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 a new sickle cell disease (SCD) therapy is challenging in part because the traditional endpoint used in trials—acute pain episodes or vaso-occlusive crises (VOCs)—measures care utilization rather than full disease burden
- Voxelotor (GBT440) is a first-in-class, oral, once-daily therapy that is designed to modulate hemoglobin’s affinity for oxygen and is in clinical development for the treatment of SCD.2
- Oxygenated sickle hemoglobin (Hb) does not polymerize (Figure 1). By maintaining Hb in an oxygenated state, voxelotor inhibits polymerization and the resultant sickling of RBCs, potentially interrupting the molecular pathogenesis of the disease (Figure 1).3

Figure 1. Voxelotor Clinical Hypothesis: Increase in HbO2 Affinity Inhibits HbS Polymerization

STUDY DESIGN

- To accelerate clinical trials to support voxelotor development, the HOPE study combines a phase 2 exploratory, dose-sequence phase (Groups 1 and 2) with a phase 3 pivotal phase (Groups 2 and 3) (Figure 3).
- Participants in Group 1 (n=60) will be randomly assigned 1:1 to voxelotor 900 mg/d or 1500 mg/d or placebo
- Participants in Group 2 (n=180) will continue enrollment with random assignment 1:1 until dose selection is made
- Group 2 will allow for a transition into Group 3 for the pivotal phase, which will randomly assign participants 1:1 to the selected dose or placebo
- Participants from Group 2 (up to 90) may be combined with those from Group 1 for the dose-analysis selection
- All selection for the dose-sequence phase (Part A) will occur when the final participant has received at least 12 weeks of treatment
- Part A analysis will enable selection of PRO-defined symptom exacerbations or traditionally defined VOC end points as the key secondary end points
- Participants in Group 3 (n=190) will be randomly assigned 1:1 to the selected dose or placebo
- The final data analysis set for the pivotal phase will include Group 2 participants who received placebo or the selected dose and all Group 3 participants (Main Population, n=250)
- Participant data used to inform dose selection will not be included in the final data analysis dataset
- Once they have completed the study, all participants are eligible to enroll in the open-label extension study under another protocol

Figure 2. HOPE Trial Worldwide Sites

INCLUSION AND EXCLUSION CRITERIA

Table 1. HOPE Trial Key Inclusion and Exclusion Criteria

CONCLUSIONS

- The HOPE trial is an ongoing study evaluating the efficacy and safety of voxelotor compared with placebo in patients aged 12 to 65 years with SCD
- The trial 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 to allow for seamless and efficient transition to the pivotal portion
- This maximizes probability of success based on selection of optimal dose and key secondary endpoint, while minimizing the time delay
- Uses a clinically relevant measure, Hb, as a primary and point that is based on the mechanism of action of voxelotor

- Enables selection of PRO-defined symptom exacerbations or traditionally defined VOC as the key secondary endpoint based on the dose decision analysis

- Enrollment is ongoing and is expected to be completed by late 2018

REFERENCES

5. Howard J, Hemmaway CJ, Telfer P, et al. Long-term dosing in sickle cell disease subjects with GBT440, a novel HbS polymerization inhibitor. Presented at the 58th ASH Annual Meeting & Exposition; December 3-6, 2016; San Diego, CA
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