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SAFETY AND EFFICACY OF VOXELOTOR IN PEDIATRIC PATIENTS WITH SICKLE CELL DISEASE AGED 4-11 YEARS

Topic: 26. Sickle cell disease

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Background: Sickle cell disease (SCD) is an inherited, lifelong disorder characterized by polymerization of deoxygenated sickle hemoglobin (HbS), chronic hemolytic anemia, and vaso-occlusive crises (VOCs). Lifelong ischemic injury and inflammation that begins during childhood in patients with SCD is associated with progressive end-organ damage, substantial morbidity, and early mortality. Voxelotor, an oral, once-daily HbS polymerization inhibitor, is approved in the United States for the treatment of SCD in adults and pediatric patients aged ≥12 years. Here we report the evaluation of safety and efficacy of voxelotor in pediatric patients with SCD aged 4 to 11 years.

Aims: To assess the safety and efficacy of weight-based, 1500-mg-equivalent, once-daily doses of voxelotor in pediatric patients with SCD (HbSS or HbSβ^0-thalassemia) aged 4 to 11 years.

Methods: Patients with SCD aged 4 to 11 years received once-daily voxelotor 1500 mg or 1500-mg weight-based-equivalent dosing for up to 48 weeks. Patients were included if they had a hemoglobin (Hb) concentration of 5.5 to 10.5 g/dL at baseline. Concomitant hydroxyurea was allowed if the dose was stable for ≥3 months at enrollment. Study outcomes included the change from baseline to week 24 in Hb and changes in markers of hemolysis (indirect bilirubin, lactate dehydrogenase, and reticulocyte count). Other outcomes included safety as assessed by adverse events (AEs).

Results: A total of 45 pediatric patients (median [range] age, 7.0 [4-11] years; median [range] weight, 24.0 [12-41] kg; 51.1% female) were enrolled to receive the weight-based dosing of voxelotor equivalent to 1500 mg. Of these patients, 95.6% had HbSS and 4.4% had HbSβ^0 genotypes. At baseline, 84.4% were receiving hydroxyurea, and 53.3% had ≥1 VOC in the year prior to enrollment. At baseline, the mean (SD) Hb level was 8.6 (1.0) g/dL. At week 24, the mean change (SD) in Hb from baseline was +1.0 (1.1) g/dL, and 47.1% (95% CI, 29.8%>64.9%) of patients achieved a Hb response, defined as a >1 g/dL increase in Hb. Reductions in markers of hemolysis, as measured by mean percent change from baseline, were observed for indirect bilirubin (−38.6%), lactate dehydrogenase (−2.6%), and reticulocytes (−3.3%). Improvements in Hb and markers of hemolysis were also observed in those who were managed at the maximally tolerated dose of hydroxyurea. Correlation of Hb response with observed pharmacokinetics and percent Hb occupancy will be presented. Treatment-related AEs not related to SCD were reported in 48.9% of patients; most were grade 1 or 2, and treatment discontinuation rates due to treatment-

related AEs were low (9%). The most commonly reported treatment-related AEs were diarrhea (11%), vomiting (11%), and rash (grouped term; 11%).

Summary/Conclusion: Voxelotor increased Hb and decreased markers of hemolysis in pediatric patients with SCD aged 4 to 11 years, the majority of whom were receiving stable hydroxyurea. Additionally, the drug was well tolerated, and no new adverse safety signals were detected. These results were consistent with those in adults and adolescent patients aged ≥12 years treated with voxelotor 1500 mg once daily in the HOPE trial. Overall, these results support the use of voxelotor in pediatric patients with SCD ≥4 years of age as a potential strategy for early mitigation of the morbidity and mortality associated with SCD.

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