Results From The Randomized Placebo-Controlled Phase 3 HOPE Trial Of Voxelotor In Adults And Adolescents With Sickle Cell Disease

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Background: Sickle cell disease (SCD) is an inherited disorder caused by a single amino acid substitution in the β-chain of hemoglobin (Hb) resulting in the production of sickle hemoglobin (HbS). When deoxygenated, HbS polymerizes, leading to red blood cell sickling and damage. This results in a triad of clinical features (anemia, hemolysis, and vaso-occlusion), which contribute to the acute and chronic manifestations of SCD. These long-term complications contribute to the decreased quality of life and reduced life expectancy observed in patients with SCD. Voxelotor is an oral, once-daily hemoglobin-oxygen affinity modulator designed to inhibit HbS polymerization, thus improving anemia and reducing hemolysis. The randomized phase 3 HOPE trial (NCT03036813) evaluates the efficacy and safety of voxelotor in patients with SCD aged 12 to 65 years.

Aims: To present the results of the pre-specified Part A analysis of the first approximately 150 randomized patients in the HOPE trial.

Methods: Patients with SCD (HbSS, HbSC, HbSβ0 thalassemia, or other variants), Hb ≥5.5 and ≤10.5 g/dL, and between 1 and 10 vaso-occlusive crises in the prior 12 months were eligible. Concurrent hydroxyurea was allowed if the dose had been stable for ≥90 days. Patients were randomly assigned to receive voxelotor 1500 mg/day, 900 mg/day, or placebo for at least 24 weeks. The primary endpoint was the proportion of patients with a >1.0-g/dL increase in Hb from baseline at week 24. Secondary endpoints included change from baseline to week 24 in measures of hemolysis (absolute and percent reticulocyte counts, indirect bilirubin levels, and lactate dehydrogenase levels) and safety.

Results: 154 patients were included in the preliminary Part A analysis; median age was 25 years (range, 12–59), and 42% were male. Most patients were HbSS/HbSβ0: 92% (1500 mg), 94% (900 mg), and 90% (placebo). Hydroxyurea use at study entry was 62% (1500 mg), 67% (900 mg), and 64% (placebo), and median baseline Hb was 8.6 g/dL (1500 mg; range, 5.9–10.8), 8.3 g/dL (900 mg; range, 6.3–10.8), and 8.5 g/dL (placebo; range, 6.1–10.4). At week 24, the proportion of patients with a >1.0-g/dL increase in Hb from baseline was significantly higher for both voxelotor 1500 mg (65%; P<0.0001) and 900 mg (33%; P=0.0159) compared with placebo (10%) (Figure). The mean change in Hb from baseline to week 24 was 1.5 g/dL with 1500 mg, 0.6 g/dL with 900 mg, and 0 g/dL with placebo. Consistent with improvement in Hb, voxelotor also resulted in concordant improvements in measures of hemolysis (Table). Overall, the treatment-emergent adverse events (TEAEs) were similar across all treatment arms except for

diarrhea, which was higher with voxelotor (1500 mg, 21%; 900 mg, 19%) compared with placebo (10%). The majority of TEAEs were grade 1 or 2 in severity. The efficacy and safety data from the full patient population of the phase 3 HOPE trial (N=274) will be presented.

Summary/Conclusion: Voxelotor treatment demonstrated a dose-dependent increase in Hb, with the majority of patients on voxelotor 1500 mg achieving a >1.0-g/dL improvement in Hb from baseline to week 24. In addition, there was a dose-dependent decrease in measures of hemolysis with voxelotor. Furthermore, voxelotor was generally well tolerated. These results suggest that voxelotor has the potential to be disease-modifying by improving anemia and reducing hemolysis and their associated morbidity and mortality.

Figure. Change in Hemoglobin From Baseline to Week 24.

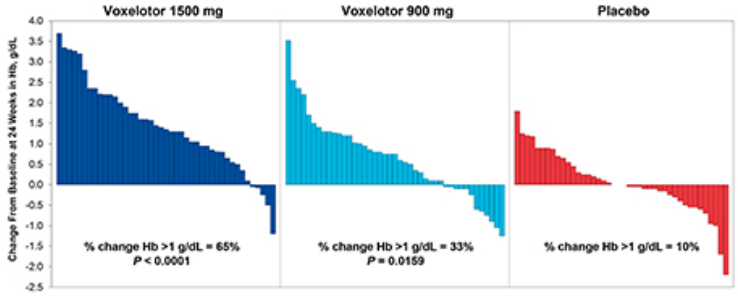

Table. Percent Change From Baseline to Week 24 in Markers of Hemolysis.

	Voxelotor 1500 mg		Voxelotor 900 mg		Placebo	
	n	Change from baseline, %	n	Change from baseline, %	n	Change from Baseline, %
Absolute reticulocytes	43	−14.6	43	−6.2	42	3.2
Percent reticulocytes	42	−27.2	43	−14.1	41	3.8
Indirect bilirubin	40	−36.5	41	−21.8	39	0.7
Lactate dehydrogenase	43	−12.1	42	−4.4	41	−0.9