# Luspatercept for the treatment of anaemia in non-transfusion-dependent β-thalassaemia (BEYOND): a phase 2, randomised, double-blind, multicentre, placebo-controlled trial

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## Summary

**Background** In patients with non-transfusion-dependent β-thalassaemia, haemoglobin concentrations lower than 10 g/dL are associated with a higher risk of morbidity, mortality, and impaired quality of life. No drugs are specifically approved for anaemia management in patients with non-transfusion-dependent β-thalassaemia, other than transfusion therapy administered infrequently in accordance with patients' needs. We assessed the efficacy and safety of luspatercept versus placebo in patients with non-transfusion-dependent β-thalassaemia.

**Methods** We did a phase 2, randomised, double-blind, multicentre, placebo-controlled trial in 12 centres in six countries (Thailand [n=1], Lebanon [n=1], Greece [n=2], Italy [n=5], the UK [n=1], and the USA [n=2]). Eligible patients were aged 18 years or older, had confirmed diagnosis of β-thalassaemia or haemoglobin E/β-thalassaemia (concomitant α-globin deletion, mutation, or duplication were allowed), and a baseline haemoglobin concentration of 10·0 g/dL or lower. All patients were non-transfusion-dependent. Patients were randomly assigned (2:1) to luspatercept or placebo using an interactive response technology system and stratified by baseline haemoglobin concentration (≥8·5 g/dL *vs* <8·5 g/dL) and baseline Non-Transfusion-Dependent β-thalassaemia-Patient-Reported Outcome Tiredness/Weakness domain score (≥3 *vs* <3). All patients, study site staff, and sponsor representatives (who reviewed the data), except for designated individuals, were masked to drug assignment until the time the study was unblinded. Luspatercept or placebo was given once subcutaneously every 3 weeks for 48 weeks in the double-blind treatment period. Luspatercept was started at 1·0 mg/kg with titration up to 1·25 mg/kg, or reduction in the event of toxicity or excessive haemoglobin concentration increase. The primary endpoint was achievement of an increase from baseline of 1·0 g/dL or higher in mean haemoglobin concentration over a continuous 12-week interval during weeks 13–24, in the absence of transfusions. The primary efficacy and safety analyses were done in the intention-to-treat population. This trial is registered at ClinicalTrials.gov, NCT03342404, and is ongoing.

**Findings** Between Feb 5, 2018, and Oct 14, 2019, 160 patients were screened for eligiblity, of whom 145 were randomly assigned to luspatercept (n=96) or placebo (n=49). 82 (57%) patients were female and 63 (43%) were male. 44 (30%) patients were Asian, 87 (60%) were White, and 14 (10%) identified as another race. The study met its primary endpoint: 74 (77%) of 96 patients in the luspatercept group and none in the placebo group had an increase of at least 1·0 g/dL in haemoglobin concentration (common risk difference 77·1 [95% CI 68·7–85·5]; p<0·0001). The proportion of patients with serious adverse events was lower in the luspatercept group than in the placebo group (11 [12%] *vs* 12 [25%]). Treatment-emergent adverse events most commonly reported with luspatercept were bone pain (35 [37%]), headache (29 [30%]), and arthralgia (28 [29%]). No thromboembolic events or deaths were reported during the study.

**Interpretation** Luspatercept represents a potential treatment for adult patients with non-transfusion-dependent β-thalassaemia, for whom effective approved treatment options are scarce.

**Funding** Celgene and Acceleron Pharma.



*Lancet Haematol 2022*

Published **Online** August 22, 2022 https://doi.org/10.1016/S2352-3026(22)00208-3

See **Online/Comment** https://doi.org/10.1016/S2352-3026(22)00256-3

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## Introduction

Patients with β-thalassaemia are commonly classified by their red blood cell transfusion requirements as having either transfusion-dependent β-thalassaemia or non-transfusion-dependent β-thalassaemia.[1,2] Patients with non-transfusion-dependent β-thalassaemia usually have less severe anaemia than do patients with transfusion-dependent β-thalassaemia, but most experience long-term serious health complications and impaired health-related quality of life (HRQoL).[3–5] Ineffective erythropoiesis and

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See Online for appendix

## Research in context

### Evidence before this study

Patients with non-transfusion-dependent β-thalassaemia have chronic anaemia resulting in serious health complications, which affect their survival and quality of life. Symptoms of anaemia are managed with occasional red blood cell transfusions and supportive care; beyond this, there is an unmet need for effective treatment options for anaemia. We searched PubMed for clinical trials with the search terms "non-transfusion-dependent thalassaemia" + "anaemia" + "clinical trial"; and ClinicalTrials.gov for active trials investigating treatments for anaemia in patients with non-transfusion-dependent β-thalassaemia. The search was done from Nov 15 to Nov 22, 2021, without language restrictions, and used PubMed's publication range option of 10 years. Active clinical trials were considered. We found that most published articles reported the results of clinical trials focused on iron overload, specific comorbidities, or both, in patients with non-transfusion-dependent β-thalassaemia, while studies addressing the underlying anaemia and ineffective erythropoiesis were limited to small trials with equivocal findings. A few active clinical trials (NCT04411082, NCT04432623, NCT04718844, NCT04059406, NCT03692052, NCT04770753, and NCT04364269) are investigating treatments for anaemia in non-transfusion-dependent β-thalassaemia through various pathways (foetal haemoglobin inducers, stimulators of hepcidin production, pyruvate kinase activators associated with red blood cells, and ferroportin inhibitors).

### Added value of this study

In the BEYOND study, a significant proportion of patients in the luspatercept group achieved 1·0 g/dL or higher haemoglobin concentration increase from baseline. Improvement in Non-Transfusion-Dependent β-thalassaemia Patient-Reported Outcomes Tiredness/Weakness domain score was more noticeable in patients receiving luspatercept than in patients receiving placebo, although it was not significant. Although luspatercept, a first-in-class erythroid maturation drug, was previously found to be effective in patients with transfusion-dependent β-thalassaemia in the phase 3 BELIEVE trial (NCT02604433), to our knowledge this is the first time that the efficacy and safety of luspatercept have been evaluated in a randomised, placebo-controlled trial of patients with non-transfusion-dependent β-thalassaemia.

### Implications of all the available evidence

The haemoglobin concentration increases observed in adult patients receiving luspatercept in the randomised BEYOND trial suggest the potential benefits of luspatercept for the treatment of chronic anaemia in patients with non-transfusion-dependent β-thalassaemia, for whom currently available treatments are often focused on alleviating comorbid disease symptoms and their complications. Luspatercept was well tolerated and had a safety profile similar with those reported in previous studies. These findings might lead to the incorporation of luspatercept in clinical treatment algorithms to guide the management of patients with anaemia due to non-transfusion-dependent β-thalassaemia.

chronic haemolytic anaemia in non-transfusion-dependent β-thalassaemia can lead to a hypercoagulable state and iron overload,[2,6,7] and often result in complications such as thrombosis, pulmonary hypertension, extramedullary haematopoiesis, and hepatic and endocrine disease.[3,8–11] As a result, the life expectancy of these patients is compromised compared with that of healthy individuals.[12]

Several studies have linked low haemoglobin concentrations with development of clinical complications and poor HRQoL and mental health in patients with non-transfusion-dependent β-thalassaemia,[8,13,14] and patients with a haemoglobin concentration of less than 10 g/dL are at high risk for clinical complications and mortality. Data from several observational studies[15–17] indicated that increasing haemoglobin by 1·0 g/dL can significantly alter complication and mortality odds and improve patient outcomes. However, treatment is limited to on-demand red blood cell transfusions.[18,19] Although hydroxyurea (also known as hydroxycarbamide) with or without erythropoietin has been evaluated previously,[20] these drugs are not approved specifically for treatment of non-transfusion-dependent β-thalassaemia-associated anaemia or ineffective erythropoiesis, thus highlighting the high unmet need in this patient population.

Luspatercept is a first-in-class erythroid maturation drug, which binds to select transforming growth factor-β ligands, inhibiting Smad 2/3 signalling to enhance late-stage erythropoiesis.[21] In several studies,[22,23] luspatercept reduced red blood cell transfusion burden in patients with transfusion-dependent β-thalassaemia, increased haemoglobin concentrations, improved HRQoL in patients with non-transfusion-dependent β-thalassaemia,[22] and had a manageable safety profile.[22–24] We report the efficacy and safety of luspatercept in adults with non-transfusion-dependent β-thalassaemia enrolled in the phase 2 BEYOND trial.

## Methods

### Study design and participants

We did a phase 2, randomised, double-blind, placebo-controlled, multicentre trial at 12 sites in six countries (Thailand [n=1], Lebanon [n=1], Greece [n=2], Italy [n=5], the UK [n=1], and the USA [n=2]; appendix pp 5–7). One site (Italy) did not find any patients who fulfilled our eligibility criteria. Eligible patients were aged 18 years or older, had a confirmed diagnosis of β-thalassaemia or haemoglobin E/β-thalassaemia (concomitant α-globin deletion, mutation, or duplication were allowed), and a

baseline haemoglobin concentration of 10·0 g/dL or lower. All patients were non-transfusion-dependent (≤5 red blood cell units per 24 weeks, and red blood cell transfusion free >8 weeks before randomisation). Patients were ineligible to participate in the study if they had a confirmed diagnosis of haemoglobin S/β-thalassaemia or α-thalassaemia; active hepatitis B, hepatitis C, or HIV infection; any medical condition or laboratory abnormality that would have prevented them from study participation, placed them under unacceptable risk if they were to participate in the study, or confounded the interpretation of study data; and had been previously treated with sotatercept or luspatercept. All additional inclusion and exclusion criteria are provided in the appendix (p 8). The trial design and additional details are provided in the appendix (pp 7, 45). The study was approved by institutional review boards of participating centres and done in compliance with the Declaration of Helsinki. All patients provided written informed consent. The sponsor, authors, and investigators designed the trial with the external steering committee. An independent data and safety monitoring board monitored the trial; authors evaluated the results.

### Randomisation and masking

Patients were randomly assigned in a 2:1 ratio to luspatercept or placebo using a block randomisation method (40 blocks of six randomisation numbers and 120 blocks of three randomisation numbers) and stratification. Patients were stratified by baseline haemoglobin concentration (≥8·5 *vs* <8·5 g/dL), as a haemoglobin concentration of 8·5 g/dL represents a midpoint for values associated with definite (<7 g/dL) and absent (>10 g/dL) complications in non-transfusion-dependent β-thalassaemia,[15] and by baseline Non-Transfusion-Dependent β-thalassaemia-Patient-Reported Outcome (PRO) Tiredness/Weakness domain score (≥3 *vs* <3), with a score of 3 or higher indicative of symptomatic non-transfusion-dependent β-thalassaemia.[25,26] Randomisation (via the interactive response technology system) was outsourced to an independent vendor (Endpoint). All patients, study site staff, and sponsor representatives (who reviewed the data), except for designated individuals (eg, designated staff at the investigational site), were masked to all study drug assignments until such time that the study was unblinded and the database was locked. The designated site individual (eg, the pharmacist) at the study site used a syringe that exactly matched the syringe used for reconstituted luspatercept and sterile normal saline (0·9% sodium chloride for injection) to prepare a matching placebo. Thus, only the designated individual at the study site, who gave investigators and other study site staff luspatercept and placebo syringes in a blinded manner, was unmasked. The success of masking was assessed by unmasked monitors. The study was unmasked 48 weeks after the last patient received the first dose of study drug. Additional study details are provided in the appendix (pp 7–8).

### Procedures

Luspatercept or placebo was given once subcutaneously every 3 weeks for 48 weeks in the double-blind treatment period. After the study was unblinded, if patients continued to benefit from treatment, they could access an open-label phase in which they could receive luspatercept for a maximum of 15 months or continue treatment in the rollover protocol (appendix p 45). Luspatercept was started at 1·0 mg/kg with titration up to 1·25 mg/kg, or reduction in the event of toxicity or excessive haemoglobin concentration increase (appendix p 10). Patients in both groups received best supportive care, including red blood cell transfusions and iron chelation therapy. Patients will be followed up every 24 weeks for up to 3 years from their last luspatercept dose for the assessment of malignancies, premalignancies, and luspatercept-related serious adverse events. Further details and rationale on procedures are provided in the appendix (pp 8–12). We used the Non-Transfusion-Dependent β-thalassaemia-PRO tool to evaluate tiredness, weakness, and shortness of breath. The Non-Transfusion-Dependent β-thalassaemia-PRO tool is, to our knowledge, the first PRO instrument developed specifically for non-transfusion-dependent β-thalassaemia.[25,26] It contains six items assessing the severity of tiredness, weakness, and shortness of breath with or without physical activity. The Tiredness/Weakness domain is the weekly scores average from four tiredness and weakness items. The tool employs a 24-h recall method, with scores ranging from 0 (absent) to 10 (extreme). A decrease in Non-Transfusion-Dependent β-thalassaemia-PRO tool Tiredness/Weakness domain score is considered an improvement and scores of 3 or higher are indicative of symptomatic non-transfusion-dependent β-thalassaemia.[25,26] Treatment-emergent adverse event severity was graded according to the Common Terminology Criteria for Adverse Events report system (version 4.03). Events of interest included thromboembolic events and malignancies. Serious treatment-emergent adverse events were defined as events that were life-threatening or resulting in death, hospitalisation, disability, or congenital anomaly.

### Outcomes

The primary efficacy endpoint was the proportion of patients with a mean haemoglobin concentration increase of 1·0 g/dL or higher from baseline over a continuous 12-week interval (weeks 13–24), in the absence of red blood cell transfusions. The first key secondary efficacy endpoint was the mean change from baseline in Non-Transfusion-Dependent β-thalassaemia-PRO tool Tiredness/Weakness domain score over a continuous 12-week interval (weeks 13–24). The second and third key secondary efficacy endpoints were mean change from baseline in haemoglobin concentration

over a continuous 12-week interval (weeks 13–24) and proportion of patients with a mean haemoglobin increase of 1·0 g/dL or higher from baseline over a continuous 12-week interval (weeks 37–48). Other reported secondary efficacy endpoints included proportion of patients with a mean haemoglobin concentration increase of 1·5 g/dL or higher from baseline over a continuous 12-week interval (weeks 13–24 and weeks 37–48) in the absence of red blood cell transfusions, mean change from baseline in Non-Transfusion-Dependent β-thalassaemia-PRO tool Tiredness/Weakness domain score over a continuous 12-week interval (weeks 37–48), mean change from baseline in serum ferritin at weeks 24 and 48, mean change from baseline in liver iron concentration at week 24, and duration of mean haemoglobin concentration increase of 1·0 g/dL or higher from baseline. Remaining efficacy, safety, pharmacokinetics, and exploratory endpoints were: mean change from baseline in mean Functional Assessment of Chronic Illness Therapy-Fatigue, Fatigue Subscale score; Non-Transfusion-Dependent β-thalassaemia-PRO tool Shortness of Breath domain score over a continuous 12-week interval (weeks 13–24); mean change from baseline in mean Functional Assessment of Chronic Illness Therapy-Fatigue, Fatigue Subscale score and mean Non-Transfusion-Dependent β-thalassaemia-PRO tool Shortness of Breath domain score over a continuous 12-week interval (weeks 37–48); mean change from baseline in mean haemoglobin values over a continuous 12-week interval (weeks 37–48) in the absence of transfusions; proportion of patients with an increase from baseline of 3 or higher in mean Functional Assessment of Chronic Illness Therapy-Fatigue, Fatigue Subscale score (weeks 13–24 and 37–48); mean change from baseline in the Physical Component Summary and Mental Component Summary scores of the Medical Outcomes Study 36-item Short Form Health Survey at weeks 24 and 48; proportion of patients with improvement of iron overload (weeks 24 and 48), as measured by (1) a 20% or higher reduction in liver iron concentration or a 33% or higher decrease in iron chelation therapy daily dose (for patients with a baseline liver iron concentration of ≥3 mg/g dry weight), or (2) no increase in liver iron concentration of more than 1 mg/g dry weight and not starting treatment with iron chelation therapy or no increase in iron chelation therapy daily dose of 33% or higher, if on iron chelation therapy at baseline (for patients with baseline liver iron concentration of <3 mg/g dry weight); mean change from baseline in serum ferritin up to last assessment; mean change from baseline in liver iron concentration at week 48 and up to last assessment; proportion of patients who were transfusion free over 24 weeks and 48 weeks; mean change from baseline in the 6-min walk test distance (weeks 24 and 48); proportion of patients with a decrease from baseline of at least 1 point (responder definition) in mean Non-Transfusion-Dependent β-thalassaemia-PRO tool Tiredness/Weakness domain score (weeks 13–24 and weeks 37–48); assessment of safety and tolerability, including immunogenicity; pharmacokinetics parameters (including exposure–response relationship); change in extramedullary haematopoietic mass volume by MRI, spleen volume by MRI, and tricuspid valve regurgitation velocity by echocardiography or MRI; change in bone mineral density by dual-energy x-ray absorptiometry at week 48; mean change in leg ulcer size (when present); change from baseline in the non-transfusion-dependent β-thalassaemia severity score system (weeks 24 and 48); mean change in serum growth differentiation factor (GDF) 11 and other related biomarkers correlation with the haemoglobin response; mean change in haemoglobin F; and mean change in measures of health-care resource use. Additional details are provided in the appendix (pp 12–16). Additional analyses included post-hoc analysis of correlation between the change in Non-Transfusion-Dependent β-thalassaemia-PRO tool Tiredness/Weakness domain score and haemoglobin response, and Non-Transfusion-Dependent β-thalassaemia-PRO tool Tiredness/Weakness domain score improvement by clinical response status and by visit. We did a post-hoc analysis of primary and key secondary efficacy endpoints, excluding patients with haemoglobin concentrations of 5–7 g/dL (appendix p 40).

### Statistical analysis

The planned sample size of 150 was based on the assumption of targeted primary endpoint response rates of 50% or higher in the luspatercept group and 10% in the placebo group (based on the results from a phase 2 clinical trial of luspatercept [NCT02268409]), and a randomisation ratio of 2:1. Therefore, a total sample size of 150 patients (100 individuals in the luspatercept group and 50 individuals in the placebo group) would have at least 99% power to detect the difference between the two groups with a two-sided α of 0·05 and an assumed dropout of 10%. For Non-Transfusion-Dependent β-thalassaemia-PRO tool Tiredness/Weakness domain scores, the assumption of mean change from baseline scores at week 24 of –1·2 for the luspatercept group and –0·5 for the placebo group, with a common SD of 1·2, the statistical power would be 91%. However, the study was closed with 145 patients because of challenges with recruitment. The reduced number of enrolled patients did not compromise the assumptions of the planned statistical analyses, which still retained 99% power to detect the difference between the two groups for the primary endpoint and 89% power to detect the difference between the two groups for the key secondary efficacy endpoint.

All efficacy evaluations were done using the intention-to-treat population. The Non-Transfusion-Dependent β-thalassaemia-PRO tool Tiredness/Weakness domain scores were analysed in both the intention-to-treat and

the HRQoL-evaluable populations. The HRQoL-evaluable population comprised all patients in the intention-to-treat population who had a valid HRQoL assessment at baseline and at least one valid post-baseline HRQoL assessment. The primary and key secondary efficacy endpoints were also analysed based on the per-protocol populations as sensitivity analyses (all described in detail in the appendix pp 33–39).

Gate-keeping methods were used to control the overall type 1 error rate for the key secondary efficacy endpoints and full details are included in the appendix (p 20). The primary endpoint was assessed using the Cochran–Mantel–Haenszel test with baseline haemoglobin (≥8·5 *vs* <8·5 g/dL) and Non-Transfusion-Dependent β-thalassaemia-PRO tool Tiredness/Weakness domain score (≥3 *vs* <3) as stratification factors, to compare luspatercept and placebo groups with a two-sided 0·05 α level, with corresponding 95% CI values. Similar methods were used to determine haemoglobin response during a continuous 12-week interval (weeks 37–48). Change in Non-Transfusion-Dependent β-thalassaemia-PRO tool Tiredness/Weakness domain score was assessed using ANCOVA with treatment group in the model, and baseline Non-Transfusion-Dependent β-thalassaemia-PRO tool Tiredness/Weakness domain score and haemoglobin stratification factors as covariates. Change in haemoglobin concentration was assessed using ANCOVA with treatment group in the model and baseline haemoglobin and Non-Transfusion-Dependent β-thalassaemia-PRO tool Tiredness/Weakness domain score stratification factors as covariates. Full details and the description of remaining statistical analyses for subgroups and secondary endpoints, as well as sensitivity and post-hoc analyses, are provided in the appendix (pp 19–27). Handling of missing data is described in detail in the appendix (pp 23–24). Statistical analyses were done in SAS, version 9.4. This trial is registered at ClinicalTrials.gov, NCT03342404, and is ongoing.

### Role of the funding source

The funders of the study had a role in study design, data collection, data analysis, data interpretation, or writing of the report.

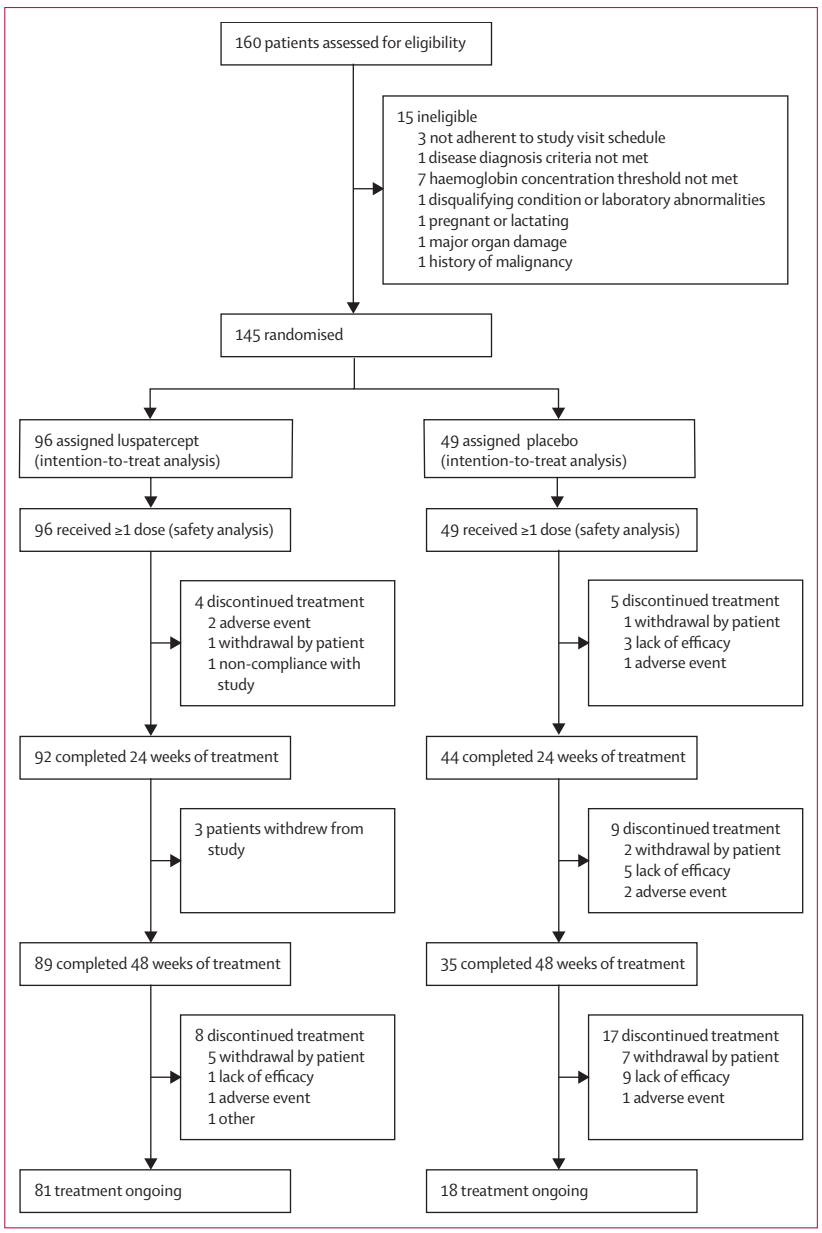


***Figure 1:*** **Trial profile**

## Results

Between Feb 5, 2018 and Oct 14, 2019, of the 160 patients assessed for eligibility, 145 patients were randomly assigned to either luspatercept (n=96) or placebo (n=49). Primary data cut-off date was Sept 14, 2020. The intention-to-treat and safety populations comprised 96 individuals in the luspatercept group and 49 in the placebo group. The per-protocol population comprised of 90 individuals in the luspatercept group and 48 in the placebo group. Patient disposition is summarised in figure 1 and additional details are provided in the appendix (pp 27–28). Baseline characteristics can be found in table 1. In the luspatercept group, there was a higher proportion of patients aged 32 years or younger than in the placebo group (35 [37%] *vs* 12 [25%]), and a lower proportion of patients aged 33–50 years (41 [43%] *vs* 26 [53%]). There was a higher proportion of people with a body-mass index between 25 kg/m² and less than 30 kg/m² in the placebo versus the luspatercept group (table 1). Overall, the median age was 40·0 years (IQR 29·0–47·0), 82 (57%) patients were female, 39 (27%) had haemoglobin E/β-thalassaemia, 87 (60%) were White, and 44 (30%) were Asian. 13 (14%) patients receiving luspatercept and seven (14%) patients receiving placebo, received 1–5 red blood cell units per 24 weeks before randomisation. Median baseline haemoglobin concentration was

| | Luspatercept (n=96) | Placebo (n=49) | Total (n=145) |
|---|---|---|---|
| **Age, years** | | | |
| Median age (IQR) | 39·5 (28·0–48·5) | 41·0 (33·0–47·0) | 40·0 (29·0–47·0) |
| ≤32 years | 35 (37%) | 12 (25%) | 47 (32%) |
| 33–50 years | 41 (43%) | 26 (53%) | 67 (46%) |
| >50 years | 20 (21%) | 11 (22%) | 31 (21%) |
| **Sex** | | | |
| Female | 56 (58%) | 26 (51%) | 82 (57%) |
| Male | 40 (42%) | 23 (47%) | 63 (43%) |
| **Country and site identification** | | | |
| Thailand | 27 (28%) | 11 (22%) | 38 (26%) |
| 401 | 27 (28%) | 11 (22%) | 38 (26%) |
| Lebanon | 9 (9%) | 8 (16%) | 17 (12%) |
| 301 | 9 (9%) | 8 (16%) | 17 (12%) |
| Greece | 22 (23%) | 14 (29%) | 36 (25%) |
| 101 | 11 (12%) | 7 (14%) | 18 (12%) |
| 102 | 11 (12%) | 7 (14%) | 18 (12%) |
| Italy | 31 (32%) | 12 (25%) | 43 (30%) |
| 201 | 6 (6%) | 3 (6%) | 9 (6%) |
| 202 | 3 (3%) | 2 (4%) | 5 (3%) |
| 203 | 9 (9%) | 2 (4%) | 11 (8%) |
| 204 | 8 (8%) | 2 (4%) | 10 (7%) |
| 206 | 5 (5%) | 3 (6%) | 8 (6%) |
| UK | 2 (2%) | 3 (6%) | 5 (3%) |
| 601 | 2 (2%) | 3 (6%) | 5 (3%) |
| USA | 5 (5%) | 1 (2%) | 6 (4%) |
| 501 | 4 (4%) | 0 | 4 (3%) |
| 503 | 1 (1%) | 1 (2%) | 2 (1%) |
| **Race** | | | |
| Asian | 31 (32%) | 13 (27%) | 44 (30%) |
| White | 59 (62%) | 28 (57%) | 87 (60%) |
| Other | 6 (6%) | 8 (16%) | 14 (10%) |
| **Body-mass index, kg/m²** | | | |
| Median (IQR) | 21·6 (19·5–24·4) | 21·5 (19·3–24·7) | 21·6 (19·3–24·4) |
| <20 | 35 (37%) | 18 (37%) | 53 (37%) |
| ≥20 to <25 | 46 (48%) | 20 (41%) | 66 (46%) |
| ≥25 to <30 | 12 (13%) | 9 (18%) | 21 (15%) |
| ≥30 | 3 (3%) | 2 (4%) | 5 (3%) |
| **Eastern Cooperative Oncology Group performance status score*** | | | |
| 0 | 62 (65%) | 38 (78%) | 100 (69%) |
| 1 | 34 (35%) | 11 (22%) | 45 (31%) |
| **β-thalassaemia diagnosis** | | | |
| β-thalassaemia | 63 (66%) | 34 (69%) | 97 (67%) |
| Haemoglobin E/β-thalassaemia | 28 (29%) | 11 (22%) | 39 (27%) |
| β-thalassaemia combined with α-thalassaemia | 5 (5%) | 4 (8%) | 9 (6%) |
| **β-thalassaemia genotype** | | | |
| [β0/β0, β+/β+, β+/β0] without α-thalassaemia | 69 (72%) | 33 (67%) | 102 (70%) |
| [β0/β0, β+/β+, β+/β0] with α-thalassaemia | 6 (6%)† | 4 (8%) | 10 (7%) |
| [β0/β, β+/β] with α-gene duplication | 21 (22%) | 12 (25%) | 33 (23%) |

(Table 1 continues on next page)

8·2 g/dL (7·3–9·2); 84 (58%) patients had baseline haemoglobin concentration <8·5 g/dL. Median baseline Non-Transfusion-Dependent β-thalassaemia-PRO tool Tiredness/Weakness domain score was 4·3 (2·5–5·7); 101 (70%) patients had baseline score 3 or higher.

The study achieved its primary endpoint: 74 (77%) of 96 patients in the luspatercept group and none in the placebo group had a mean haemoglobin concentration increase of 1·0 g/dL or higher from baseline over a continuous 12-week interval (weeks 13–24), in the absence of red blood cell transfusions (common risk difference 77·1 [95% CI 68·7–85·5]; p<0·0001; table 2; appendix p 46). Subgroup and sensitivity analyses of the primary endpoint are described in the appendix (pp 28–29, 33–36).

Although the study did not meet the first key secondary efficacy endpoint, improvement in Non-Transfusion-Dependent β-thalassaemia-PRO tool Tiredness/Weakness domain score, indicated by score decrease from baseline, was greater in patients receiving luspatercept than in patients receiving placebo during weeks 13–24 (least squares mean [LSM] –0·68 *vs* –0·20; LSM difference –0·48 [95% CI –1·03 to 0·08]; p=0·092; table 2; appendix p 47). Patients in luspatercept group had a greater mean haemoglobin increase from baseline than did patients in the placebo group during weeks 13–24 (LSM 1·48 *vs* 0·07 g/dL; LSM difference 1·42 [95% CI 1·16–1·67]; p<0·0001; table 2; appendix p 48) and a mean haemoglobin increase of at least 1·0 g/dL from baseline (weeks 37–48) was observed in 68 (71%) patients receiving luspatercept and in one (2%) patient receiving placebo (common risk difference 68·6 [95% CI 58·5–78·7]; p<0·0001).

During weeks 13–24, 50 (52%) patients in the luspatercept group versus no patients in the placebo group (common risk difference 52·3 [95% CI 42·3–62·3]; p<0·0001) had a mean haemoglobin increase of at least 1·5 g/dL from baseline. During weeks 37–48, 47 (49%) patients in the luspatercept group versus no patients in the placebo group (common risk difference 49·1 [95% CI 39·1–59·1]; p<0·0001) had a mean haemoglobin increase of at least 1·5 g/dL from baseline. Subgroup and sensitivity analyses for the key secondary efficacy endpoints are described in the appendix (pp 30–33, 36–39). During weeks 37–48, patients in the luspatercept group had a greater mean haemoglobin increase from baseline than did patients in the placebo group (LSM 1·50 *vs* 0·01 g/dL; LSM difference 1·49 [95% CI 1·2–1·79]; p<0·0001; data not shown). The improvement in Non-Transfusion-Dependent β-thalassaemia-PRO tool Tiredness/Weakness domain score was greater in the luspatercept group during weeks 37–48 (LSM –0·78 *vs* 0·01; LSM difference –0·79 [95% CI –1·58 to 0·00]; p=0·051), although the difference was not significant (data not shown). Increase from baseline in serum ferritin concentrations was observed in both the luspatercept group and the placebo group at week 24 (LSM 29·32 *vs* 2·18 µg/L; LSM difference 27·14 [95% CI –46·77 to 101·06]; p=0·59) and week 48

(LSM 84·98 *vs* 71·48 µg/L; LSM difference 13·50 [95% CI −60·96 to 87·96]; p=0·35). However, the difference between treatment groups was not significant. Decrease from baseline in liver iron concentration was greater in the luspatercept group than in the placebo group at week 24, although the difference was not significant (LSM −0·40 *vs* −0·28 mg/g dry weight; LSM difference −0·12 [95% CI −0·52 to 0·28]; p=0·55). A total of 28 (29%) patients in the luspatercept group and 16 (33%) patients in the placebo group were receiving iron chelation therapy at baseline (table 1). Duration of mean haemoglobin increase during any 12-week rolling interval was 611·7 days (SD 243·3) in the luspatercept group versus 176·5 days (SD 132·9) in the placebo group (data not shown). Data collection and analysis of remaining endpoints is ongoing, unless stated otherwise (appendix pp 12–16), and the results will be reported elsewhere.

Median treatment duration was 99·7 weeks (IQR 77·0–117·5) in the luspatercept group and 61·1 weeks (37·1–96·9) in the placebo group. Data on treatment exposure are reported in the appendix (pp 41–42). Overall, 144 (99%) patients experienced one or more treatment-emergent adverse events and 39 (27%) experienced one or more grade 3–4 treatment-emergent adverse events (table 3). The most common any grade treatment-emergent adverse events in luspatercept versus placebo were bone pain (35 [37%] *vs* three [6%]), headache (29 [30%] *vs* ten [20%]), arthralgia (28 [29%] *vs* seven [14%]), back pain (27 [28%] *vs* five [10%]), prehypertension (22 [23%] *vs* seven [14%]), and hypertension (19 [20%] *vs* one [2%]); the highest incidence of treatment-emergent adverse events (including bone pain, headache, and prehypertension) generally occurred during treatment cycles 1–4 and decreased thereafter. Treatment-emergent adverse events in patients in the luspatercept and placebo groups led to treatment discontinuation (three [3%] *vs* four [8%]), dose reductions (ten [10%] *vs* none), and dose delays (23 [24%] *vs* nine [18%]). Any-grade treatment-emergent adverse events occurring at an incidence of 5% or more and more often in the luspatercept group than in the placebo group are reported in the appendix (pp 43–44). Serious adverse events occurred in 11 (12%) patients in the luspatercept group and 12 (25%) in the placebo group. The most common serious adverse events in luspatercept versus placebo were traumatic fracture (five [5%] *vs* one [2%]) and viral upper respiratory tract infection (none *vs* two [4%]). No thromboembolic events were observed in either treatment group. Extramedullary haematopoiesis was reported in six (6%) patients in the luspatercept group and in one (2%) patient in the placebo group. Data collection and analysis of change from baseline in extramedullary haematopoietic masses and of correlation of mean change in serum GDF11 and other related biomarkers with the haemoglobin response is ongoing and will be reported elsewhere. Two patients receiving placebo developed a malignancy (one diffuse large B-cell lymphoma, one hepatocellular carcinoma). No malignancies were reported in the luspatercept group. No deaths occurred during the study.

Post-hoc analysis of Non-Transfusion-Dependent β-thalassaemia-PRO tool Tiredness/Weakness domain score improvement by primary endpoint response status (mean haemoglobin increase of ≥1·0 g/dL during weeks 13–24) showed that luspatercept responders had a significantly greater magnitude of improvement in Non-Transfusion-Dependent β-thalassaemia-PRO tool Tiredness/Weakness domain score during weeks 13–24 (mean difference −0·70 [95% CI −1·32 to −0·09]; p=0·026) and weeks 37–48 (mean difference −1·28

| | Luspatercept (n=96) | Placebo (n=49) | Total (n=145) |
|---|---|---|---|
| (Continued from previous page) | | | |
| **Baseline haemoglobin concentration, g/dL‡** | | | |
| Median (IQR) | 8·2 (7·4–9·2) | 8·1 (6·9–9·2) | 8·2 (7·3–9·2) |
| ≥8·5 | 41 (43%) | 20 (41%) | 61 (42%) |
| <8·5 | 55 (57%) | 29 (59%) | 84 (58%) |
| **Baseline transfusion burden, red blood cell units per 24 weeks§** | | | |
| Median (IQR) | 0 (0–0) | 0 (0–0) | 0 (0–4) |
| 0 units per 24 weeks | 83 (87%) | 42 (86%) | 125 (86%) |
| 1–5 units per 24 weeks | 13 (14%) | 7 (14%) | 20 (14%) |
| **Baseline NTDT-PRO T/W domain score¶** | | | |
| Median (IQR) | 4·3 (2·4–5·8) | 4·1 (2·5–5·4) | 4·3 (2·5–5·7) |
| ≥3 | 66 (69%) | 35 (71%) | 101 (70%) |
| <3 | 30 (31%) | 14 (29%) | 44 (30%) |
| **Baseline serum ferritin concentration, µg/L** | | | |
| Median (IQR) | 456·5 (251·0–656·0) | 360·0 (226·0–735·5) | 441 (245·0–662·0) |
| **Baseline iron chelation therapy** | | | |
| Yes | 28 (29%) | 16 (33%) | 44 (30%) |
| Baseline serum ferritin ≤800 µg/L | 22 (23%) | 12 (25%) | 34 (23%) |
| Baseline serum ferritin >800 µg/L | 6 (6%) | 4 (8%) | 10 (7%) |
| No | 68 (71%) | 33 (67%) | 101 (70%) |
| Baseline serum ferritin ≤800 µg/L | 61 (64%) | 25 (51%) | 86 (59%) |
| Baseline serum ferritin >800 µg/L | 7 (7%) | 8 (16%) | 15 (10%) |
| **Baseline liver iron concentration, mg/g dry weight** | | | |
| Mean (SD) | 6·1 (6·2) | 5·9 (5·8) | 6·0 (6·0) |
| <3 | 35 (37%) | 17 (35%) | 52 (36%) |
| ≥3 to ≤5 | 23 (24%) | 13 (27%) | 36 (25%) |
| >5 to ≤7 | 12 (13%) | 3 (6%) | 15 (10%) |
| >7 to ≤15 | 14 (15%) | 9 (18%) | 23 (16%) |
| >15 | 11 (12%) | 5 (10%) | 16 (11%) |
| Missing | 1 (1%) | 2 (4%) | 3 (2%) |

Data are n (%), unless otherwise indicated. NTDT-PRO T/W=Non-Transfusion Dependent β-thalassaemia Patient-Reported Outcomes Tiredness/Weakness. *More patients with Eastern Cooperative Oncology Group performance status score of 1 were enrolled in the luspatercept group than in the placebo group. †This included one patient for whom haemoglobin E/β-thalassaemia was a more appropriate clinical diagnosis, while based on the α-gene deletion, this was the more appropriate gene mutation classification. ‡Baseline haemoglobin value was defined as the average of two or more haemoglobin measurements, at least 1 week apart, within 4 weeks before randomisation. §Baseline transfusion burden was defined as the number of red blood cell units transfused in the 24 weeks before the first dose of luspatercept or placebo; red blood cell units transfused on the day of the first dose of study treatment were considered part of the baseline transfusion burden. ¶NTDT-PRO T/W domain score <3 is indicative of patients with less symptomatic NTDT, whereas NTDT-PRO T/W domain scores ≥3 are indicative of patients with symptomatic NTDT.

***Table 1:*** **Baseline characteristics in the intention-to-treat population**

| | | Luspatercept (n=96) | Placebo (n=49) | Common risk difference or least squares mean difference (95% CI) | p value |
|---|---|---|---|---|---|
| Primary efficacy endpoint | Proportion of individuals who had an increase from baseline of ≥1·0 g/dL in mean of haemoglobin values over a continuous 12-week interval (weeks 13–24) in the absence of transfusions | 74 (77%) | 0 | 77·1 (68·7 to 85·5) | <0·0001 |
| First key secondary efficacy endpoint | Mean change from baseline in NTDT-PRO T/W domain score over a continuous 12-week interval (weeks 13–24) | −0·68 (0·176) | −0·20 (0·240) | −0·48 (−1·03 to 0·08) | 0·092 |
| Second key secondary efficacy endpoint | Mean change from baseline in mean of haemoglobin values over a continuous 12-week interval (weeks 13–24) in the absence of transfusions | 1·48 (0·078) | 0·07 (0·108) | 1·42 (1·16 to 1·67) | <0·0001* |
| Third key secondary efficacy endpoint | Proportion of individuals who had an increase from baseline of ≥1·0 g/dL in mean of haemoglobin values over a continuous 12-week interval (weeks 37–48) in the absence of transfusions | 68 (71%) | 1 (2%) | 68·6 (58·5 to 78·7) | <0·0001* |

Data on intention-to-treat population. NTDT-PRO T/W=Non-Transfusion-Dependent β-thalassaemia Patient-Reported Outcomes Tiredness/Weakness. *Nominal p values.

***Table 2:*** **Primary and key secondary efficacy outcomes**

[−2·12 to −0·44]; p=0·0033), than did patients receiving placebo, who were all non-responders (appendix p 49). The correlation analysis showed that as haemoglobin concentrations increased, Non-Transfusion-Dependent β-thalassaemia-PRO tool Tiredness/Weakness domain scores decreased, suggesting improvement in patient-reported tiredness and weakness (R=−0·29; p<0·0001; figure 2). Mean change from baseline in Non-Transfusion-Dependent β-thalassaemia-PRO tool Tiredness/Weakness domain score by visit (appendix p 50) showed a gradual and consistent decrease in the luspatercept group, maintained for up to 78 weeks. In contrast, scores in the placebo group decreased temporarily and to a lesser degree than in the luspatercept group before returning to baseline levels. The post-hoc analysis of primary and key secondary endpoints, excluding patients with haemoglobin concentrations of 5–7 g/dL, is reported in the appendix (pp 39–40).

## Discussion

Luspatercept has been previously shown to improve haemoglobin concentrations in patients with transfusion-dependent β-thalassaemia in the BELIEVE study,[23] and similarly, in adult patients with non-transfusion-dependent β-thalassaemia, treatment with luspatercept resulted in a sustained increase in haemoglobin concentrations. Overall, at weeks 13–24, 77% of patients in the luspatercept group had a mean haemoglobin increase of 1·0 g/dL or higher from baseline in the absence of red blood cell transfusions, compared with no patients in the placebo group, and more than 50% of patients in the luspatercept group had a mean increase of 1·5 g/dL or higher. Most importantly, the observed haemoglobin response was rapid and sustained throughout the study.

Patients in this study had a baseline haemoglobin concentration of less than 10 g/dL, prognostic of higher risk for clinical complications.[15–17] As shown in several studies, a haemoglobin increase of 1·0 g/dL or higher has been linked to lower complication rates,[15–17] but interventions that can improve anaemia remain a critical unmet need for this patient population.[2] Previous experience with drugs such as hydroxyurea or erythropoiesis stimulants highlighted irregular outcome in patients with non-transfusion-dependent β-thalassaemia, and overall benefit–risk ratio has not been shown because of a scarcity of data from large, randomised clinical trials.[27]

The observed increase in haemoglobin concentrations with luspatercept is expected to ameliorate clinical complications; however, a longer follow-up is needed to assess this. Red blood cell transfusions are often used as a last resort for non-transfusion-dependent β-thalassaemia, either occasionally in situations of worsening anaemia (eg, infections), blood loss, or more frequently to promote growth in childhood or manage specific complications.[18] However, red blood cell transfusions come with their own sequelae from iron overload, organ damage, increased risk of alloimmunisation, and overall burden to the patient and the health-care system.

The Non-Transfusion-Dependent β-thalassaemia-PRO tool is a validated instrument to assess specific non-transfusion-dependent β-thalassaemia tiredness, weakness, and shortness of breath symptoms, which greatly affect the daily lives of patients with non-transfusion-dependent β-thalassaemia.[25,26] Patients treated with luspatercept had greater improvement in Non-Transfusion-Dependent β-thalassaemia-PRO tool Tiredness/Weakness domain score, indicated by score decrease, compared with placebo, which, although not significant, was more pronounced over time. No significant difference was predominately because of a reduced magnitude of change among the subset of patients who were less symptomatic (baseline Non-Transfusion-Dependent β-thalassaemia-PRO tool Tiredness/Weakness domain score <3). Indeed, improvements in tiredness and weakness symptoms

| | Luspatercept (n=96) | | | | | | Placebo (n=49) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 | Total | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 | Total |
| Patients with ≥1 TEAE | 92 (96%) | 84 (88%) | 24 (25%) | 3 (3%) | 0 | 96 (100%) | 43 (88%) | 38 (78%) | 12 (25%) | 1 (2%) | 0 | 48 (98%) |
| Patients with ≥1 serious TEAE | NA | NA | NA | NA | NA | 11 (12%) | NA | NA | NA | NA | NA | 12 (25%) |
| Patients with ≥1 grade ≥3 TEAE | NA | NA | NA | NA | NA | 27 (28%) | NA | NA | NA | NA | NA | 12 (25%) |
| Patients with ≥1 TEAE leading to death | NA | NA | NA | NA | NA | 0 | NA | NA | NA | NA | NA | 0 |
| Patients with ≥1 treatment-related TEAE | NA | NA | NA | NA | NA | 73 (76%) | NA | NA | NA | NA | NA | 18 (37%) |
| Patients with ≥1 treatment-related serious TEAE | NA | NA | NA | NA | NA | 1 (1%) | NA | NA | NA | NA | NA | 0 |
| Patients with ≥1 treatment-related grade ≥3 TEAE | NA | NA | NA | NA | NA | 11 (12%) | NA | NA | NA | NA | NA | 0 |
| Patients with ≥1 treatment-related TEAE leading to death | NA | NA | NA | NA | NA | 0 | NA | NA | NA | NA | NA | 0 |
| Bone pain | 20 (21%) | 12 (13%) | 3 (3%) | 0 | 0 | 35 (37%) | 1 (2%) | 2 (4%) | 0 | 0 | 0 | 3 (6%) |
| Headache | 14 (15%) | 15 (16%) | 0 | 0 | 0 | 29 (30%) | 4 (8%) | 6 (12%) | 0 | 0 | 0 | 10 (20%) |
| Arthralgia | 13 (14%) | 13 (14%) | 2 (2%) | 0 | 0 | 28 (29%) | 3 (6%) | 4 (8%) | 0 | 0 | 0 | 7 (14%) |
| Back pain | 19 (20%) | 8 (8%) | 0 | 0 | 0 | 27 (28%) | 4 (8%) | 1 (2%) | 0 | 0 | 0 | 5 (10%) |
| Prehypertension | 22 (23%) | 0 | 0 | 0 | 0 | 22 (23%) | 7 (14%) | 0 | 0 | 0 | 0 | 7 (14%) |
| Upper respiratory tract infection | 3 (3%) | 17 (18%) | 0 | 0 | 0 | 20 (21%) | 2 (4%) | 9 (18%) | 0 | 0 | 0 | 11 (22%) |
| Hypertension | 4 (4%) | 12 (13%) | 3 (3%) | 0 | 0 | 19 (20%) | 0 | 1 (2%) | 0 | 0 | 0 | 1 (2%) |
| Oropharyngeal pain | 9 (9%) | 10 (10%) | 0 | 0 | 0 | 19 (20%) | 4 (8%) | 2 (4%) | 0 | 0 | 0 | 6 (12%) |
| Pharyngitis | 0 | 19 (20%) | 0 | 0 | 0 | 19 (20%) | 0 | 6 (12%) | 1 (2%) | 0 | 0 | 7 (14%) |
| Cough | 9 (9%) | 8 (8%) | 0 | 0 | 0 | 17 (18%) | 0 | 1 (2%) | 0 | 0 | 0 | 1 (2%) |
| Diarrhoea | 12 (13%) | 4 (4%) | 0 | 0 | 0 | 16 (17%) | 3 (6%) | 3 (6%) | 0 | 0 | 0 | 6 (12%) |
| Fatigue | 12 (13%) | 4 (4%) | 0 | 0 | 0 | 16 (17%) | 6 (12%) | 3 (6%) | 1 (2%) | 0 | 0 | 10 (20%) |
| Influenza-like illness | 5 (5%) | 10 (10%) | 1 (1%) | 0 | 0 | 16 (17%) | 2 (4%) | 1 (2%) | 0 | 0 | 0 | 3 (6%) |
| Pain in extremity | 9 (9%) | 7 (7%) | 0 | 0 | 0 | 16 (17%) | 3 (6%) | 2 (4%) | 0 | 0 | 0 | 5 (10%) |
| Pyrexia | 7 (7%) | 7 (7%) | 0 | 0 | 0 | 14 (15%) | 7 (14%) | 2 (4%) | 0 | 0 | 0 | 9 (18%) |
| Asthenia | 9 (9%) | 4 (4%) | 0 | 0 | 0 | 13 (14%) | 2 (4%) | 3 (6%) | 0 | 0 | 0 | 5 (10%) |
| Influenza | 5 (5%) | 7 (7%) | 0 | 0 | 0 | 12 (13%) | 4 (8%) | 0 | 1 (2%) | 0 | 0 | 5 (10%) |
| Irregular menstruation* | 8 (8%) | 1 (1%) | 3 (3%) | 0 | 0 | 12 (21%) | 2 (4%) | 1 (2%) | 0 | 0 | 0 | 3 (12%) |
| Toothache | 4 (4%) | 8 (8%) | 0 | 0 | 0 | 12 (13%) | 0 | 1 (2%) | 0 | 0 | 0 | 1 (2%) |
| Insomnia | 6 (6%) | 5 (5%) | 0 | 0 | 0 | 11 (12%) | 1 (2%) | 0 | 0 | 0 | 0 | 1 (2%) |
| Myalgia | 8 (8%) | 2 (2%) | 1 (1%) | 0 | 0 | 11 (12%) | 3 (6%) | 2 (4%) | 0 | 0 | 0 | 5 (10%) |
| Gastroenteritis | 5 (5%) | 5 (5%) | 0 | 0 | 0 | 10 (10%) | 0 | 2 (4%) | 1 (2%) | 0 | 0 | 3 (6%) |
| Iron overload† | 3 (3%) | 5 (5%) | 2 (2%) | 0 | 0 | 10 (10%) | 1 (2%) | 4 (8%) | 0 | 0 | 0 | 5 (10%) |
| Nausea | 9 (9%) | 1 (1%) | 0 | 0 | 0 | 10 (10%) | 4 (8%) | 2 (4%) | 0 | 0 | 0 | 6 (12%) |
| Abdominal pain | 7 (7%) | 2 (2%) | 0 | 0 | 0 | 9 (9%) | 3 (6%) | 2 (4%) | 0 | 0 | 0 | 5 (10%) |
| Upper abdominal pain | 6 (6%) | 3 (3%) | 0 | 0 | 0 | 9 (9%) | 3 (6%) | 0 | 0 | 0 | 0 | 3 (6%) |
| Epistaxis | 8 (8%) | 1 (1%) | 0 | 0 | 0 | 9 (9%) | 1 (2%) | 0 | 0 | 0 | 0 | 1 (2%) |
| Vitamin D deficiency | 2 (2%) | 7 (7%) | 0 | 0 | 0 | 9 (9%) | 1 (2%) | 3 (6%) | 0 | 0 | 0 | 4 (8%) |
| Dizziness | 7 (7%) | 1 (1%) | 0 | 0 | 0 | 8 (8%) | 4 (8%) | 0 | 0 | 0 | 0 | 4 (8%) |
| Rhinitis | 5 (5%) | 3 (3%) | 0 | 0 | 0 | 8 (8%) | 4 (8%) | 1 (2%) | 0 | 0 | 0 | 5 (10%) |
| Traumatic fracture | 2 (2%) | 2 (2%) | 4 (4%) | 0 | 0 | 8 (8%) | 0 | 0 | 1 (2%) | 0 | 0 | 1 (2%) |
| Dyspepsia | 3 (3%) | 4 (4%) | 0 | 0 | 0 | 7 (7%) | 0 | 1 (2%) | 0 | 0 | 0 | 1 (2%) |
| Neck pain | 4 (4%) | 3 (3%) | 0 | 0 | 0 | 7 (7%) | 0 | 2 (4%) | 0 | 0 | 0 | 2 (4%) |
| Erythema | 5 (5%) | 1 (1%) | 0 | 0 | 0 | 6 (6%) | 0 | 0 | 0 | 0 | 0 | 0 |
| Extramedullary haematopoiesis | 1 (1%) | 5 (5%) | 0 | 0 | 0 | 6 (6%) | 0 | 0 | 1 (2%) | 0 | 0 | 1 (2%) |
| Migraine | 4 (4%) | 2 (2%) | 0 | 0 | 0 | 6 (6%) | 0 | 0 | 0 | 0 | 0 | 0 |
| Musculoskeletal pain | 5 (5%) | 1 (1%) | 0 | 0 | 0 | 6 (6%) | 2 (4%) | 1 (2%) | 0 | 0 | 0 | 3 (6%) |
| Palpitations | 5 (5%) | 1 (1%) | 0 | 0 | 0 | 6 (6%) | 5 (10%) | 1 (2%) | 0 | 0 | 0 | 6 (12%) |
| Anxiety | 3 (3%) | 2 (2%) | 0 | 0 | 0 | 5 (5%) | 0 | 0 | 0 | 0 | 0 | 0 |
| Injection-site erythema | 5 (5%) | 0 | 0 | 0 | 0 | 5 (5%) | 0 | 0 | 0 | 0 | 0 | 0 |
| Muscle strain | 3 (3%) | 2 (2%) | 0 | 0 | 0 | 5 (5%) | 0 | 0 | 0 | 0 | 0 | 0 |

(Table 3 continues on next page)

| | Luspatercept (n=96) | | | | | | Placebo (n=49) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 | Total | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 | Total |
| (Continued from previous page) | | | | | | | | | | | | |
| Nasopharyngitis | 3 (3%) | 2 (2%) | 0 | 0 | 0 | 5 (5%) | 0 | 0 | 0 | 0 | 0 | 0 |
| Skin ulcer | 0 | 5 (5%) | 0 | 0 | 0 | 5 (5%) | 0 | 1 (2%) | 0 | 0 | 0 | 1 (2%) |
| Spinal pain | 5 (5%) | 0 | 0 | 0 | 0 | 5 (5%) | 1 (2%) | 0 | 0 | 0 | 0 | 1 (2%) |
| Vomiting | 3 (3%) | 2 (2%) | 0 | 0 | 0 | 5 (5%) | 0 | 0 | 0 | 0 | 0 | 0 |
| Allergic rhinitis | 0 | 4 (4%) | 0 | 0 | 0 | 4 (4%) | 3 (6%) | 0 | 0 | 0 | 0 | 3 (6%) |
| Rhinorrhoea | 2 (2%) | 1 (1%) | 0 | 0 | 0 | 3 (3%) | 3 (6%) | 0 | 0 | 0 | 0 | 3 (6%) |
| Vertigo | 2 (2%) | 1 (1%) | 0 | 0 | 0 | 3 (3%) | 3 (6%) | 0 | 0 | 0 | 0 | 3 (6%) |
| Ear pain | 1 (1%) | 1 (1%) | 0 | 0 | 0 | 2 (2%) | 2 (4%) | 2 (4%) | 0 | 0 | 0 | 4 (8%) |
| Gastro-oesophageal reflux disease | 2 (2%) | 0 | 0 | 0 | 0 | 2 (2%) | 1 (2%) | 2 (4%) | 0 | 0 | 0 | 3 (6%) |
| Muscular weakness | 2 (2%) | 0 | 0 | 0 | 0 | 2 (2%) | 3 (6%) | 0 | 0 | 0 | 0 | 3 (6%) |
| Tonsillitis | 0 | 2 (2%) | 0 | 0 | 0 | 2 (2%) | 0 | 5 (10%) | 1 (2%) | 0 | 0 | 6 (12%) |

All data are n (%). Data on all events, regardless of causality, occurring in 5% or more of patients in either treatment group. NA=not applicable. TEAE=treatment-emergent adverse event. *Irregular menstruation patient proportion calculated per 56 female patients in the luspatercept group and 26 female patients in the placebo group. †Iron overload was defined as serum ferritin concentration of more than 800 µg/L or a liver iron concentration of more than 5 mg/g dry weight.

***Table 3:*** **TEAEs in the safety population**

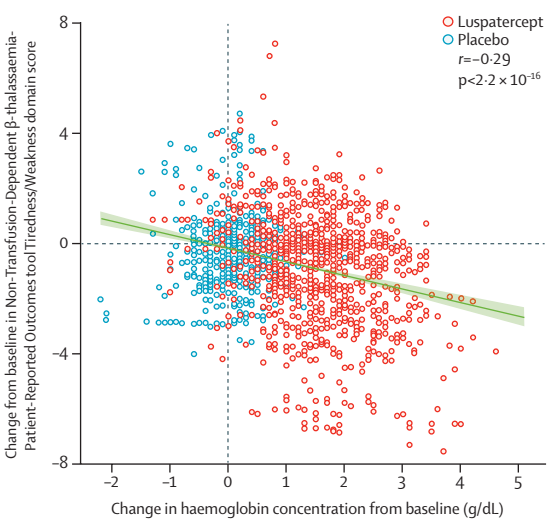


***Figure 2:*** **Correlation between change from baseline in haemoglobin concentration and change in Non-Transfusion-Dependent β-thalassaemia-Patient-Reported Outcomes tool Tiredness/Weakness domain score**
Decrease from baseline in Non-Transfusion-Dependent β-thalassaemia-Patient-Reported Outcome tool Tiredness/Weakness domain score indicates improvement.

might not be as readily detected by patients with fewer symptoms at baseline. Post-hoc analyses have shown that Non-Transfusion-Dependent β-thalassaemia-PRO tool Tiredness/Weakness domain scores were inversely correlated with increased haemoglobin concentration, and an improvement in Non-Transfusion-Dependent β-thalassaemia-PRO tool Tiredness/Weakness domain scores was observed in patients treated with luspatercept, who had a 1·0 g/dL or higher increase in haemoglobin concentration, which is in line with clinical expectations. Previous studies have shown the association between haemoglobin concentrations and HRQoL or mental health in patients with non-transfusion-dependent β-thalassaemia.[4,5,13,14,28,29] The relationship between haemoglobin increase and improvement in Non-Transfusion-Dependent β-thalassaemia-PRO tool Tiredness/Weakness domain score found in this study indicate the potential for meaningful improvement of anaemia-related symptoms affecting patients' HRQoL.

Anaemia improvement directly reflects amelioration of ineffective erythropoiesis.[7] This, in turn, should lead to lower levels of iron overload or improved chelator efficiency.[7,22] Serum ferritin and liver iron concentration did not show significant changes from baseline during the treatment; however, the effects on hepatic iron overload require longer periods of observation to be recognised fully.[30] In addition, the iron chelation therapy in the study was not standardised in terms of type and dosing, thus adding to the complexity of data analysis.

Luspatercept was generally well tolerated, with a lower rate of serious adverse events in the luspatercept group (11 [12%] patients) versus placebo group (12 [25%] patients). Consistent with previous studies,[21–23] the most common treatment-emergent adverse events were bone pain, headache, and arthralgia, which were manageable with over-the-counter analgesics. Bone pain was considered transient, as it was reported more frequently at initial treatment cycles. Most treatment-emergent adverse events were of low-grade severity, and the discontinuation due to treatment-emergent adverse events was low. Notably, no malignancies or thromboembolic events were reported in patients treated with luspatercept during this short follow-up. Thromboembolic events are of particular interest as hypercoagulability, iron overload, and anaemia contribute to the development of cardiovascular disease, which is the leading cause of death in patients with non-transfusion-dependent β-thalassaemia.[2,12] As luspatercept binds to

select transforming growth factor-β ligands and enhances erythropoiesis, premalignancies and malignancies, especially of haematological origin, were considered as adverse events of special interest and were monitored during the study.

The BEYOND study had some limitations. First, one site out of 13 failed to recruit patients for the study, which led to 145 patients being randomly assigned, instead of the assumed 150. The power calculation of the study was based on the assumption of 150 participants in the primary analysis population. Although the analysis of the primary efficacy endpoint included 145 patients instead of 150, this had little effect on the power of the study, which met the primary endpoint, with a two-sided α of 0·05 and an assumed 10% dropout rate. Second, definitive statements of effect cannot be made for phase 2 trials; however, the design of the BEYOND trial (double-blinding, randomisation, and placebo treatment group as control) was aimed to showcase that luspatercept is a safe and efficacious treatment in this patient population, which currently has no alternative options to red blood cell transfusion therapy to manage their detrimental anaemia.

In summary, a significant proportion of luspatercept-treated patients with non-transfusion-dependent β-thalassaemia had increased haemoglobin concentrations compared with patients receiving placebo in the BEYOND study. Moreover, despite no significant difference, the improvement in Non-Transfusion-Dependent β-thalassaemia-PRO tool Tiredness/Weakness domain score was more pronounced with longer luspatercept treatment, and future studies should aim to confirm the long-term efficacy and safety. These findings suggest that luspatercept could be considered a potential first treatment to sustainably improve haemoglobin concentrations and quality of life in patients with non-transfusion-dependent β-thalassaemia, with the potential to decrease the risk of developing serious complications, and to favourably affect long-term outcomes.

#### Contributors

ATT and MDC designed the trial and ATT is the chief investigator. ATT, MDC, AK, EV, SP, AGP, AF, JBP, TDC, GLF, AAT, IT, and VV contributed to data acquisition. DM, ACG, and W-LK accessed and verified the data and W-LK did the statistical analysis. All authors contributed to data interpretation. All authors carefully reviewed and approved the final version. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

#### Declaration of interests

ATT reports receiving consulting fees from Agios Pharmaceuticals; and research funding and consulting fees from Celgene/Bristol Myers Squibb, Ionis Pharmaceuticals, Novartis Pharmaceuticals, and Vifor Pharma. MDC reports receiving advisory board fees from Agios Pharmaceuticals, Celgene/Bristol Myers Squibb, CRISPR Therapeutics/Vertex, Novo Nordisk, Sanofi Genzyme, Silence Therapeutics, and Vifor Pharma. AK reports receiving advisory board fees and consulting fees from Agios Pharmaceuticals, Amgen, Celgene/Bristol Myers Squibb, CRISPR Therapeutics/Vertex, Ionis Pharmaceuticals, Novartis, and Vifor Pharma; and research support, paid to his institution, from Celgene/Bristol Myers Squibb and Novartis; honoraria for lectures, presentations or speakers' bureau from Bristol Myers Squibb, Chiesi Farmaceutuici, CRISPR Therapeutics/Vertex, and Novartis; and personal fees from Bristol Myers Squibb. SP reports receiving grant support, paid to his institution, from Novartis, and personal fees from bluebird bio and Celgene. AGP reports receiving grant support, paid to his institution, from Acceleron Pharma and Celgene, and advisory board fees from Celgene. AF reports advisory board fees from Celgene and grant support, paid to his institution, from bluebird bio and Novartis. JBP reports receiving advisory board fees from bluebird bio, Bristol Myers Squibb, Silence Therapeutics, and Vifor Pharma. TDC reports receiving consultancy fees from Agios Pharmaceuticals, bluebird bio, Bristol Myers Squibb/Celgene, Chiesi Farmaceutici, and Vifor Pharma. GLF reports receiving consulting fees and grant support, paid to his institution, from Agios Pharmaceuticals, Bristol Myers Squibb, and Novartis; and advisory board fees from Bristol Myers Squibb and Novartis; honoraria for lectures, presentations or speakers' bureau from Bristol Myers Squibb and Novartis. AA Thompson reports receiving grant support from Baxalta, Biomarin, bluebird bio, Celgene/Bristol Myers Squibb, CRISPR Therapeutics/Vertex, Editas Medicine, and Novartis; and consulting fees from bluebird bio, Celgene/Bristol Myers Squibb, and CRISPR Therapeutics/Vertex; fees for leadership of fiduciary role in a committee or advocacy group from Global Blood Therapeutics; previous employment (last 12 months) at Ann & Robert H. Lurie Children's Hospital of Chicago, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA; and current employment at Children's Hospital of Philadelphia, Philadelphia, PA, USA. IT reports receiving honoraria from Celgene. KMM reports receiving consulting fees from Agios Pharmaceuticals, Celgene/Bristol Myers Squibb, CRISPR Therapeutics, Novartis, and Vifor Pharma. JTB reports ending employment at Acceleron Pharma in the last 12 months and owning stock in Acceleron Pharma, and Bristol Myers Squibb. OE, W-LK, and DM report being employed by Bristol Myers Squibb. ACG, JL-B, AY, and JKS report being employed by and owning stock in Bristol Myers Squibb. TZ reports ending employment at Bristol Myers Squibb in the last 24 months and owning stock in Bristol Myers Squibb. EV and VV report no conflicts of interest.

#### Data sharing

Bristol Myers Squibb details their data sharing process via the following website: https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html. The data available might vary depending upon the study or request. Each proposal for data sharing is reviewed when received. Given that requests for data sharing are reviewed as they are received, Bristol Myers Squibb cannot specify what data might be shared or when. A request for data sharing can be made through the portal link: Bristol Myers Squibb at: https://vivli.org/ourmember/bristol-myers-squibb/. Upon execution of an agreement, the de-identified or anonymised data sets will be available within the Vivli Research environment at: https://vivli.org/ourmember/bristol-myers-squibb/. Data will be made available to qualified researchers who submit an in-scope proposal approved by the Independent Review Committee as detailed at: https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html.

#### Acknowledgments

We thank all the patients and families who participated in the trial. We thank Prof Emanuele Angelucci, Prof Evangelos Terpos, Prof Jeffrey M Lipton, and Dr Stéphane Ederhy for their role in clinical trial data monitoring. Writing and editorial assistance were provided by Karolina Lech, PhD, of Excerpta Medica, funded by Bristol Myers Squibb. Study was funded by Celgene, a Bristol-Myers Squibb Company in collaboration with Acceleron Pharma Inc., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

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