ORIGINAL ARTICLE

A Phase 3 Trial of Luspatercept in Patients with Transfusion-Dependent β-Thalassemia

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ABSTRACT

BACKGROUND

Patients with transfusion-dependent β-thalassemia need regular red-cell transfusions. Luspatercept, a recombinant fusion protein that binds to select transforming growth factor β superfamily ligands, may enhance erythroid maturation and reduce the transfusion burden (the total number of red-cell units transfused) in such patients.

METHODS

In this randomized, double-blind, phase 3 trial, we assigned, in a 2:1 ratio, adults with transfusion-dependent β-thalassemia to receive best supportive care plus luspatercept (at a dose of 1.00 to 1.25 mg per kilogram of body weight) or placebo for at least 48 weeks. The primary end point was the percentage of patients who had a reduction in the transfusion burden of at least 33% from baseline during weeks 13 through 24 plus a reduction of at least 2 red-cell units over this 12-week interval. Other efficacy end points included reductions in the transfusion burden during any 12-week interval and results of iron studies.

RESULTS

A total of 224 patients were assigned to the luspatercept group and 112 to the placebo group. Luspatercept or placebo was administered for a median of approximately 64 weeks in both groups. The percentage of patients who had a reduction in the transfusion burden of at least 33% from baseline during weeks 13 through 24 plus a reduction of at least 2 red-cell units over this 12-week interval was significantly greater in the luspatercept group than in the placebo group (21.4% vs. 4.5%, P<0.001). During any 12-week interval, the percentage of patients who had a reduction in transfusion burden of at least 33% was greater in the luspatercept group than in the placebo group (70.5% vs. 29.5%), as was the percentage of those who had a reduction of at least 50% (40.2% vs. 6.3%). The least-squares mean difference between the groups in serum ferritin levels at week 48 was −348 μg per liter (95% confidence interval, −517 to −179) in favor of luspatercept. Adverse events of transient bone pain, arthralgia, dizziness, hypertension, and hyperuricemia were more common with luspatercept than placebo.

CONCLUSIONS

The percentage of patients with transfusion-dependent β-thalassemia who had a reduction in transfusion burden was significantly greater in the luspatercept group than in the placebo group, and few adverse events led to the discontinuation of treatment. (Funded by Celgene and Acceleron Pharma; BELIEVE ClinicalTrials.gov number, NCT02604433; EudraCT number, 2015-003224-31.)

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The β-thalassemias are a group of inherited hemoglobin disorders that represent a substantial global health burden.[1,2] Defective production of β-globin chains of adult hemoglobin causes an imbalanced ratio of α-globin to β-globin.[2,3] Genetic mutations and secondary modifiers that affect this imbalance determine the severity of ineffective erythropoiesis and chronic anemia.[2,3] β-thalassemia may be classified clinically as transfusion-dependent or non–transfusion-dependent.[2,3] Patients with transfusion-dependent β-thalassemia present in early childhood and need regular red-cell transfusions to maintain adequate hemoglobin levels.[2,3]

Red-cell transfusion carries infectious and noninfectious risks.[4] Despite the availability of iron-chelation therapy, many patients with transfusion-dependent β-thalassemia still have complications related to secondary iron overload that may result in end-organ failure and death in early adulthood.[4-6] Iron-chelation therapy also carries risks of adverse effects.[6] The lifelong need for blood transfusions and iron-chelation therapy negatively affects the quality of life of patients with transfusion-dependent β-thalassemia.[4,7,8] Allogeneic hematopoietic stem-cell transplantation and gene therapy are potentially curative but carry inherent risks and are suitable only in a limited population of patients.[9-12]

Luspatercept is a recombinant fusion protein that binds to select transforming growth factor β superfamily ligands and enhances late-stage erythropoiesis. This erythroid maturation agent increased hemoglobin levels in mouse models[13,14] by a mechanism that is not yet fully understood.[13,15,16] Luspatercept increased hemoglobin levels in a phase 1 study involving healthy postmenopausal women.[15] In a subsequent open-label, dose-ranging, phase 2 study, the transfusion burden (the total number of red-cell units transfused) during any 12-week interval was reduced by at least 20% from baseline in 26 of 32 patients with transfusion-dependent β-thalassemia (81%) who received luspatercept at a dose of 0.60 to 1.25 mg per kilogram of body weight.[17] Here, we report the results of the phase 3 BELIEVE trial, which evaluated the efficacy and safety of luspatercept in adults with transfusion-dependent β-thalassemia.

Methods

Trial Design and Oversight

This randomized, double-blind, placebo-controlled trial was performed at 65 sites in 15 countries (Australia and countries across Europe, the Middle East, North Africa, North America, and Southeast Asia). The sponsors, in collaboration with an independent steering committee and with advice from regulatory agencies, participated in the design and conduct of the trial (including the development of the trial protocol and statistical analysis plan, available with the full text of this article at NEJM.org); in the collection, management, analysis, and interpretation of the data; and in the preparation and review of the manuscript. The trial was conducted in accordance with the tenets of the Declaration of Helsinki. The trial was approved by an institutional review board or ethics committee at each participating site. All the patients provided written informed consent. An independent data monitoring committee assessed the conduct of the trial and safety outcomes, and the authors evaluated the findings. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The manuscript was written by the authors (with assistance from a medical writer paid by the sponsors). An overview of the trial design is provided in Figure S1 in the Supplementary Appendix, available at NEJM.org.

Patients

Patients 18 years of age or older who had confirmed β-thalassemia or hemoglobin E–β-thalassemia and were regularly receiving transfusions (6 to 20 units of packed red cells, with no transfusion-free period of >35 days, within 24 weeks before randomization) were eligible for inclusion in the trial. Additional key inclusion and exclusion criteria are provided in the Supplementary Appendix.

Randomization and Trial Groups

Patients were randomly assigned in a 2:1 ratio to receive luspatercept or placebo subcutaneously every 21 days for at least 48 weeks. Randomization was stratified according to geographic region (North America and Europe, Middle East and North Africa, or Asia–Pacific) to ensure a balanced global distribution. The starting dose of luspatercept was 1.00 mg per kilogram of body weight and was adjusted up to 1.25 mg per kilogram according to rules specified in the protocol. All the patients also received best supportive care, including red-cell transfusion and iron-chelation therapy, according to local guidelines.

Patients who completed the 48-week double-

blind treatment period could continue to receive luspatercept or placebo in a double-blind manner until all the patients completed the initial 48-week period. The trial-group assignments were then unblinded.

END POINTS AND ASSESSMENTS

The primary end point was the percentage of patients who had an erythroid response, defined as a reduction in the transfusion burden of at least 33% from baseline (the 12-week period before the first dose of luspatercept or placebo) during weeks 13 through 24 plus a reduction of at least 2 red-cell units over this 12-week interval. Key secondary end points were a reduction in the transfusion burden of at least 33% from baseline during weeks 37 through 48 plus a reduction of at least 2 red-cell units over this 12-week interval, a reduction in the transfusion burden of at least 50% from baseline during weeks 13 through 24 plus a reduction of at least 2 red-cell units over this 12-week interval, a reduction in the transfusion burden of at least 50% from baseline during weeks 37 through 48 plus a reduction of at least 2 red-cell units over this 12-week interval, and the mean change from baseline in the transfusion burden during weeks 13 through 24.

Other efficacy end points were reductions in the transfusion burden of at least 33% and at least 50% from baseline during any 12-week interval plus a reduction of at least 2 red-cell units over the interval; reductions of at least 33% and at least 50% from baseline during any 24-week interval; duration of the longest continuous erythroid response and time to the first erythroid response during any 12-week interval; transfusion independence (defined as the absence of transfusion) and the duration of transfusion independence during any 8-week and 12-week interval; the mean reduction from baseline in the transfusion burden during any 24-week interval; the mean change from baseline in the pretransfusion hemoglobin level (in defined 12-week intervals), which was evaluated to identify any variation in transfusion practice; the serum ferritin level during weeks 37 through 48 or in the 12-week period before discontinuation of luspatercept or placebo; the liver iron concentration at week 48, as assessed by means of magnetic resonance imaging (MRI); and myocardial iron deposition at week 48, as assessed by T2*-weighted MRI (which allows for distortions in the magnetic field due to hemosiderin or ferritin to quantify effective T2). Safety analyses included assessments of the incidence and severity of adverse events; all adverse events that occurred or worsened during the treatment period or a 9-week follow-up period are reported, as well as adverse events that occurred later but were considered by the investigator to be related to the trial drug.

STATISTICAL ANALYSIS

We estimated that a target sample of 300 patients would provide the trial with 90% power, at a two-sided alpha level of 0.05 and an assumed dropout rate of 10%, to detect a 20% difference between the luspatercept group and the placebo group with respect to the primary end point. All efficacy analyses were performed in the intention-to-treat population, which comprised all patients who underwent randomization, regardless of whether they received the assigned intervention. For the patients who did not complete the double-blind treatment period, transfusion records were collected up to 48 weeks or 9 weeks after the last dose, whichever was later. With respect to the primary end point and the first three key secondary end points of reductions in the transfusion burden from baseline, the patients who discontinued luspatercept or placebo during a 12-week interval were considered not to have had a response. With respect to the fourth key secondary end point (the mean change from baseline in the transfusion burden during weeks 13 through 24), the patients who discontinued luspatercept or placebo were excluded from the analysis.

In the primary end-point analysis, the difference between the luspatercept group and the placebo group in the percentage of patients who had an erythroid response was evaluated with the use of the Cochran–Mantel–Haenszel test, with stratification according to geographic region (North America and Europe, Middle East and North Africa, or Asia–Pacific). The odds ratio and corresponding two-sided 95% confidence interval and P value were calculated; luspatercept would be shown to be superior to placebo if a greater percentage of patients in the luspatercept group than in the placebo group had an erythroid response, with a P value of 0.05 or less for the between-group difference. In the analyses of the key secondary end points, the reduction in the transfusion burden was evaluated with the use of methods similar to those in the analysis of the pri-

mary end point. The mean change in the transfusion burden was evaluated with the use of analysis of covariance with the stratification factor (geographic region) and baseline transfusion burden as covariates. To control for overall type 1 error, gate-keeping methods were used for the key secondary efficacy end points, which were evaluated sequentially after the result with respect to the primary end point was shown to be statistically significant. Control for multiple comparisons was not planned for other efficacy evaluations. Additional information on the statistical analyses is provided in the Methods section in the Supplementary Appendix.

RESULTS

PATIENTS

From July 2016 through June 2017, a total of 336 patients were randomly assigned to the luspatercept group (224 patients) or the placebo group (112 patients); these patients were included in the intention-to-treat population. A total of 332 of the 336 patients received the assigned intervention and were included in the safety population (223 patients in the luspatercept group and 109 in the placebo group) (Fig. 1).

The median age of the patients in the intention-to-treat population was 30 years; 30.7% had a β^0/β^0 genotype, and 57.7% had undergone splenectomy (Table 1). Patients had a median hemoglobin threshold for transfusion of 9.3 g per deciliter and received a median of 14 units of red cells during the 24-week baseline period (12 weeks of historical information plus 12 weeks of prospectively collected run-in data). Baseline characteristics were broadly similar in both trial groups.

REDUCTION IN THE TRANSFUSION BURDEN

The percentage of patients who had a reduction in the transfusion burden of at least 33% from baseline during weeks 13 through 24 plus a reduction of at least 2 red-cell units over this 12-week interval (the primary end point) was significantly greater in the luspatercept group than in the placebo group (21.4% [48 of 224 patients] vs. 4.5% [5 of 112 patients]; odds ratio, 5.79; 95% confidence interval [CI], 2.24 to 14.97; P<0.001) (Fig. 2). Similarly, a significantly greater percentage of patients in the luspatercept group than in the placebo group had reductions in the transfusion burden of at least 33% from baseline during weeks 37 through 48 plus a reduction of at least 2 red-cell units over this 12-week interval (19.6% vs. 3.6%, P<0.001), of at least 50% during weeks 13 through 24 plus a reduction of at least 2 red-cell units over this interval (7.6% vs. 1.8%, P=0.03), and of at least 50% during weeks 37 through 48 plus a reduction of at least 2 red-cell units over this interval (10.3% vs. 0.9%, P=0.002) — all key secondary end points (Fig. 2). The transfusion burdens during fixed 12-week and 24-week intervals are shown in Figure S2 in the Supplementary Appendix.

The results with respect to the primary end point favored luspatercept across all prespecified subgroups; a significant benefit for luspatercept over placebo was observed in most patient subgroups (Fig. S3A). With respect to the secondary end points related to reductions in the transfusion burden of at least 33% or at least 50% from baseline, the results favored luspatercept over placebo across most subgroups (Fig. S3B through S3D). The findings from these subgroup analyses also suggest that the magnitude of response to luspatercept may be lower in patients with a β^0/β^0 genotype than in those with a non-β^0/β^0 genotype.

The percentage of patients who had a reduction in the transfusion burden of at least 33% from baseline was greater in the luspatercept group than in the placebo group during any 12-week interval (70.5% vs. 29.5%; odds ratio, 5.69; 95% CI, 3.46 to 9.35) or any 24-week interval (41.1% vs. 2.7%; odds ratio, 25.02; 95% CI, 7.76 to 80.71). The percentage of patients who had a reduction in the transfusion burden of at least 50% from baseline was also greater in the luspatercept group than in the placebo group during any 12-week interval (40.2% vs. 6.3%; odds ratio, 9.95; 95% CI, 4.44 to 22.33) or any 24-week interval (16.5% vs. 0.9%; odds ratio, 20.37; 95% CI, 2.86 to 144.94) (Fig. 2). Among the patients who had a reduction in the transfusion burden of at least 33% from baseline and those who had a reduction of at least 50%, we estimated that the reduction in the number of red-cell units from baseline per patient per 24 weeks would be 6.55 units and 8.27 units, respectively. The reductions in the transfusion burden according to luspatercept dose groups are reported in the Results section in the Supplementary Appendix.

ADDITIONAL EFFICACY ANALYSES

The least-squares mean difference in the key secondary end point of mean change from baseline in

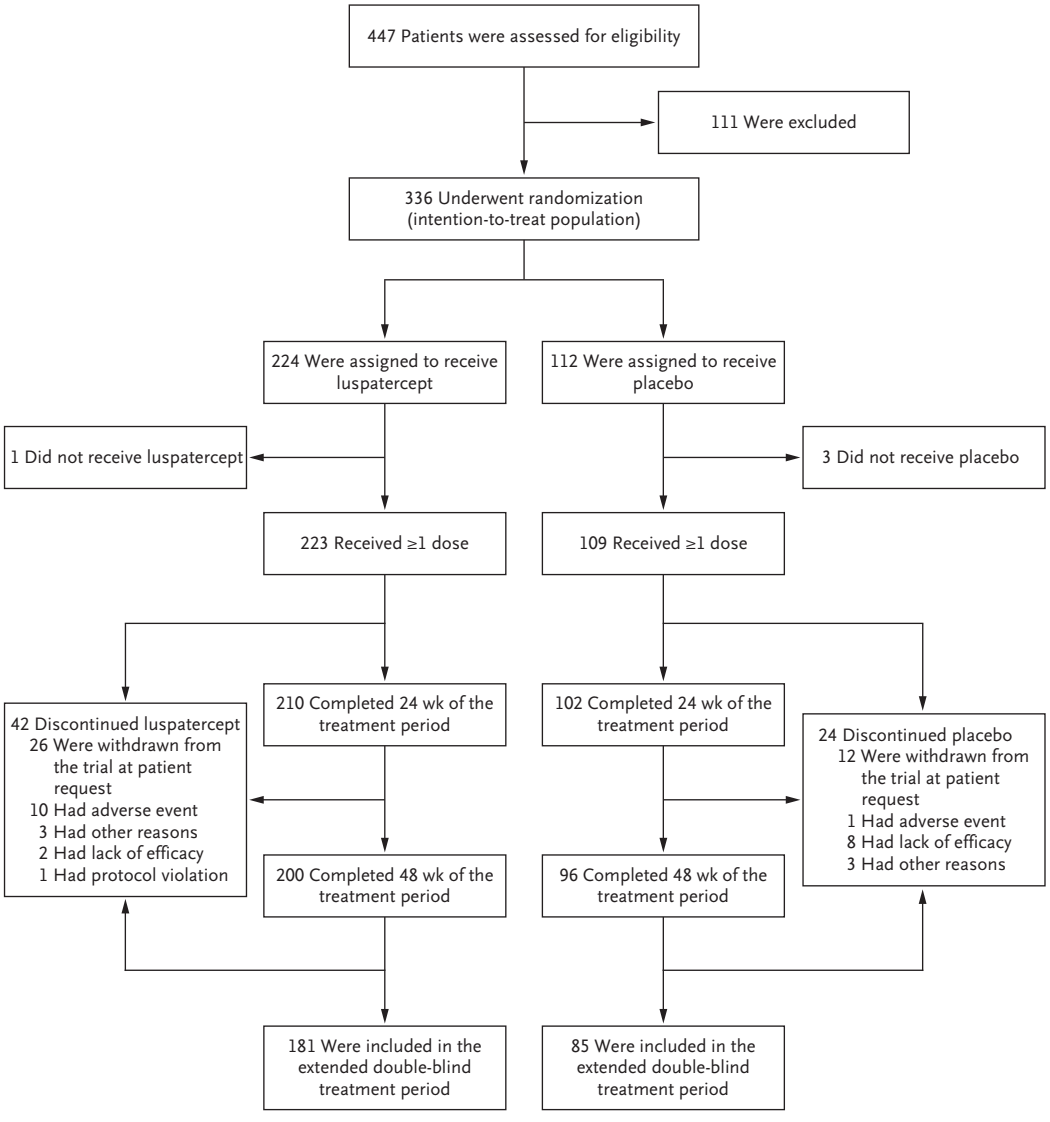

Figure 1. Screening, Randomization, and Follow-up.

The intention-to-treat population comprised 336 patients who underwent randomization, in a 2:1 ratio, to receive luspatercept or placebo; the safety population comprised 332 patients who received at least one dose of luspatercept or placebo. In addition to luspatercept or placebo, all the patients received best supportive care according to local guidelines. For any patients who did not complete 24 or 48 weeks of the double-blind treatment period, transfusion records were collected up to 48 weeks or 9 weeks after the last dose, whichever was later. Among the 10 patients who had adverse events that led to the discontinuation of luspatercept, 1 had pulmonary embolism; 1 had deep-vein thrombosis and superficial thrombophlebitis; 1 had myalgia and headache; 1 had chest discomfort, malaise, arthralgia, back pain, and exertional dyspnea; 1 had drug-induced liver injury; 1 had portal-vein thrombosis; 1 had arthralgia and deep-vein thrombosis; 1 had bone pain; 1 had sinus tachycardia; and 1 had pain, an increased uric acid level, an increased urine albumin-to-creatinine ratio, and facial swelling. The one adverse event that led to discontinuation of placebo was acute cholecystitis. These data are not equivalent to the adverse events that led to discontinuation, because adverse events were not reported as the primary reason for discontinuation for 2 patients. Other reasons given for discontinuation of luspatercept were interest in other clinical studies, plan to get pregnant, transferred residence, and personal reasons, and those given for discontinuation of placebo were personal reasons and not wishing to enter the optional extended double-blind treatment period.

Table 1. Baseline Demographic and Disease Characteristics.*

Characteristic	Luspatercept Group (N=224)	Placebo Group (N=112)	Total (N=336)
Median age (range) — yr	30 (18–66)	30 (18–59)	30 (18–66)
Female sex — no. (%)	132 (58.9)	63 (56.3)	195 (58.0)
Geographic region — no. (%)			
North America and Europe	100 (44.6)	51 (45.5)	151 (44.9)
Asia–Pacific	72 (32.1)	35 (31.3)	107 (31.8)
Middle East and North Africa	52 (23.2)	26 (23.2)	78 (23.2)
Diagnosis of hemoglobin E–β-thalassemia — no. (%)	31 (13.8)	21 (18.8)	52 (15.5)
Presence of a β^0/β^0 genotype — no. (%)	68 (30.4)	35 (31.3)	103 (30.7)
Median pretransfusion hemoglobin level (range) — g/dl†	9.3 (4.5–11.4)	9.2 (5.8–11.7)	9.3 (4.5–11.7)
Median transfusion burden (range) — no. of red-cell units in 24 wk‡	14 (6–24)	15 (6–26)	14 (6–26)
Transfusion burden category — no. (%)			
≤10 red-cell units in 24 wk	33 (14.7)	14 (12.5)	47 (14.0)
>10 to ≤15 red-cell units in 24 wk	96 (42.9)	47 (42.0)	143 (42.6)
>15 red-cell units in 24 wk	95 (42.4)	51 (45.5)	146 (43.5)
Previous splenectomy — no. (%)	129 (57.6)	65 (58.0)	194 (57.7)
Mean total bilirubin level — μmol/liter	35.4	35.9	NA
Median liver iron concentration (range) — mg/g of dry liver weight	6.14 (0.8–125.0)	5.05 (0.2–53.2)	5.69 (0.2–125.0)
Liver iron concentration category — no. (%)			
0–3 mg/g of dry liver weight	70 (31.3)	37 (33.0)	107 (31.8)
>3–7 mg/g of dry liver weight	51 (22.8)	30 (26.8)	81 (24.1)
>7–15 mg/g of dry liver weight	38 (17.0)	19 (17.0)	57 (17.0)
>15 mg/g of dry liver weight	65 (29.0)	26 (23.2)	91 (27.1)
Median myocardial iron deposition (range) — msec§	34.7 (3.0–205.9)	36.3 (6.4–57.5)	35.0 (3.0–205.9)
Median serum ferritin level (range) — μg/liter	1441.3 (88.0–6400.0)	1301.5 (136.0–6400.0)	NA
Current iron-chelation therapy — no. (%)¶	222 (99.6)	109 (100.0)	331 (99.7)

* Data on all baseline demographics and disease characteristics, except current iron-chelation therapy, are shown for the intention-to-treat population (all patients who underwent randomization). Percentages may not total 100 because of rounding. To convert the values for bilirubin to milligrams per deciliter, divide by 17.1. NA denotes not available.

† The baseline pretransfusion hemoglobin level in a patient was defined as the median of all documented pretransfusion hemoglobin levels measured in the 24 weeks (12 weeks of historical information plus 12 weeks of prospectively collected run-in data) before the first dose of luspatercept or placebo.

‡ The baseline transfusion burden was defined as the number of red-cell units transfused in the 24 weeks before the first dose of luspatercept or placebo; red-cell units transfused on the day of the first dose of were considered part of the baseline transfusion burden.

§ Myocardial iron deposition was assessed by means of T2*-weighted magnetic resonance imaging (which allows for distortions in the magnetic field due to hemosiderin or ferritin to quantify effective T2); a value higher than 10 msec indicates minimal risk of heart failure.[18]

¶ Current iron-chelation therapy was assessed in the safety population (all patients who underwent randomization and received ≥1 dose of luspatercept or placebo — 223 in the luspatercept group and 109 in the placebo group). Combination iron-chelation therapy was permitted.

the transfusion burden during weeks 13 through 24 was significantly in favor of luspatercept over placebo (–1.35 red-cell units per 12 weeks; 95% CI, –1.77 to –0.93; P<0.001). A reduction in the transfusion burden with luspatercept (and an increase with placebo) was observed consistently across the other fixed time intervals that were assessed.

The median time to the first response with luspatercept was within the first treatment cycle (12.0 days or 24.5 days among the patients who had reductions in the transfusion burden of ≥33% or ≥50%, respectively, during any 12-week interval). Three quarters of patients (75%) who had at least a 33% reduction in transfusion burden dur-

ing any rolling 12-week interval with luspatercept had a response within 86 days (four treatment cycles). Post hoc analyses indicate that the response was faster among the patients with a non-β^0/β^0 genotype than among those with a β^0/β^0 genotype. Additional data regarding the time to the first response are provided in the Results section in the Supplementary Appendix.

The median longest duration of response with luspatercept was 104 days or 98 days

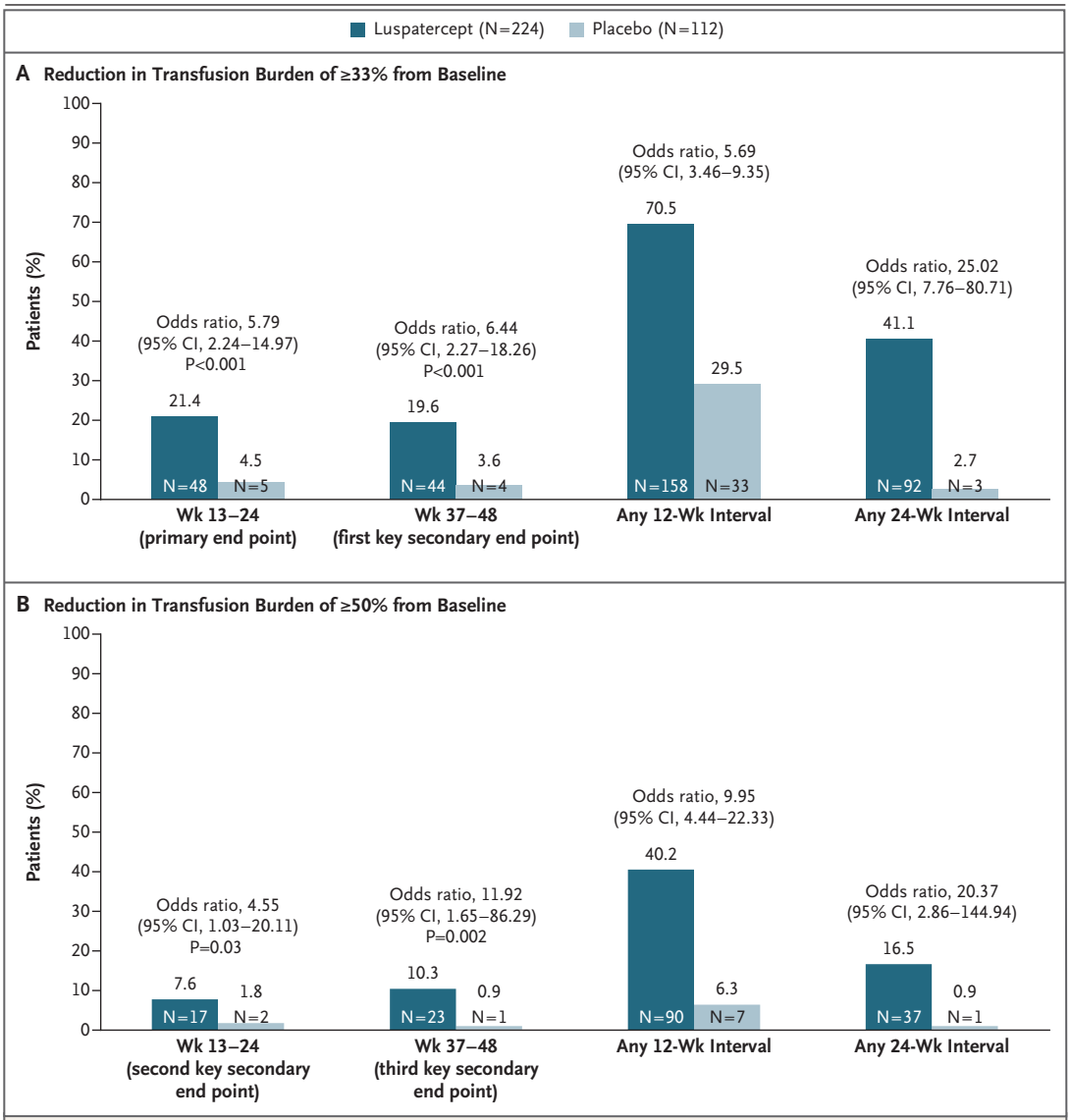

Figure 2. Percentage of Patients Who Had a Reduction in the Transfusion Burden of at Least 33% or at Least 50% from Baseline.

Reductions in the transfusion burden (defined as the total number of red-cell units transfused in a specified time interval) were assessed in the intention-to-treat population. Panel A shows the percentages of patients who had a reduction in the transfusion burden of at least 33% from baseline during weeks 13 through 24 (primary end point), during weeks 37 through 48 (first key secondary end point), and during any 12-week or 24-week interval. Panel B shows the percentages of patients who had a reduction in the transfusion burden of at least 50% from baseline during weeks 13 through 24 (second key secondary end point), during weeks 37 through 48 (third key secondary end point), and during any 12-week or 24-week interval. A reduction of at least 2 red-cell units over the fixed and nonfixed 12-week intervals was also required for those end points. To control for multiple comparisons, key secondary end points were evaluated in sequential order once the primary efficacy analysis had shown statistical significance.

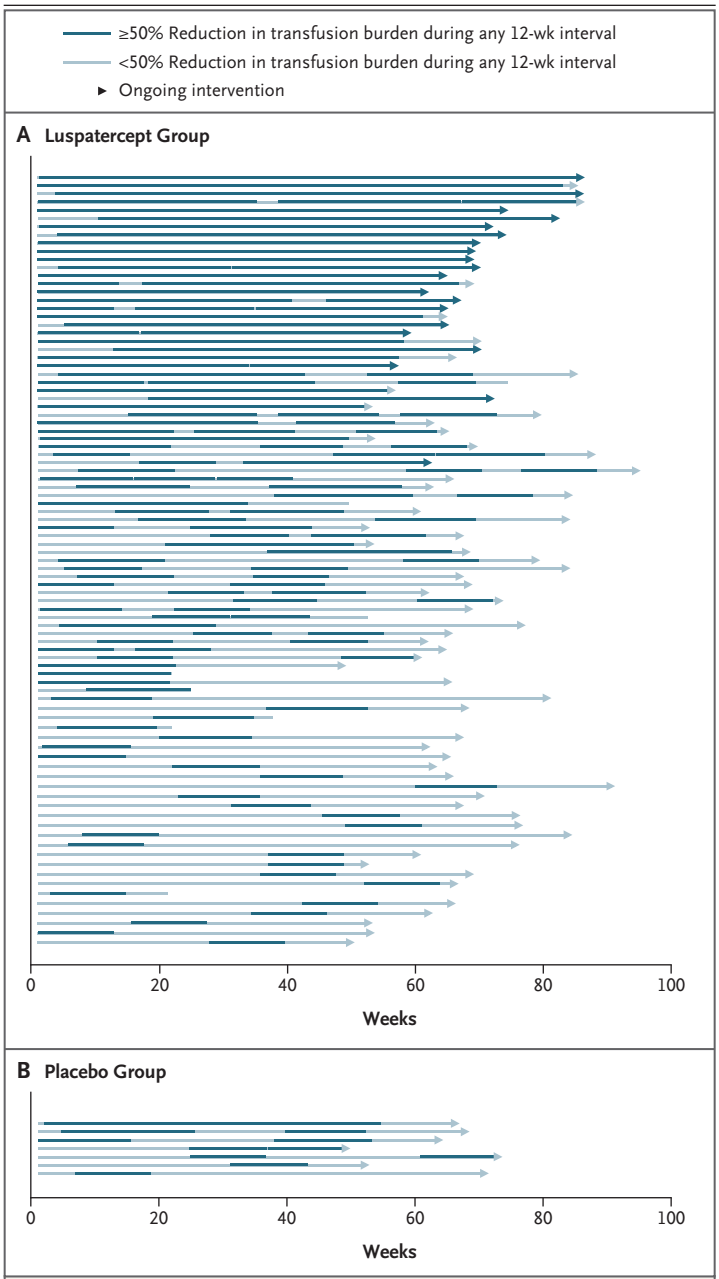

Figure 3. Swimmer Plot of Response Periods for Patients Who Had a Reduction in the Transfusion Burden of at Least 50% from Baseline During any 12-Week Interval in the Intention-to-Treat Population.

Each row (swim lane) on the y axis represents an individual patient in the luspatercept group (Panel A) or the placebo group (Panel B). A response period was defined as a continuous period in which a patient had a reduction in the transfusion burden of at least 50% from baseline during any 12-week interval. Different response periods may have overlapped. All patients received best supportive care in addition to luspatercept or placebo.

among the patients who had reductions in the transfusion burden from baseline of at least 33% (158 patients) or at least 50% (90 patients), respectively, during any 12-week interval (Fig. S4A and S4B). Data regarding the cumulative duration of response are provided in the Results section in the Supplementary Appendix.

Most patients (80.4%) in the luspatercept group who had a reduction in the transfusion burden of at least 33% from baseline during any 12-week interval had at least two distinct episodes of response, and 51.3% had at least four episodes of response. Similarly, 68.9% of the patients in the luspatercept group who had at least a 50% reduction in the transfusion burden in any 12-week interval had at least two distinct responses and 33.3% had at least four responses (Fig. 3).

A greater percentage of patients in the luspatercept group than in the placebo group had transfusion independence during any 8-week interval (10.7% [24 patients] vs. 1.8% [2 patients]; odds ratio, 6.76; 95% CI, 1.56 to 29.28). Additional data regarding transfusion independence are provided in the Results section in the Supplementary Appendix.

Pretransfusion hemoglobin levels did not decrease over the course of the trial. The mean pretransfusion hemoglobin levels increased slightly from baseline in all fixed 12-week intervals (range, 0.09 to 0.38 g per deciliter) among the patients receiving luspatercept at any dose. Among the patients in the placebo group, a minimal change from baseline in the mean pretransfusion hemoglobin level was observed during the fixed 12-week intervals (range, −0.04 to 0.03 g per deciliter) (Table S1).

IRON STUDIES

Serum ferritin levels at week 48 were reduced from baseline in the luspatercept group (mean [±SD] change, −248±800 μg per liter) and were increased from baseline in the placebo group (mean change, 107±526 μg per liter) (Fig. S5A). The least-squares mean difference (the value in the luspatercept group minus the value in the placebo group) was −348 μg per liter (95% CI, −517 to −179). No clinically meaningful changes from baseline in liver iron concentration or myocardial iron deposition were observed during the assess-

ment period (Fig. S5B through S5C, and the Results section in the Supplementary Appendix).

SAFETY

Luspatercept or placebo was administered for a median of approximately 64 weeks in both groups (range, 3 to 97 weeks in the luspatercept group and 9 to 92 weeks in the placebo group). Among the 223 patients who received luspatercept, 120 (53.8%) received a maximum dose of 1.00 mg per kilogram of body weight and 103 (46.2%) received a maximum dose of 1.25 mg per kilogram.

Most patients had at least one adverse event (214 of 223 patients [96.0%; 95% CI, 92.5 to 98.1] in the luspatercept group and 101 of 109 patients [92.7%; 95% CI, 86.0 to 96.8] in the placebo group). Adverse events that occurred in at least 5% of the patients in the luspatercept group and for which the incidence was at least 5% greater in the luspatercept group than in the placebo group were bone pain (19.7% vs. 8.3%), arthralgia (19.3% vs. 11.9%), dizziness (11.2% vs. 4.6%), hypertension (8.1% vs. 2.8%), and hyperuricemia (7.2% vs. 0%) (Table 2). Bone pain was reported more frequently during the first 24 weeks than during the last 24 weeks of the trial in both groups (18.4% [41 patients] and 4.9% [11 patients], respectively, in the luspatercept group and 7.3% [8 patients] and 0.9% [1 patient], respectively, in the placebo group). Bone pain was generally of short duration and low grade and was managed with the use of simple analgesic medications.

A greater percentage of patients in the luspatercept group than in the placebo group had at least one adverse event of grade 3 or higher during the treatment period (29.1% [95% CI, 23.3 to 35.6] vs. 15.6% [95% CI, 9.4 to 23.8]). The most common adverse events of grade 3 or higher that occurred in the luspatercept group during the treatment period were anemia (3.1%, as compared with 0% in the placebo group), increased liver iron concentration (2.7%, as compared with 0.9% in the placebo group), and hyperuricemia (2.7%, as compared with 0% in the placebo group) (Table 2, and the Results section in the Supplementary Appendix).

At least one serious adverse event was reported during the treatment period in 15.2% (95% CI, 10.8 to 20.6) of the patients in the luspatercept group and in 5.5% (95% CI, 2.0 to 11.6) of the patients in the placebo group (Table 2, and the Results section in the Supplementary Appendix). No malignant or premalignant conditions were reported. Clinically confirmed thromboembolic adverse events occurred during the treatment period in 8 patients (3.6%) in the luspatercept group (including two grade ≥3 events) and in 1 patient (0.9%) in the placebo group. A total of 8 patients in the luspatercept group had deep-vein thrombosis (3 patients), ischemic stroke (3 patients), superficial thrombophlebitis (2 patients), portal-vein thrombosis (1 patient), and pulmonary embolism (1 patient), and phlebitis occurred in 1 patient in the placebo group. All such events occurred in patients who had undergone splenectomy and had at least one other risk factor for thromboembolic disease, including a history of venous thrombosis or thrombocytosis at baseline.

Discontinuation of luspatercept or placebo because of an adverse event that occurred during the treatment period was reported in 12 patients (5.4%) in the luspatercept group and in 1 patient (0.9%) in the placebo group. No deaths related to luspatercept or placebo were reported. Additional data regarding discontinuation of luspatercept or placebo and dose reduction are reported in the Results section in the Supplementary Appendix.

DISCUSSION

This multinational, phase 3, randomized, placebo-controlled trial established the efficacy and safety of luspatercept in reducing the transfusion burden among patients with transfusion-dependent β-thalassemia. The results of all primary and key secondary efficacy analyses were in favor of luspatercept over placebo. Furthermore, a greater percentage of patients in the luspatercept group than in the placebo group had reductions in the transfusion burden of at least 33% or at least 50% from baseline during any 12-week or 24-week interval; in the luspatercept group, reductions in the transfusion burden of at least 33% and at least 50% were attained by 71% and 40%, respectively, of the patients during any 12-week interval. Transfusion independence was attained by 11% of the patients in the luspatercept group during any 8-week interval.

Table 2. Adverse Events, Regardless of Causality, Occurring during the Treatment Period in at Least 5% of Patients in Either Trial Group.*

Adverse Event†	Luspatercept Group (N=223)		Placebo Group (N=109)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number (percent)			
Patients with ≥1 adverse event	214 (96.0)	65 (29.1)	101 (92.7)	17 (15.6)
Back pain	61 (27.4)	3 (1.3)	32 (29.4)	1 (0.9)
Upper respiratory tract infection	59 (26.5)	2 (0.9)	36 (33.0)	0
Headache	58 (26.0)	1 (0.4)	26 (23.9)	1 (0.9)
Bone pain	44 (19.7)	3 (1.3)	9 (8.3)	0
Arthralgia	43 (19.3)	0	13 (11.9)	0
Pyrexia	36 (16.1)	0	23 (21.1)	0
Cough	32 (14.3)	1 (0.4)	12 (11.0)	0
Fatigue	30 (13.5)	0	14 (12.8)	0
Oropharyngeal pain	28 (12.6)	0	12 (11.0)	0
Diarrhea	27 (12.1)	1 (0.4)	11 (10.1)	0
Dizziness	25 (11.2)	0	5 (4.6)	0
Myalgia	22 (9.9)	0	11 (10.1)	0
Asthenia	22 (9.9)	0	11 (10.1)	0
Pain in extremity	21 (9.4)	0	9 (8.3)	0
Pharyngitis	20 (9.0)	1 (0.4)	13 (11.9)	0
Nausea	20 (9.0)	0	6 (5.5)	0
Influenza	19 (8.5)	0	6 (5.5)	0
Abdominal pain	18 (8.1)	0	7 (6.4)	0
Vomiting	18 (8.1)	1 (0.4)	8 (7.3)	0
Hypertension	18 (8.1)	4 (1.8)	3 (2.8)	0
Influenza-like illness	17 (7.6)	0	8 (7.3)	0
Hyperuricemia	16 (7.2)	6 (2.7)	0	0
Abdominal pain upper	15 (6.7)	0	7 (6.4)	0
Viral upper respiratory tract infection	14 (6.3)	1 (0.4)	2 (1.8)	0
Musculoskeletal pain	14 (6.3)	0	9 (8.3)	0
Pain	13 (5.8)	0	4 (3.7)	0
Gastroenteritis	12 (5.4)	2 (0.9)	8 (7.3)	0
Nasal congestion	12 (5.4)	0	5 (4.6)	0
Liver iron concentration increased	12 (5.4)	6 (2.7)	2 (1.8)	1 (0.9)
Neck pain	10 (4.5)	0	8 (7.3)	0
Osteoporosis	9 (4.0)	0	6 (5.5)	0
Musculoskeletal chest pain	5 (2.2)	0	7 (6.4)	0
Urinary tract infection	4 (1.8)	0	7 (6.4)	0
Fall	4 (1.8)	0	7 (6.4)	0

* Data are shown for the safety population. An adverse event that occurred during the treatment period was defined as any adverse event that occurred or worsened on or after the day of first dose of luspatercept or placebo, up to 63 days after the last dose; any adverse event with later onset that was determined by the investigator to be related to luspatercept or placebo was also considered to have occurred during the treatment period. All the patients received best supportive care in addition to luspatercept or placebo.

† Adverse events were classified according to preferred term in the *Medical Dictionary for Regulatory Activities*, version 20.0, and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. A patient was counted only once for multiple events within each preferred term. Serious adverse events that occurred during the treatment period included abdominal pain, back pain, gastroenteritis, pain, and viral upper respiratory tract infection (reported in 1 patient [0.4%] in the luspatercept group for each event); pyrexia (reported in 2 patients [0.9%] in the luspatercept group); and urinary tract infection (reported in 1 patient in the placebo group [0.4%]). Additional serious adverse events and adverse events of grade 3 or higher that occurred during the treatment period, for which an event of any grade occurred in less than 5% of patients, are listed in the Results section in the Supplementary Appendix.

Pretransfusion hemoglobin levels were maintained; therefore, the observed benefit of luspatercept on the reduction in the transfusion burden was not due to variation in hemoglobin thresholds for transfusion.

Patients with β-thalassemia have varying degrees of bone marrow suppression caused by their baseline transfusion regimen. Therefore, long-term clinical assessment and evaluation of treatment effects are essential. In the current trial, pretransfusion hemoglobin levels for each patient were maintained according to local practice guidelines. In addition, multiple assessments of reduction in the transfusion burden were used at various fixed and nonfixed time intervals. Analyses of reductions during nonfixed time intervals show the percentage of patients deriving a benefit from the intervention at any time and, we believe, better reflect real-world clinical practice than do fixed-interval analyses.

Reductions in the transfusion burden of at least 33% and at least 50% from baseline were estimated to avoid the need for approximately 7 and 8 red-cell units, respectively, per patient over 6 months. In practice, patients could receive fewer red-cell units per visit or have a longer duration between transfusion visits. Either of these outcomes may reduce the iron load, improve patient convenience, and reduce the associated burden of disease. A clinical benefit of luspatercept was observed in all patient subgroups, but the percentage of patients who had a response may have been greater among those with a non-β^0/β^0 genotype than among those with a β^0/β^0 genotype.

The cornerstone of disease management for most patients with β-thalassemia is supportive care, which typically includes regular red-cell transfusions and iron-chelation therapy.[4] These available therapies have resulted in an improved prognosis and longer survival, but high morbidity and mortality persist.[19,20] Access to red-cell transfusion is a challenge, particularly in resource-constrained countries where β-thalassemia is more prevalent.[1,21] As a result, some patients had suboptimal hemoglobin levels and delays in the initiation of transfusion therapy.

A major challenge of regular red-cell transfusion therapy is secondary iron overload with associated damage to cardiac, hepatic, and endocrine tissues.[4] Despite developments in iron-chelation therapy, limitations to its efficacy and safety exist, and access and adherence to treatment are not uniform.[2,4,22] A reduction in the transfusion burden should decrease ongoing iron intake and, thus, the iron-chelation therapy requirements.

The reduction in the serum ferritin level observed with luspatercept, as compared with placebo, suggests favorable early effects on iron balance. However, we were unable to assess the full effect of luspatercept on iron status in the current analysis owing to the slow dynamics of iron loading and unloading, especially in target organs.[18] The observed reduction in the serum ferritin level with luspatercept could be due to improved iron utilization (by reducing ineffective erythropoiesis and promoting red-cell production),[13,14] reduced transfusional iron intake augmenting the efficiency of iron-chelation therapy, or both.

The safety of luspatercept was consistent with previous experience in this and other patient populations.[17,23] Luspatercept was associated with an increased incidence of bone pain, arthralgia, dizziness, hypertension, and hyperuricemia. Bone pain was generally of short duration and low grade. The percentage of patients who had thromboembolic events was somewhat increased with luspatercept but was in line with the finding in a previous study involving patients with transfusion-dependent β-thalassemia (3.6% in the current trial, as compared with 6.3% in a previous study).[24] All thromboembolic events occurred in patients who had undergone splenectomy and had additional risk factors for thromboembolism.[25] We recommend that patients receiving luspatercept are assessed and assigned prophylactic intervention according to local or international risk-stratification guidelines for the prevention of thromboembolic events.

Among patients with transfusion-dependent β-thalassemia, a reduction in the transfusion burden was observed in a significantly greater percentage of patients who received luspatercept than in those who received placebo. The response with luspatercept was sustained, and multiple episodes of response were observed. Luspatercept was associated with mainly low-grade adverse events, although the percentage of patients who had thromboembolic events appeared to be somewhat increased. A 5-year open-label extension phase is under way to provide long-term data on the safety of luspatercept and its effects on the transfusion burden and iron outcomes.

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APPENDIX

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