Abstract: S291

Title: PRELIMINARY RESULTS FROM A MULTICENTER PHASE 2/3 STUDY OF NEXT-GENERATION HBS POLYMERIZATION INHIBITOR OSIVELOTOR (GBT021601) FOR THE TREATMENT OF PATIENTS WITH SICKLE CELL DISEASE

Abstract Type: Oral Presentation

Session Title: Sickle cell disease

Background:

Osivelotor (previously GBT021601) is a next-generation sickle hemoglobin (HbS) polymerization inhibitor in development for sickle cell disease (SCD). Compared with the first-in-class HbS polymerization inhibitor voxelotor, osivelotor has improved pharmacokinetic properties, which may enable higher Hb occupancies at lower doses to potentially reduce treatment burden and improve clinical outcomes.

Aims:

To report preliminary phase 2 data from an ongoing phase 2/3 study of osivelotor in SCD.

Methods:

Preliminary data are reported from Part A of a 3-part, multicenter phase 2/3 study (NCT05431088). Part A is a randomized (1:1), open-label, 12-week, dose-finding study of oral osivelotor in patients (pts) with SCD (HbSS/HbSβ0 genotype) aged 18–65 y and Hb 5.5−10.5 g/dL. After signing the consent form, pts received a loading dose twice-daily for 4 days then once-daily maintenance doses (100 or 150 mg) through Week 12 (W12). The primary endpoint was change from baseline (BL) in Hb at W12. Secondary endpoints included ektacytometry (Oxygenscan) to assess red blood cell (RBC) deformability as a function of partial pressure of oxygen, expressed as elongation index (EI).

Results:

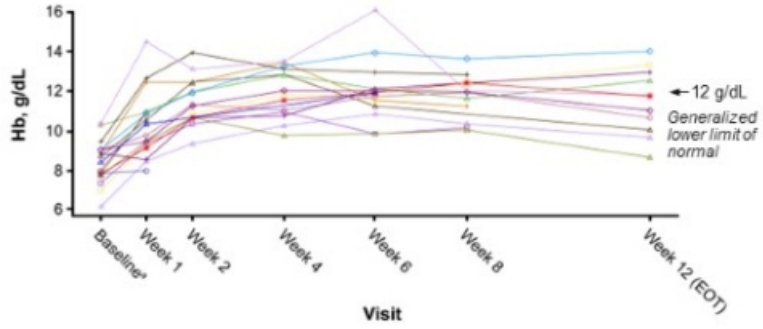
At data cutoff (June 20, 2023), 35 pts had been treated (osivelotor 100 mg, n=17; 150 mg, n=18); 28 had completed 12 weeks' treatment. Mean (range) age was 29.7 (18–59) y, 32/35 pts were HbSS, and 16/35 were on stable hydroxyurea at BL. At W12, median (range) %Hb occupancy was ~34.6% (19.1–54.6%) for 100 mg (n=7) and 54.3% (39.9–73.1%) for 150 mg (n=8). Increases in Hb from BL were observed from W1 and sustained to W12 (**Figure**). At W12, for the 100-mg (n=12) and 150-mg (n=11) groups, mean (SD) increases from BL in Hb (g/dL) were 2.67 (1.52) and 3.17 (1.82) and in hematocrit (%) were 7.87 (4.25) and 9.61 (4.60); mean (SD) changes in erythropoietin (mU/mL) were −140.4 (375.9) (n=11) and −106.2 (286.7) (n=8). Indirect bilirubin and reticulocytes also showed reductions from BL. On ektacytometry, median EI increased and median point of sickling (PoS) during deoxygenation decreased from BL to W12 (EImax: 100 mg, from 0.37 to 0.53 [n=6]; 150 mg, from 0.42 to 0.50 [n=8]; EImin:100 mg, from 0.09 to 0.33 [n=6]; 150 mg, from 0.11 to 0.35 [n=8]; PoS (mmHg): 100 mg, from 37.8 to 20.8 [n=6]; 150 mg, from 32.5 to 15.3 [n=8]). For 27 pts with ≥1 vaso-occlusive crisis (VOC) at BL, the annualized VOC rate (95% CI) was 2.30 (1.81–2.92) at BL and 1.16 (0.55–2.43) on-study, with median (range) on-study duration 0.4 (0.03–0.41) y. Treatment-emergent adverse events (TEAEs) were reported for 22 pts (62.9%). Treatment-related TEAEs, reported for 8/35 pts (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). One death, deemed unrelated to osivelotor, was due to a cerebrovascular accident (CVA), in a pt with history of CVA and seizures, after new-onset high fever and no change from BL Hb (8.0 g/dL).

Summary/Conclusion:

In preliminary results from Part A of this phase 2/3 study, loading and daily doses of osivelotor for 12 weeks were well tolerated in adults with SCD. Results to date show large increases in mean Hb accompanied by

improvements in markers of hemolysis. Although oxygen delivery was not directly measured, no impairment was suggested by indicators of oxygen delivery (i.e. no increases in erythropoietin levels or VOCs). Ektacytometry suggested improvement in RBC deformability and delayed HbS polymerization. These results support ongoing clinical development of osivelotor as a potential SCD therapy.

Figure: Individual Hb responses with osivelotor 150 mg



EOT=end of treatment.
[a] Baseline is the average of all values prior to the first treatment.

Keywords: Sickle cell disease, Clinical trial, Therapy