INTRODUCTION

Sickle Cell Disease
- Sickle cell disease (SCD) is an autosomal recessive disease resulting from a point mutation in the globin gene
- The mutation causes the red blood cells (RBCs) to develop an abnormal sickle shape
- Sickle-shaped cells can block blood vessels, leading to other complications

Figure 1. SCD is caused by a point mutation in the beta-globin gene

GPH101 Mechanism of Action and Preclinical Data

- GPH101 is an investigational drug product (DP) intended for the treatment of patients with severe SCD
- GPH101 is intended to reprogram the blood and immune system of SCD patients by restoring a healthy RBC compartment and eliminating the existing erythropoiesis responsible for SCD-related morbidity and mortality
- GPH101 harnesses the natural homology-directed repair (HDR) pathway to precisely correct the beta-globin gene mutation (Figure 2)
- Single-stranded guide RNA (gRNA) paired with HiFi Cas9 results in a sequence-specific double-strand break
- Novel gene editing approaches follow the non-homologous and joining (NIHL) pathway, which disrupts gene expression through the creation of insertions and deletions (Figure 2)
- Utilizing the HDR pathway, the CRISPR-Cas9 complex in combination with adeno-associated virus type 5 (AAV) delivery template corrects beta-globin gene mutation to reduce HbS production and restore HbA expression

Figure 2. High efficiency HDR via CRISPR/HF Cas9 precisely corrects the SCD mutation

Optimized GPH101 Gene Correction Protocol
- The GPH101 gene correction protocol was optimized in healthy donor-derived hematopoietic stem cells (HSCs) and results in efficient correction of SCD patient HSCs
- Erythropoietic differentiation in vitro demonstrated >90% HbA production (Figure 4A)
- Long-term engraftment of gene-corrected HSCs with multilineage reconstitution was demonstrated in vivo following transplantation into immunodeficient mice (Figure 4B)
- Translational data show robust and reproducible gene correction of the beta-globin gene

Figure 4. Translational data show robust and reproducible gene correction of the beta-globin gene

GPH101 Patient Journey

- Clinical trial site
  - Participants are screened for trial eligibility, including screening for pre-existing cytogenetic abnormalities (Figure 5)
  - Participants will undergo physical examination and assessment at the clinical site (CEDAR) for cell selection and cryopreservation of the approache
  - Cell product will be delivered on a weekly basis to the clinical site for storage

Figure 5. GPH101 treatment process

Clinical trial site
- Participants will be evaluated before and after engraftment and will be monitored for adverse events
- Participants will be evaluated for the following outcomes over time
  - HbA levels
  - Frequency of painful crises
  - Need for transfusions and blood products
  - Risk of transplantation-related mortality
  - Quality of life

Figure 6. CEDAR trial design (NCT04819841)

Clinical trial site
- Participants with severe SCD
- Key Inclusion Criteria
  - ≥18 years old
  - Diagnosis of severe SCD (HbS >80%)
- Randomized controlled trial
- Primary outcomes
  - Changes in HbA levels
  - Changes in transfusion requirements
- Exploratory objectives
  - Central hemodynamics and oxygen delivery (by MRI)
  - Improvements in SCD-related events and changes in organ function (e.g., heart, brain, liver)
  - Measurements of RBC health and function
  - Measurement of HbAs, off-target editing, and gene correction levels in peripheral immune cells

Figure 7. CEDAR key study endpoints

References

Poster presented at the 2021 ASH Annual Meeting & Expo.