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

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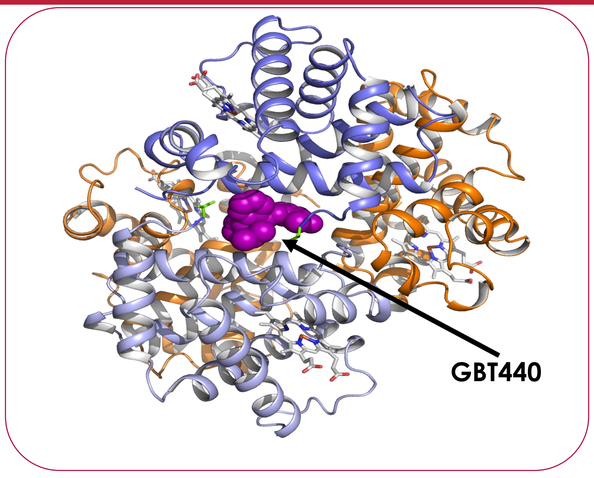
Introduction

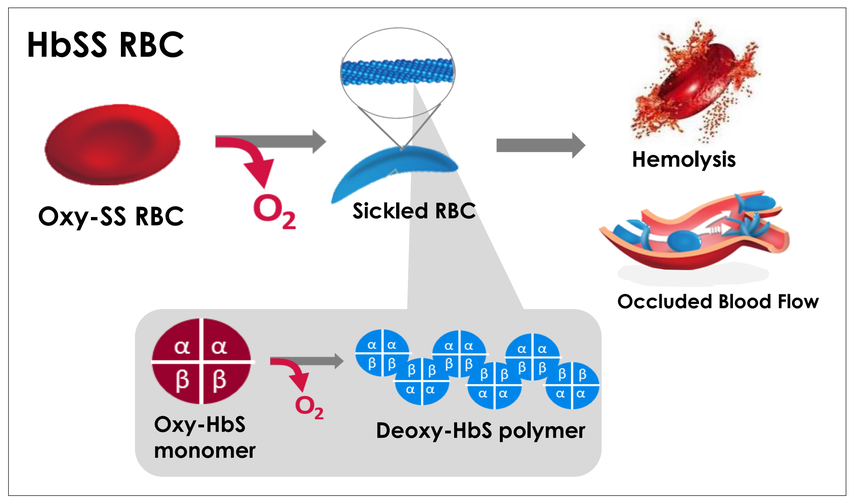
- Sickle cell disease (SCD) is an inherited disorder caused by a point mutation in the β-globin gene leading to abnormal hemoglobin production (HbS)
- Polymerization of deoxyHbS in sickle cell disease (SCD) triggers the downstream effects of red cell distortion (sickling), hemolysis, occlusion of blood 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
- Management strategies have evolved very slowly, and treatment of SCD remains a serious unmet medical need. Most clinical trials exclude HbSC patients, and no approved therapies currently exist for patients with HbSC disease
- GBT440 is an oral, once-daily therapy that modulates hemoglobin affinity for oxygen, thereby inhibiting hemoglobin polymerization
- We present results on a single patient with HbSC disease who participated in the GBT440 Phase 1/2 study to describe the clinical course in this SCD variant

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



- Reversible covalent binding to N-terminus of hemoglobin a chain → stabilizes oxy-Hb conformation
- Profile confirms properties with high selectivity for hemoglobin
  - 1:1 stoichiometry of GBT440 to Hb tetramer binding
  - Preferential partitioning into RBCs
  - Potent, dose-dependent increase in Hb-O_2 affinity

Figure 2: GBT440 Clinical Hypothesis: Increase in Hb-O_2 Affinity Inhibits HbS Polymerization



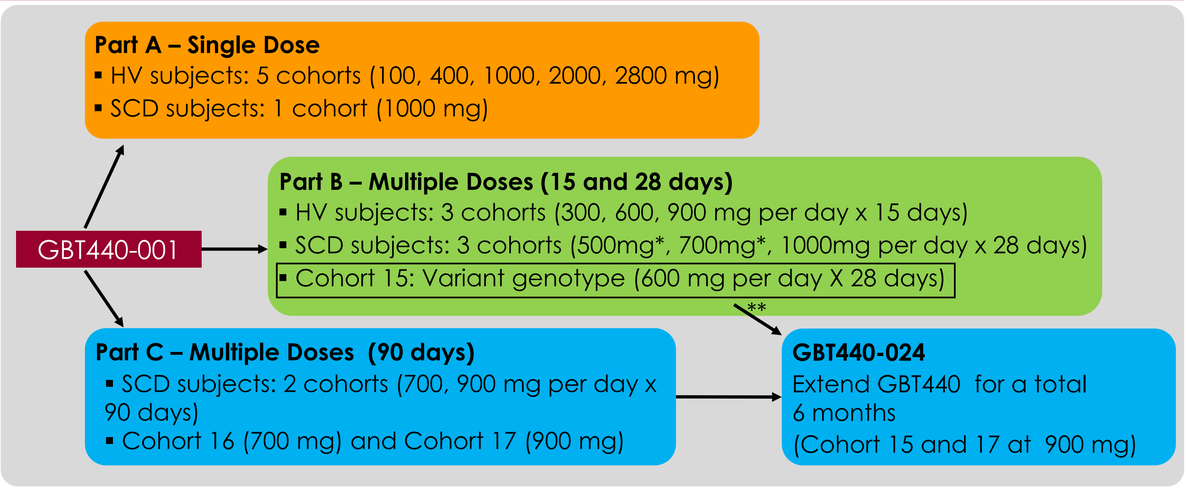
GBT440 inhibits Hb polymerization → decreases RBC damage → **Decreases hemolysis and improves anemia**

Objectives & Study Design

- Population
  - Healthy volunteers (HV)
  - Sickle cell disease (SCD) subjects:
    - HbSS, HbSβ0thalassemia – baseline Hb 6 - 10 g/dL
    - HbSC, HbS/β+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 Objective
  - To describe the effect of GBT440 on clinical measures of hemolysis and anemia in a patient with HbSC disease

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

GBT440-001: Randomized, Double-blind, Placebo Controlled Study in Adult HbSS, HbS/β0thalassemia, HbS/β+thalassemia, or HbSC Patients
GBT440-024: Open Label, extended dosing up to 6 months for subjects in GBT440-001



Each Cohort = 8 subjects (6 active, 2 placebo), except SCD subjects in Part B: 500mg* cohort (10:4); 700mg cohort* (12:4)

**Case study patient moved from Cohort 15 to the Extended Dosing

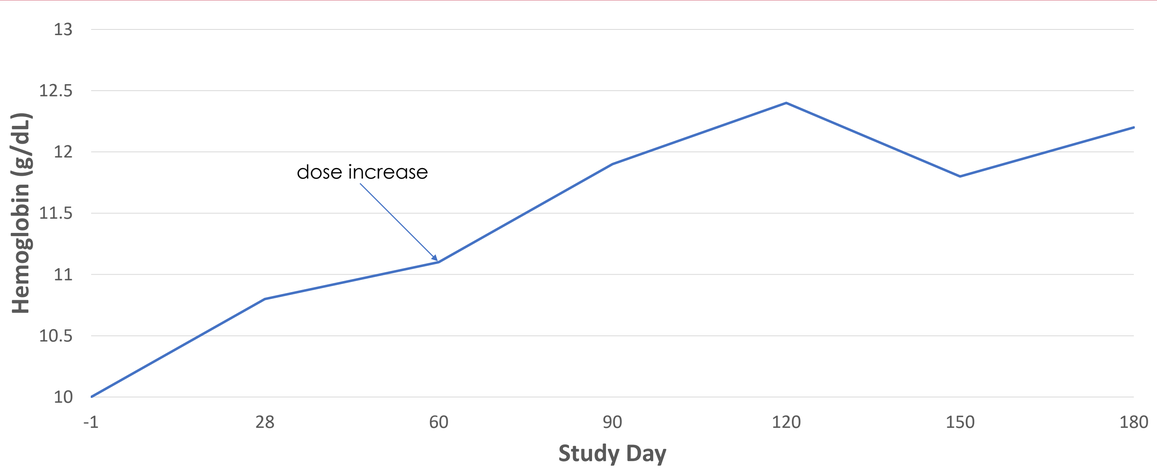
Case Presentation

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

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% decreased 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

Figure 4: Hemoglobin (g/dL) over time



Conclusions

- In this patient, GBT440 was well tolerated and raised hemoglobin more than 2 g/dL with resolution of anemia
- 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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- Trial performed at Guy's and St. Thomas' NIHR Clinical Research Facility
- Study results from Part C have been previously reported at ASH 2016

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