Voxelotor in adolescents and adults with sickle cell disease (HOPE): long-term follow-up results of an international, randomised, double-blind, placebo-controlled, phase 3 trial

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Summary

Background For decades, patients with sickle cell disease have had only a limited number of therapies available. In 2019, voxelotor (1500 mg), an oral once-daily sickle haemoglobin polymerisation inhibitor, was approved in the USA for the treatment of sickle cell disease in patients aged 12 years and older on the basis of HOPE trial data. To further describe the applicability of voxelotor as a treatment for this chronic illness, we report the long-term efficacy and safety of this drug at 72 weeks of treatment; the conclusion of the placebo-controlled HOPE trial.

Methods HOPE is an international, randomised, double-blind, placebo-controlled, phase 3 trial done at 60 clinical sites in Canada, Egypt, France, Italy, Jamaica, Kenya, Lebanon, Netherlands, Oman, Turkey, the USA, and the UK. Patients (aged 12–65 years) with confirmed sickle cell disease, a haemoglobin concentration of 5·5–10·5 g/dL at enrolment, and who had between one and ten vaso-occlusive crisis events in the previous 12 months were enrolled. Patients receiving regularly scheduled transfusion therapy, who had received a transfusion in the previous 60 days, or who had been admitted to hospital for a vaso-occlusive crisis in the previous 14 days were excluded. Patients were randomly assigned (1:1:1) to receive either once-daily oral voxelotor 1500 mg, voxelotor 900 mg, or placebo for 72 weeks. Randomisation was done centrally by use of an interactive web response system, stratified by baseline hydroxyurea use (yes *vs* no), age group (adolescents [12 to <18 years] *vs* adults [18 to 65 years]), and geographic region (North America *vs* Europe *vs* other). The primary endpoint (already reported) was the proportion of patients who achieved a haemoglobin response at week 24. In this final analysis, we report prespecified long-term efficacy assessments by intention to treat, including changes in haemoglobin concentrations from baseline to week 72, changes in the concentration of haemolysis markers (absolute and percentage reticulocytes, indirect bilirubin concentrations, and lactate dehydrogenase concentrations) from baseline to week 72, the annualised incidence of vaso-occlusive crises, and patient functioning, as assessed with the Clinical Global Impression of Change (CGI-C) scale. Safety was assessed in patients who received at least one dose of treatment (modified intention-to-treat population). This trial is registered with ClinicalTrials.gov, NCT03036813.

Findings Between Dec 5, 2016, and May 3, 2018, 449 patients were screened, of whom 274 were randomly assigned to the voxelotor 1500 mg group (n=90), the voxelotor 900 mg group (n=92), or the placebo group (n=92). At week 72, the adjusted mean change in haemoglobin concentration from baseline was 1·0 g/dL (95% CI 0·7 to –1·3) in the voxelotor 1500 mg group, 0·5 g/dL (0·3 to –0·8) in the voxelotor 900 mg group, and 0·0 g/dL (–0·3 to 0·3) in the placebo group, with a significant difference observed between the voxelotor 1500 mg group and the placebo group (p<0·0001), and between the voxelotor 900 mg group and the placebo group (p=0·014). Significant improvements in markers of haemolysis, as assessed by the difference in adjusted mean percentage change from baseline at week 72 versus placebo, were observed in the voxelotor 1500 mg group in indirect bilirubin concentrations (–26·6% [95% CI –40·2 to –12·9]) and percentage of reticulocytes (–18·6% [–33·9 to –3·3]). The proportion of patients in the voxelotor 1500 mg group who were rated as "moderately improved" or "very much improved" at week 72 with the CGI-C was significantly greater than in the placebo group (39 [74%] of 53 *vs* 24 [47%] of 51; p=0·0057). Serious adverse events unrelated to sickle cell disease were reported in 25 (28%) of 88 patients in the voxelotor 1500 mg group, 20 (22%) of 92 patients in the voxelotor 900 mg group, and 23 (25%) of 91 patients in the placebo group. Grade 3 or 4 adverse events were infrequent (ie, occurred in <10% of patients); anaemia occurred in five or more patients (two [2%] patients in the voxelotor 1500 mg group, seven [8%] patients in the voxelotor 900 mg group, and three [3%] patients in the placebo group). Of all 274 patients, six (2%) deaths occurred during the study (two deaths in each treatment group), all of which were judged as unrelated to treatment.

Interpretation Voxelotor 1500 mg resulted in rapid and durable improvements in haemoglobin concentrations maintained over 72 weeks and has potential to address the substantial morbidity associated with haemolytic anaemia in sickle cell disease.

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Research in context

Evidence before this study

We searched PubMed on Dec 10, 2020, using the search terms "sickle cell disease" and "HbS polymerisation", filtered by "article type: clinical trial". We searched for clinical trials assessing therapies that modified sickle haemoglobin polymerisation in sickle cell disease, published in any language from database inception to Dec 10, 2020. We identified only two previous clinical trials evaluating voxelotor: one phase 1–2 ascending-dose, open-label study of voxelotor, and one previous report of the HOPE trial showing the efficacy and safety of voxelotor at 24 weeks.

Added value of this study

The results of this study show the durable efficacy and safety of once-daily voxelotor 1500 mg. Voxelotor resulted in rapid and robust improvements in haemoglobin concentrations and reductions in markers of haemolysis from baseline that were maintained up to week 72. Most (approximately 90%) patients had an increase in haemoglobin concentration of more than 1 g/dL from baseline at one or more timepoints during the study. Improvements in patient functioning with voxelotor were shown as per clinician assessments. No new safety signals were identified in this long-term investigation of voxelotor.

Implications of all the available evidence

Our results support the sustained and chronic use of voxelotor to reduce anaemia and haemolysis, and show that the chronic use of this drug is as an important new treatment option that has the potential to address the substantial morbidity of haemolytic anaemia in sickle cell disease.

Introduction

Sickle cell disease is an inherited disorder characterised by lifelong complications and severe morbidity.[1,2] Sickle haemoglobin (HbS), which arises from mutations in the gene encoding haemoglobin subunit β, polymerises when deoxygenated, causing red blood cells to develop a characteristic sickle shape.[1] Repeated episodes of sickling and unsickling damage the red blood cell membrane, which results in intravascular haemolysis and recurrent episodes of acute pain caused by vaso-occlusive crises, leading to ischaemia and inflammation.[1,2]

The unmet needs of the sickle cell disease population are substantial. Despite previously available therapies, individuals with sickle cell disease can continue to have persistent haemolytic anaemia, with steady-state average haemoglobin concentrations of 7–9 g/dL in patients with sickle cell anaemia, reduced health-related quality of life, and premature mortality.[1,3,4] Lower haemoglobin concentrations and increased haemolysis are associated with increased morbidity due to acute and chronic complications, including chronic kidney disease, pulmonary hypertension, and stroke.[5,6] Increasing haemoglobin concentrations and reducing haemolysis are therefore crucial in preventing complications in patients with sickle cell disease.[3]

Voxelotor is a HbS polymerisation inhibitor that has been approved by the US Food and Drug Administration for the treatment of sickle cell disease in adult and adolescent patients (aged 12 years and older) at a dose of 1500 mg orally once daily. The efficacy and safety of voxelotor in the Hemoglobin Oxygen Affinity Modulation to Inhibit HbS Polymerization (HOPE) trial has been reported at 24 weeks.[7] The primary endpoint of this study was haemoglobin response at week 24. A significantly greater proportion of patients in the voxelotor 1500 mg group (46 [51%; 95% CI 41–61] of 90) had a haemoglobin response than in the placebo group (six [7%; 1–12] of 92). Significant voxelotor-associated increases in haemoglobin concentrations were equivalent between patients with and without concomitant hydroxyurea use. Treatment with voxelotor also resulted in substantial reductions in markers of haemolysis when compared with placebo. Patients with the greatest reductions in haemolysis had the greatest increases in haemoglobin concentrations.

Herein we report the final evaluation of efficacy and safety of voxelotor at 72 weeks; the conclusion of the placebo-controlled HOPE trial.

Methods

Study design and participants

The HOPE trial is an international, randomised, double-blind, placebo-controlled, phase 3 trial done at 60 clinical sites in Canada, Egypt, France, Italy, Jamaica, Kenya, Lebanon, Netherlands, Oman, Turkey, the USA, and the UK (appendix pp 6–7). The study included patients (aged 12–65 years) with confirmed sickle cell disease (homozygous for sickle cell disease [HbSS], heterozygous for sickle cell disease [HbSC], sickle β^0 thalassaemia [HbSβ^0], and sickle β plus thalassaemia [HbSβ+], and other genotypic variants), a haemoglobin concentration of 5·5–10·5 g/dL at enrolment, and who had between one and ten vaso-occlusive crises in the previous 12 months (defined as an acute painful crisis or acute chest syndrome, for which there was no explanation other than a vaso-occlusive crisis [appendix p 2]). Concurrent hydroxyurea was allowed if the dose had been stable for 90 days or more. Patients were excluded if they were receiving regularly scheduled transfusion therapy, had received a transfusion in the previous 60 days, or had been admitted to hospital for a vaso-occlusive crisis in the previous 14 days.

This trial was done 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. Written informed consent was obtained from patients before enrolment. For paediatric patients, both the

See Online for appendix

consent of the participant's legal representative or legal guardian and the participant's assent were obtained. The study protocol was reviewed and approved by an independent ethics committee at each participating trial site. The study protocol is included in the appendix (pp 14–62).

Randomisation and masking

Patients were randomly assigned (1:1:1) to receive either voxelotor 1500 mg, voxelotor 900 mg, or placebo for up to 72 weeks. Randomisation was done centrally by use of an interactive web response system for concealed allocation. Permuted blocks (size three or six) within randomisation strata were used. Patients were stratified by baseline hydroxyurea use (yes *vs* no), age group (adolescents [12 to <18 years] *vs* adults [18 to 65 years]), and geographic region (North America *vs* Europe *vs* other). The trial medications (voxelotor and placebo) had an identical appearance. All individuals involved in the direct conduct of the study (investigators, patients, site staff, contract research organisation personnel, and the Global Blood Therapeutics [GBT] clinical team) were masked to individual treatment assignment. No patients were unmasked by the investigators during the conduct of the trial.

Procedures

The full procedures for the HOPE trial have been reported previously.[7] Briefly, patients in the study received oral voxelotor (1500 mg or 900 mg dose) or placebo once daily for 72 weeks or until withdrawal from the study. Dose modification was allowed for management of suspected treatment-related adverse events, and the original dose was resumed upon adverse event resolution, at the discretion of the investigator.

Patients were assessed at the screening visit, the baseline visit, every 2 weeks (up to week 8), every 4 weeks (up to week 24), and every 12 weeks (up to week 72). Safety was monitored at every assessment throughout the 72-week treatment period. Patients were monitored for adverse events from the time that informed consent was given to study completion or discontinuation. Adverse events that occurred after study initiation or pre-existing adverse events that worsened during the treatment period for up to 28 days after the previous dose were assessed and graded in severity with the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Adverse events were categorised as related or unrelated to sickle cell disease. Adverse events related to sickle cell disease included sickle cell anaemia with crisis, acute chest syndrome, all pneumonia events, priapism, and osteonecrosis. The safety assessment included treatment-emergent adverse events, serious adverse events (defined as an adverse event that resulted in death, a threat to life, inpatient hospitalisation or prolongation of an existing hospitalisation, or a congenital anomaly, or based on investigator opinion), and adverse events that led to treatment discontinuation. Changes in patient health-related quality of life were assessed by use of the EQ-5D-5L questionnaire (scored on the basis of the US crosswalk value set, with a maximum value of 1) and visual analogue scale scores (ranging from 0 to 100), with higher scores representing a better patient-reported health status. Patient status was evaluated by the Clinical Global Impression of Change (CGI-C), which is a single-item, seven-point scale and clinician-reported outcome that evaluates a patient's global functioning according to the physician's judgement. Status was assessed at selected timepoints, including at week 72, and rated by the investigator as "very much improved", "moderately improved", "minimally improved", "no change", "minimally worse", "moderately worse", or "very much worse" compared with their status at baseline.

Patients who completed the 72-week treatment period were offered continued treatment in the open-label extension study (NCT03573882).

Outcomes

The primary endpoint was the proportion of patients with a haemoglobin response at week 24, defined as the proportion of patients who had a haemoglobin change from baseline of >1 g/dL. Secondary endpoints were the change in haemoglobin concentration from baseline at week 24, the change in markers of haemolysis (absolute and percentage reticulocytes, indirect bilirubin concentrations, and lactate dehydrogenase concentrations) at week 24, the annualised incidence of vaso-occlusive crises by treatment group, and the incidence of severe anaemic episodes, defined as having haemoglobin concentrations less than 5·5 g/dL at any time during the trial. Results for the primary and secondary endpoints were reported previously.[7]

Prespecified exploratory analyses were changes from baseline in the concentrations of haemoglobin and markers of haemolysis at week 72, time to first vaso-occlusive crisis, incidence and time to first red blood cell transfusion, time to first acute chest syndrome or pneumonia, measures of pathophysiology and their utility as pharmacodynamic markers (including inflammatory biomarkers, kidney function and red blood cell rheology), measures predictive of response to voxelotor, health-related quality of life, disease severity (measured according to the Sickle Cell Disease Severity Measure), school or work attendance, use of opioid during the treatment period (recorded with an eDiary), and disease status (measured with the CGI-C). The CGI-C assessment was added as an exploratory endpoint after the study had started. Safety and pharmacokinetic endpoints were also evaluated.

Additional post-hoc analyses included the incidence of acute anaemic episodes, defined as a decrease in haemoglobin concentration of 2 g/dL or more from baseline at any time during the trial, the maximal change in haemoglobin concentration and peak haemoglobin concentration achieved during the 72-week treatment

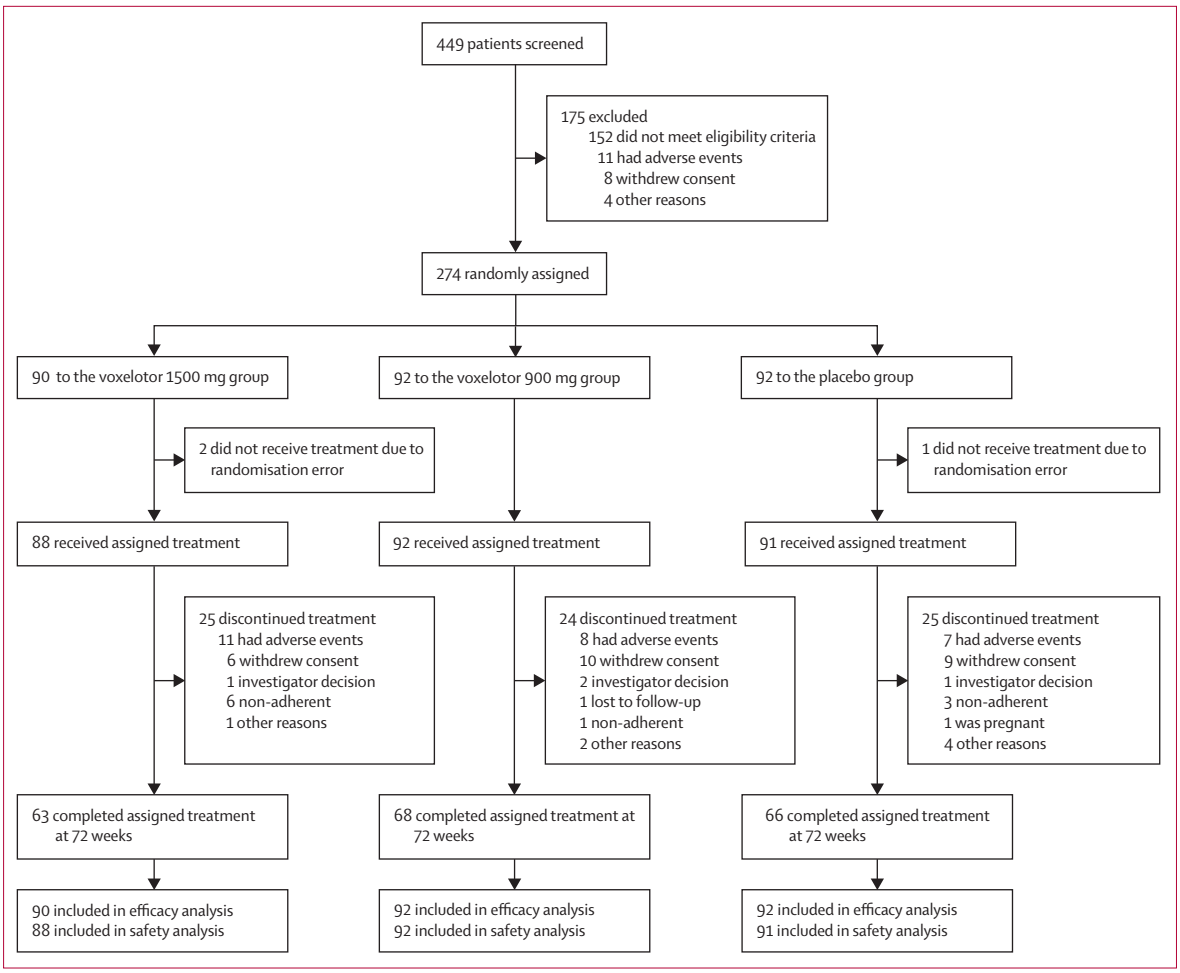

Figure 1: **Trial profile**
Among the 197 patients who completed 72 weeks of treatment in the study, 179 (91%) enrolled in the open-label extension study.

period, and the proportion of patients in each group who had an increase in haemoglobin concentration of more than 1 g/dL, more than 2 g/dL, and more than 3 g/dL at any timepoint between baseline and week 72.

Statistical analysis

With the sample size of 274 patients, the study had more than 95% power to detect a targeted treatment difference of 30% for the primary endpoint of haemoglobin response in the voxelotor 1500 mg group versus the placebo group at week 24, assuming that 10% of patients in the placebo group had a haemoglobin response, and using Fisher's exact test with a two-sided α level of 0·0481.

Efficacy analyses included all randomised patients (intention-to-treat population). Change from baseline in haemoglobin concentration over time was analysed by use of a regression model for repeated measures. A single model was fit using all available data up to week 72. Independent variables included treatment group assignment, study visit (as a categorical variable), treatment by visit interaction, baseline hydroxyurea use, age group, and geographic region. Baseline haemoglobin concentration was also included. Intrapatient variability was modelled with an unstructured covariance matrix. Haemoglobin measurements taken within 8 weeks of a red blood cell transfusion were replaced with the last observed haemoglobin value before the transfusion, and measurements obtained after hydroxyurea initiation in patients who initiated hydroxyurea treatment after randomisation were excluded from the analysis. The adjusted mean change from baseline in haemoglobin concentration was estimated from the regression model for each treatment group and each study timepoint, including week 72.

The proportions of patients who had an increase in haemoglobin concentration of more than 1 g/dL, more than 2 g/dL, and more than 3 g/dL from baseline at one or more timepoints during the 72-week treatment period were calculated by treatment group. The corresponding 95% CIs were calculated by the asymptotic (Wald) method based on normal approximation. For each

patient, the average post-baseline haemoglobin concentration reached, the change from baseline to the average haemoglobin concentration reached, the peak haemoglobin concentration reached, and the change from baseline to the peak haemoglobin concentration reached during the 72-week treatment period were ascertained and summarised descriptively by treatment group as unadjusted means (SDs).

Relative change from baseline in markers of haemolysis were analysed by use of a similar methodology as that used for assessing change from baseline in haemoglobin concentrations, including replacing the values obtained within 8 weeks of a red blood cell transfusion with the last observed values obtained before the transfusion.

The mean cumulative function of vaso-occlusive crisis incidence over time was estimated by treatment group for the overall study population and for patients who had at least two vaso-occlusive crises in the 12 months before screening, then stratified by average haemoglobin concentration over the patients' duration of treatment. The annualised incidence rate of vaso-occlusive crisis events was modelled by use of a negative binomial regression model with the independent variable of treatment group and adjusted for baseline hydroxyurea use, age group, and geographic region. Time at risk was from randomisation to the earliest of either treatment discontinuation, hydroxyurea initiation in patients not receiving hydroxyurea at baseline, withdrawal of consent, or the end of the study. The incidence rate ratio (IRR) was defined as the ratio of the annualised incidence rate for voxelotor versus placebo.

CGI-C data were summarised descriptively by treatment group and timepoint. The proportion of patients with sickle cell disease rated as either "very much improved" or "moderately improved" was calculated and compared between groups with a χ^2 test. Statistical testing was not adjusted for multiplicity.

Safety was assessed in all patients who received at least one dose of voxelotor or placebo during the 72-week treatment period (modified intention-to-treat population). Safety assessments, including adverse events, were summarised descriptively by treatment group.

All statistical analyses were done with SAS, version 9.4. This study is registered with ClinicalTrials.gov, NCT03036813.

Role of the funding source

The funder of the study was involved in study design, data collection, data management, data analysis, data interpretation, and writing of the report.

Results

Between Dec 5, 2016, and May 3, 2018, 449 patients were screened and 274 patients were randomly assigned to receive voxelotor 1500 mg (n=90), voxelotor 900 mg (n=92), or placebo (n=92; figure 1). 88 (98%) patients in the voxelotor 1500 mg group, 92 (100%) patients in the voxelotor 900 mg group, and 91 (99%) patients in the placebo group received their assigned treatment.

The median duration of follow-up was 72·1 weeks (IQR 42·3–73·0) in the voxelotor 1500 mg group, 72·5 weeks (71·3–74·0) in the voxelotor 900 mg group, and 72·1 weeks (61·2–72·9) in the placebo group. Baseline characteristics and demographics of all patients were well balanced among the groups (table 1). Most patients (248 [91%] of 274) had sickle cell disease genotypes HbSS or HbSβ⁰. 179 (65%) of 274 patients were receiving hydroxyurea at baseline. Median haemoglobin concentrations at baseline were also similar across the three groups (table 1).

At week 72, the adjusted mean change in haemoglobin concentration from baseline was 1·0 g/dL (95% CI 0·7 to –1·3) in the voxelotor 1500 mg group, 0·5 g/dL (0·3 to –0·8) in the voxelotor 900 mg group, and 0·0 g/dL (–0·3 to 0·3) in the placebo group in the intention-to-treat analysis, with a significant difference observed

	Voxelotor 1500 mg group (n=90)	Voxelotor 900 mg group (n=92)	Placebo group (n=92)
Median age, years	24·0 (19·0–32·0)	24·0 (19·0–34·0)	28·0 (19·0–35·5)
12 to <18	14 (16%)	15 (16%)	17 (18%)
18 to 65	76 (84%)	77 (84%)	75 (82%)
Sex			
Female	58 (64%)	51 (55%)	50 (54%)
Male	32 (36%)	41 (45%)	42 (46%)
Region			
North America	34 (38%)	36 (39%)	35 (38%)
Europe	19 (21%)	19 (21%)	18 (20%)
Other regions	37 (41%)	37 (40%)	39 (42%)
Genotype			
HbSS	61 (68%)	71 (77%)	74 (80%)
HbSβ⁰	18 (20%)	13 (14%)	11 (12%)
HbSC	3 (3%)	2 (2%)	2 (2%)
Other*	8 (9%)	6 (7%)	5 (5%)
Patients on hydroxyurea at baseline	58 (64%)	63 (68%)	58 (63%)
Median baseline haemoglobin concentration, g/dL	8·7 (7·9–9·5)	8·3 (7·4–9·2)	8·6 (8·0–9·5)
Mean baseline haemolysis markers			
Indirect bilirubin, µmol/L	45·3 (44·3)	44·2 (34·2)	50·3 (43·2)
Reticulocytes, %	10·5% (5·0)	11·7% (5·4)	11·0% (4·9)
Absolute reticulocyte count, $\times 10^9$ cells per L	299·0 (123·4)	322·1 (141·7)	318·3 (130·3)
Lactate dehydrogenase, U/L	385·1 (150·6)	432·9 (179·1)	439·2 (188·7)
Number of vaso-occlusive crises in previous 12 months†			
1	35 (39%)	41 (45%)	39 (42%)
2–10	55 (61%)	51 (55%)	53 (58%)
Median follow-up, weeks	72·1 (42·3–73·0)	72·5 (71·3–74·0)	72·1 (61·2–72·9)

Data are median (IQR), n (%), or mean (SD). HbSS=homozygous for sickle cell disease. HbSβ⁰=sickle cell β⁰ thalassaemia. HbSC=heterozygous for sickle cell disease. HbSβ+=sickle β plus thalassaemia. *Included HbSβ+ and other sickle cell disease variants. †Baseline vaso-occlusive crisis was defined as a documented episode of acute chest syndrome or acute painful crisis that required prescription or use of analgesics for moderate to severe pain, as instructed by a health-care professional.

Table 1: **Baseline patient characteristics and demographics**

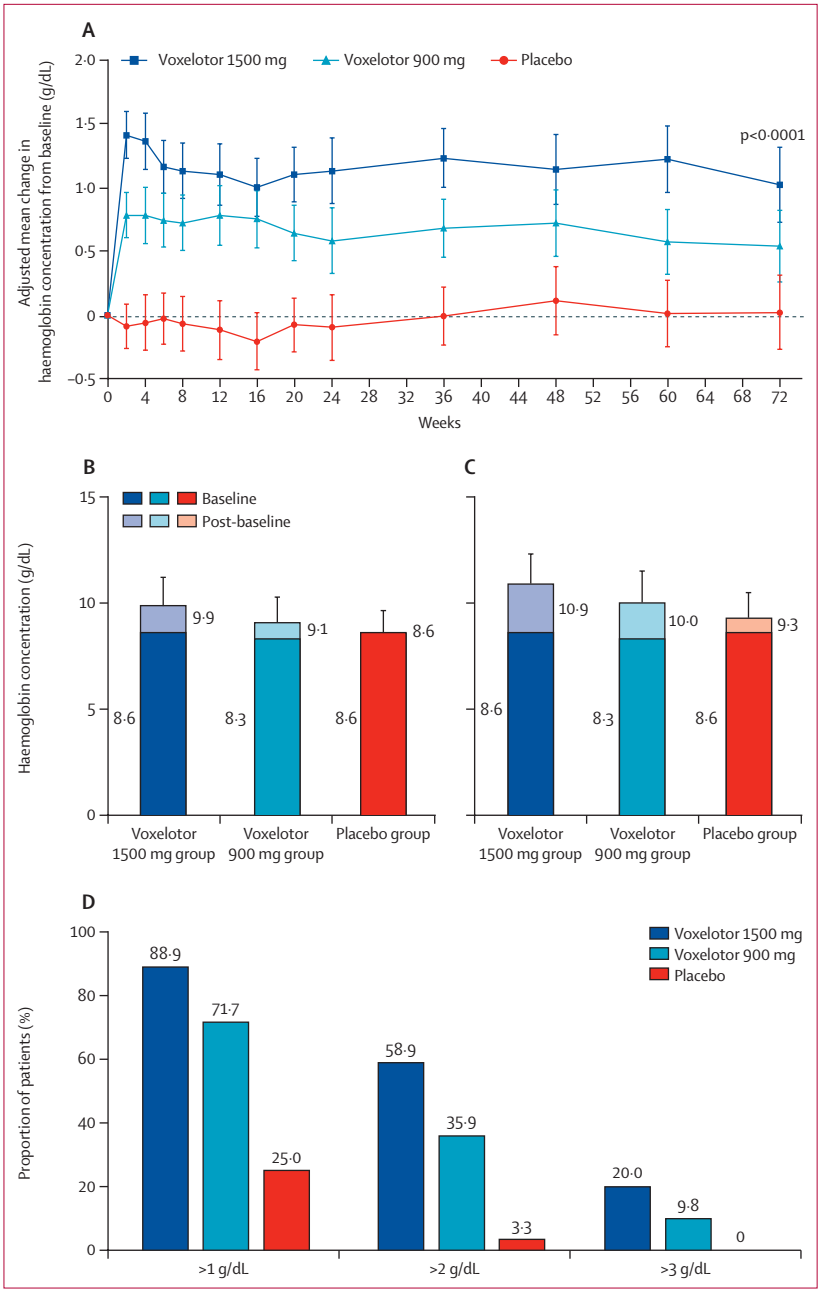

Figure 2: **Change in haemoglobin from baseline to week 72**
(A) Adjusted mean change in haemoglobin concentrations from baseline to week 72, calculated by use of a regression model for repeated measures. Error bars represent 95% CIs. The p value was derived from comparing the voxelotor 1500 mg group with the placebo group at week 72. (B) Mean baseline and average post-baseline haemoglobin concentration reached during the 72-week treatment period. For each patient, the average post-baseline haemoglobin value is the mean of all haemoglobin values obtained at each post-baseline summary visit up to week 72. Error bars indicate SDs. (C) Mean baseline and peak (maximal) post-baseline haemoglobin concentration achieved during the 72-week treatment period. For each patient, the peak haemoglobin value is the highest value obtained at a post-baseline summary visit up to week 72. Error bars indicate SDs. (D) The proportion of patients with haemoglobin response at any time during the 72-week treatment period. In A, C, and D, haemoglobin values within 8 weeks after the red blood cell transfusion were imputed as the last value before the transfusion. In A–D, haemoglobin values obtained after hydroxyurea had been initiated post-randomisation were excluded for eight patients who had not been receiving hydroxyurea at baseline.

between the voxelotor 1500 mg group and the placebo group (p<0·0001), and between the voxelotor 900 mg group and the placebo group (p=0·014; figure 2A). Over the entire 72-week treatment period, the mean change in haemoglobin concentration from baseline was 1·3 g/dL (SD 0·9) in the voxelotor 1500 mg group, 0·7 g/dL (0·8) in the voxelotor 900 mg group, and 0·0 g/dL (0·5) in the placebo group. The mean haemoglobin concentration reached during the 72-week period was 9·9 g/dL (1·3) in the voxelotor 1500 mg group, 9·1 g/dL (1·2) in the voxelotor 900 mg group, and 8·6 g/dL (1·1) in the placebo group (figure 2B). The peak haemoglobin concentration reached was 10·9 g/L (1·4) in the voxelotor 1500 mg group, 10·0 g/dL (1·5) in the voxelotor 900 mg group, and 9·3 g/dL (1·2) in the placebo group (figure 2C), and the mean change from baseline to peak haemoglobin concentration was 2·3 g/dL (1·0) in the voxelotor 1500 mg group, 1·7 g/dL (1·1) in the voxelotor 900 mg group, and 0·7 g/dL (0·6) in the placebo group.

A total of 80 (89% [95% CI 82–95]) of 90 patients in the voxelotor 1500 mg group, 66 (72% [63–81]) of 92 patients in the voxelotor 900 mg group, and 23 (25% [16–34%]) of 92 patients in the placebo group had an increase in haemoglobin concentration of more than 1 g/dL from baseline at any timepoint by week 72 (figure 2D). Of those patients who did not have a haemoglobin response by week 24 with follow-up data after week 24, three (38%) of eight patients in the voxelotor 1500 mg group, five (21%) of 24 in the voxelotor 900 mg group, and eight (13%) of 61 in the placebo group had a haemoglobin response by week 72. Greater proportions of patients in the voxelotor 1500 mg group (53 [59%; 95% CI 49–69] of 90 patients) and the voxelotor 900 mg group (33 [36%; 26–46] of 92 patients) had an increase in haemoglobin concentrations of more than 2 g/dL from baseline to week 72 compared with the placebo group (three [3%; 0–7] of 92 patients). Similarly, higher proportions of patients in the voxelotor 1500 mg group (18 [20%; 12–28] of 90 patients) and the voxelotor 900 mg group (nine [10%; 4–16] of 92 patients) had an increase in haemoglobin concentrations of more than 3 g/dL from baseline to week 72 compared with the placebo group (0 [0%; 0–0] of 92 patients).

Acute anaemic episodes occurred less frequently in patients receiving voxelotor than placebo, with an annualised incidence three times lower in the voxelotor 1500 mg group (0·05 episodes per year) and four times lower in the voxelotor 900 mg group (0·04 episodes per year) than in the placebo group (0·15 episodes per year).

Significant improvements in markers of haemolysis, as assessed by the difference in adjusted mean percentage change from baseline at week 72 relative to placebo, were observed in the voxelotor 1500 mg group in indirect bilirubin (–26·6% [95% CI –40·2 to –12·9]) and percentage of reticulocytes (–18·6% [–33·9 to –3·3]). Differences in the adjusted mean percentage change from baseline at week 72 between voxelotor 1500 mg and the placebo group in absolute reticulocyte count (–5·8% [–23·4 to 11·9]) and

lactate dehydrogenase concentration (–4·8% [–13·8 to 4·1]) were also observed. Differences in markers of haemolysis in the voxelotor 900 mg group relative to the placebo group were observed (indirect bilirubin –17·9% [–31·2 to –4·5]; percentage of reticulocytes –7·5% [–22·6 to 7·6]; absolute reticulocyte count 5·6% [–11·8 to 23·0]; lactate dehydrogenase concentration –9·4% [–18·2 to –0·6]). Patients receiving voxelotor had substantially lower nadirs in markers of haemolysis during the 72-week treatment period, with mean nadirs in absolute reticulocyte counts of $164·5\times10^9$ cells per L (SD 88·0) in the voxelotor 1500 mg group and $195·9\times10^9$ cells per L (103·9) in the voxelotor 900 mg group versus $220·6\times10^9$ cells per L (126·3) in the placebo group; in percentage of reticulocytes of 4·8% (2·9) in the voxelotor 1500 mg group and 6·6% (3·7) in the voxelotor 900 mg group versus 7·8% (4·3) in the placebo group; in indirect bilirubin concentrations of 15·6 µmol/L (15·7) in the voxelotor 1500 mg group and 20·7 µmol/L (14·9) in the voxelotor 900 mg group versus 35·6 µmol/L (34·5) in the placebo group; and in lactate dehydrogenase concentrations of 271·2 U/L (94·7) in the voxelotor 1500 mg group and 322·0 U/L (145·1) in the voxelotor 900 mg group versus 361·2 U/L (174·2) in the placebo group.

The proportion of patients who underwent red blood cell transfusions during the study was similar among the treatment groups (32 [36%] of 90 patients in the voxelotor 1500 mg group, 33 [36%] of 92 patients in the voxelotor 900 mg group, and 33 [36%] of 92 patients in the placebo group). Red blood cell transfusions were given to treat sickle cell disease-related complications as part of routine standard of care and were most commonly administered for the treatment of vaso-occlusive crises. Hydroxyurea initiation in patients not receiving hydroxyurea at baseline was infrequent (n=8). Overall, fetal haemoglobin percentages were unchanged between baseline and week 72 across all groups.

The annualised incidence rate of vaso-occlusive crises was 2·4 (95% CI 1·8–3·1) in the voxelotor 1500 mg group, 2·4 (1·9–3·1) in the voxelotor 900 mg group, and 2·8 (2·2–3·6) in the placebo group, with an IRR of 0·85 (95% CI 0·60–1·21) in the voxelotor 1500 mg and 0·86 (0·61–1·22) in the voxelotor 900 mg group versus the placebo group during the 72-week treatment period (figure 3). Among participants who had at least two vaso-occlusive crises in the 12 months before screening, the annualised incidence rate of vaso-occlusive crisis events was 2·5 events (95% CI 1·8–3·5) in the voxelotor 1500 mg group, 3·0 events (2·2–4·2) in the voxelotor 900 mg group, and 3·1 events (2·3–4·2) in the placebo group, with an IRR of 0·81 (95% CI 0·52–1·28) in the voxelotor 1500 mg group and 0·98 (0·63–1·53) in the voxelotor 900 mg group versus the placebo group at week 72 (appendix p 3).

When stratified by average haemoglobin concentration reached during the entire 72-week treatment period, the incidence of vaso-occlusive crises was lowest among patients in the voxelotor 1500 mg and 900 mg groups who reached the highest haemoglobin concentrations (ie, ≥12 g/dL) compared with those who reached lower haemoglobin concentrations (ie, <12 g/dL) or those receiving placebo (appendix p 4). The highest average haemoglobin concentration reached in the voxelotor 1500 mg group over the 72-week treatment period was 13·3 g/dL, and the highest individual haemoglobin concentration observed was 14·3 g/dL.

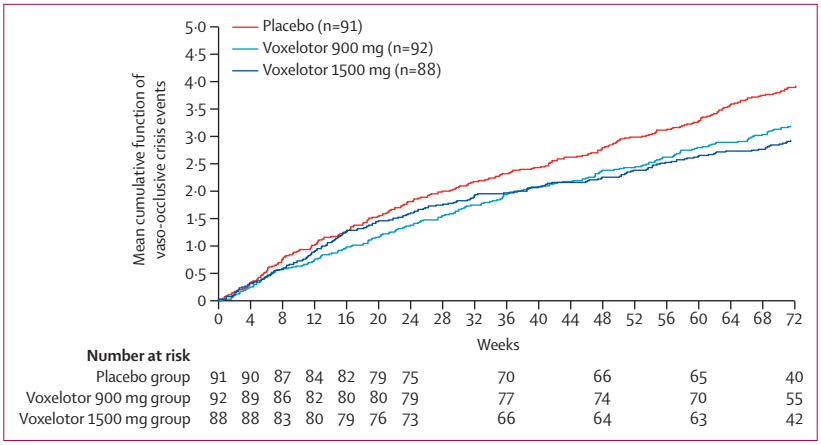

Figure 3: **Mean cumulative vaso-occlusive crisis events on treatment up to week 72 in the modified intention-to-treat population**

The modified intention-to-treat population included all patients who received at least one dose of voxelotor or placebo during the 72-week treatment period. Vaso-occlusive events after treatment discontinuation and events after post-randomisation hydroxyurea initiation in patients not receiving hydroxyurea at baseline were excluded. The sample sizes shown are the number of patients remaining at risk at each specific timepoint.

Among the 162 patients who received CGI-C ratings (53 patients in the voxelotor 1500 mg group, 58 patients in the voxelotor 900 mg group, and 51 patients in the placebo group), a greater proportion of patients in the voxelotor 1500 mg group (39 [74%] patients; p=0·0057) and voxelotor 900 mg group (32 [55%] patients; p=0·398) were rated as "very much improved" or "moderately improved" at week 72 compared with the placebo group (24 [47%] patients; appendix p 5). A lower proportion of patients were given a rating of "no change", "minimally worse", "moderately worse", or "very much worse" in the voxelotor 1500 mg group (six [11%] patients) and the voxelotor 900 mg group (13 [22%] patients) compared with the placebo group (21 [41%] patients).

Patient health-related quality of life at baseline was similar among the treatment groups in terms of mean EQ-5D-5L index scores (0·86 [SD 0·12] in the voxelotor 1500 mg group, 0·86 [0·18] in the voxelotor 900 mg group, and 0·86 [0·19] in the placebo group) and mean visual analogue scale scores (81·0 [20·8] in the voxelotor 1500 mg group, 78·4 [21·2] in the voxelotor 900 mg group, and 77·8 [25·0] in the placebo group). Small fluctuations in mean scores were observed across all treatment groups during the study, and no appreciable trends were observed (appendix p 8).

Adverse events unrelated to sickle cell disease that occurred or worsened during the treatment period were observed in 85 (97%) of 88 patients in the voxelotor

	Voxelotor 1500 mg group (n=88)				Voxelotor 900 mg group (n=92)				Placebo group (n=91)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any event	56 (64%)	26 (30%)	1 (1%)	2 (2%)	56 (61%)	27 (29%)	2 (2%)	1 (1%)	48 (53%)	30 (33%)	3 (3%)	1 (1%)
Headache	26 (30%)	2 (2%)	0	0	19 (21%)	1 (1%)	0	0	21 (23%)	2 (2%)	0	0
Diarrhoea	19 (22%)	1 (1%)	0	0	14 (15%)	3 (3%)	0	0	10 (11%)	0	0	0
Arthralgia	17 (19%)	2 (2%)	0	0	14 (15%)	0	0	0	13 (14%)	0	0	0
Nausea	16 (18%)	1 (1%)	0	0	17 (18%)	0	0	0	9 (10%)	0	0	0
Pain	15 (17%)	0	0	0	13 (14%)	2 (2%)	0	0	15 (16%)	3 (3%)	0	0
Back pain	14 (16%)	1 (1%)	0	0	13 (14%)	0	0	0	12 (13%)	0	0	0
Upper respiratory tract infection	13 (15%)	0	0	0	22 (24%)	0	0	0	13 (14%)	1 (1%)	0	0
Abdominal pain	13 (15%)	0	0	0	13 (14%)	0	0	0	9 (10%)	1 (1%)	0	0
Pyrexia	13 (15%)	0	0	0	10 (11%)	2 (2%)	0	0	4 (4%)	3 (3%)	0	0
Fatigue	12 (14%)	0	0	0	13 (14%)	0	0	0	10 (11%)	2 (2%)	0	0
Pain in arms or legs	11 (13%)	1 (1%)	0	0	19 (21%)	1 (1%)	0	0	18 (20%)	1 (1%)	0	0
Vomiting	11 (13%)	0	0	0	13 (14%)	0	0	0	15 (16%)	0	0	0
Rash*	9 (10%)	4 (5%)	0	0	13 (14%)	0	0	0	10 (11%)	0	0	0
Non-cardiac chest pain	8 (9%)	2 (2%)	0	0	13 (14%)	0	0	0	8 (9%)	2 (2%)	0	0
Urinary tract infection	8 (9%)	1 (1%)	0	0	5 (5%)	1 (1%)	0	0	12 (13%)	1 (1%)	0	0
Abdominal pain (upper)	8 (9%)	0	0	0	14 (15%)	0	0	0	4 (4%)	2 (2%)	0	0
Cough	8 (9%)	0	0	0	6 (7%)	0	0	0	10 (11%)	0	0	0

Data are n (%). Data are adverse events occurring in at least 10% of patients in any group. *Includes the following preferred terms from the Medical Dictionary for Regulatory Activities (version 22.0): rash, urticaria, rash generalised, rash maculopapular, rash pruritic, rash papular, rash erythematous, rash vesicular, and rash macular.

Table 2: **Treatment-emergent adverse events unrelated to sickle cell disease**

1500 mg group, 86 (93%) of 92 patients in the voxelotor 900 mg group, and 82 (90%) of 91 patients in the placebo group. The most frequently reported adverse events unrelated to sickle cell disease with an incidence of 20% or higher in any group were headache, diarrhoea, arthralgia, upper respiratory tract infection, and pain in the arms or legs (table 2; appendix pp 9–11). Grade 3 or 4 adverse events unrelated to sickle cell disease were infrequent, and events that occurred in five or more patients included anaemia (two [2·3%] of 88 patients in the voxelotor 1500 mg group, seven [7·6%] of 92 patients in the voxelotor 900 mg group, and three [3·3%] of 91 patients in the placebo group). There were no adverse events of stroke or transient ischaemic attack in the voxelotor 1500 mg group. One patient in the voxelotor 900 mg group had a cerebrovascular accident, which was considered as unrelated to the study drug by the study investigator; one patient in the placebo group had cerebral infarction and cerebral microhaemorrhage; both were considered as unrelated to the study drug by the study investigator. Most adverse events were considered by the study investigators to be unrelated to the study drug or placebo. The proportion of patients with sickle cell disease-related adverse events was not substantially different between the treatment groups (69 [78%] of 88 patients in the voxelotor 1500 mg group, 69 [75%] of 92 patients in the voxelotor 900 mg group, and 73 [80%] of 91 patients in the placebo group; appendix p 12).

Adverse events leading to dose reductions occurred in all treatment groups (13 [15%] of 88 patients in the voxelotor 1500 mg group, five [5%] of 92 patients in the voxelotor 900 mg group, and six [7%] of 91 patients in the placebo group). The occurrence of adverse events that led to study drug discontinuation were low and similar between treatment groups (11 [13%] patients in the voxelotor 1500 mg group, eight [9%] patients in the voxelotor 900 mg group, and seven [8%] patients in the placebo group). Serious adverse events unrelated to sickle cell disease were generally balanced across the treatment groups (25 [28%] patients in the voxelotor 1500 mg group, 20 [22%] patients in the voxelotor 900 mg group, and 23 [25%] patients in the placebo group).

Two patients in each treatment group had fatal adverse events (appendix p 13). Of adverse events unrelated to sickle cell disease, one grade 4 event (respiratory failure) and two grade 5 events (encephalopathy or brain abscess in one patient and pulmonary sepsis in one patient) occurred in the voxelotor 1500 mg group, two grade 4 events (type 2 diabetes mellitus and anaemia), and one grade 5 event (death of unknown aetiology) occurred in the voxelotor 900 mg group, and three grade 4 events (depressed level of consciousness, pulmonary embolism, and respiratory failure) and one grade 5 event (cardiac arrest) occurred in the placebo group. All fatal adverse events were determined to be unrelated to the received study drug or placebo by the trial investigators.

Discussion

Voxelotor 1500 mg once daily resulted in rapid and robust improvements in haemoglobin concentrations and

reductions in markers of haemolysis that were maintained up to week 72. In the voxelotor 1500 mg group, most patients (80 [89%; 95% CI 82–95] of 90) had an increase in haemoglobin concentration of more than 1 g/dL from baseline at any timepoint by week 72. Among the few patients who did not reach a haemoglobin response at week 24, a greater proportion of patients who continued treatment with voxelotor 1500 mg had an increase in haemoglobin concentration of more than 1 g/dL by week 72 than those who received placebo, indicating that sustained treatment is advantageous in optimising a haemoglobin response. A higher proportion of patients in the voxelotor 1500 mg group had greater increases in haemoglobin (ie, a >2 g/dL increase from baseline) compared with the voxelotor 900 mg and placebo groups. These improvements corresponded with the greater maximal haemoglobin change from baseline and peak haemoglobin concentration reached in this treatment group compared with the other two treatment groups. Treatment with voxelotor 1500 mg resulted in significant reductions in markers of haemolysis between baseline and week 72, including indirect bilirubin and percentage of reticulocytes.

It is noteworthy that the patients in the voxelotor 1500 mg group who had the highest haemoglobin concentrations showed the lowest annualised incidence of vaso-occlusive crises. Specifically, when stratified by average on-treatment haemoglobin concentrations, patients in the voxelotor groups with the highest haemoglobin concentrations had the least number of vaso-occlusive crises, with a stepwise reduction in vaso-occlusive crisis incidence with each increase in haemoglobin concentration stratum. Also, 39 (74%) of 53 patients in the voxelotor 1500 mg group had their overall clinical status rated by CGI-C as "moderately improved" or "very much improved" by their clinicians at week 72. Treatment with voxelotor remained generally well tolerated, and the incidence of adverse events was similar among the three treatment groups over 72 weeks.

Despite the urgent need for effective chronic therapies, the paucity of research and investment in sickle cell disease, until recently, compared with other rare diseases (eg, cystic fibrosis) has led to few new therapies being developed within the past 30 years.[8] Patients with sickle cell disease are at a high risk of early mortality due to end-organ complications, which are highly associated with the haemolytic anaemia that occurs from ongoing HbS polymerisation.[5,9,10] Complicated by overall disparities in access to quality care, life expectancy in this underserved population remains decades shorter than that of the general population, with an estimated median life expectancy of 54–61 years.[11,12] Even though improving the health outcomes for individuals living with sickle cell disease requires multifaceted efforts, therapies that address the underlying pathophysiology of the disease can potentially protect against end-organ damage, leading to reduced morbidity and mortality.

In this study, patients receiving voxelotor 1500 mg maintained mean haemoglobin concentrations of approximately 10 g/dL throughout the duration of the study; an important finding given the graded inverse association observed between haemoglobin concentration and end-organ damage.[6] Increasing haemoglobin concentration has been identified as the mechanism for reducing stroke risk and cerebral time-averaged mean blood flow velocities, as assessed by transcranial Doppler ultrasound.[13,14] Early evidence has suggested mitigation of haemolytic anaemia-associated end-organ damage with voxelotor treatment compared with placebo, specifically with leg ulcerations, which are a common complication of sickle cell disease.[15] The long-term efficacy and safety of voxelotor shown in our study highlight its potential applicability for use in this chronic condition to meaningfully improve patient outcomes. The effect of voxelotor on the incidence of chronic complications of sickle cell disease is being further evaluated in ongoing investigations.

The appropriate haemoglobin concentration target is a key consideration in the treatment of sickle cell disease. Patients with this disease have abnormally elevated blood viscosity due to the presence of sickled cells, and an excessive, rapid increase in haemoglobin concentrations without modifying HbS polymerisation has been recognised as a contributing factor to hyperviscosity that can increase the incidence of vaso-occlusive crises.[16,17] Recent (2020) American Society of Hematology treatment guidelines have recommended 10 g/dL as the maximal threshold for increasing haemoglobin concentrations with simple transfusion due to concerns about viscosity-related complications.[16] However, with low HbS concentrations (ie, <30%), the post-transfusion haemoglobin concentration can be safely increased to more than 10 g/dL, and up to 12–13 g/dL.[16,18]

In this report, patients given voxelotor 1500 mg reached haemoglobin concentrations in excess of 12 g/dL, which did not lead to an increased incidence in vaso-occlusive crises. This outcome could be attributed to voxelotor-associated inhibition of HbS polymerisation, improvements in red blood cell health, including increased deformability and reduced sickling, and decreased blood viscosity, as shown in clinical and preclinical studies.[19–21] Additionally, no adverse consequences from sustained increases in the affinity of haemoglobin for oxygen were observed. Previous studies and reports have shown that the mechanism of action of voxelotor does not affect oxygen offloading or delivery to tissues. Cardiopulmonary exercise testing of patients with sickle cell disease receiving voxelotor showed no appreciable differences in exercise capacity, as assessed by maximum rate of oxygen consumption and heart rate, compared with those receiving placebo.[22] Among seven patients with severe sickle cell disease granted compassionate use of voxelotor, four patients with baseline oxygen saturation of less than 95% had their oxygen saturation improve to 98–99%

by week 24 of treatment, with two patients discontinuing use of long-term supplemental oxygen.[23] Cerebral blood flow analysis by MRI of three adolescents receiving voxelotor revealed that cerebral blood flow was unchanged or reduced compared with baseline, suggesting no impairment of oxygen delivery to cerebral tissues.[24] Collectively, these data reinforce the safety of the mechanism of action of voxelotor, highlight the importance of the mechanism whereby haemoglobin concentrations are increased in individuals with sickle cell disease, and suggest that therapies that improve red blood cell health could potentially inform the consideration of haemoglobin concentration thresholds in this patient population that are higher than those currently used.

In this study, patients receiving voxelotor were rated as having an improved health-related quality of life status, as measured by use of the CGI-C, which is a holistic assessment of a patient's wellbeing that does not focus on specific symptoms, but instead considers changes in other aspects of a patient's life (eg, daily functioning, work or school attendance, or improved jaundice). Experienced clinicians familiar with the interpatient and intrapatient symptom variability of sickle cell disease are uniquely suited to assess the overall sickle cell disease status of patients. Intermittent CGI-C assessments with longer intervals between assessments could have allowed detection of improvements that would have been less evident than if assessments had been more frequent with shorter intervals between assessments. Investigators remained masked to the patients' haematological data at the time of the CGI-C ratings, thereby mitigating the potential confounding of the ratings based on laboratory findings alone. Additionally, in a single-centre report of 27 patients with sickle cell anaemia who received voxelotor, clinician assessments with the CGI-C were positively associated with patient self-reported assessments done by use of the Patient Global Impression of Change scale.[25]

The double-blinded, randomised, placebo-controlled, international design of this study allowed for impartial evaluation of voxelotor in a broad demographic range of patients with sickle cell disease. The 72-week efficacy and safety results for voxelotor constitute the longest registrational trial of recently approved therapies for sickle cell disease, including L-Glutamine and crizanlizumab, published to date.

This study has some limitations. Even though the annualised incidence of vaso-occlusive crises was reported, the HOPE study patient population was not enriched or powered to evaluate the incidence of vaso-occlusive crises as an efficacy endpoint. The CGI-C assessment was added after the study had begun, and scores were not collected for all patients. Although the investigators, including those who assessed patients using the CGI-C, remained masked to central laboratory findings throughout the study, we recognise that there was potential for clinicians to infer treatment effect, despite the study blinding procedures. Furthermore, with regard to health-related quality of life assessments, baseline scores were high for the EQ-5D-5L index and visual analogue scale, which indicated that the patients might have been insufficiently symptomatic at baseline for any effect of treatment on symptoms to be observed with these instruments. Of note, clinician rating is valuable in assessing patient status; however, patient self-assessment of their overall health status is paramount and needs to be considered with appropriate and validated instruments. Finally, although the distribution of sickle cell disease genotypes was generally balanced across the three treatment groups, the haemoglobin concentration analyses were not adjusted for sickle cell disease genotype.

Voxelotor use provided significant, durable increases in haemoglobin concentrations and reductions in markers of haemolysis and a favourable safety profile. Long-term use is appropriate to treat haemolytic anaemia, thereby potentially mitigating the morbidity and mortality of sickle cell disease.

Contributors

JH, KIA, JL-G, and EV conceptualised and designed the study, and MT and SG statistically analysed the data. All authors were involved in the analysis and interpretation of the data. JH, IA, JL-G, and EV contributed to drafting the manuscript, and all authors contributed to critically reviewing and revising the manuscript. Administrative, technical, or material support was provided by IA, MT, SG, and JL-G. This study was supervised by JH, KIA, RCB, MA, VN, AE-B, HH, and EV. All authors had full access to the data in the study and had the final responsibility for the decision to submit for publication.

Declaration of interests

JH reports serving as a consultant for GBT, Agios Pharmaceuticals, Novartis, Forma Therapeutics, and Imara; receiving honoraria from Novartis, Imara, and Resonance Health; and receiving grants from bluebird bio. KIA reports serving as a consultant for Novartis and Forma Therapeutics; receiving grants from GBT and Pfizer; receiving honoraria from GBT, Novartis, Modus Therapeutics, Bioverativ, and Novo Nordisk; and serving on the member advisory boards for GBT, Bioverativ, and Novo Nordisk. RCB reports serving as a consultant for GBT and Imara and receiving grants from GBT, Novartis, and Pfizer. MA reports serving as a consultant for GBT. AE-B reports receiving grants from GBT, Novartis, and ApoPharma. HH reports receiving grants from GBT. IA, MT, and SG report being employees and shareholders of GBT. JL-G reports being a former employee and shareholder of GBT. EV reports serving as a consultant for GBT and receiving grants from Agios and Pfizer. VN declares no competing interests.

Data sharing

Study data will not be made publicly available. The study protocol and statistical analysis plan are included in the appendix (pp 14–110).

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