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ORAL ABSTRACTS

114.SICKLE CELL DISEASE, SICKLE CELL TRAIT AND OTHER HEMOGLOBINOPATHIES, EXCLUDING THALASSEMIAS: CLINICAL AND EPIDEMIOLOGICAL

Preliminary Results from a Multicenter Phase 2/3 Study of Next-Generation HbS Polymerization Inhibitor GBT021601 for the Treatment of Patients with Sickle Cell Disease

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Introduction: Sickle cell disease (SCD) is a lifelong inherited disorder resulting in polymerization of sickle hemoglobin (HbS) and is characterized by chronic hemolytic anemia, vaso-occlusive crises (VOCs), and cumulative end-organ damage. Voxelotor is a first-in-class HbS polymerization inhibitor approved in the US for the treatment of patients with SCD aged ≥4 years and in Europe for the treatment of hemolytic anemia due to SCD in patients aged ≥12 years. GBT021601 is a next-generation HbS polymerization inhibitor with improved pharmacokinetic (PK) properties that increases hemoglobin (Hb)-oxygen affinity and stabilizes Hb in the oxygenated state to inhibit polymerization. GBT021601 has the potential for higher Hb occupancies at lower doses than voxelotor and could potentially reduce treatment burden and improve clinical outcomes. Here we report preliminary safety, efficacy, and pharmacodynamic (PD) data from an ongoing phase 2/3 study of orally administered GBT021601 (NCT05431088) in patients with SCD.

Methods: This is a 3-part, multicenter phase 2/3 study in SCD. Part A is a randomized, open-label, 12-week, dose-finding study of GBT021601 in adult participants. Part B is a placebo-controlled study in adult and adolescent participants. Part C is an open-label study in pediatric participants. Here, we report data at Week 12 from Part A, which enrolled participants aged 18-65 years with SCD (HbSS/HbSβ^0 genotype) and Hb 5.5-10.5 g/dL at screening. Eligible participants were randomly assigned 1:1 to GBT021601 100 mg or 150 mg and received a loading dose twice daily for 4 days followed by once-daily maintenance doses through to Week 12. The primary endpoint was change from baseline in Hb at Week 12; secondary endpoints included Hb response (increase from baseline >1 g/dL) and change from baseline in hemolysis markers at Week 12, PK, PD, and safety. Vascular cell adhesion molecule-1 (VCAM-1) levels are elevated during VOCs, with flow adhesion of whole blood on VCAM-1 previously reported as a prognostic biomarker for VOC risk. The effect of GBT021601 on adherent cells was evaluated using a microfluidic device coated with VCAM-1.

Results: At data cutoff (June 20, 2023), 35 patients were treated in Part A; 28 had completed 12 weeks of treatment. The 100-mg group consisted of 17/35 patients (48.6%), with a mean (range) age of 29.1 (18-49) years; 7/17 patients (41.2%) were on hydroxyurea (HU). The 150-mg group had 18/35 patients (51.4%), with a mean (range) age of 30.2 (18-59) years; 9/18 patients (50.0%) were on HU. Most patients (32/35 [91.4%]) had the HbSS genotype. After 12 weeks of treatment, the mean (SD) increase in Hb from baseline was 2.67 (1.52) g/dL for the 100-mg group (n=12) and 3.17 (1.82) g/dL for the 150-mg group (n=11). A favorable trend towards reduction from baseline was observed in markers of hemolysis. Flow adhesion data showed patients taking GBT021601 had a reduction in adherent cells, which could correlate with a reduction in the probability of a VOC event (Figure). At data cutoff, the safety data showed GBT021601 was well tolerated. For 27 patients with ≥1 VOC at baseline, the

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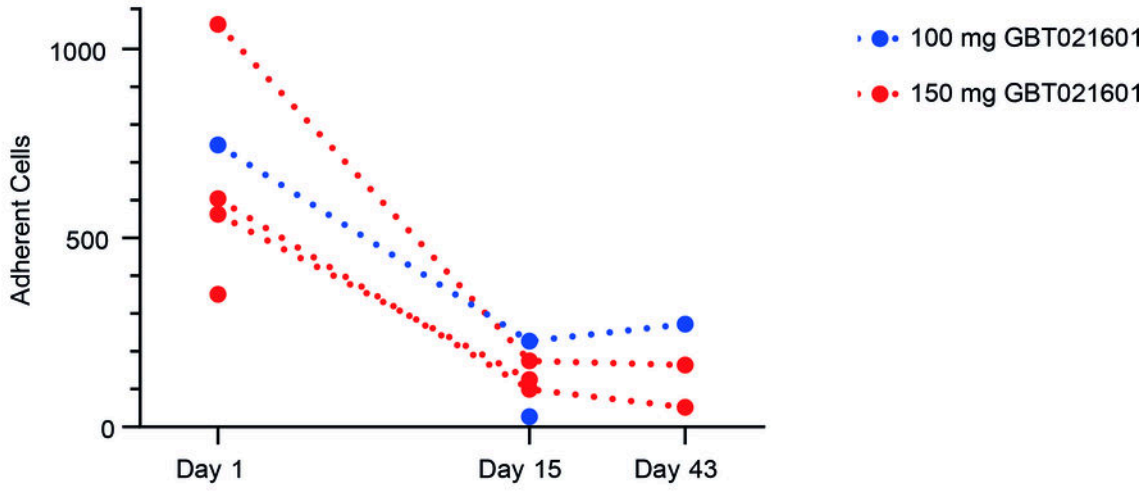
baseline annualized VOC rate was 2.30 (95% CI 1.81-2.92), and the on-study annualized VOC rate was 1.16 (95% CI 0.55-2.43) with a median (range) on-study duration of 0.4 (0.03-0.41) years. Treatment-emergent adverse events (TEAEs), predominantly grade 1 and 2 (15/35 [42.9%]) and unrelated to treatment (14/35 [40.0%]), were reported for 22 patients (62.9%). Treatment-related TEAEs in 8/35 patients (22.9%) were headache (n=4), diarrhea (n=2), and abdominal discomfort, nausea, suspected seizure (uncoded), sickle cell anemia with crisis, upper abdominal pain, and urticaria (n=1 each). There was 1 TEAE, unrelated to treatment, that led to study discontinuation (sepsis, in the 100-mg group). One death deemed unrelated to GBT021601 was due to a cerebrovascular (CVA) event, in a patient with history of CVA and seizures, after new onset high fever and no change from baseline Hb 8.0 g/dL.

Conclusions: Loading and daily doses of GBT021601 for 12 weeks were well tolerated in adult participants with SCD. Despite large increases in mean Hb levels, pain episodes did not increase and there was a reduction of adherent cells in a flow adhesion assay with VCAM-1, a potential biomarker for VOC risk. Data from Part A of this phase 2/3 study support the ongoing clinical development of GBT021601 as a potential treatment for individuals with SCD.

Disclosures Saraf: *Novartis:* Consultancy, Other: Advisory board, Research Funding; *GBT/Pfizer:* Consultancy, Other: Advisory board, Research Funding, Speakers Bureau; *BEAM Therapeutics:* Consultancy, Other: Advisory board; *Forma Therapeutics:* Consultancy, Other: Advisory board, Research Funding; *Agios:* Consultancy, Other: Advisory board. **Idowu:** *Vertex:* Consultancy; *Novo Nordisk:* Consultancy, Research Funding; *Global Blood Therapeutics:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Forma Therapeutics:* Research Funding; *Pfizer:* Consultancy, Research Funding, Speakers Bureau; *Bluebird Bio:* Consultancy; *Novartis:* Consultancy, Research Funding; *Alexion:* Research Funding; *Agios Pharmaceuticals, Inc.:* Research Funding. **Pennington:** *Global Blood Therapeutics:* Other: Advisory board. **Ershler:** *Novartis:* Other: Advisory board; Responder's office, Speakers Bureau; *Pharmacosmos:* Other: Advisory board, Speakers Bureau; *Pfizer:* Other: Advisory board, Research Funding, Speakers Bureau; *Global Blood Therapeutics:* Other: Advisory board; Responder's office. **Chin:** *Pfizer Inc:* Current Employment; *Global Blood Therapeutics:* Ended employment in the past 24 months. **Zimmerman:** *Pfizer Inc:* Current Employment; *Global Blood Therapeutics:* Ended employment in the past 24 months. **Adenola:** *Global Blood Therapeutics:* Ended employment in the past 24 months; *Pfizer:* Current Employment. **Pochron:** *Pfizer:* Current Employment, Current holder of *stock options* in a privately-held company; *Global Blood Therapeutics:* Ended employment in the past 24 months. **Lisbon:** *Pfizer:* Current Employment, Current holder of *stock options* in a privately-held company; *Global Blood Therapeutics:* Ended employment in the past 24 months.

Figure. Flow Adhesion of Whole Blood to VCAM-1



VCAM-1=vascular cell adhesion molecule-1.

Figure 1

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