Novel trial design to evaluate oral voxelotor for the treatment of sickle cell disease: protocol of the phase 3 Hemoglobin Oxygen Affinity Modulation to Inhibit HbS Polymerization (HOPE) trial (GBT440-031)

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BACKGROUND
- Clinical development of new sickle cell disease (SCD) therapies is challenging in part because the traditional and sole approach used in the past requires the isolation of severe, -core sickle crystals (VOCs) — a rare event and a major source of pain and vaso-occlusive crises (VOCs) — measures health care utilization rather than full disease burden
- Voxelotor (GBT440-031) is a first-in-class oral therapy that is designed to modulate hemoglobin's affinity for oxygen and is in clinical development for the treatment of SCD.
- Oxygenated sickle hemoglobin (HbS) does not polymerize (Figure 1), which decreases RBC damage, improves anemia, and reduces Hemolysis and improves O2 delivery.

Figure 1. Voxelotor Clinical Hypothesis: Increase in Hb O2 Affinity Inhibits HbS Polymerization

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OBJECTIVES
- Primary objective:
- To assess the efficacy of voxelotor in adolescents and adults (aged 12-65 years) with SCD, measured as an increase in Hb >1 g/dL, from baseline to 24 weeks
- Secondary objectives:
- To assess the efficacy of voxelotor compared with placebo on:
  - SCD symptom exacerbation and total symptom score using a PRO measurement from a 12-week end point
  - SCDSM is an electronic PRO (ePRO), developed specifically for the HOPE trial following US Food and Drug Administration (FDA) guidance, to evaluate changes in SCD symptom score from baseline to 24 weeks
- To assess the safety of voxelotor in adolescents and adults (aged 12-65 years) with SCD, measured as treatment-emergent adverse events

Figure 2. HOPE Trial Worldwide Sites

NCT03036813 is an ongoing, phase 3 randomized, double-blind, placebo-controlled, multicenter trial to evaluate the safety and efficacy of voxelotor in patients with SCD aged 12 to 65 years (ClinicalTrials.gov identifier: NCT03036813).

Figure 3. HOPE Trial Design

INCLUSION AND EXCLUSION CRITERIA

Table 1. HOPE Trial Key Inclusion and Exclusion Criteria

Inclusion Criteria
- Aged 12 to 65 years
- Hemoglobin S (HbS) >30% of total hemoglobin
- Receiving regularly scheduled RBC transfusion therapy or has received an RBC transfusion within 30 days of signing the informed consent
- Hospitalized for sickle cell-related complications or other medical reasons at any time before enrollment
- No receive of donor RBC transfusion therapy
- No prior participation in another clinical trial of an investigational agent (or medical device) within 30 days or 5 half-lives of study drug, whichever is longer
- Receiving prophylactic antibiotics for a documented infection within 30 days or 5 half-lives of study drug, whichever is longer
- No need for such agents during the study

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References

Conclusions
- The trial design takes an innovative approach to address some of the key challenges in SCD trials and accelerate clinical development
- Combines phase 2 dose selection with a transition to a phase 3 registrational phase
- Uses a clinically relevant laboratory measure, 4b, as a primary end point that is based on the mechanism of action of voxelotor
- Enables selection of RDO-defined symptom exacerbations or traditionally defined VOC as the key secondary end point based on the dose-exposure analysis
- Enrollment is ongoing and is expected to be completed by late 2018

Disclosures
- No disclosures were made regarding competing financial interests, relevant past relationships, or ownership interests.

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