



Health-related quality of life in patients with β -thalassemia: Data from the phase 3 BELIEVE trial of luspatercept

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Abstract

Background: Patients with transfusion-dependent (TD) β -thalassemia require long-term red blood cell transfusions (RBCTs) that lead to iron overload, impacting health-related quality of life (HRQoL).

Methods: The impact of luspatercept, a first-in-class erythroid maturation agent, versus placebo on HRQoL of patients with TD β -thalassemia was evaluated in the phase 3 BELIEVE trial. HRQoL was assessed at baseline and every 12 weeks using the 36-item Short Form Health Survey (SF-36) and Transfusion-dependent Quality of Life questionnaire (TranQoL). Mean change in HRQoL was evaluated from baseline to week 48 for patients receiving luspatercept + best supportive care (BSC) and placebo + BSC and between luspatercept responders and non-responders.

Results: Through week 48, for both groups, mean scores on SF-36 and TranQoL domains were stable over time and did not have a clinically meaningful change. At week 48, more patients who achieved clinical response ($\geq 50\%$ reduction in RBCT burden over 24 weeks) in the luspatercept + BSC group had improvement in SF-36 Physical Function compared with placebo + BSC (27.1% vs. 11.5%; $p = .019$).

Conclusions: Luspatercept + BSC reduced transfusion burden while maintaining patients' HRQoL. HRQoL domain improvements from baseline through 48 weeks were also enhanced for luspatercept responders.

KEYWORDS

beta-thalassemia, iron overload, quality of life

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Funding information

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Novelty statement**What is the new aspect of your work?**

The phase 3 BELIEVE study showed that luspatercept, a first-in-class erythroid maturation agent that enhances late-stage erythropoiesis, is effective in reducing red blood cell transfusion (RBCT) burden; however, the impact of luspatercept on health-related quality of life (HRQoL) has not yet been reported.

What is the central finding of your work?

We found that luspatercept reduced transfusion burden while maintaining patients' HRQoL with improvements observed from baseline through 48 weeks for patients attaining a clinical response to luspatercept.

What is (or could be) the specific clinical relevance of your work?

Our study suggests that luspatercept may offer a treatment option that reduces RBCT burden while maintaining the quality of life of patients with transfusion-dependent β -thalassemia.

1 | INTRODUCTION

Beta (β)-thalassemia is an inherited blood disorder caused by a reduction or absence of β -globin chains that leads to alpha (α)/ β -globin chain imbalance and ineffective erythropoiesis.^{1,2} Patients with β -thalassemia experience anemia, which may or may not require regular red blood cell transfusions (RBCTs), depending on the severity of anemia.¹ Patients with transfusion-dependent (TD) β -thalassemia typically present at a young age and require frequent RBCTs to maintain hemoglobin (Hb) levels.^{2,3} Although the use of RBCTs can provide short-term relief from the symptoms of anemia, long-term receipt of RBCTs can lead to iron overload, which is toxic to many tissues and can cause complications such as heart failure, cirrhosis, liver cancer, growth retardation, and endocrine abnormalities.^{1,2} Many patients, therefore, receive iron chelation therapy to prevent iron overload. While recent advances in iron chelation therapy, from infusional to oral formulations, have improved adherence, there are still challenges associated with iron chelation therapy, and reducing RBCT burden can potentially prevent iron overload.^{4,5}

The effects of anemia and fatigue, together with the effects of treatment regimens (i.e., RBCTs and iron chelation therapy) can have a considerable impact on the health-related quality of life (HRQoL) of patients with β -thalassemia. Adults with TD β -thalassemia have been found to have worse physical, emotional, and social functioning HRQoL scores compared with the general population.^{6–8} Anxiety/depression and perceived barriers to treatment, including the difficulties and expenses associated with ongoing treatment, are significant negative predictors of HRQoL among adults with TD β -thalassemia.⁹ The supply of red blood cells needed for RBCTs and the availability of transfusions are often limited, and only a proportion of those in need may receive RBCTs, exacerbating their clinical and HRQoL burden.^{10,11} Patients report a high burden from their transfusion regimen related to lack of blood availability, fear of adverse events, and negative impact on their employment.¹²

Increases in life expectancy observed over the past few decades have highlighted the need for improvements in HRQoL as working-age adults face particular challenges related to employment, higher education, and mental health issues.⁸ As such, there is a need to reduce RBCT burden while maintaining or improving HRQoL for these patients.

Luspatercept is a first-in-class erythroid maturation agent that enhances late-stage erythropoiesis.¹³ Luspatercept has been approved by the US Food and Drug Administration and European Medicines Agency for the treatment of anemia due to β -thalassemia in adult patients who require regular RBCTs. The phase 3 BELIEVE study (NCT02604433) showed that luspatercept is effective in reducing RBCT burden,¹⁴ but the impact of luspatercept on HRQoL has not yet been evaluated. This analysis of the BELIEVE study aimed to assess the effect of luspatercept + best supportive care (BSC) versus placebo + BSC on HRQoL using the generic 36-item Short Form Health Survey (SF-36) and the disease-specific Transfusion-dependent Quality of Life questionnaire (TranQoL).^{15,16}

2 | METHODS

2.1 | Study design

The BELIEVE study (NCT02604433) was a phase 3, double-blind, randomized, placebo-controlled, multicenter study to determine the efficacy and safety of luspatercept (ACE-536) + BSC versus placebo + BSC in adult patients (≥ 18 years of age) who required regular RBCTs (6 to 20 units of packed red blood cells with no transfusion-free period of >35 days within 24 weeks of randomization) due to β -thalassemia as described previously.¹⁴ The study was conducted at 65 sites in 15 countries across Australia, Europe, Middle East, North Africa, North America, and Southeast Asia. Patients were randomized in a 2:1 ratio to receive either luspatercept (starting dose of 1.0 mg/kg with titration up to 1.25 mg/kg every 3 weeks) or placebo,



subcutaneously for ≥ 48 weeks + BSC, which included RBCTs and iron chelation therapy as needed.¹⁴ HRQoL, a secondary endpoint of the BELIEVE study, was assessed at baseline (≤ 4 weeks prior to first study dose), every 12 weeks up to 48 weeks of treatment, and every 12 weeks during the long-term treatment period beyond 49 weeks.

2.2 | HRQoL assessments

HRQoL was evaluated using the TranQoL and SF-36 questionnaires. The TranQoL questionnaire includes the domains Physical Health, Emotional Health, Sexual Activity, Family Functioning, and School/Career Functioning, with scores ranging from 0 to 100 for each domain. In addition, a TranQoL total score was calculated as follows:

$$100 \times \left(1 - \frac{\text{Sum of valid responses}}{\text{Total number of valid responses} \times 4} \right).$$

Higher scores denote better HRQoL in all domains and in total score. The TranQoL has been demonstrated to have good validity, reliability, and responsiveness in β -thalassemia.^{15,16}

The SF-36 questionnaire consists of eight domains: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Mental Health, Role-Emotional, and Social Functioning. To obtain domain scores, raw scores from each domain of the SF-36 were transformed to 0–100-point scales, which were then normalized using T-score transformation with a mean of 50 and standard deviation (SD) of 10 in order to facilitate interpretation in the context of other populations and published norms. T-score allows comparisons across different SF-36 scales since each scale has the same average score and standard deviation (50 ± 10). Without referring to published norms, this method makes it clear that whenever an individual respondent's scale score is below 45, or a group mean scale score is below 47, the implication is that health status is below the average range. Then, composites of these domain scores were used to form the two-component summary scales, Physical Component Summary and Mental Component Summary. For domains and component summary scales, higher T-scores indicate better HRQoL.

2.3 | Endpoints

As the primary HRQoL endpoint, differences in mean change in TranQoL and SF-36 total and domain scores from baseline to week 48 were evaluated between and within treatment groups. There were five primary domains of interest, two for the TranQoL (total score and Physical Health) and three for SF-36 (Physical Component Summary, Physical Functioning, and General Health). TranQoL Total Score is a summary measure of the overall HRQoL of the target population. TranQoL Physical Health and SF-36 Physical Functioning domains were considered to be anemia-related concepts, and the SF-36 Physical Component Summary domain is a summary measure of overall HRQoL and considered to be related to anemia symptoms. The SF-36 General Health domain was the only domain where patients with TDT have been shown to have scores

noticeably worse than the general population.¹⁷ For the SF-36 Mental Health domain, patients with TDT have been shown to have scores comparable with the general population.¹⁷ Therefore, the SF-36 Mental Health domain was not included as a primary domain of interest.

As the secondary HRQoL endpoints, the proportion of patients experiencing a clinically meaningful improvement in HRQoL scores were assessed at week 48 and differences in mean change in HRQoL over time were compared between clinical responders and non-responders to luspatercept.

2.4 | Population

The data cutoff for these HRQoL analyses was July 1, 2019. Two sets of study populations were created for the analyses: (1) the intent-to-treat (ITT) population, which included all patients who were randomized in the study, and (2) the HRQoL-evaluable population. The disposition of randomized participants in the BELIEVE trial has been detailed previously.¹⁴ The HRQoL-evaluable population included all patients who completed the HRQoL assessment at baseline and completed ≥ 1 post-baseline assessment visit. The TranQoL was considered complete if $\geq 75\%$ of items were answered at a given time point. SF-36 was considered complete if $\geq 50\%$ of items were answered at a given time point.

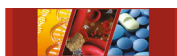
2.5 | Statistical analyses

P values estimated from the analyses were considered descriptive (i.e., non-inferential) as there was no formal hypothesis testing since the study was not powered to detect between-group differences in HRQoL endpoints, and unadjusted for multiplicity. Continuous variables are summarized using mean and SD, while categorical variables are summarized with frequency and percentage. A one-sample, two-sided, paired *t*-test was used to assess the within-group change from baseline; a pooled two-sample, two-sided *t*-test was used to assess between-group differences in the observed mean change from baseline.

Summary statistics were used to report observed changes from baseline at each time point as well as between-group differences in mean changes from baseline in HRQoL measures.

In analyses comparing the proportion of patients with a clinical response to luspatercept + BSC who achieved a clinically meaningful improvement in domain scores at week 48 with those receiving placebo + BSC, clinical response to luspatercept was defined in four distinct ways: a $\geq 50\%$ reduction in RBCT burden for any 24 rolling consecutive weeks in the study period; a $\geq 33\%$ reduction in RBCT burden for any 24 rolling consecutive weeks; transfusion independence for any 8 weeks; or transfusion independence for any 12 weeks.

For each SF-36 domain, the ranges of possible T-scores, the minimally important differences (MID; defining the thresholds of a clinically meaningful change between groups), and the responder definitions (RD; which were the individual patients' HRQoL score change, defining the thresholds of a clinically meaningful change within groups) are provided in Table S1.^{15–19}



For the TranQol total score, a within-group clinically meaningful improvement was defined as a ≥ 4 -point improvement from baseline based on the TranQol validation study by Klaassen et al. (2013).²⁰ For TranQol domains, it was defined as $0.5 \times SD$ of the pooled domain score at baseline. Differences between treatment arms were clinically meaningful if the change from baseline between arms exceeded the MID threshold defined as $\geq 0.5 \times SD$ of the pooled domain score at baseline for the TranQol domains and a score of ≥ 4 for the TranQol total score.²¹ No imputation of missing data was performed. In the analysis of treatment response, those with missing post-baseline responses were considered non-responders.

3 | RESULTS

3.1 | Patients

A total of 336 patients were randomized to receive treatment (224 patients receiving luspatercept + BSC; 112 receiving placebo + BSC). The HRQoL-evaluable population ($N = 316$) comprised 212/224 (94.6%) and 104/112 (92.9%) of the ITT patients in the luspatercept + BSC and placebo + BSC arms, respectively (Figure S1). Baseline characteristics were similar between patients receiving luspatercept + BSC and placebo + BSC (Table 1). The mean (SD) liver iron content by magnetic resonance imaging was 12.3 (15.13) mg/g dry weight in the luspatercept group and 10.2 (11.66) mg/g dry weight in the placebo group from the HRQoL-evaluable population; baseline use of iron chelation therapy was not evaluated in the HRQoL-evaluable population. HRQoL questionnaire compliance rates at

baseline were $\geq 99\%$ in both treatment groups for the TranQol and SF-36 questionnaires and were $\geq 87.5\%$ for both questionnaires among patients who were still on treatment at week 48.

3.2 | Mean change from baseline in HRQoL scores

Baseline SF-36 scores among patients with β -thalassemia were similar between treatment groups and similar to the US general population for most domains (Figure 1); however, General Health, Role-Emotional, and Role-Physical domain scores were negatively impaired at baseline in the BELIEVE population. For the domains of interest, mean scores on the SF-36 Physical Component Summary, Physical Functioning, and General Health domains were stable over time and did not reach the MID threshold for patients receiving either luspatercept + BSC or placebo + BSC at any time point through week 48. There was no statistically significant difference in mean changes from baseline to week 48 between and within treatment groups (Figures 2A–C). There was no marked score difference in the TranQol scores between treatment groups at baseline (Figure S2). TranQol total and Physical Health scores remained stable over time in both treatment groups up to week 48 (Figure 3). This was generally maintained in the long-term treatment period through week 96, with no significant difference over time between and within treatment groups, with the exception of the SF-36 General Health domain. Although not significantly different from the luspatercept + BSC group, the placebo + BSC group showed a consistent decline in SF-36 General Health domain scores from baseline, which approached a clinically meaningful deterioration, but with a reduced sample size, by week 84 (Figure 2C).

3.3 | HRQoL by clinical response status

The luspatercept + BSC group had numerically greater proportions of patients with clinically meaningful improvements in all five primary domains of interest at week 48 compared to the placebo + BSC group, although the differences were not statistically significant (Figure S3).

When meaningful improvements in HRQoL were analyzed by clinical response status, numerically greater proportions of luspatercept + BSC responders showed clinically meaningful improvements in all primary domains of interest at week 48 than patients treated with placebo + BSC, across clinical response definitions. None of the primary HRQoL domains were significantly different between luspatercept + BSC non-responders and placebo + BSC across clinical response definitions (Figure 4). Proportions of patients with clinically meaningful improvements in TranQol domains were not statistically significantly different across clinical response analyses, though numerically greater proportions of luspatercept responders achieved meaningful improvements in the TranQol total score across most response criteria (Figure 4).

Within the clinical response definition of $\geq 33\%$ reduction in RBCT burden, 23.6% of luspatercept + BSC responders ($n = 25/106$) and

TABLE 1 Patient baseline characteristics.

Characteristic	Luspatercept + BSC ($n = 212$)	Placebo + BSC ($n = 104$)
Age, mean (SD), year	32.1 (10.8)	31.6 (9.8)
Sex, n (%)		
Male	87 (41.0)	47 (45.2)
Region, n (%)		
North America and Europe	90 (42.5)	47 (45.2)
Middle East and North Africa	51 (24.1)	25 (24.0)
Asia-Pacific	71 (33.5)	32 (30.8)
Baseline transfusion rate		
≤ 6 units/12 weeks	107 (50.5)	52 (50.0)
> 6 units/12 weeks	105 (49.5)	52 (50.0)
Liver iron content by MRI, mg/g dry weight, mean (SD)	12.3 (15.13) $n = 212$	10.2 (11.66) $n = 104$

Abbreviations: BSC, best supportive care; MRI, magnetic resonance imaging; SD, standard deviation.

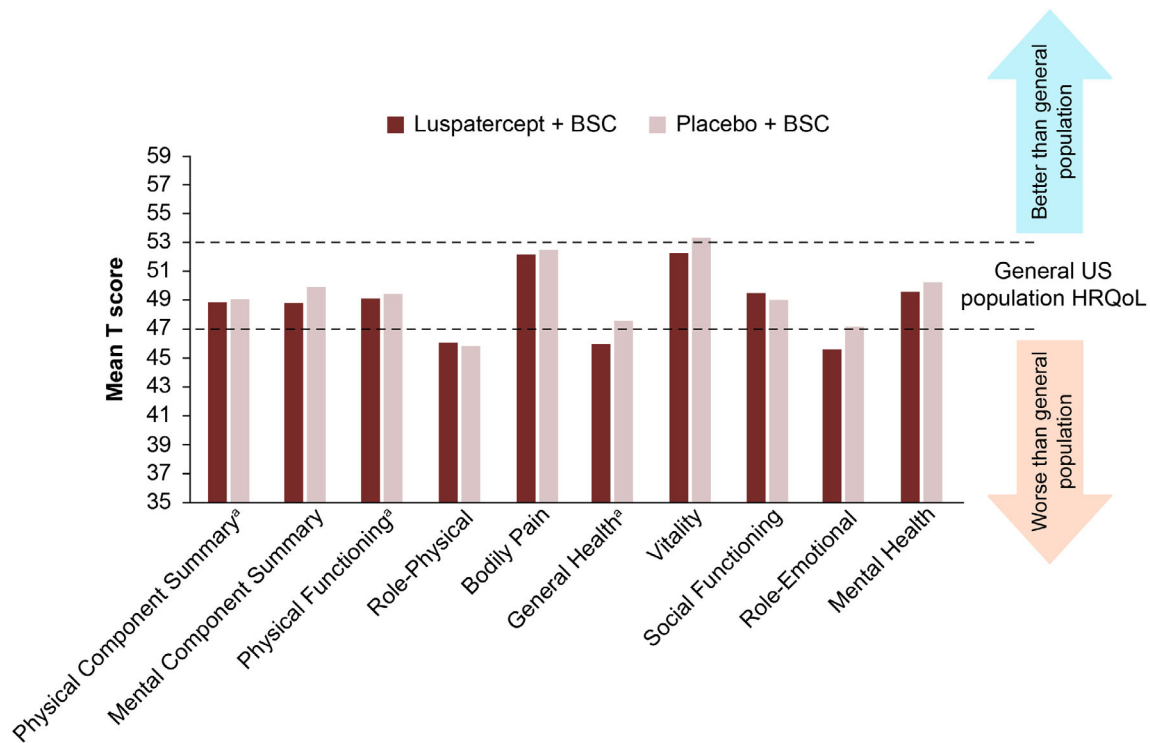


FIGURE 1 Comparison of baseline SF-36 scores in patients with β -thalassemia (HRQoL-evaluable population) to the 2009 US general population.¹⁴ ^aDomain of interest for the present study. BSC, best supportive care; HRQoL, health-related quality of life; SF-36, 36-item Short Form Health Survey.

11.5% of the placebo + BSC group ($n = 12/104$) achieved clinically meaningful improvements in the SF-36 Physical Functioning domain (odds ratio [OR]: 2.37 [95% confidence interval (CI): 1.12–5.01]; $p = .025$) (Figure 4A). In the SF-36 Physical Component Summary domain, 27.4% ($n = 29/106$) and 14.4% ($n = 15/104$) of luspatercept responders and placebo patients, respectively, achieved clinically meaningful improvements (OR: 2.23 [95% CI: 1.12–4.47]; $p = .023$) (Figure 4A). Within the clinical response definition of $\geq 50\%$ reduction in RBC burden, 27.1% of luspatercept + BSC responders ($n = 13/48$) and 11.5% of the placebo + BSC group ($n = 12/104$) achieved clinically meaningful improvements in the SF-36 Physical Functioning domain (OR: 2.85 [95% CI: 1.19–6.84]; $p = .019$) (Figure 4B). The difference in proportions of patients achieving clinically meaningful improvement in the SF-36 Physical Component Summary was in favor of luspatercept + BSC responders versus placebo + BSC at the higher reduction in RBC burden threshold of $\geq 50\%$, but such a difference was not significant (OR: 1.98 [95% CI: 0.84–4.64]; $p = .117$) (Figure 4B).

Within the clinical response criterion of transfusion independence for any 8-week period, greater proportions of luspatercept + BSC responders than patients receiving placebo + BSC achieved clinically meaningful improvements in HRQoL. Differences were significant for the SF-36 Physical Functioning (OR: 5.93 [95% CI: 2.00–17.55]; $p = .002$) and Physical Component Summary domains (OR: 3.68 [95% CI: 1.27–10.70]; $p = .026$) (Figure 4C). Differences were similar in the 12-week transfusion independence criterion but did not reach significance for luspatercept + BSC responders as compared with placebo + BSC (Figure 4D) as the

sample size was very small for the luspatercept + BSC responders ($n = 9$ based on the SF-36).

4 | DISCUSSION

In this analysis of HRQoL from the phase 3 BELIEVE study of luspatercept in patients with β -thalassemia, the addition of luspatercept to BSC reduced transfusion burden while maintaining baseline HRQoL scores over time to week 48 of treatment and continued through the long-term treatment period through week 96. In addition, a greater number of patients who responded to luspatercept + BSC achieved clinically meaningful improvements across all primary domains of interest compared with placebo + BSC, regardless of clinical response criteria examined in the analysis. Such improvements were particularly pronounced in SF-36 Physical Functioning and Physical Component Summary. Furthermore, those patients who did not respond to luspatercept + BSC displayed similar results to placebo + BSC, suggesting luspatercept did not worsen patients' HRQoL.

It is important to note that baseline HRQoL scores in the BELIEVE population were generally comparable with the US general population, leaving little room for improvement, which is consistent with previous reports of patients with β -thalassemia. Sobota et al. (2011) showed HRQoL among adolescents and adults with β -thalassemia were comparable with the US general population.¹⁷ This is likely due to patients having adapted to living with the illness since early age, leading to a change in their internal standards, values, or conceptualization of

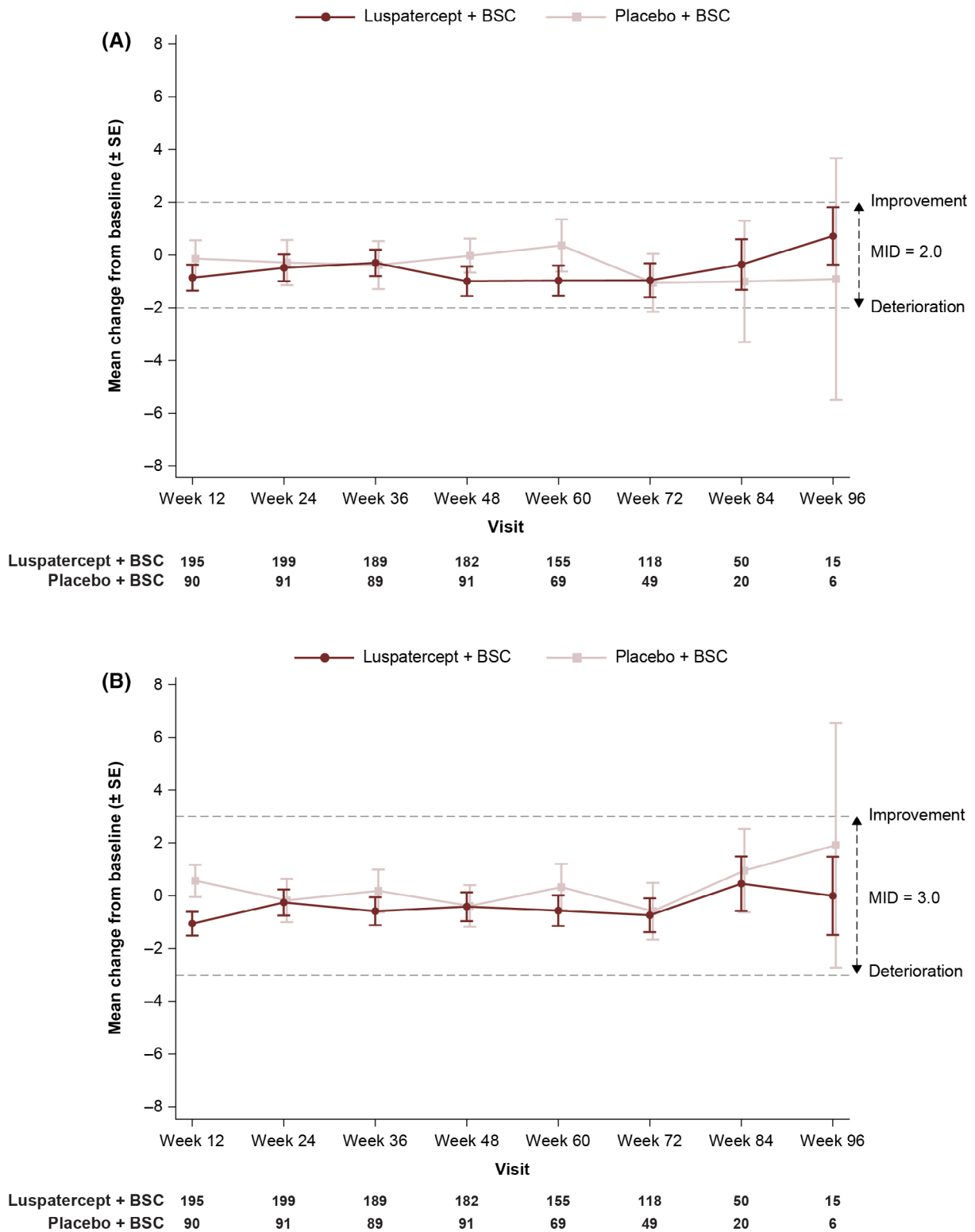


FIGURE 2 SF-36 scores for patients receiving luspatercept + BSC or placebo + BSC. Physical component summary (A), physical functioning (B), and general health (C) domains. Directional indicators of improvement or deterioration of the scores are provided for illustrative purposes; dashed lines indicate the MID thresholds. BSC, best supportive care; MID, minimally important difference; SE, standard error; SF-36, 36-item Short Form Health Survey.

HRQoL. Musallam et al. (2011) also reported that longer durations since diagnosis of β -thalassemia were significantly associated with better mental health.²² Since HRQoL in the BELIEVE population was

generally good (i.e., comparable to the general US population) at the study's entry (based on the SF-36), reducing transfusion burden is less likely to result in substantial improvement in HRQoL, but more likely

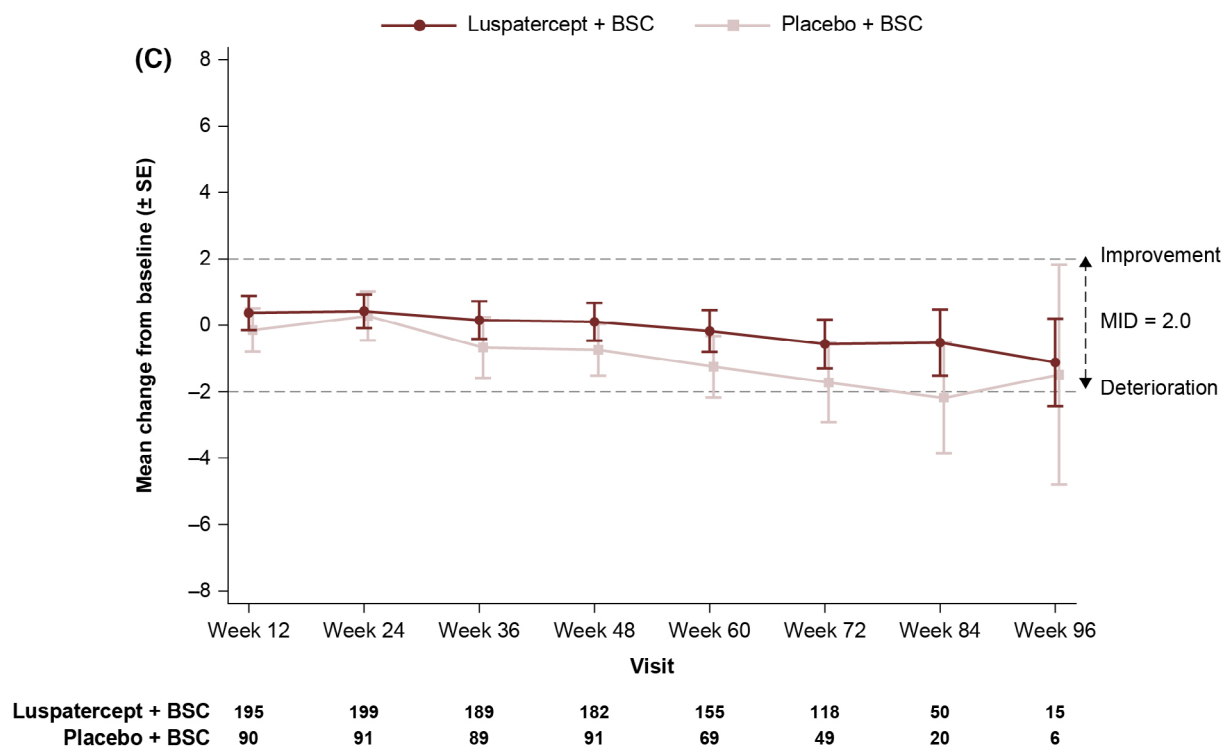
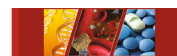


FIGURE 2 (Continued)

to maintain a good level of HRQoL. Ultimately, positive baseline and post-treatment HRQoL scores observed in the BELIEVE study illustrate the humanistic value of lusatercept to reduce RBCT dependence while maintaining patients' HRQoL. It should be noted that Arian et al. (2019) reported worse HRQoL across several domains of the SF-36 in a meta-analysis of 26 cross-sectional and case-control studies of patients with β -thalassemia in the Mediterranean and Middle East as compared with the general populations of Norway and the United Kingdom.²³ However, the Arian meta-analysis did not appear to specify the use of mean scores and/or T-scores in its analysis, which would have important implications for interpretation of HRQoL findings. Both Arian et al. and the baseline lusatercept population in BELIEVE showed worse SF-36 scores for the General Health and Role-Emotional domains among patients with β -thalassemia.²³ The consistency of findings between the Arian meta-analysis and the BELIEVE clinical trial were mixed for other SF-36 domains. While the patient and reference populations, study designs, and settings were different, this point nonetheless underscores the need for continued examination of HRQoL among patients with β -thalassemia as compared with comparable reference populations and in the context of research design and sociocultural factors.

Since BELIEVE patients were allowed to continue to receive RBCTs and iron chelation therapy alongside lusatercept or placebo, this may explain the similar findings between treatment groups, as patients generally have an improvement in anemia-related symptoms following RBCT, thereby alleviating negative effects on HRQoL. In the BELIEVE trial, lusatercept reduced transfusion burden (frequency of RBCTs) but placebo did not.¹⁴ Therefore, the placebo group was likely

to receive a greater RBCT-related HRQoL benefit than patients treated with lusatercept. Participation in the BELIEVE trial, including regular follow-up visits and care, may have also contributed to the instances of positive HRQoL benefits observed in the placebo + BSC group.

Factors reported to be significantly associated with worse HRQoL across multiple domains of the SF-36 among patients with β -thalassemia include older age, greater number of side effects from iron chelation therapy, country of origin, greater number of complications, and Asian race.¹⁷ Multiplicity of complications were also found in another study to be significantly associated with worse physical health.²² This study showed that lusatercept improved clinical outcomes while maintaining HRQoL, which may suggest a meaningful impact of lusatercept on the totality of care. However, a larger difference between treatment arms may have been more evident if a much longer follow-up time was possible, as shown in other studies. Findings from the literature regarding the determinants of HRQoL among the study population seem to suggest that a positive effect on HRQoL for a novel anemic treatment is most likely to occur by reducing or avoiding the use of iron chelation therapy and/or iron overload-related complications as a result of reduction in transfusion burden; studies have shown unloading even half the iron from the liver and heart could take about 6 and 17 months, respectively.^{18,19,24,25} This may suggest that more benefit would take many months to observe and the time frame of the BELIEVE study may be insufficient to show HRQoL benefits gained by the decrease in transfusion burden with lusatercept. It should also be noted that there are very limited data from the literature on how reduction in transfusion burden would

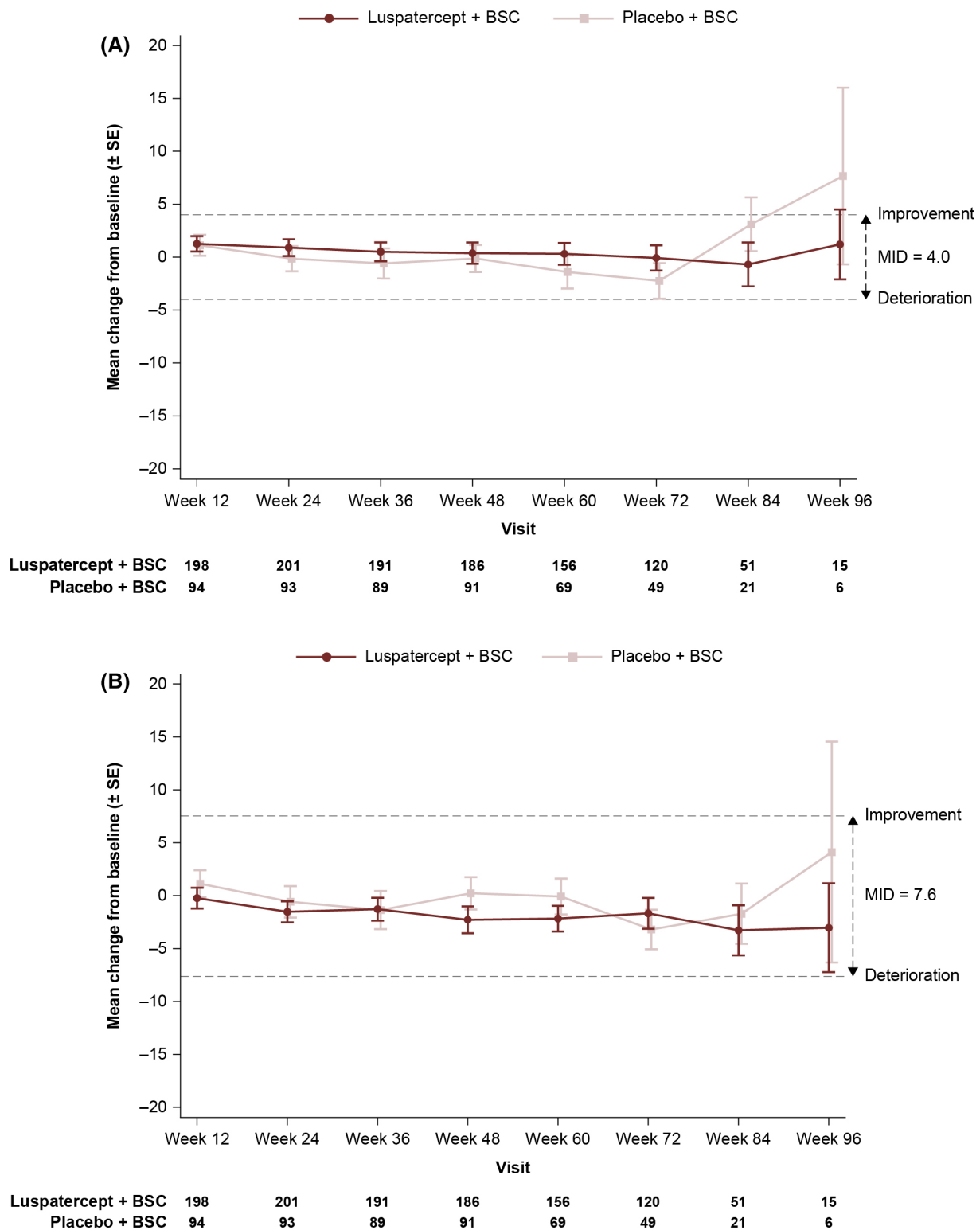


FIGURE 3 TranQol total score (A) and TranQol Physical Health scores (B) for patients with β -thalassaemia receiving luspatercept + BSC and placebo + BSC. Directional indicators of improvement or deterioration of the scores are provided for illustrative purposes; dashed lines indicate the MID thresholds. BSC, best supportive care; MID, minimally important difference; SE, standard error; TranQol, Transfusion-dependent Quality of Life questionnaire.

impact HRQoL in patients with TD β -thalassaemia. This may be due to the lack of effective anemia treatments for these patients to enable such an investigation. It should be noted that baseline iron overload

was similar between treatment groups in the HRQoL-evaluable population, suggesting that changes in HRQoL measures were more likely attributable to differences in reductions of transfusion burden.

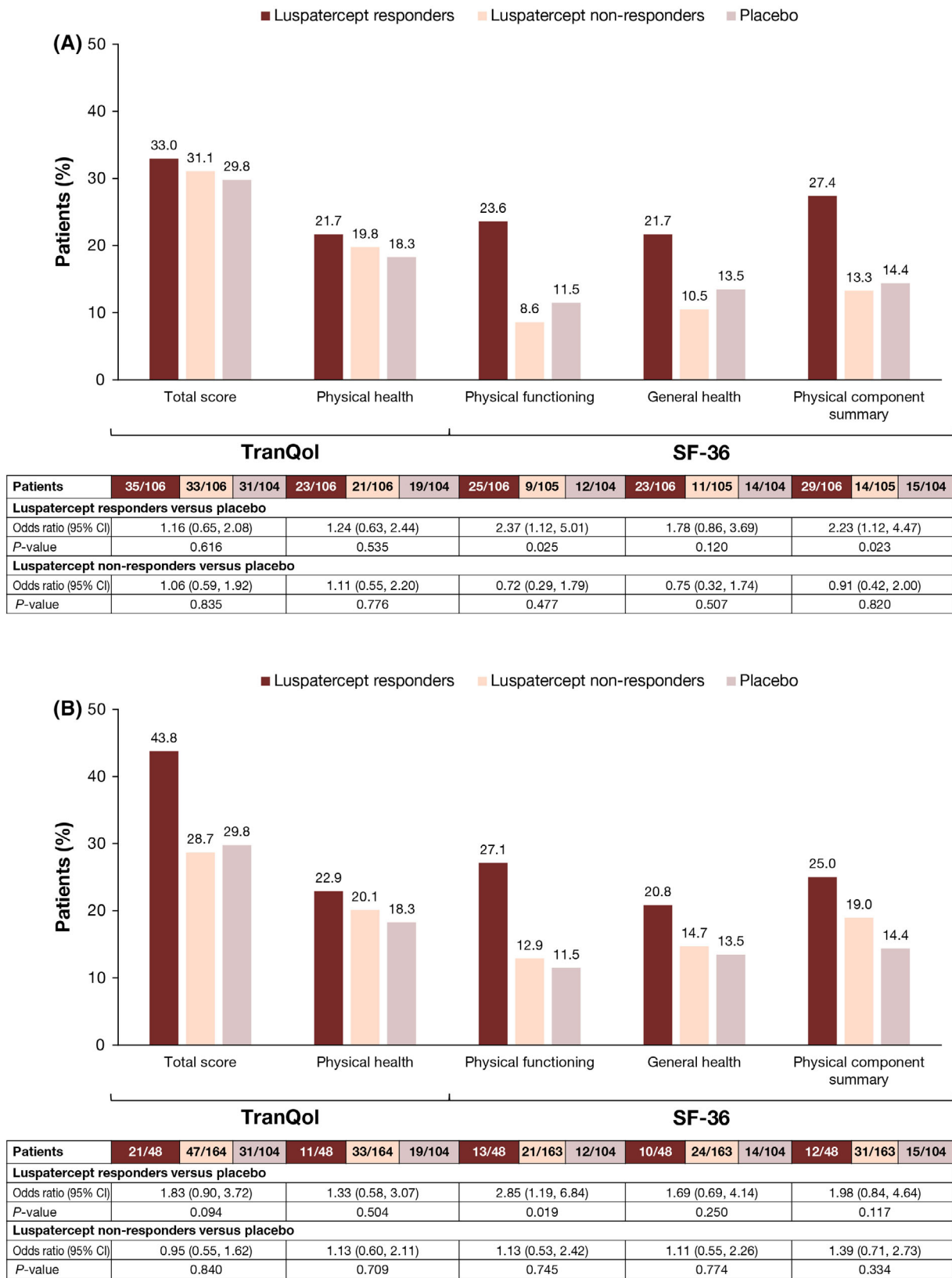


FIGURE 4 Proportion of patients with clinically meaningful improvement in the primary HRQoL domain scores at week 48 who responded. $\geq 33\%$ reduction in RBCT burden (A) and $\geq 50\%$ reduction in RBCT burden over 24 consecutive weeks (B)^a; transfusion independence at any 8-week interval (C); and transfusion independence at any 12-week interval (D)^b. ^aResponse rates based on the number of HRQoL-evaluable population at baseline, assuming those with missing data are non-responders. ^bResponse rates based on the number of HRQoL-evaluable patients with non-missing data at week 48. CI, confidence interval; HRQoL, health-related quality of life; RBCT, red blood cell transfusion; SF-36, 36-item Short Form Health Survey; TranQoL, Transfusion-dependent Quality of Life questionnaire.

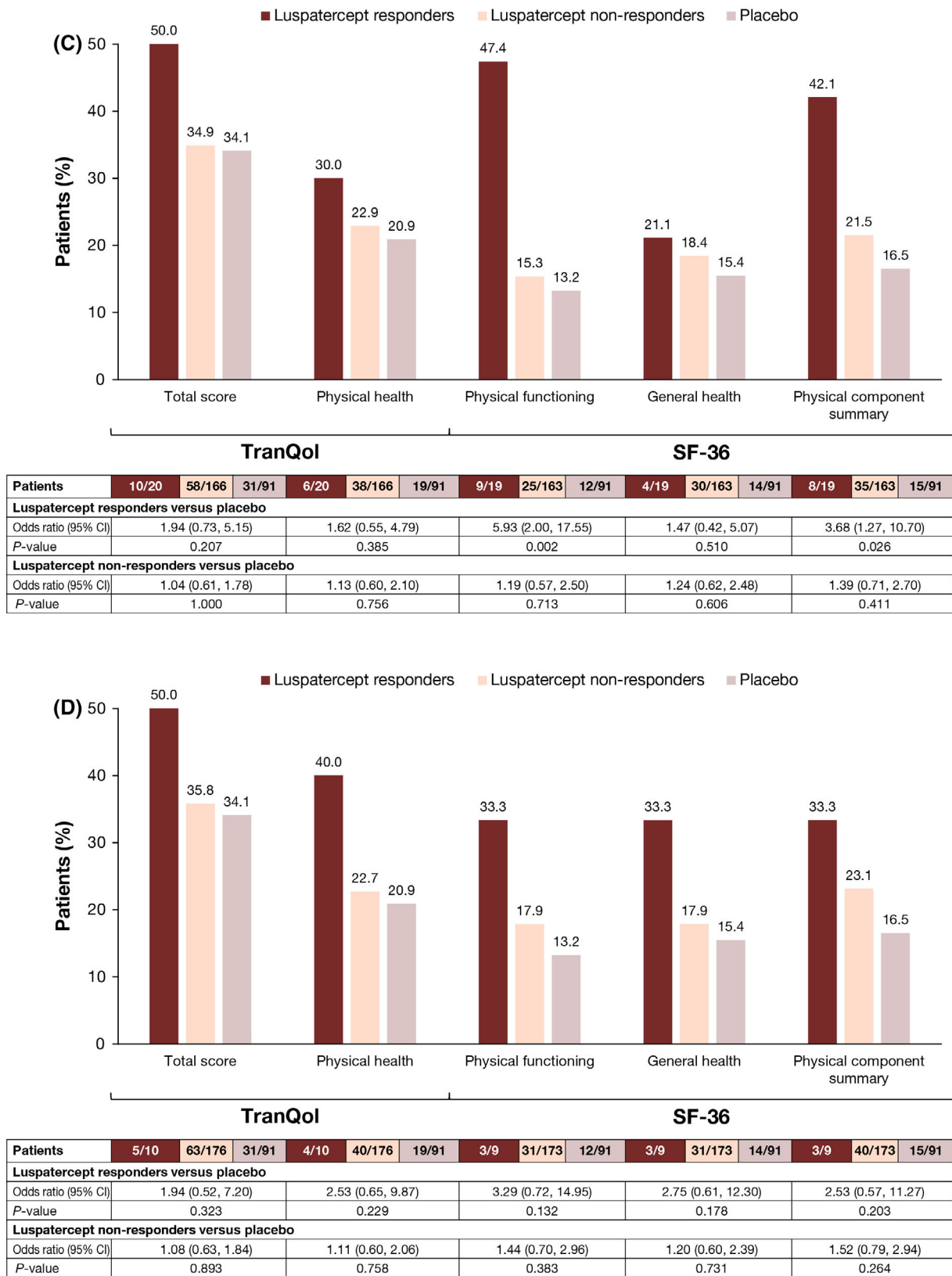


FIGURE 4 (Continued)

There are some important contextual considerations and limitations to this study. The HRQoL compliance rates remained high (>84%) during the 48-week, double-blind treatment period and were

similar between the treatment groups for both HRQoL measures when using the number of eligible patients at a given visit as the denominator. Considering the low number of patients excluded from



the HRQoL-evaluable population, it was likely representative of the overall ITT population, which is further supported by the similar baseline characteristics between the HRQoL-evaluable and non-evaluable populations within each group, with the exception of age (64% of non-evaluable patients were >32 years of age; the majority of HRQoL-evaluable patients were ≤32 years of age). While the SF-36 and TranQoL^{15,16} are validated instruments, they may have lacked some specificity related to aspects of the patient experience that would likely have been improved with the luspatercept treatment. As discussed earlier, while HRQoL was assessed at prespecified time points, patients were allowed to receive RBCTs as needed at any time during the study, which could have impacted HRQoL assessments, particularly in key domains related to anemia (e.g., Physical Functioning). Nonetheless, this study demonstrated that reduced transfusion burden with luspatercept can be achieved without diminishing patient-reported HRQoL.

5 | CONCLUSIONS

The addition of luspatercept to BSC reduced transfusion burden while maintaining patients' HRQoL over time throughout the study period. Improvements in HRQoL, particularly Physical Functioning, may be observed in some patients with significant and durable reduction in transfusion burden and/or those who achieve transfusion independence.

AUTHOR CONTRIBUTIONS

Maria Domenica Cappellini, Ali T. Taher, Derek Tang, Jeevan K. Shetty, Dimana Miteva, Tatiana Zinger, and Jay T. Backstrom were involved in conception/design, data acquisition, and data interpretation. Antonio Piga, Farrukh Shah, Ersi Voskaridou, Vip Viprakasit, John B. Porter, Olivier Hermine, Ellis J. Neufeld, Alexis A. Thompson, Aylin Yucel, Jennifer Lord-Bessen, Peiwen Yu, Shien Guo, and Esther Natalie Oliva participated in data acquisition and data interpretation.

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CONFLICT OF INTEREST STATEMENT

Maria Domenica Cappellini has received honoraria from Bristol Myers Squibb and Genzyme/Sanofi; reports membership on an entity's board of directors of CRISPR Therapeutics, Genzyme/Sanofi, Novartis Pharmaceuticals, and Vifor Pharma. Ali T. Taher discloses consultancy for Bristol Myers Squibb, Ionis Pharmaceuticals, Novartis Pharmaceuticals, Silence Therapeutics, and Vifor Pharma; has received research

funding from Bristol Myers Squibb, Novartis Pharmaceuticals, and Vifor Pharma. Antonio Piga has received research funding from Bristol Myers Squibb and Novartis Pharmaceuticals. Farrukh Shah reports consultancy for Bristol Myers Squibb; honoraria from bluebird bio, Inc., and Novartis; reports membership in an adjunction committee of IQVIA. Ersi Voskaridou declares consultancy for Acceleron Pharma Inc., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, Addmedica, Bristol Myers Squibb, and Genesis; has received research funding from Acceleron Pharma Inc., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, Addmedica, Bristol Myers Squibb, Genesis, Novartis Pharmaceuticals, and Protagonist. Vip Viprakasit reports consultancy for Agios Pharmaceuticals, Bristol Myers Squibb, Ionis Pharmaceuticals, La Jolla Pharmaceuticals, Novartis, Protagonist Therapeutics, and Vifor Pharma; has received honoraria from Bristol Myers Squibb and Novartis; has received research funding from Agios Pharmaceuticals, Bristol Myers Squibb, Ionis Pharmaceuticals, La Jolla Pharmaceuticals, Novartis, Protagonist Therapeutics, and Vifor Pharma; has received speakers bureau from Bristol Myers Squibb and Novartis; reports employment and stock for Acceleron Pharma Inc., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. John B. Porter reports consultancy for Agios Pharmaceuticals, bluebird bio, Inc., and Bristol Myers Squibb; and has received honoraria from Agios Pharmaceuticals, bluebird bio, Inc., Bristol Myers Squibb, La Jolla Pharmaceuticals, Protagonist Therapeutics, Silence Therapeutics, and Vifor Pharma. Olivier Hermine reports consultancy, equity, research funding, honoraria, patents and royalties from AB Science; and research funding from Alexion, Bristol Myers Squibb, Inaterys, and Novartis Pharmaceuticals. Ellis J. Neufeld declares consultancy for Acceleron Pharma Inc., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA and Bristol Myers Squibb; DSMB membership for Acceleron Pharma Inc., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, ApoPharma/Chiezi, and Imara Pharma; and is an advisory committee member for Pfizer. Alexis A. Thompson reports consultancy and research funding from bluebird bio, Inc. Derek Tang, Aylin Yucel, Jennifer Lord-Bessen, Jeevan K. Shetty, Dimana Miteva, and Tatiana Zinger declare employment and equity ownership for Bristol Myers Squibb. Peiwen Yu and Shien Guo report consultancy for Bristol Myers Squibb. Jay T. Backstrom reports employment by Acceleron Pharma Inc., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA and equity ownership for Merck & Co., Inc., Rahway, NJ, USA and equity ownership in Bristol Myers Squibb. Esther Natalie Oliva reports consultancy for AbbVie, Alexion, Amgen, Apellis, Bristol Myers Squibb and Novartis; and discloses honoraria, patents, royalties, and speaker's bureau from Bristol Myers Squibb.

DATA AVAILABILITY STATEMENT

The Bristol Myers Squibb policy on data sharing may be found at: www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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