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 end points used are based on outcomes that, while health-related, often do not capture disease modification.
- 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. In an oxygenated state, voxelotor inhibits polymerization and the resulting sickling of RBCs, potentially interrupting the molecular pathogenesis of the disease (Figure 1).

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

- Voxelotor is one of the first products designed specifically to treat SCD and is being studied across all SCD genotypes.
- The final HOPE trial design is based on successful dose selection in Part A of the HOPE trial which was designed to identify a safe and efficacious dose of voxelotor in treatment-naïve patients with sickle cell disease.
- The trial design takes an innovative approach to address some of the key challenges in SCD clinical trials and is scheduled to start enrollment in the third quarter of 2018.

Figure 2. HOPE Trial Worldwide Sites

NOVEL STUDY END POINTS

- The primary end point, an increase in Hb >1 g/dL, is an objective and clinically relevant measure of disease modification based on the voxelotor mechanism of action (inhibition of Hb polymerization).

Figure 3. HOPE Trial Design

- To achieve clinical trial support for voxelotor development, the HOPE study combines a phase 2 exploratory, dose-escalation phase (Groups 1 and 2) with a phase 3 pivotal phase (Groups 2 and 3) (Figure 3).

Table 1. HOPE Trial Key Inclusion and Exclusion Criteria

- Participant data used to inform dose selection will not be included in the final analysis dataset.
- Total number of participants enrolled into Group 3 determined by Group 2 enrollment.
- Total Main Population (Groups 2 and 3) = approximately 250 participants.

CONCLUSIONS

- The HOPE trial is an ongoing study evaluating the efficacy and safety of voxelotor compared with placebo in patients aged 16 to 65 years with SCD.
- The HOPE trial is an innovative response to address some of the key challenges in SCD and accelerates clinical development.

Table 2. HOPE Trial Key Inclusion and Exclusion Criteria

- Dose selection phase with a transition to a phase 3 pivotal phase to allow for seamless and efficient transition to the pivotal portion.

Figure 4. HOPE Trial Enrollment

- Enables selection of RDO-defined syndrome exacerbations or traditionally defined VOD in the key efficacy and safety end point based on the dose escalation analysis.
- Enrollment is ongoing and is expected to be completed by late 2019.

Inclusion Criteria

- Medical writing and editorial assistance were provided by ApotheCom (San Francisco, CA) and supported by Global Blood Therapeutics.
- The trial is sponsored by Global Blood Therapeutics, Inc.
- There are no contraindications identified for voxelotor.
- Multiple doses of voxelotor (GBT440) were well tolerated in patients with sickle cell disease in a Phase 2 dose-escalation study.
- Safety data from the Phase 2 study support the conduct of the Phase 3 HOPE trial.

Acknowledgments

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References

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