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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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Abstract

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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