Efficacy of GBT440 in a Patient with HbSC Genotype Sickle Cell Disease

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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).
- Polymerization of deoxyHbs in sickle cell disease (SCD) triggers the downstream effects of red cell distortion (sickling), hemolysis, occlusion of blood flow, and inflammation.
- While the most common SCD genotype is HbSS, approximately 1/3 of patients have the variant genotype HbSC.
- Although patients with HbSC disease generally experience a somewhat milder clinical course than those with HbSS, the pathogenic properties of polymerized hemoglobin can still lead to significant complications including proliferative retinopathy, osteonecrosis, painful crisis, and acute chest syndrome.

Objectives & Study Design

- Population
  - Healthy volunteers (HV)
  - Sickle cell disease (SCD) subjects:
    - HbSS, HbSβ0thalassemia – baseline Hb 6 - 10 g/dL
    - HbSC, HbSβ+thalassemia – baseline Hb 6 - <ULN g/dL
    - No vaso-occlusive crisis (VOC) or RBC transfusion within 30 days; stable hydroxyurea allowed
- Study Objectives
  - Safety
  - Pharmacokinetics (PK), pharmacodynamics (PD)
  - SCD subjects: Assess the effect of GBT440 on clinical measures of hemolysis and anemia
- Case Study Objectives
  - To describe the effect of GBT440 on clinical measures of hemolysis and anemia in a patient with HbSC disease

Case Presentation

- The patient is a 21-year-old Black female with HbSC disease.
- Past medical history includes VOC, abdominal pain, cholelithiasis.
- No prior use of hydroxyurea.
- Fatigue was the primary SCD-related symptom

Results

- The patient’s baseline hemoglobin of 10.0 g/dL increased by 1.1 g/dL at 2 months.
- By the end of 6 months, hemoglobin was 12.2 g/dL (normal 11.5 – 15.5 g/dL).
- Unconjugated bilirubin normalized, decreasing by 57% from a baseline of 28 µmol/L to 12 µmol/L at 6 months (normal 0 – 19 µmol/L).
- Baseline reticulocyte count of 3.11 increased by 17% at 6 months.
- Patient reported decreased fatigue while receiving GBT440-001 and no sickle cell crisis events occurred during the study.
- The patient tolerated the drug well with no treatment related AEs

Conclusions

- In this patient, GBT440 was well tolerated and raised hemoglobin more than 2 g/dL.
- Concurrent marked reduction of other clinical measures of hemolysis support the in vivo inhibition of polymerization by GBT440, consistent with prior published data.
- Further evaluation of GBT440 as a potential disease-modifying therapy across a broad population of genotypes including HbSC in SCD is ongoing in the Phase 3 HOPE Study

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- Study results from Part C have been previously reported at ASH 2016

Figure 1: GBT440: Designed to Bind Hemoglobin with High Selectivity

Figure 2: GBT440 Clinical Hypothesis: Increase in Hb-O2 Affinity Inhibits HbS Polymerization

Figure 3: Study Design: Chronic Dosing for 90 Days and Beyond

Figure 4: Hemoglobin (g/dL) over time

- The patient received GBT440 once daily for 6 months:
  - 2 months at 600 mg (GBT440-001)
  - 4 months at 900mg (GBT440-024)