Incidence of Vaso-occlusive Crisis Does Not Increase With Achieving Higher Hemoglobin Levels on Voxelotor Treatment or After Discontinuation: Analyses of the HOPE Study

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BACKGROUND
- Sickle cell disease (SCD) is an inherited disorder in which pathology is driven by hemoglobin (Hb) polymerization and red blood cell sickling, leading to chronic hemolytic anemia, and intermittent vaso-occlusion with subsequent ischemia-reperfusion injury.
- Hemolytic anemia has been associated with innate immune system and endothelial cell activation resulting in an inflammatory, pro-inflammatory state that leads to vaso-occlusive crisis (VOC) and damage to organs.
- Voxelotor is a first-in-class soluble hemoglobin (Hb) polymerization inhibitor in development for the treatment of SCD (Figure 3).
- In the Phase 3 HOPE Trial, voxelotor 1500 mg and 900 mg daily demonstrated robust, rapid, and sustained dose-dependent improvements in patient Hb levels, with numerically lower VOCs compared with placebo, which suggests that voxelotor was not increasing with voxelotor treatment.

Figure 1. Voxelotor Inhibits Hb Polymerization and Is Potentially Disease Modifying

Figure 3. Indicators for Study Design

Figure 3. Cumulative Incidence of VOCs by Hb Level During Treatment Period

CONCLUSIONS
- There was no evidence that increased Hb with voxelotor treatment led to an increased risk of VOC. Patients who achieved the absolute highest Hb levels after 24 weeks of treatment with voxelotor had numerically fewer VOCs than patients who received placebo.
- Patients who reached a Hb occupancy of 23% and those with Hb levels of ≥13 g/dL with voxelotor experienced the lower VOC rates and lower VOC compared with those receiving placebo, consistent with a treatment-induced inhibition of Hb polymerization.

- Although the patient population of the HOPE study was not enriched or powered to evaluate VOC as an efficacy endpoint, the results of this safety analysis provide important reassurance regarding the safety of voxelotor and are consistent with voxelotor treatment safely mobilizing Hb without causing a previously-observed increased risk of VOC.

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REFERENCES

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