**GBT440, a Novel HbS Polymerization Inhibitor, Increases Hb Oxygen Affinity and Results in a Rapid Improvement in Hemolysis and Anemia**

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**INTRODUCTION**

- Sickle cell disease (SCD) is an inherited disorder caused by a point mutation in the β-globin gene leading to abnormal hemoglobin production (HbS).
- The pathophysiology mechanism involves the polymerisation of deoxygenated HbS resulting in the sickling of red blood cells (RBC), hemolytic anemia and vaso-occlusion.
- Management strategies have evolved very slowly, and treatment of SCD remains a serious unmet medical need with progressive end-organ damage, life-long pain, disability, and early death despite standard of care therapies.

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**RESULTS**

- **Baseline Characteristics and Subject Disposition**
  - SCF subjects who received multiple doses of GBT440
  - Median increase in Hb of ~1.1 g/dL

- **Efficacy: 28-day Cohort Data**
  - Unassessed bilirubin levels:
    - <1 mg/dL: 28%, 6.7% (GBT440), 2.3% (Placebo)
    - >1 mg/dL: 22%, 10.2% (GBT440), 9.6% (Placebo)

- **Efficacy Summary**
  - Hb response variable: bone marrow compartment is dynamic and has not reached equilibrium
  - 30-day treatment
  - Profound and rapid reduction in hemolysis and sickle cell sickle

- **Pharmacokinetics and Pharmacodynamics at Steady State**
  - Dose proportional increase in Hb
  - Hemoglobin modification is proportional to dose

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**CONCLUSIONS**

- GBT440 treatment leads to a rapid, profound, and durable reduction in hemolysis and sickle cells in 100% of SCD patients dosed to date
- Decrease in bilirubin
- Reduction in reticulocytosis
- Stabilization and increase in median hemoglobin >1 g/dL
- Approximately 70% reduction in irreversible sickled cells
- Dose dependent increase in oxygen affinity as measured by PSO (left shifting to normal-range)

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**Safety Data**

- No evidence of tissue hypoxia with GBT440 treatment

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**GBT440 Clinical Hypothesis: Increase in Hb-O2 affinity inhibits HbS polymerization**

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**GBT440-001: STUDY DESIGN**

- Randomized, double-blind, Phase 1B Controlled Study in Adult HbS Patients

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**GBT440-003**

- Part A - Single Dose
  - 60 mg (n=4), 120 mg (n=16), 180 mg (n=16), 240 mg (n=16), 300 mg (n=16), 360 mg (n=16), 480 mg (n=16)

- Part B - Multiple Doses (25 and 28 days)
  - 60 mg (n=4), 120 mg (n=16), 180 mg (n=16), 240 mg (n=16), 300 mg (n=16), 360 mg (n=16), 480 mg (n=16)

- Part C - Multiple Doses (30 days)
  - 60 mg (n=4), 120 mg (n=16), 180 mg (n=16), 240 mg (n=16), 300 mg (n=16), 360 mg (n=16), 480 mg (n=16)

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**No Evidence of Tissue Hypoxia with GBT440 Treatment**

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