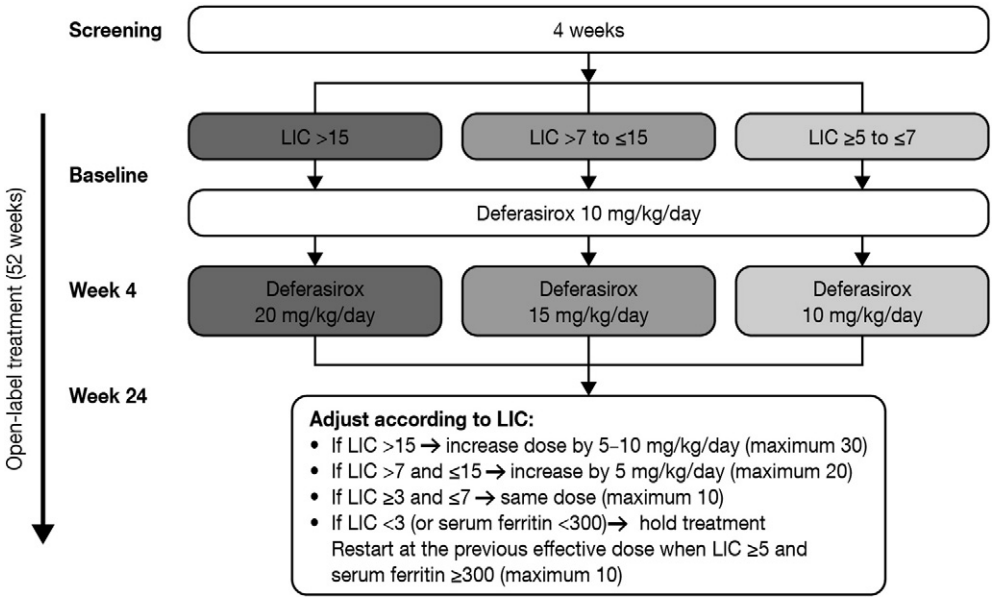


Fig. 1. Deferasirox dosing algorithm. LIC is measured in mg Fe/g dw; deferasirox dose is measured in mg/kg/day; serum ferritin is measured in ng/mL. dw, dry weight; LIC, liver iron concentration.

Table 1
Patient demographic, disease and baseline characteristics.

Variable	All patients (N = 134)
Disease, n (%)	
β thalassaemia intermedia	69 (51.5)
Hb H disease[a]	40 (29.9)
Hb E/β thalassaemia	24 (17.9)
Congenital dyserythropoietic anaemia	1 (0.7)
Mean age ± SD, years	28.0 ± 11.1
Median age (range), years	27 (10–63)
Paediatric patients (10–<18 years), n (%)	25 (18.7)
Male:female, n	76:58
Race, n (%)	
Asian	85 (63.4)
Caucasian	47 (35.1)
Other	2 (1.5)
Splenectomy, n (%)	77 (57.5)
Prior transfusions received, n (%)	115 (85.8)
Previous chelation, n (%)	64 (47.8)
Deferoxamine	18 (13.4)
Deferiprone	17 (12.7)
Deferasirox	29 (21.6)
Mean LIC ± SD	15.13 ± 10.72
Median LIC (range)	11.35 (5.0–50.5)
LIC category, n (%)	
5–≤7	36 (26.9)
>7–≤15	49 (36.6)
>15	49 (36.6)
Mean serum ferritin ± SD	1427 ± 1118
Median serum ferritin (range)	1001 (232–6638)
Serum ferritin category, n (%)	
<300	1 (0.7)[b]
≥300–≤500	17 (12.7)
>500–≤1000	49 (36.6)
>1000–≤2500	51 (38.1)
>2500–≤5000	14 (10.4)
>5000	2 (1.5)

LIC is measured in mg Fe/g dw; serum ferritin is measured in ng/mL.
dw, dry weight; Hb, haemoglobin; LIC, liver iron concentration; SD, standard deviation.
[a] Hb H Constant Spring ($-^{SEA}/\alpha^{CS}\alpha$; n = 7), Homozygous Hb Constant Spring ($\alpha^{CS}\alpha/\alpha^{CS}\alpha$; n = 2), deletional Hb H ($-^{SEA}/-\alpha^{4.2}$; n = 1), triple alpha gene deletion (n = 1), +861 G–A (n = 1), $-/-\alpha^{3.7}$ (n = 1), genotype unknown (n = 27).
[b] This patient was ineligible for inclusion, removed from the study and considered a protocol deviation.

accounted for dose adjustments or drug interruptions in 30 (22.4%) patients; the principal causes were diarrhoea (n = 6, 4.5%) and vomiting (n = 5, 3.7%). The dose was increased at week 24 in 48 (38.7%) patients, reduced in 30 (24.2%) patients and interrupted in two (1.6%) patients. Between week 24 and week 52, dose increases were required in six (5.4%) patients, 32 (28.8%) had dose reductions and 19 (17.1%) received interruptions as per protocol. Overall, 22 (17.7%) and 10 (9.0%) patients received the maximum daily dose of 30 mg/kg/day at week 24 and week 52, respectively. Compliance with medication was high, with 97.1% of the planned doses taken.

3.3. Transfusions

The majority of patients did not receive transfusions during the study (n = 112, 83.6%); seven (5.2%), five (3.7%), four (3.0%), one (0.7%) and five (3.7%) patients received 1, 2, 3, 4 and >4 transfusions, respectively.

3.4. Efficacy of deferasirox

Mean LIC ± SD decreased significantly from 15.13 ± 10.72 mg Fe/g dw at baseline to 8.46 ± 6.25 mg Fe/g dw at week 52 (absolute change from baseline, −6.68 ± 7.02 mg Fe/g dw [95% confidence interval (CI): −7.91, −5.45]; $P < 0.0001$). This is equivalent to a change in total body iron of approximately −0.18 mg/kg/day, based on a formula [25] that accounts for iron accumulation in untreated NTDT patients [19]. At the last assessment, an absolute decrease in LIC of ≥3 mg Fe/g dw was observed in 86 (64.2%) patients, while a ≥30% relative reduction in LIC was observed in 81 (60.4%) patients. There was a markedly greater absolute reduction in mean LIC at both week 24 and week 52 in patients with higher baseline LIC (≥15 mg Fe/g dw), with patients receiving a higher mean actual deferasirox dose (Table 2). Data by serum ferritin subgroups ≥300–500, >500–1000 and >1000 ng/mL are shown in Supplementary Table 1. Overall, the majority of patients moved to a lower iron burden category by week 52 (66.9%; Table 3), with 15 patients (12.7%) achieving LIC < 3 mg Fe/g dw; as such, treatment was suspended.

Median serum ferritin (range) decreased from 1001 (232–6638) ng/mL at baseline to 669 (200–4315) ng/mL at week 52 (absolute

Table 2
Change in LIC by baseline LIC at week 24 and week 52.

	Baseline LIC		
Mean ± SD	5–≤7 (n=36)	>7–≤15 (n=49)	>15 (n = 49)
Baseline LIC	6.06 ± 0.55	10.37 ± 2.46	26.56 ± 9.68
Week 24 LIC	4.90 ± 1.67	7.63 ± 3.06	19.97 ± 8.95
Week 24 absolute change in LIC	−1.18 ± 1.53	−2.77 ± 2.11	−6.28 ± 4.53
Change in total body iron*	−0.02	−0.07	−0.17
Deferasirox dose over 24 weeks	9.66 ± 0.82	13.26 ± 1.30	17.34 ± 1.79
Week 52 LIC	4.25 ± 1.63	5.72 ± 2.80	13.48 ± 7.23
Week 52 absolute change in LIC	−1.82 ± 1.60	−4.49 ± 2.17	−13.64 ± 8.09
Change in total body iron*	−0.04	−0.12	−0.39
Deferasirox dose over 52 weeks	8.95 ± 1.87	13.37 ± 2.90	20.27 ± 3.72

LIC is measured in mg Fe/g dw; deferasirox dose and change in total body iron are measured in mg/kg/day.
Patients included had a value at baseline and at the considered time point. Week 24 and 52 data are based on the last available LIC during days 2–198 and days 199–378, respectively.
dw, dry weight; LIC, liver iron concentration; SD, standard deviation.
[a] Estimated based on a formula [25] that took into account the mean rate of iron accumulation in placebo-treated NTDT patients [19].

median change of −304 [−5307 to −1669] ng/mL). The absolute reduction in both LIC and serum ferritin was progressive over the course of the study across all baseline LIC categories (Fig. 2A and B). There was a moderate correlation between LIC and serum ferritin at baseline (r = 0.730; Supplementary Fig. 1A) and at week 52 (r = 0.634; Supplementary Fig. 1B). There was also a moderate correlation between absolute changes in serum ferritin and LIC (r = 0.694; Fig. 3A), indicating a reduction in both LIC and serum ferritin in the majority of patients. A strong correlation was identified between change in LIC and baseline LIC (r = −0.844; Fig. 3B).

3.5. Safety parameters

3.5.1. Adverse events

Investigator-reported AEs regardless of causality were reported in 97 (72.4%) patients and were unaffected by average daily dose received. AEs with a suspected relationship to deferasirox were reported in 42 (31.3%) patients and were predominantly gastrointestinal (Table 4). Overall, during deferasirox treatment, eight patients received concomitant hydroxyurea.

One patient was reported with a suspected SAE (pancreatitis) related to study drug that lasted for 11 days; deferasirox was withheld for the duration of this AE and then restarted. One patient discontinued treatment because of an AE (extramedullary haematopoiesis), although a relationship to deferasirox was not suspected. One death occurred during the study as a result of pneumonia leading to cardiac failure; this was not suspected to be related to study drug.

At week 52, three patients (baseline LICs of 30.1, 28.5 and 6.8 mg Fe/g dw), with unspecified clinically insignificant audiological abnormalities detected during screening, developed clinically

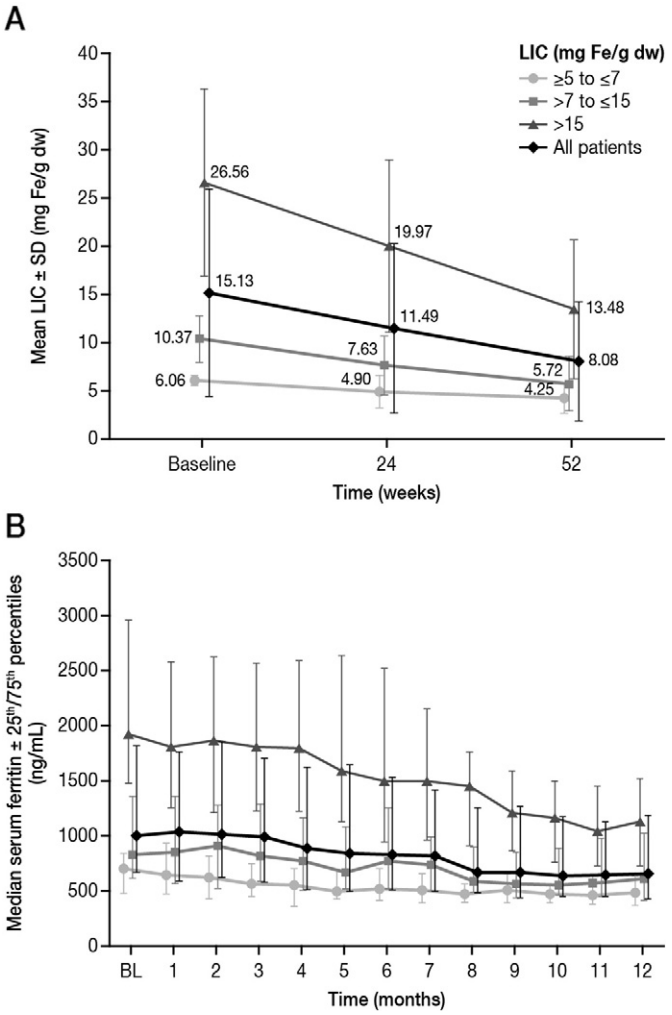


Fig. 2. LIC and serum ferritin assessments over time by baseline LIC categories. A) Mean LIC ± SD; B) median serum ferritin ± 25th/75th percentiles. Patients included had a value at baseline and at the considered time point. Week 24 and 52 LIC data are based on the last available LIC during days 2–198 and days 199–378, respectively. dw, dry weight; LIC, liver iron concentration; SD, standard deviation.

Table 3
Changes in iron overload status between baseline and week 52.

		Week 52 LIC				
Baseline LIC	n (%)	<3, n (%)	3–<5, n (%)	5–7, n (%)	>7–15, n (%)	>15, n (%)
n (%)		15 (12.7)	32 (27.1)	21 (17.8)	35 (29.7)	15 (12.7)
5–7	32 (27.1)	**9 (28.1)**	**12 (37.5)**	9 (28.1)	2 (6.3)	0
>7–15	44 (37.3)	**5 (11.4)**	**18 (40.9)**	**8 (18.2)**	13 (29.5)	0
>15	42 (35.6)	**1 (2.4)**	**2 (4.8)**	**4 (9.5)**	**20 (47.6)**	15 (35.7)

LIC is measured in mg Fe/g dw.
Bold indicates patients who moved to a lower iron burden range. Patients included had a value at baseline and week 52 (last available LIC during days 199–378).
dw, dry weight; LIC, liver iron concentration.

significant audiological abnormalities noted as moderate sensorineural hearing loss, moderate conductive hearing loss, and sensorineural hearing loss, respectively. At week 52, these patients were receiving deferasirox doses of 30, 25 and 10 mg/kg/day and LIC had changed to 12.5, 34.3 and 5.5 mg Fe/g dw, respectively. The first two cases were reported as AEs of special interest and as related to deferasirox. In the patient with sensorineural hearing loss (not suspected to be related to deferasirox), large cupping and mild cortical cataract were also reported, both of which were suspected to be related to deferasirox.

3.5.2. Laboratory parameters

One patient had an elevated baseline ALT 2 × ULN that increased to >5 × ULN on one occasion; baseline bilirubin levels were 2 × ULN and alkaline phosphatase 1.5 × ULN. Without dose adjustment or interruption, all parameters improved better than baseline values by week 52. No patient had two consecutive serum creatinine increases of >33% above baseline and >ULN. Two consecutive CrCl measurements <60 mL/min were recorded in three patients, all with baseline levels >60 mL/min. Of these three, two patients continued treatment without dose adjustment and at week 52, CrCl was >60 mL/min in one patient and remained <60 mL/min in the other. The third patient's dose was decreased from 30 to 20 mg/kg/day and at week 52, CrCl was >60 mL/min. UPCR increased to >1.0 mg/mg on two consecutive measurements in

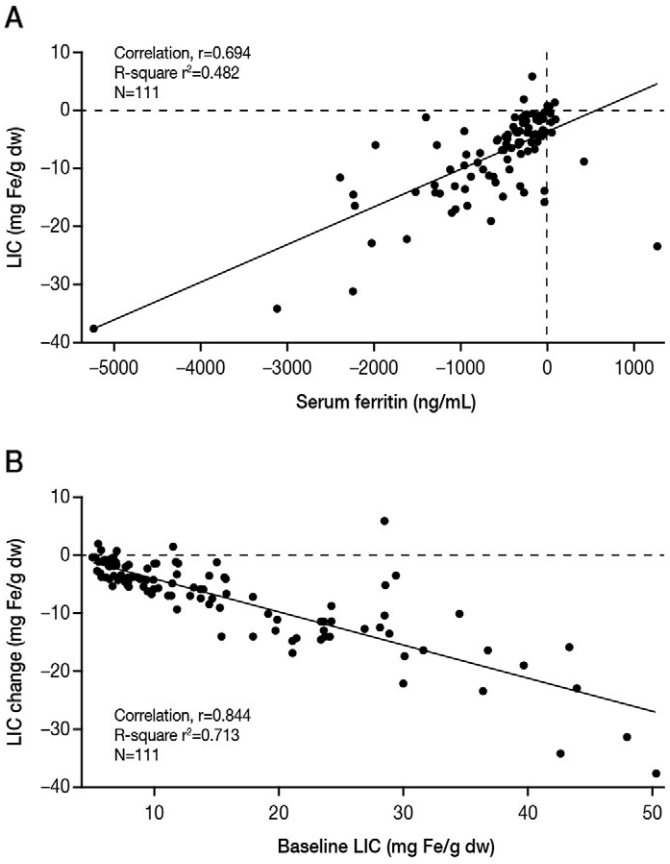


Fig. 3. Relationship between change in LIC versus A) change in serum ferritin at week 52 and B) baseline LIC. dw, dry weight; LIC, liver iron concentration.

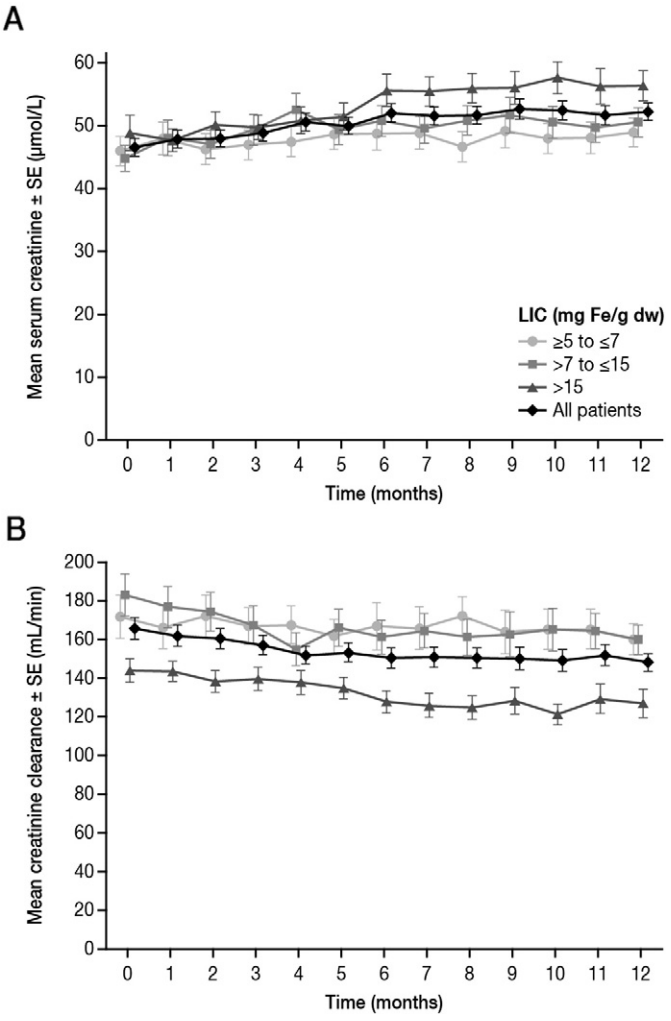


Fig. 4. Serum creatinine and creatinine clearance over time by baseline LIC category. A) Mean serum creatinine ± SE; B) mean creatinine clearance ± SE. dw, dry weight; LIC, liver iron concentration; SE, standard error.

one patient receiving deferasirox at 10 mg/kg/day. Treatment was interrupted for 2 weeks, and UPCR decreased to ≤1.0 mg/mg. Treatment was restarted at 10 mg/kg/day, and UPCR remained stable. Although remaining within the normal range, there was a trend for increasing SCr and declining CrCl over time (Fig. 4A and B). Analysis by age group indicated that patients <18 years old had twice the increase in the last available SCr measurements and a four-fold decrease in the last available CrCl; there was also high intervariability from month to month. There was no discernible relationship between baseline LIC categories and increases in SCr or decreases in CrCl. Mean aminotransferase elevations showed a decreasing trend over time and there were no progressive changes in UPCR (Supplementary Fig. 2). No patient with notable renal or liver laboratory values discontinued treatment.

Overall, 23 patients (17.2%) had notable reductions in absolute neutrophil count (ANC: $<1.5 \times 10^9$/L after baseline); ANC was >1.0 to $<1.5 \times 10^9$/L after baseline in 16 of these patients (eight of whom had post-baseline infections), none had ANC $<0.5 \times 10^9$/L and three had ANC $< 1.5 \times 10^9$/L at baseline. None of the infections represented a new safety signal. There were no episodes of drug-induced neutropenia, agranulocytosis or thrombocytopenia. Nine patients (6.7%) had notable reductions in platelet count ($<100 \times 10^9$/L after baseline; range $63–99 \times 10^9$/L).

Table 4
Most common (≥2 patients) investigator-assessed drug-related AEs.

AE, preferred term, n (%)	All patients (N = 134)
Abdominal discomfort	6 (4.5)
Diarrhoea	6 (4.5)
Nausea	6 (4.5)
Abdominal pain	5 (3.7)
Upper abdominal pain	5 (3.7)
Dyspepsia	3 (2.2)
Rash	3 (2.2)
Increased blood creatinine	2 (1.5)
Insomnia	2 (1.5)
Increased UPCR	2 (1.5)
Vomiting	2 (1.5)

Note: A patient with multiple occurrences of the same event is counted only once.
AE, adverse event; UPCR, urine protein/urine creatinine ratio.

4. Discussion

The 1-year analysis from THETIS provides further evidence to support the efficacy and safety of initiating deferasirox 10 mg/kg/day, escalating earlier at week 4 according to baseline LIC to a maximum of 20 mg/kg/day, then up to a maximum of 30 mg/kg/day according to LIC response at week 24 and every 6 months thereafter. This dosing regimen was selected based on the results from the THALASSA study, which indicated improved efficacy of 10 mg/kg/day as a starting dose, escalated to 20 mg/kg/day to significantly reduce LIC and serum ferritin [19]. Hence, patients with a higher baseline and ongoing iron burden received correspondingly higher deferasirox doses. Treatment was administered to patients with LIC ≥ 5 mg Fe/g dw, the threshold above which there is a greater risk of iron-overload-related complications [10,11,23]. Treatment was withheld if LIC was <3 mg Fe/g dw or repeated serum ferritin levels were <300 ng/mL, in order to reduce the risk of over-chelation at normal body iron levels. The primary endpoint was

met by demonstrating a significant absolute reduction in LIC from baseline to week 52 ($P < 0.0001$), equivalent to a decrease in total body iron of approximately 0.18 mg/kg/day. The absolute change in LIC from baseline was strongly correlated with baseline LIC. The largest reductions in LIC occurred in patients with greater iron overload at baseline, who had also received higher average deferasirox doses. Furthermore, absolute LIC reduction of ≥3 mg Fe/g dw or relative reduction of ≥30% were observed in approximately 60% of patients.

Despite some differences in patient demographics and baseline iron overload, with an earlier dose escalation and higher deferasirox doses permitted in THETIS, the absolute reduction in LIC and serum ferritin at week 52 was greater than that in THALASSA [19]. In THETIS, more patients achieved LIC <3 mg Fe/g dw, mainly in patients with a lower baseline LIC. However, it can be speculated that more patients will achieve this therapeutic target, irrespective of baseline LIC, on optimised treatment as the study continues. Although doses up to 30 mg/kg/day were permitted, most patients required the maximum dose for a relatively short time before being titrated down.

Prior to the study, the majority of patients received intermittent transfusions, which contributed to the development of iron loading in combination with underlying ineffective erythropoiesis associated with non-transfusion-dependent congenital and chronic anaemias. With the known associations between iron overload and morbidity in NTDT patients [10,11], the need for guidance in optimising chelation therapy is apparent. These data support earlier dose escalation following initiation of treatment, followed by further optimisation based on response to chelation therapy as assessed by LIC. LIC assessment by MRI is robust and recommended for the assessment of iron overload in NTDT patients [23]. Results from THETIS and other published studies [26–29] indicate a positive correlation between serum ferritin and LIC in patients with NTDT, though with variable strengths of association. THETIS also demonstrated that this correlation is maintained during treatment with deferasirox. However, serum ferritin trends should not be used to make treatment decisions when MRI analysis is available.

Safety data from THETIS were similar to safety findings in THALASSA [19]. Despite higher deferasirox doses and use of concomitant treatments, such as hydroxyurea, no new safety signals were identified. Investigator-assessed drug-related AEs were predominantly gastrointestinal, as previously observed in both NTDT [19] and TDT [30] patients treated with deferasirox. Although the majority of dose reductions were a result of AEs, the incidence of drug-related AEs (31.3%) was similar to that observed in THALASSA (24.1%) [19] and considerably lower than that reported in TDT patients (50.3%) [30]. The absence of progressive changes over 1 year in renal and hepatic laboratory parameters was consistent with previous observations [19], and there was a decreasing trend in aminotransferases over time. Although remaining within normal limits, the slight trend of worsening SCr and CrCl over 1 year may be a result of growth of paediatric patients with increasing muscle mass who had notably increased SCr and correspondingly decreased CrCl at the last available measurement in this 1-year study.

In conclusion, deferasirox effectively reduced iron overload in NTDT patients at a starting dose of 10 mg/kg/day, with dose escalations from week 4 according to baseline LIC and further dose adjustments up to 30 mg/kg/day according to LIC response. These findings will help to guide physicians in optimising iron chelation therapy with deferasirox in NTDT patients based on continuous monitoring with either LIC or serum ferritin and to inform updates to treatment guidelines. The THETIS trial is ongoing to provide long-term follow-up of NTDT patients for up to 5 years.

Authorship contributions

ATT, MDC, YA and JBP served as investigators in this trial, enrolling patients, and as Study Steering Committee members, overseeing the conduct of the trial from study design to analysis planning and data interpretation. Y-RL, ZK, VV, NS and AK served as investigators in this trial, enrolling patients; Y-RL contributed substantially to patient recruitment. CW, VJ and MJU contributed to the analysis, interpretation and reporting of the trial data. ZZ served as the trial statistician. All authors contributed to data interpretation, reviewed and provided their comments on this manuscript, and approved the final version.

Conflicts of interest

ATT reports receiving honoraria for participating in advisory boards for Novartis Pharmaceuticals; YA reports receiving research funding from Novartis Pharmaceuticals and being a member of an advisory committee and participation in a Novartis speakers' bureau; JBP reports participation in advisory boards for Novartis Pharmaceuticals and is supported by the NIHR University College London Hospitals Biomedical Research Centre; ZK reports receiving research grants and speaker's honoraria from Novartis Pharmaceuticals; VV reports receiving research grant support and lecture fees from Novartis Pharmaceuticals and research grant support from FerroKin Biosciences, Shire and Faculty of Medicine Siriraj Hospital, Thailand; NS reports receiving research funding from Novartis Pharmaceuticals; AK reports receiving honoraria and research funding from Novartis Pharmaceuticals and participating in a speakers' bureau; CW, VJ, MJU and ZZ are full-time employees of Novartis Pharmaceuticals; MDC reports receiving honoraria for participating in advisory boards for Novartis Pharmaceuticals and Genzyme. Y-RL has no relevant conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.bcmd.2015.11.002.

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