Preliminary Safety and Efficacy Results from PRECIZN-1: An Ongoing A Phase 1/2 Study on Zinc Finger Nuclease-Mediated CD34+ HSPCs for Sickle Cell Disease (SCD)

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Introduction

- Sickle cell disease (SCD) is an autosomal recessive disorder characterized by a substitution of glutamic acid to valine in the sixth amino acid of the globin peptide, generating sickle hemoglobin (HbS), which polymerizes into inflexible polymers under hypoxic conditions, altering red blood cells (RBCs) in a wedge shape and other protein cell deformity.2,3
- SCD affects ~150,000 patients in the US, and while almost all affected persons survive into adulthood in the US and UK, that survival is shortened by 3–10 years compared with the general population.4
- Clinical phenotypes of SCD include hemolytic anemia and cyclic microvascular occlusion, leading to injury in virtually all organs.5
- Elevated fetal hemoglobin (HbF) levels in patients with SCD are shown to ameliorate multiple clinical and laboratory hemolysis markers, total hemoglobin (Hb) and HbF, percentage of F cells, and engraftment.6
- Time to initial neutrophil recovery following infusion (first of three consecutive days with absolute neutrophil count ≥ 0.5 x 10⁹/L) in non-erythroid cells
- Patients were scheduled for a total of 114 weeks

Key study endpoints

- Primary endpoints (to evaluate safety and tolerability of SAR445136)
  - Survival post transplantation: Day 100, Week 52, and Week 104 (last study visit)
  - Clinical assessments after SAR445136 infusion, including quality of life (QoL) measures
  - Total-Hb and clinical markers of hemolysis stabilized by Week 26 post-SAR445136 infusion in all four subjects
  - Percent Hb level (≥ 11%) at screening increased from 14–39 to 26% in all four subjects, and was 36% in one subject at 99 weeks' follow-up (Figure 2)

Baseline characteristics

- Table 1. Baseline characteristics and clinical history

Safety and tolerability

- Pharmacologic and surgical were generally well tolerated in patients with SCD, and most AEs reported in the skin, the initial transplantation, and conditioning periods were SCD-related events (Figure 5)
- Two SAs of sickle cell emergency crisis in two patients were reported by the investigator as possibly related
- One SAE of nausea was reported by the investigator as related to busulfan
- SAR445136 infusion in one patient, other SCD-related events reported in four patients
- There were no AEs associated to SAR445136 by the investigator or sponsor

Table 1. Baseline characteristics and clinical history

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References


Acknowledgments

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Disclosures

Asif Alavi has no relevant disclosures.

Mehrdad Abedi has participated in advisory committees or speakers bureaus for Athersys, BMS/Genzyme, and others. He has no relevant disclosures.

Mark C. Walters has served as a consultant to Alexion, BioCryst, and Vercro Pharmaceuticals. He has no relevant disclosures.

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