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A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease

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ABSTRACT

BACKGROUND

Deoxygenated sickle hemoglobin (HbS) polymerization drives the pathophysiology of sickle cell disease. Therefore, direct inhibition of HbS polymerization has potential to favorably modify disease outcomes. Voxelotor is an HbS polymerization inhibitor.

METHODS

In a multicenter, phase 3, double-blind, randomized, placebo-controlled trial, we compared the efficacy and safety of two dose levels of voxelotor (1500 mg and 900 mg, administered orally once daily) with placebo in persons with sickle cell disease. The primary end point was the percentage of participants who had a hemoglobin response, which was defined as an increase of more than 1.0 g per deciliter from baseline at week 24 in the intention-to-treat analysis.

RESULTS

A total of 274 participants were randomly assigned in a 1:1:1 ratio to receive a once-daily oral dose of 1500 mg of voxelotor, 900 mg of voxelotor, or placebo. Most participants had sickle cell anemia (homozygous hemoglobin S or hemoglobin Sβ^0-thalassemia), and approximately two thirds were receiving hydroxyurea at baseline. In the intention-to-treat analysis, a significantly higher percentage of participants had a hemoglobin response in the 1500-mg voxelotor group (51%; 95% confidence interval [CI], 41 to 61) than in the placebo group (7%; 95% CI, 1 to 12). Anemia worsened between baseline and week 24 in fewer participants in each voxelotor dose group than in those receiving placebo. At week 24, the 1500-mg voxelotor group had significantly greater reductions from baseline in the indirect bilirubin level and percentage of reticulocytes than the placebo group. The percentage of participants with an adverse event that occurred or worsened during the treatment period was similar across the trial groups. Adverse events of at least grade 3 occurred in 26% of the participants in the 1500-mg voxelotor group, 23% in the 900-mg voxelotor group, and 26% in the placebo group. Most adverse events were not related to the trial drug or placebo, as determined by the investigators.

CONCLUSIONS

In this phase 3 randomized, placebo-controlled trial involving participants with sickle cell disease, voxelotor significantly increased hemoglobin levels and reduced markers of hemolysis. These findings are consistent with inhibition of HbS polymerization and indicate a disease-modifying potential. (Funded by Global Blood Therapeutics; HOPE ClinicalTrials.gov number, NCT03036813.)

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*A complete list of the investigators in the HOPE trial is provided in the Supplementary Appendix, available at NEJM.org.

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A Quick Take is available at NEJM.org

Sickle cell disease affects approximately 100,000 persons in the United States and reduces life expectancy by approximately 30 years.[1] The disease is caused by a single amino acid substitution resulting in the production of sickle hemoglobin (HbS).[2] HbS polymerizes when deoxygenated, resulting in red-cell sickling and membrane damage.[2,3] These abnormalities lead to hemolysis, chronic anemia, inflammation, and vaso-occlusion, which cause the acute and chronic manifestations of sickle cell disease.[2,3] Chronic hemolysis and anemia result in vascular damage and tissue hypoxia, which contribute to multiorgan damage and an increased risk of death.[4-7] Although two medications approved by the Food and Drug Administration are available (hydroxyurea and L-glutamine [USAN, glutamine]),[8,9] chronic medical complications and early death in persons with sickle cell disease remain a substantial burden. In particular, chronic organ dysfunction has become a leading cause of death in adults with sickle cell disease in the United States.[10,11]

Deoxygenated HbS polymerization drives the molecular pathogenesis of sickle cell disease; thus, inhibiting HbS polymerization in red cells could have a disease-modifying effect. Because the rate of HbS polymerization is extremely sensitive to deoxygenated HbS concentration, small changes in concentration can have substantial effects on polymerization.[12,13] This hypothesis is supported by the absence of symptoms of sickle cell disease in persons who are compound heterozygotes for HbS and deletional hereditary persistence of fetal hemoglobin, who have antisickling fetal hemoglobin levels of approximately 30%.[13]

Voxelotor is an HbS polymerization inhibitor that reversibly binds to hemoglobin to stabilize the oxygenated hemoglobin state.[14,15] Once-daily oral administration of voxelotor has been shown to reduce red-cell sickling and blood viscosity and improve red-cell deformability in vitro[14-16] and to extend red-cell half-life and reduce anemia and hemolysis in vivo.[15,17] In a phase 1/2 trial, voxelotor showed favorable pharmacokinetics and dose-dependent increases in hemoglobin–oxygen affinity; daily doses of up to 1000 mg for 28 days and 900 mg for at least 90 days were associated with only low-grade toxic effects in persons with sickle cell disease.[17] The phase 3 HOPE (Hemoglobin Oxygen Affinity Modulation to Inhibit HbS Polymerization) trial was designed to evaluate the efficacy and safety of voxelotor, as compared with placebo, in adolescents and adults with sickle cell disease.

METHODS

TRIAL DESIGN AND OVERSIGHT

The phase 3 HOPE trial is an international, multicenter, randomized, placebo-controlled, double-blind, parallel-group trial. Global Blood Therapeutics, the trial sponsor, provided the investigational agent and collaborated with academic investigators on the design of the trial and the analysis and interpretation of the data. All the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, available with the full text of this article at NEJM.org. This trial was conducted in accordance with the International Conference on Harmonisation for Good Clinical Practice guidelines, the principles of the Declaration of Helsinki, and all applicable country-specific regulatory guidelines. The conduct of the trial was overseen by IQVIA, a contract research organization, and an independent data and safety monitoring board performed periodic assessments. Written informed consent was obtained from the adult participants (18 to 65 years of age) and from the parents or guardians of the adolescent participants (12 to 17 years of age). The protocol and consent form were approved by an independent ethics committee at each participating trial site. All drafts of the manuscript were prepared by the authors, with writing assistance from a medical writer funded by the sponsor. The sponsor and all authors and institutions agreed to data confidentiality during manuscript development.

PARTICIPANTS

Eligible participants were between 12 and 65 years of age, had confirmed sickle cell disease (homozygous hemoglobin S, sickle hemoglobin C disease, hemoglobin Sβ-thalassemia, or other genotypic variants of sickle cell disease), had a hemoglobin level between 5.5 and 10.5 g per deciliter during screening, and had had 1 to 10 vaso-occlusive crises in the past 12 months (defined as acute painful crisis or acute chest syndrome for which there was no explanation other than vaso-occlusive crisis and that met the protocol-specified criteria [see the Supplementary

Appendix, available at NEJM.org]). Participants who were receiving hydroxyurea at a dose that had been stable for at least 3 months before they provided informed consent were eligible. Participants who were receiving regular red-cell transfusion therapy, had received a transfusion in the past 60 days, or had been hospitalized for vaso-occlusive crisis within 14 days before providing informed consent were excluded. Participants could be rescreened at the discretion of an investigator.

TRIAL REGIMEN

Participants were randomly assigned in a 1:1:1 ratio to receive a once-daily oral dose of 1500 mg of voxelotor, 900 mg of voxelotor, or placebo. The trial included a screening period (28 to 35 days), a treatment period (up to 72 weeks), and an end-of-trial visit at 4 weeks (range, 3 to 5) after the last dose of the trial drug or placebo. Stratification factors included hydroxyurea use (yes or no), geographic region (North America, Europe, or other), and age (adolescent [12 to 17 years] or adult [18 to 65 years]).

END POINTS AND ASSESSMENTS

The primary end point was the percentage of participants who had a hemoglobin response, which was defined as an increase from baseline of more than 1.0 g per deciliter at week 24. Secondary end points included the change in hemoglobin level from baseline to week 24, laboratory markers associated with hemolysis (indirect bilirubin level, absolute reticulocyte count and percentage of reticulocytes, and lactate dehydrogenase level), and the annualized incidence rate of vaso-occlusive crisis. Clinical assessments were performed at screening, at baseline, every 2 weeks for the first 8 weeks of the treatment period, every 4 weeks up to week 24, and every 3 months until the end of the treatment period. Serum erythropoietin levels were assessed at baseline and every 3 months until the end of the treatment period. All laboratory studies were performed at a central laboratory.

Pharmacokinetic and pharmacodynamic modeling was used to correlate voxelotor exposure and response (e.g., changes in the levels of hemoglobin and markers of hemolysis). Hemoglobin occupancy was defined as the percentage of hemoglobin bound by voxelotor, calculated as the concentration of voxelotor in red cells divided by the concentration of hemoglobin in red cells, as previously described.[17,18]

Participants who received at least one dose of the trial drug or placebo were assessed for safety. Adverse events that occurred on or after initiation of the trial drug or placebo or preexisting adverse events that worsened during the treatment period for up to 28 days after the last dose were assessed and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. The relationship of an adverse event to the trial drug or placebo was adjudicated by the investigators. Adverse events not related to sickle cell disease and those related to sickle cell disease were tabulated separately. Attribution of an adverse event to a cause other than a new therapeutic agent may be inexact.

STATISTICAL ANALYSIS

All participants who underwent randomization (intention-to-treat population) were included in the primary efficacy analysis, which was performed when the last trial participant reached week 24. Two protocol-specified interim analyses preceded the primary analysis (see the Supplementary Appendix).[19] To maintain an overall type I error rate of 5% (two-sided), the Lan–DeMets alpha-spending function with an O'Brien–Fleming boundary was used to determine the alpha allocation for the analyses (an alpha level of 0.0481 was used in the primary analysis). A hierarchical testing procedure was implemented in the following order until the P value exceeded 0.0481: percentage of participants who had a hemoglobin response, absolute change in hemoglobin level, relative change in indirect bilirubin level, relative change in the percentage of reticulocytes, and relative change in lactate dehydrogenase level; the comparisons between the 1500-mg dose and placebo were tested with respect to all end points before the comparisons between the 900-mg dose and placebo.

The exact Cochran–Mantel–Haenszel test was used to compare the percentages of participants who had a hemoglobin response in each voxelotor dose group with the placebo group, with the same stratification factors as those used for randomization. Baseline values were calculated as the mean values of the data collected at screening and on the day of randomization, and the values at week 24 were calculated as the mean

values of the data collected at weeks 20 and 24. If one time point was missing, data from the other time point were used.

Absolute change in hemoglobin level, relative change in indirect bilirubin level, absolute reticulocyte count and percentage of reticulocytes, and lactate dehydrogenase level from baseline to week 24 were analyzed with the use of a regression model for repeated measures. Independent variables included trial-group assignment, trial visit, interaction between trial-group assignment and visit, baseline hydroxyurea use, geographic region, and age group. Intrapatient variability was modeled with the use of an unstructured covariance matrix.

In the intention-to-treat analysis, hemoglobin measurements taken within 8 weeks after red-cell transfusion were replaced with the last-observed hemoglobin value before the red-cell transfusion. Participants who had missing data at weeks 20 and 24, initiated hydroxyurea therapy after baseline, or received a red-cell transfusion because of anemia before week 24 were considered not to have had a hemoglobin response in the primary end-point analysis. In a per-protocol analysis of observed hemoglobin response, participants who completed 24 weeks of the assigned regimen and did not initiate hydroxyurea treatment after randomization and before week 24 were included; no adjustment was made for red-cell transfusions.

RESULTS

PARTICIPANTS

From January 2017 through May 2018, a total of 274 participants were enrolled at 60 institutions across 12 countries — 90 were assigned to the 1500-mg voxelotor group, 92 to the 900-mg voxelotor group, and 92 to the placebo group (Fig. 1). Baseline characteristics of the three trial groups were generally well balanced (Table 1). Most participants had sickle cell anemia (homozygous hemoglobin S or hemoglobin Sβ^0-thalassemia), and approximately two thirds were receiving hydroxyurea at baseline. As of October 31, 2018 (the date of data cutoff for the primary end-point analysis), the median duration of follow-up was 42.3 weeks (range, 0.1 to 73.3) in the 1500-mg voxelotor group, 38.1 weeks (range, 4.0 to 72.4) in the 900-mg voxelotor group, and 37.2 weeks (range, 8.1 to 72.9) in the placebo group.

HEMOGLOBIN RESPONSE AND MARKERS OF HEMOLYSIS

In the intention-to-treat analysis, a hemoglobin response at week 24 was observed in a significantly greater percentage of participants in the 1500-mg voxelotor group (51% [46 of 90]; 95% confidence interval [CI], 41 to 61) than in the placebo group (7% [6 of 92]; 95% CI, 1 to 12) (P<0.001). In the 900-mg voxelotor group, 33% (30 of 92) (95% CI, 23 to 42) had a hemoglobin response at week 24. In the per-protocol analysis of observed data, the percentage of participants who had a hemoglobin response was 59% (44 of 74) in the 1500-mg voxelotor group, 38% (30 of 79) in the 900-mg voxelotor group, and 9% (7 of 76) in the placebo group (Fig. 2A). The percentage of participants who had a hemoglobin response was higher in the 1500-mg voxelotor group than in the placebo group, regardless of concurrent hydroxyurea use or anemia severity at baseline (Fig. S1 in the Supplementary Appendix). Acute anemic episodes (defined as a decrease in the hemoglobin level of >2.0 g per deciliter from baseline at any time during the trial) occurred in fewer participants in each voxelotor dose group than in those receiving placebo, with annualized incidence rates that were lower by a factor of three for the 1500-mg voxelotor group (0.06 vs. 0.18 episodes per person-year) and by a factor of 4.5 for the 900-mg voxelotor group (0.04 vs. 0.18 episodes per person-year).

In the intention-to-treat analysis, the adjusted mean change in hemoglobin level from baseline to week 24 was 1.1 g per deciliter (95% CI, 0.9 to 1.4; P<0.001) in the 1500-mg voxelotor group, 0.6 g per deciliter (95% CI, 0.3 to 0.8) in the 900-mg voxelotor group, and −0.1 g per deciliter (95% CI, −0.3 to 0.2) in the placebo group (Fig. 2B). In the per-protocol analysis, the mean change in hemoglobin level was 1.3 g per deciliter in the 1500-mg voxelotor group, 0.7 g per deciliter in the 900-mg voxelotor group, and 0 g per deciliter in the placebo group (Fig. S2 in the Supplementary Appendix). Hemoglobin levels of at least 10 g per deciliter at week 24 were observed in 41% of the participants in the 1500-mg voxelotor group, 20% in the 900-mg voxelotor group, and 9% in the placebo group. The mean increase in hemoglobin level among the participants receiving voxelotor was consistent across patient subgroups, regardless of concurrent hydroxyurea use or baseline anemia severity (Table

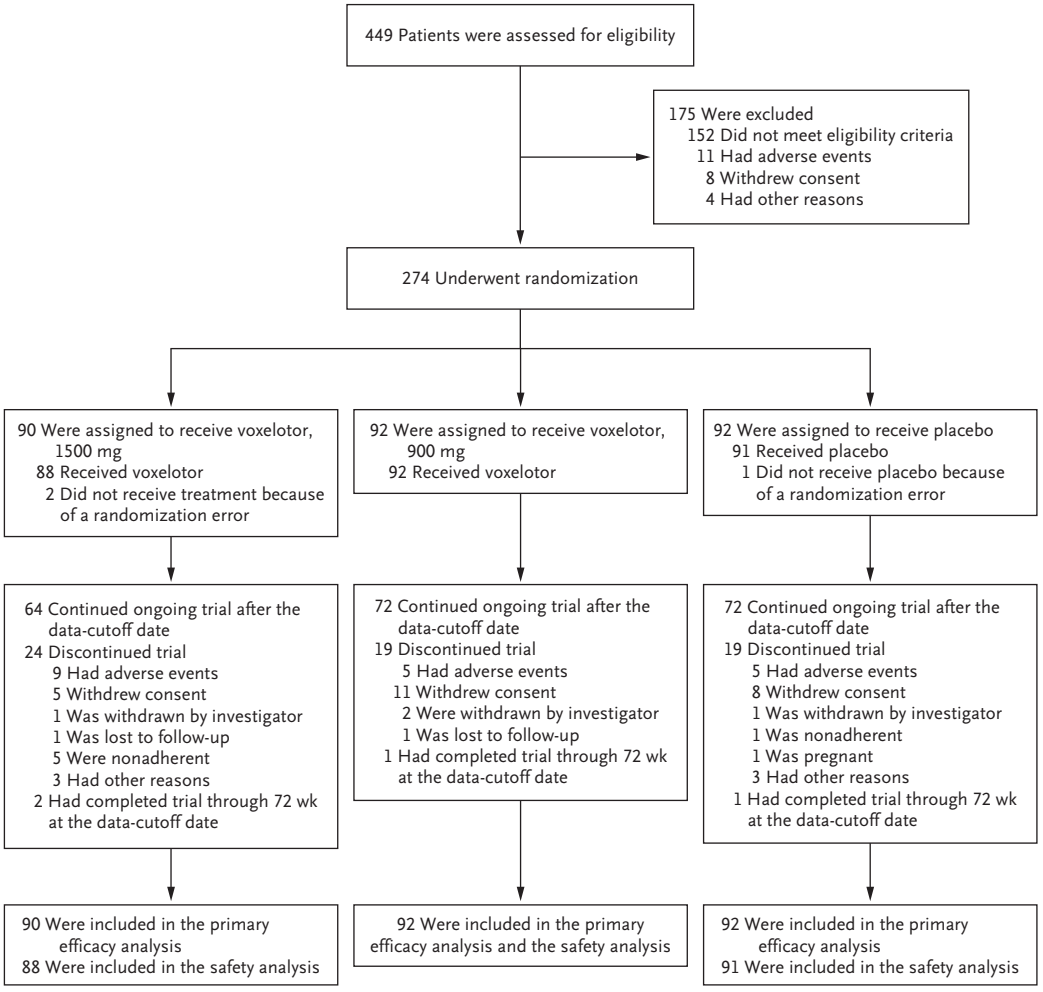

Figure 1. Screening, Randomization, and Follow-up.

Shown is the disposition of the trial participants at the time of the primary analysis, performed when the last participant in the trial reached week 24.

S1 in the Supplementary Appendix). Hemoglobin occupancy (geometric mean percentage) was 26.5% in the 1500-mg voxelotor group and 17.1% in the 900-mg voxelotor group.

The decrease in indirect bilirubin level from baseline to week 24 was significantly greater in the 1500-mg voxelotor group than in the placebo group (mean change, –29.1% vs. –3.2%; P<0.001), and the relative change in the percentage of reticulocytes was significantly greater in the 1500-mg voxelotor group (a mean decrease of –19.9%) than in the placebo group (a mean increase of 4.5%) (P<0.001) (Table 2). Absolute reticulocyte count and lactate dehydrogenase level showed numerical but nonsignificant decreases from baseline to week 24 with the 1500-mg dose of voxelotor as compared with placebo (Table 2). Reductions in these markers from baseline were observed at several time points (Fig. S3 in the Supplementary Appendix). All four measures of hemolysis showed a response that improved with increasing whole-blood concentrations of voxelotor.

Although the median baseline erythropoietin levels were similar across the trial groups, a trend toward a lower median erythropoietin level was observed in the 1500-mg voxelotor group through week 24 (Table S2 in the Supplementary Appen-

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Voxelotor, 1500 mg (N=90)	Voxelotor, 900 mg (N=92)	Placebo (N=92)
Age — yr			
Median	24	24	28
Range	12–59	12–59	12–64
Age group — no. (%)			
12 to <18 yr	14 (16)	15 (16)	17 (18)
≥18 yr	76 (84)	77 (84)	75 (82)
Female sex — no. (%)	58 (64)	51 (55)	50 (54)
Race or ethnic group — no. (%)†			
Black	59 (66)	61 (66)	63 (68)
Arab or Middle Eastern	20 (22)	20 (22)	20 (22)
White	12 (13)	7 (8)	5 (5)
Asian	1 (1)	1 (1)	0
Other	2 (2)	5 (5)	6 (7)
Geographic region — no. (%)			
North America	34 (38)	36 (39)	35 (38)
Europe	19 (21)	19 (21)	18 (20)
Other	37 (41)	37 (40)	39 (42)
Sickle cell disease genotype — no. (%)			
Homozygous hemoglobin S	61 (68)	71 (77)	74 (80)
Hemoglobin Sβ^0-thalassemia	18 (20)	13 (14)	11 (12)
Hemoglobin Sβ^+-thalassemia	7 (8)	2 (2)	3 (3)
Hemoglobin SC	3 (3)	2 (2)	2 (2)
Other variant	1 (1)	4 (4)	2 (2)
Baseline hemoglobin level — g/dl			
Median	8.7	8.3	8.6
Range	5.9–10.8	5.9–10.8	6.1–10.5
No. of vaso-occlusive crises in the past 12 months — no. of patients (%)			
1	35 (39)	41 (45)	39 (42)
2–10	55 (61)	51 (55)	53 (58)
Patients receiving hydroxyurea at baseline — no. (%)	58 (64)	63 (68)	58 (63)

* There were no significant between-group differences in demographic and clinical characteristics at baseline. Percentages may not total 100 because of rounding.
† Race or ethnic group was self-reported; participants could be included in more than one category of race or ethnic group.

dix). No exposure-related increase in the erythropoietin level was observed in the two voxelotor dose groups, as compared with the placebo group (Fig. S4 in the Supplementary Appendix).

The percentages of participants who underwent red-cell transfusions during the trial period were similar in the three trial groups (33% in the 1500-mg voxelotor group, 32% in the 900-mg voxelotor group, and 25% in the placebo group). Most transfusions were performed because of acute vaso-occlusive crises.

ANNUALIZED INCIDENCE RATE OF VASO-OCCLUSIVE CRISIS

The annualized adjusted incidence rate of vaso-occlusive crisis (the number of crises per person-

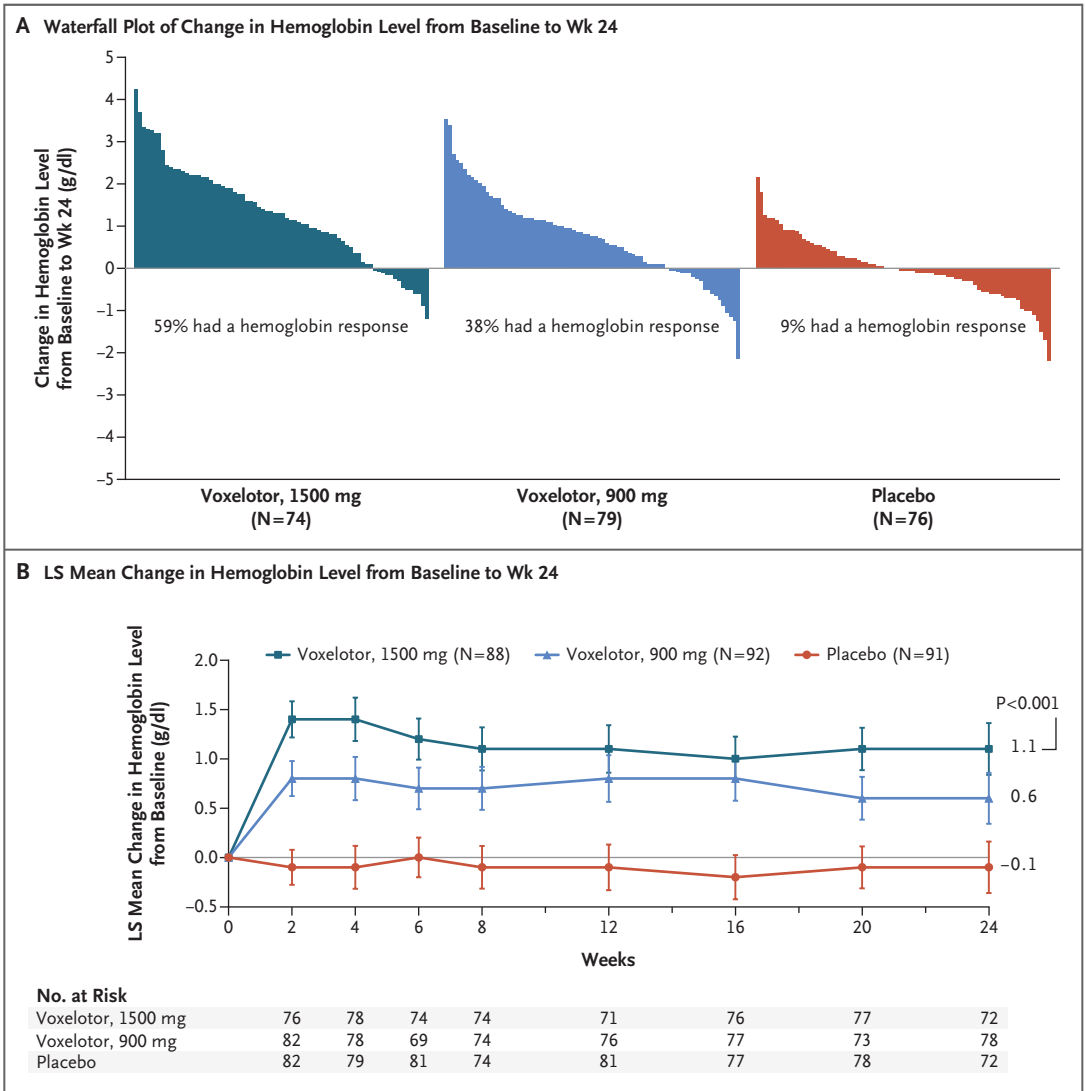

Figure 2. Change in Hemoglobin Level from Baseline to Week 24.

Panel A shows a waterfall plot of change in hemoglobin level from baseline to week 24 for the 1500-mg dose of voxelotor, the 900-mg dose of voxelotor, and placebo in the per-protocol analysis that included observed data from the participants who completed 24 weeks of the assigned regimen and did not initiate hydroxyurea after randomization and before week 24; vertical bars in the plot represent individual participants. The percentage of participants who had a hemoglobin response (defined as an increase in the hemoglobin level of >1.0 g per deciliter from baseline at week 24) is reported for each trial group. Baseline values were calculated as the mean values of the data collected at screening and on the day of randomization. Values for the response at week 24 were calculated as the mean values of the data collected at weeks 20 and 24. Panel B shows the least-squares (LS) mean change, with 95% confidence intervals, in hemoglobin level from baseline to week 24 in the intention-to-treat analysis. The total number of participants in each trial group represents those who had any data included in the regression model for repeated measures (data were not included for two patients in the 1500-mg voxelotor group and one in the placebo group); the sample sizes varied over time. Laboratory values within 8 weeks after any red-cell transfusion were imputed as the last value before the transfusion. Laboratory values obtained after hydroxyurea treatment had been initiated after randomization were excluded for the participants who had not been receiving hydroxyurea at baseline (1 participant in the 1500-mg voxelotor group and 3 participants in the placebo group). P<0.001 is for the comparison between the 1500-mg voxelotor group and the placebo group at week 24.

Table 2. Change in the Levels of Hemoglobin and Markers of Hemolysis from Baseline to Week 24.*

Variable	Voxelotor, 1500 mg		Voxelotor, 900 mg		Placebo	
	No. of Participants†	Change from Baseline to Week 24‡	No. of Participants†	Change from Baseline to Week 24‡	No. of Participants†	Change from Baseline to Week 24‡
		LS mean (95% CI)		*LS mean (95% CI)*		*LS mean (95% CI)*
Absolute change in hemoglobin level — g/dl	88	1.1 (0.9 to 1.4)§	92	0.6 (0.3 to 0.8)	91	–0.1 (–0.3 to 0.2)
Relative change in indirect bilirubin level — %	85	–29.1 (–35.9 to –22.2)§	88	–20.3 (–27.1 to –13.6)	85	–3.2 (–10.1 to 3.8)
Relative change in percentage of reticulocytes — %	88	–19.9 (–29.0 to –10.9)§	92	–1.3 (–10.3 to 7.7)	91	4.5 (–4.5 to 13.6)
Relative change in absolute reticulocyte count — %	88	–8.0 (–18.1 to 2.1)	92	5.1 (–4.9 to 15.2)	91	3.1 (–7.0 to 13.2)
Relative change in lactate dehydrogenase level — %	88	–4.5 (–11.9 to 2.8)	90	1.4 (–5.9 to 8.7)	87	3.4 (–4.0 to 10.9)

* Laboratory values within 8 weeks after any red-cell transfusion were imputed as the last value before the transfusion. Laboratory values after hydroxyurea had been initiated after randomization were excluded for participants who had not been receiving hydroxyurea at baseline (four participants in the 1500-mg voxelotor group and three participants in the placebo group). LS denotes least-squares.
† The number of participants represents those for whom any observations were included in the regression model for repeated measures.
‡ Baseline values were calculated as the mean values of the data collected at screening and on the day of randomization.
§ P<0.001 for the comparison with placebo.

year) was 2.77 in the 1500-mg voxelotor group, 2.76 in the 900-mg voxelotor group, and 3.19 in the placebo group (Table 3). For participants who had had at least two crises in the past year, the incidence rate was 2.88 in the 1500-mg voxelotor group, 3.39 in the 900-mg voxelotor group, and 3.50 in the placebo group. The percentages of participants who had had at least one vaso-occlusive crisis were 67% in the 1500-mg voxelotor group, 66% in the 900-mg voxelotor group, and 69% in the placebo group. A trend of reduced incidence of crises over time with voxelotor, as compared with placebo, was observed (Fig. S5 in the Supplementary Appendix). A total of 179 crises occurred in the 1500-mg voxelotor group, 183 occurred in the 900-mg voxelotor group, and 219 occurred in the placebo group.

SAFETY

The median duration of treatment was 42.6 weeks (range, 4.0 to 73.1) in the 1500-mg voxelotor group, 38.1 weeks (2.0 to 72.3) in the 900-mg voxelotor group, and 36.4 weeks (0.3 to 72.7) in the placebo group. Adverse events not related to sickle cell disease that occurred or worsened during the treatment period were reported in 83 of 88 participants (94%) in the 1500-mg voxelotor group, 86 of 92 participants (93%) in the 900-mg voxelotor group, and 81 of 91 participants (89%) in the placebo group (Table 3). The most common adverse events, with an incidence of at least 20%, were headache and diarrhea (Table 3). The majority of adverse events were grade 1 or 2; the percentages of participants who had an adverse event of at least grade 3, a serious adverse event, and treatment discontinuation because of an adverse event did not differ substantially among the three trial groups. Most adverse events were judged by the investigators to be unrelated to the trial drug or placebo. Additional details are provided in Tables S3 and S4 in the Supplementary Appendix.

No substantial differences in the percentages of participants who had sickle cell disease–related adverse events among the trial groups were observed (76% [67 of 88] in the 1500-mg voxelotor group, 73% [67 of 92] in the 900-mg voxelotor group, and 73% [66 of 91] in the placebo group). Four participants had fatal adverse events (one participant in the 1500-mg voxelotor group had pulmonary sepsis, sickle cell anemia with crisis, and acute sickle hepatic crisis; one in the 900-mg

Table 3. Annualized Incidence Rate of Vaso-Occlusive Crisis and the Most Common Adverse Events That Occurred or Worsened during the Treatment Period.

Variable	Voxelotor, 1500 mg (N=88)	Voxelotor, 900 mg (N=92)	Placebo (N=91)
Annualized incidence rate of vaso-occlusive crisis — no. of crises per person-yr (95% CI)*	2.77 (2.15 to 3.57)	2.76 (2.15 to 3.53)	3.19 (2.50 to 4.07)
Participants with ≥1 vaso-occlusive crisis — no. (%)	59 (67)	61 (66)	63 (69)
Total no. of vaso-occlusive crises	179	183	219
Adverse events not related to sickle cell disease — no. (%)†			
Incidence of adverse events of any grade	83 (94)	86 (93)	81 (89)
Adverse events with ≥10% incidence			
Headache	23 (26)	14 (15)	20 (22)
Diarrhea	18 (20)	16 (17)	9 (10)
Nausea	15 (17)	15 (16)	9 (10)
Arthralgia	13 (15)	11 (12)	11 (12)
Upper respiratory tract infection	12 (14)	17 (18)	10 (11)
Abdominal pain	12 (14)	13 (14)	7 (8)
Fatigue	12 (14)	12 (13)	9 (10)
Rash‡	12 (14)	10 (11)	9 (10)
Pyrexia	11 (12)	10 (11)	6 (7)
Pain in extremity	10 (11)	18 (20)	16 (18)
Back pain	10 (11)	13 (14)	10 (11)
Vomiting	10 (11)	12 (13)	11 (12)
Pain	8 (9)	10 (11)	6 (7)
Noncardiac chest pain	7 (8)	12 (13)	8 (9)
Upper abdominal pain	6 (7)	11 (12)	6 (7)

* The annualized incidence rate of vaso-occlusive crisis was adjusted for baseline hydroxyurea use, age, and geographic region.
† Adverse events related to sickle cell disease (sickle cell anemia with crisis, acute chest syndrome, pneumonia, priapism, and osteonecrosis) are excluded.
‡ "Rash" includes the following preferred terms in the *Medical Dictionary for Regulatory Activities*, version 19.1: rash, urticaria, rash generalized, rash maculopapular, rash pruritic, rash erythematous, rash vesicular, rash macular, and rash papular.

voxelotor group had sickle cell anemia with crisis; one in the placebo group had sickle cell anemia with crisis; and one in the placebo group had cardiac arrest); all fatal adverse events were determined to be unrelated to the trial drug or placebo by the investigators. Additional details are provided in Tables S5 and S6 in the Supplementary Appendix.

DISCUSSION

Among persons with sickle cell disease, the 1500-mg dose of voxelotor increased hemoglobin levels and reduced the incidence of worsening anemia as compared with placebo. In the 1500-mg voxelotor group, more than half of the participants had an increase in the hemoglobin level of more than 1.0 g per deciliter, and reductions in anemia were observed irrespective of baseline anemia severity or hydroxyurea use. Furthermore, at week 24, the 1500-mg voxelotor group had significantly greater reductions from baseline in indirect bilirubin level and percentage of reticulocytes than the placebo group; these findings were consistent with reduced hemolysis. The increase in hemoglobin level and reduction in hemolysis occurred within 2 weeks after initiation of the trial drug, indicating a rapid pharmacodynamic and biologic effect. Subsequently, a steady state was reached that was sustained throughout the treatment period. A clear relationship was observed between voxelo-

tor exposure and all hematologic measures of efficacy, including lactate dehydrogenase level and absolute reticulocyte count. The incidence of vaso-occlusive crisis did not differ significantly among the trial groups. The percentage of participants who had adverse events of at least grade 3 and serious adverse events were similar in both voxelotor and placebo groups.

The hemoglobin occupancy target was based on the pancellular fetal hemoglobin level of approximately 30% observed in persons who are compound heterozygotes for HbS and hereditary persistence of fetal hemoglobin, who generally have no symptoms of sickle cell disease.[13] This finding suggests that binding approximately 30% of HbS in all red cells with voxelotor to stabilize the oxygenated HbS state may be sufficient to inhibit polymerization, red-cell sickling, and clinical sequelae of sickle cell disease. The observed hemoglobin occupancy for the 1500-mg dose of voxelotor was 26.5%, which was therapeutically efficacious, with no evidence of impaired oxygen delivery. This finding was supported by the similar erythropoietin levels observed with voxelotor and placebo, a reduction in the percentage of reticulocytes with voxelotor, and no pattern of adverse events suggestive of impaired tissue oxygenation.

We specifically chose to use an increase in hemoglobin level of more than 1 g per deciliter as a primary end point because validated natural history studies indicated that an increase in hemoglobin level significantly decreases the rate of multiorgan failure and death. Long-term follow-up studies are planned to evaluate the effect of the increase in hemoglobin level and decrease in hemolysis induced by voxelotor on morbidity and mortality among persons with sickle cell disease.

Persons with sickle cell disease have abnormally elevated blood viscosity and are generally recognized to have an increased risk of vaso-occlusive crisis with excessive increases in the hemoglobin level (e.g., after simple transfusion).[20] The absence of an increased incidence rate of vaso-occlusive crisis with voxelotor despite significant increases in the hemoglobin level suggests that voxelotor raises hemoglobin levels without negatively affecting blood viscosity. This may be due to the upstream mechanism of action of voxelotor (inhibition of HbS polymerization), which results in improved red-cell deformability and reduced blood viscosity with voxelotor in vitro.[16] Longer-term follow-up is needed to further characterize the effect of voxelotor on the incidence of vaso-occlusive crisis. A follow-up analysis after the last participant reached week 72 in this trial was planned. Participants who complete 72 weeks of voxelotor treatment are eligible for enrollment in the open-label, phase 3 extension study (NCT03573882) to assess the long-term effects of voxelotor.

In conclusion, voxelotor provided a significant, sustained increase in hemoglobin level and reduced the incidence of worsening anemia and hemolysis in persons with sickle cell disease.

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APPENDIX

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