Revisiting erythroid response in the phase 3 BELIEVE trial of luspatercept in patients with transfusion-dependent ß-thalassemia using real-world criteria

1139

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Introduction

- In the phase 3, randomized, double-blind, placebo-controlled BELIEVE trial (NCT02604433), significantly more patients with transfusion-dependent (TD) ß-thalassemia achieved an erythroid response with luspatercept (21.4%) versus placebo (4.5%)[1]
  - Erythroid response was defined as ≥ 33% reduction in red blood cell (RBC) transfusion burden (TB) from baseline plus a reduction of ≥ 2 RBC units in weeks 13–24
- Additional clinically meaningful benefits, such as increased depth of TB reduction with continued treatment or responses beyond 24 weeks, as well as improvement or maintenance of pretransfusion hemoglobin (Hb) level,[1-3] have been reported
- To allow for more practical evaluation of response to luspatercept in clinical practice, a revised framework for response evaluation was proposed[4]
- Retrospective application of this response framework to a large cohort of patients with TD ß-thalassemia highlighted its utility in evaluating the real-world benefit of luspatercept[5]

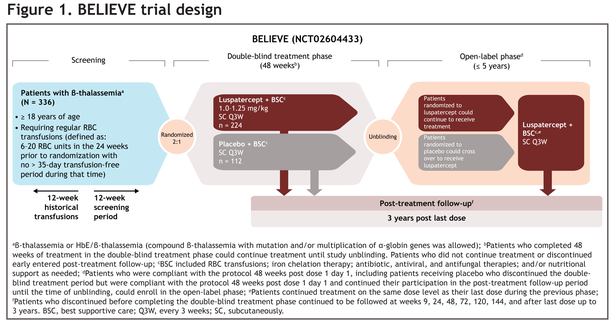
Objective

- To recategorize erythroid response among patients with TD ß-thalassemia in the BELIEVE trial using a revised framework for response evaluation reflective of real-world clinical benefit

Methods

- This post hoc study reanalyzed erythroid response data from the BELIEVE trial (**Figure 1**) (cutoff date: Jan 5, 2021) using a modified version of the revised framework[4] (**Figure 2**)
  - Patients who did not meet these response criteria were considered to have no response
  - Patients could meet more than 1 criterion per response category
  - Baseline TB was defined as the total number of RBC units transfused in the 12 weeks prior to or on dose 1 day 1 of BELIEVE
  - Baseline pretransfusion Hb level was defined as the mean level in the 24 weeks prior to dose 1 day 1
- Modifications to the original criteria[4] were made to align with the BELIEVE trial protocol, including the following:
  - Additional requirement for reduction of ≥ 2 RBC units concomitant with decreased RBC TB for excellent and good responses
  - Consideration of RBC-TI ≥ 12 weeks as excellent response, given that patients in the BELIEVE trial were required to be TD (6–20 RBC units/24 weeks) and have no ≥ 35-day transfusion-free period before randomization
  - Omission of quality of life requirements for excellent response, due to difficulty in standardizing assessment of subjective improvements in a trial setting
- Odds ratios (ORs), *P* values, and 95% confidence intervals (CIs) were estimated using unstratified Cochran-Mantel-Haenszel test

Figure 1. BELIEVE trial design



[a]ß-thalassemia or HbE/ß-thalassemia (compound ß-thalassemia with mutation and/or multiplication of α-globin genes was allowed); [b]Patients who completed 48 weeks of treatment in the double-blind treatment phase could continue treatment until study unblinding. Patients who did not continue treatment or discontinued early entered post-treatment follow-up; [c]BSC included RBC transfusions; iron chelation therapy; antibiotic, antiviral, and antifungal therapies; and/or nutritional support as needed; [d]Patients who were compliant with the protocol 48 weeks post dose 1 day 1, including patients receiving placebo who discontinued the double-blind treatment period but were compliant with the protocol 48 weeks post dose 1 day 1 and continued their participation in the post-treatment follow-up period until the time of unblinding, could enroll in the open-label phase; [e]Patients continued treatment on the same dose level as their last dose during the previous phase; [f]Patients who discontinued before completing the double-blind treatment phase continued to be followed at weeks 9, 24, 48, 72, 120, 144, and after last dose up to 3 years. BSC, best supportive care; Q3W, every 3 weeks; SC, subcutaneously.

Figure 2. Criteria for achieving erythroid response

	Excellent	Good	Satisfactory
Musallam et al. criteria[4]	• ≥ 50% TB reduction within 6 months of therapy with same or better pretransfusion Hb level • ≥ 2 g/dL increase in previously suboptimal pretransfusion Hb level with same or lower TB • Any TB reduction or increase in pretransfusion Hb level within 6 months of therapy concomitant with notable improvement in quality of life	• ≥ 33% TB reduction within 6 months of therapy with same or better pretransfusion Hb level • ≥ 1 g/dL increase in previously suboptimal pretransfusion Hb level with same or lower TB	• Any TB reduction within 6 months of therapy with same or better pretransfusion Hb level
Modified criteria applied to BELIEVE[5]	• **Criterion E1:** ≥ 50% TB reduction, reduction of ≥ 2 RBC units, and same or better Hb level over the same period • **Criterion E2:** ≥ 2 g/dL increase in Hb level, and same or lower TB over the same period • **Criterion E3:** achievement of RBC-TI for ≥ 12 weeks	• **Criterion G1:** ≥ 33% TB reduction, reduction of ≥ 2 RBC units, and same or better Hb level over the same period • **Criterion G2:** ≥ 1 g/dL increase in Hb level, and same or lower TB over the same period	• Any TB reduction with same or better Hb level over the same period

[a]Response categories were defined considering changes from baseline in RBC TB and pretransfusion Hb level over rolling 12-week periods during weeks 1-24 and weeks 1-48 of BELIEVE. TI, transfusion independence.

Results

- This analysis included 224 patients randomized to luspatercept and 112 randomized to placebo in the BELIEVE trial (**Table 1**)
- When recategorized based on the modified response criteria, a greater proportion of patients in the luspatercept group had an excellent or good erythroid response when compared with placebo in weeks 1–24 and 1–48 (**Figure 3**)
  - Subsequent analyses focused on excellent and good responses, as these were considered more clinically meaningful
- Most patients met criterion E1 when achieving an excellent response with luspatercept in weeks 1–24 (44/224) and weeks 1–48 (60/224) (**Figure 4**)
- Similar proportions of patients in either arm who achieved a good response met either of the 2 response criteria (**Figure 5**)

Table 1. Baseline characteristics of patients in the BELIEVE trial[1]

Characteristic	Luspatercept (N = 224)	Placebo (N = 112)
Age, median (range), years	30.0 (18-66)	30.0 (18-59)
Sex, female, n (%)	132 (58.9)	63 (56.3)
Race, n (%)		
Asian	81 (36.2)	36 (32.1)
White	122 (54.5)	60 (53.6)
Other[a]	21 (9.4)	16 (14.3)
Diagnosis, n (%)		
ß-thalassemia	174 (77.7)	83 (74.1)
HbE/ß-thalassemia	31 (13.8)	21 (18.8)
ß-thalassemia combined with α-thalassemia	18 (8.0)	8 (7.1)
Missing	1 (0.4)	0
TB, median (range), RBC units/12 weeks[b]	6.12 (3.0-14.0)	6.27 (3.0-12.0)
Pretransfusion Hb level (24 week), median (range), g/dL	9.31 (4.5-11.4)	9.15 (5.8-11.7)
Splenectomy, n (%)	129 (57.6)	65 (58.0)

Percentages may not sum to 100 due to rounding. [a]Includes Black or African American (n = 1 luspatercept vs n = 0 placebo), Other (n = 15 vs n = 11), and Not collected/reported (n = 5 each); [b]12-week run-in data (week −12 to day 1).

Figure 3. Recategorized responses among patients in the BELIEVE trial in weeks 1-24 and weeks 1-48

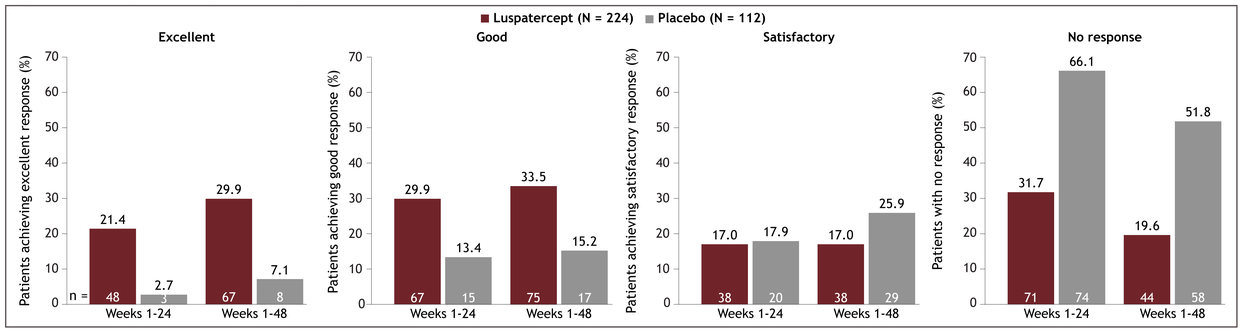
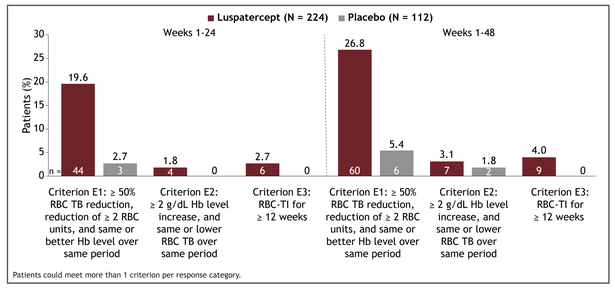
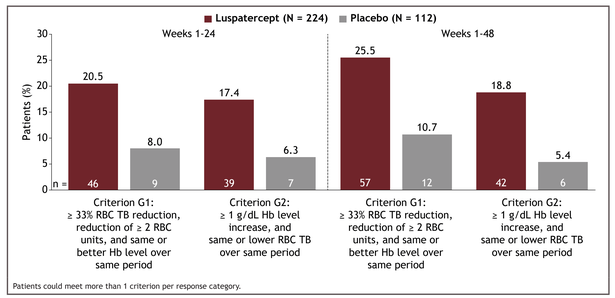


Figure 4. Individual criteria met for patients achieving excellent response in weeks 1-24 and weeks 1-48 of BELIEVE



Patients could meet more than 1 criterion per response category.

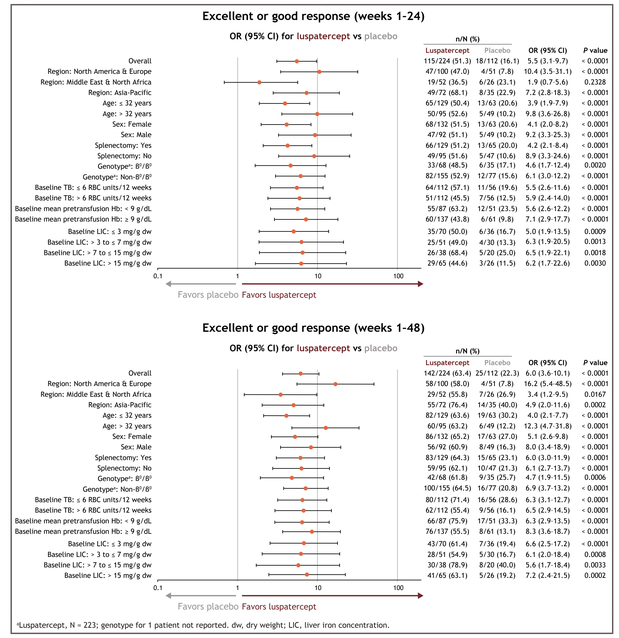
Figure 5. Individual criteria met for patients achieving good response in weeks 1-24 and weeks 1-48 of BELIEVE



Patients could meet more than 1 criterion per response category.

- Overall, and across subgroups, the odds of achieving an excellent response alone (overall: luspatercept vs placebo OR [95% CI], weeks 1-24, 9.9 [3.0-32.6]; weeks 1-48, 5.5 [2.6-12.0]), or an excellent or good response (**Figure 6**) were higher with luspatercept versus placebo in both weeks 1–24 and weeks 1–48
  - Excellent or good response rates with luspatercept were similar and significantly higher than with placebo at both time points in the genotype subgroups
    - The proportion of patients with a B^0/B^0 genotype who achieved excellent response increased with longer treatment (14.7% during weeks 1–24 vs 25.0% during weeks 1–48)
  - Significantly more patients with prior splenectomy than without achieved excellent response with luspatercept in both weeks 1–24 (24.8% vs 16.8%) and weeks 1–48 (36.4% vs 21.1%), although response rates were similar when considering excellent and good response together

Figure 6. Achievement of response by subgroup



[a]Luspatercept, N = 223; genotype for 1 patient not reported. dw, dry weight; LIC, liver iron concentration.

Conclusions

- In this post hoc analysis from the BELIEVE trial, recategorization of erythroid responses based on modified real-world criteria showed higher response rates for patients treated with luspatercept versus placebo, consistent with the original trial results[1]
- It has been reported that some patients in BELIEVE experienced delayed responses[2,3]; consistent with this, achievement of excellent or good response with luspatercept increased between weeks 1-24 and 1-48, suggesting that longer treatment may be warranted
  - Delayed response could be influenced by suboptimal dosing or protocol-mandated dose delays, which were required in the event of pretreatment Hb levels ≥ 11.5 g/dL or an increase in Hb level of > 2 g/dL[1]
- The framework used here provides a practical approach for evaluating luspatercept treatment in routine clinical practice, especially in regions where pretransfusion Hb levels are suboptimal, and may better reflect the spectrum of response and increase understanding of patient benefit

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Acknowledgments

- The patients and families who made this study possible
- The clinical study teams who participated
- The study was supported by Celgene, a Bristol-Myers Squibb Company, in collaboration with Acceleron Pharma Inc., a wholly-owned subsidiary of Merck & Co., Inc., Rahway, NJ, USA
- All authors contributed to and approved the presentation; writing and editorial assistance were provided by Breann Yanagisawa, PhD, of Excerpta Medica, funded by Bristol Myers Squibb

Presented at the American Society of Hematology (ASH) Annual Meeting; December 6-9, 2025; Orlando, FL, USA.