Impact of long-term luspatercept treatment on iron parameters in patients with transfusion-dependent and non-transfusion-dependent β-thalassemia: results from the phase 3b long-term follow-up study

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Introduction

- Iron overload is a common complication of chronic anemia and ineffective erythropoiesis among patients with transfusion-dependent β-thalassemia (TDT) and non-transfusion-dependent β-thalassemia (NTDT)[1]
  - For patients with TDT, the need for regular red blood cell (RBC) transfusions leads to iron overload, whereas in patients with NTDT, iron overload results from enhanced intestinal absorption of iron even in the absence of regular RBC transfusions[1]
- Long-term treatment with luspatercept has been associated with significant and durable erythroid responses and improvement or stabilization of iron parameters in patients with TDT and NTDT in the BELIEVE (NCT02604433) and BEYOND (NCT03342404) trials, respectively[2,3]
- In both patient populations, data from long-term treatment are important to inform robust characterization of iron outcomes

Objective

- To report long-term iron parameters up to a total of 384 weeks of treatment for patients with TDT and NTDT who received luspatercept in the BELIEVE and BEYOND trials, respectively, and continued treatment in the long-term follow-up (LTFU) study (NCT04064060)

Methods

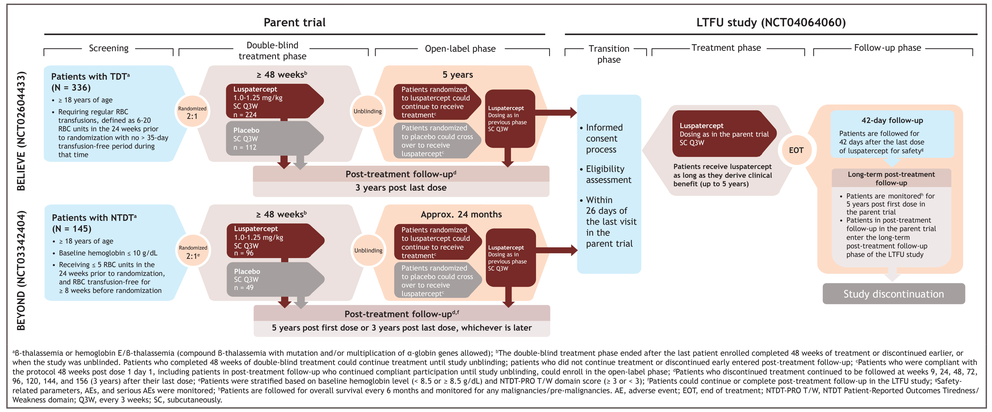
Study design and treatment received

- The LTFU study is a phase 3b, open-label, single-arm, rollover study of patients who participated in luspatercept clinical trials (**Figure 1**)
- This analysis includes patients with TDT from the BELIEVE trial and patients with NTDT from the BEYOND trial who were receiving luspatercept treatment at the time of rollover to the LTFU study and who, in the opinion of the investigator, continued to experience clinical benefit
  - Patients could continue to receive luspatercept in the LTFU study at the same dose and schedule as at the end of the parent trial for as long as they continued to demonstrate clinical benefit and did not experience unacceptable toxicities up to a maximum of 5 years
- Data cutoff dates for this analysis were January 28, 2025, for patients from the BELIEVE trial and November 8, 2024, for patients from the BEYOND trial

Assessments

- Evaluation of iron parameters included liver iron concentration (LIC; derived from T2*, R2*, or R2 magnetic resonance imaging [MRI]), serum ferritin (mean per 24 weeks), and myocardial iron level assessment (by T2* MRI)
- Treatment timing was defined from initiation of luspatercept treatment in the parent trial (baseline)
- Baseline serum ferritin values were calculated as the mean values during the 12 weeks prior to first dose for patients in the BELIEVE trial or the mean values during the 24 weeks on or prior to the first dose for patients in the BEYOND trial
- Baseline LIC and cardiac T2* levels were calculated at the last assessment on or before the first dose in the parent trial

Figure 1. BELIEVE, BEYOND, and LTFU study designs



[a]β-thalassemia or hemoglobin E/β-thalassemia (compound β-thalassemia with mutation and/or multiplication of α-globin genes allowed); [b]The double-blind treatment phase ended after the last patient enrolled completed 48 weeks of treatment or discontinued earlier, or when the study was unblinded. Patients who completed 48 weeks of double-blind treatment could continue treatment until study unblinding; patients who did not continue treatment or discontinued early entered post-treatment follow-up; [c]Patients who were compliant with the protocol 48 weeks post dose 1 day 1, including patients in post-treatment follow-up who continued complaint participation until study unblinding, could enroll in the open-label phase; [d]Patients who discontinued treatment continued to be followed at weeks 9, 24, 48, 72, 96, 120, 144, and 156 (3 years) after their last dose; [e]Patients were stratified based on baseline hemoglobin level (< 8.5 or ≥ 8.5 g/dL) and NTDT-PRO T/W domain score (≥ 3 or < 3); [f]Patients could continue or complete post-treatment follow-up in the LTFU study; †Safety-related parameters, AEs, and serious AEs were monitored; ‡Patients are followed for overall survival every 6 months and monitored for any malignancies/pre-malignancies. AE, adverse event; EOT, end of treatment; NTDT-PRO T/W, NTDT Patient-Reported Outcomes Tiredness/Weakness domain; Q3W, every 3 weeks; SC, subcutaneously.

Results

The BELIEVE trial

Patient population

- Of the 224 patients with TDT in the luspatercept group of the BELIEVE trial, 127 (56.7%) transitioned to the LTFU study to continue treatment
- Baseline characteristics for patients in the luspatercept group of the BELIEVE trial are shown in **Table 1**
  - Most (99.6%) patients received concomitant ICT
  - The majority (166/194; 85.6%) of evaluable patients had a cardiac T2* level > 20 ms at baseline
- Median treatment duration at data cutoff was 229.1 weeks (range, 1.7-438.3)

Table 1. Baseline characteristics of patients with TDT from the BELIEVE trial[4]

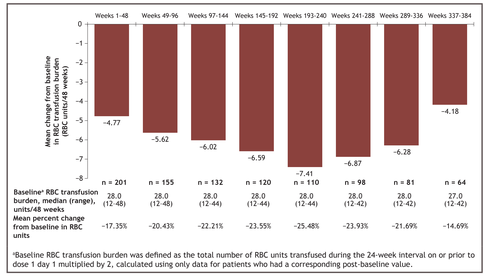
Characteristic	Luspatercept (N = 224)
Age, median (range), years	30 (18-66)
Female, n (%)	132 (58.9)
Race, n (%)	
Asian	81 (36.2)
White	122 (54.5)
Other[a]	21 (9.4)
Diagnosis, n (%)	
β-thalassemia	174 (77.7)
Hemoglobin E/β-thalassemia	31 (13.8)
β-thalassemia with α-thalassemia	18 (8.0)
Missing	1 (0.4)
Transfusion burden, median (range), RBC units/48 weeks	28 (12-48)
Pretransfusion hemoglobin level (24 weeks), median (range), g/dL	9.3 (4.5-11.4)
LIC, median (range), mg/g dw	6.1 (0.8-125.0)
Serum ferritin level, median (range), µg/L	1441.3 (88.0-6400.0)
Cardiac T2* level, median (range), ms	34.7 (3.0-205.9)
Received concomitant ICT, n (%)[b]	222 (99.6)

[a]Includes Black or African American (n = 1), Other (n = 15), and Not collected/reported (n = 5); [b]Safety population, N = 223. dw, dry weight. ICT, iron chelation therapy.

RBC transfusion burden

- Patients from the BELIEVE trial experienced a mean change from baseline in RBC transfusion burden of −6.28 RBC units/48 weeks in weeks 289-336 and −4.18 units/48 weeks in weeks 337-384 (**Figure 2**)

Figure 2. Mean change from baseline in RBC transfusion burden among patients with TDT

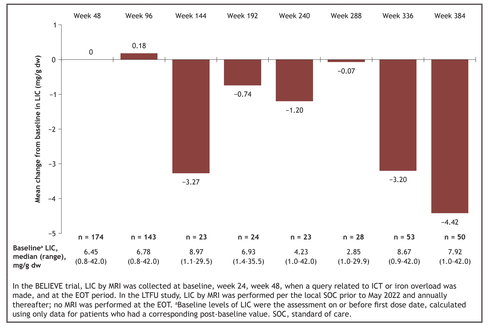


[a]Baseline RBC transfusion burden was defined as the total number of RBC units transfused during the 24-week interval on or prior to dose 1 day 1 multiplied by 2, calculated using only data for patients who had a corresponding post-baseline value.

Iron parameters

- Patients experienced a mean change in LIC from baseline of −3.20 mg/g dw (n = 53) at week 336 and −4.42 mg/g dw (n = 50) at week 384 (**Figure 3**)

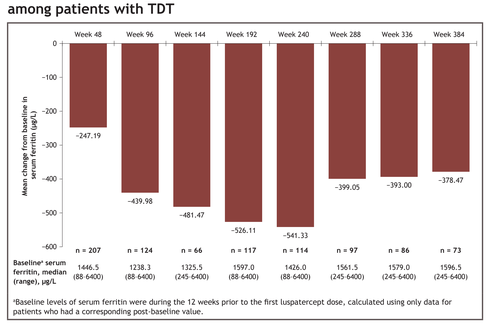
Figure 3. Mean change from baseline in LIC among patients with TDT



In the BELIEVE trial, LIC by MRI was collected at baseline, week 24, week 48, when a query related to ICT or iron overload was made, and at the EOT period. In the LTFU study, LIC by MRI was performed per the local SOC prior to May 2022 and annually thereafter; no MRI was performed at the EOT. [a]Baseline levels of LIC were the assessment on or before first dose date, calculated using only data for patients who had a corresponding post-baseline value. SOC, standard of care.

- Patients also experienced decreases in serum ferritin with mean changes of −393.00 µg/L (n = 86) and −378.47 µg/L (n = 73) at week 336 and week 384, respectively (**Figure 4**)

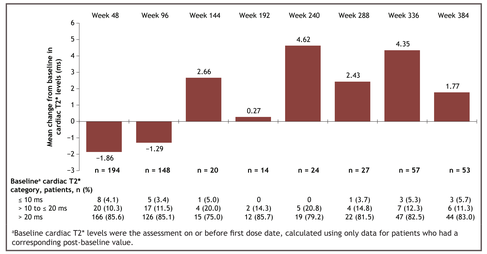
Figure 4. Mean change from baseline in mean serum ferritin level among patients with TDT



[a]Baseline levels of serum ferritin were during the 12 weeks prior to the first luspatercept dose, calculated using only data for patients who had a corresponding post-baseline value.

- Mean change in cardiac T2* levels versus baseline are shown in **Figure 5**
- Cardiac T2* levels remained > 20 ms with luspatercept treatment for 44 of 47 (93.6%) patients at week 336 and for 38 of 44 (86.4%) patients at week 384
  - Shifts from ≤ 20 ms at baseline to > 20 ms at week 336 and week 384 were experienced by 8 and 7 patients, respectively

Figure 5. Mean change from baseline in cardiac T2* levels among patients with TDT



[a]Baseline cardiac T2* levels were the assessment on or before first dose date, calculated using only data for patients who had a corresponding post-baseline value.

The BEYOND trial

Patient population

- Of the 96 patients with NTDT in the luspatercept group of the BEYOND trial, 65 (67.7%) transitioned to the LTFU study and continued treatment
- Baseline characteristics for patients in the luspatercept group of the BEYOND trial are shown in **Table 2**

Table 2. Baseline characteristics of patients with NTDT from the BEYOND trial[5]

Characteristic	Luspatercept (N = 96)
Age, median (range), years	39.5 (18.0-71.0)
Female, n (%)	56 (58.3)
Race, n (%)	
Asian	31 (32.3)
White	59 (61.5)
Other	6 (6.3)
Diagnosis, n (%)	
β-thalassemia	63 (65.6)
Hemoglobin E/β-thalassemia	28 (29.2)
β-thalassemia with α-thalassemia	5 (5.2)
Transfusion burden, median (range), RBC units/24 weeks	0 (0-4.0)
Hemoglobin level (4 weeks),[a] median (range), g/dL	8.2 (5.3-10.1)
LIC, median (range),[b] mg/g dw	3.9 (0.8-39.9)
Serum ferritin level, median (range), µg/L	456.5 (30.0-3528.0)
Received ICT at baseline,[c] n (%)	28 (29.2)

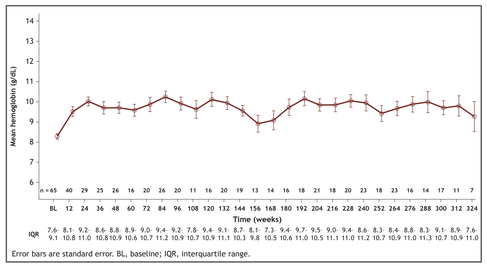
[a]Mean of ≥ 2 hemoglobin values during the 28-day screening period; [b]n = 95; [c]Defined as receiving ICT during the 24 weeks on or prior to the first dose of luspatercept.

- Of the 65 patients who continued treatment in the LTFU study, 17 were receiving ICT at baseline (defined as receipt during the 24 weeks on or prior to the first luspatercept dose)
  - Of these 17 patients, 6 (35.3%) stopped receiving ICT while in the BEYOND or LTFU studies
- In total, 31 of 65 patients received ICT during their entire trial participation and 34 of 65 did not receive ICT at any point
- Median treatment duration with luspatercept was 313.9 weeks (range, 223.3-345.0)

Hemoglobin level

- Mean hemoglobin levels increased from baseline and subsequently remained above baseline with long-term luspatercept treatment throughout the evaluation period (**Figure 6**)

Figure 6. Mean hemoglobin over time among patients with NTDT

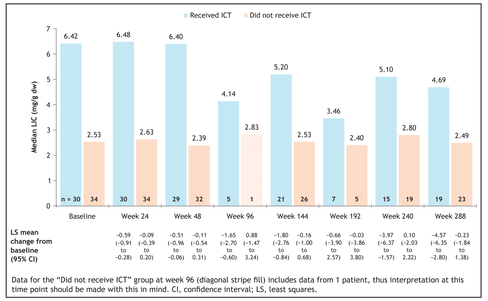


Error bars are standard error. BL, baseline; IQR, interquartile range.

Iron parameters

- LIC among patients who received ICT was reduced at week 288 compared with baseline, and was similar to baseline for patients who did not receive ICT (**Figure 7**)

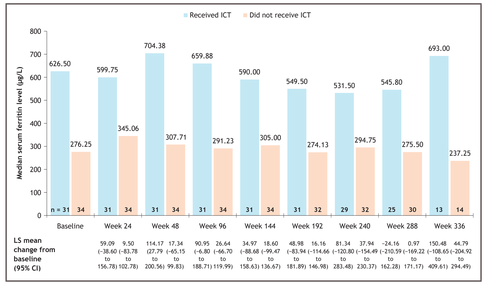
Figure 7. Median LIC among patients with NTDT



Data for the "Did not receive ICT" group at week 96 (diagonal stripe fill) includes data from 1 patient, thus interpretation at this time point should be made with this in mind. CI, confidence interval; LS, least squares.

- No clinically significant changes in serum ferritin levels were observed at week 336 compared with baseline regardless of ICT status (**Figure 8**)

Figure 8. Median serum ferritin level among patients with NTDT



Conclusions

- Results from the phase 3b LTFU study suggest that patients with TDT who receive long-term luspatercept treatment experience durable reductions from baseline in RBC transfusion burden, LIC, and serum ferritin levels, as well as stable cardiac iron markers
- Among patients with NTDT treated with luspatercept, LIC decreased from baseline for those who received ICT while it remained stable for those who did not receive ICT
  - No clinically significant changes in serum ferritin levels were observed among patients with NTDT who were treated with luspatercept regardless of ICT status
- Overall, these data suggest that long-term luspatercept treatment of patients with TDT and NTDT is associated with durable clinical benefit, including control of liver iron

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