PB2232 TRIAL IN PROGRESS: A PHASE 2, OPEN-LABEL STUDY EVALUATING THE SAFETY AND EFFICACY OF THE ERYTHROCYTE PYRUVATE KINASE ACTIVATOR ETAVOPIVAT IN PATIENTS WITH THALASSEMIA OR SICKLE CELL DISEASE

Topic: 27. Thalassemias

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Background: In sickle cell disease (SCD), a single β-globin gene mutation results in sickle hemoglobin (HbS) that polymerizes upon deoxygenation, causing red blood cells (RBCs) to sickle leading to various complications. In thalassemia, RBCs have an imbalance in the ratio of α/β globin chains and aggregated, unpaired globin chains increase metabolic demands. These stresses result in ineffective erythropoiesis and shorten RBC lifespan, leading to chronic anemia. The resultant anemias, exacerbated by impaired RBC health, are associated with lower ATP levels than in healthy RBCs. Supportive care and agents like hydroxyurea are used most in treating SCD, with some patients (pts) on regular transfusions. Regular or episodic transfusions, with their own set of complications, are the mainstay of treatment for thalassemia.

Etavopivat, an investigational, once-daily, selective, erythrocyte pyruvate kinase (PKR) activator increases ATP and decreases 2,3-DPG.1,2 In a Phase 1 study, etavopivat 300-600 mg once daily in pts with SCD not regularly transfused was well tolerated, improved hematologic markers, decreased hemolysis and improved markers of RBC health.1,2 Etavopivat 200 and 400 mg once daily (doses predicted to provide desired pharmacodynamic response profiles) are being evaluated in a Phase 2/3 study of pts with SCD not on chronic transfusions (The Hibiscus Study, NCT04624659).

Aims: Describe the design of a Phase 2, open-label, multicenter study (NCT04987489) evaluating efficacy and safety of etavopivat in pts with SCD on chronic transfusions (Cohort A), transfusion-dependent thalassemia (Cohort B) and non-transfusion-dependent thalassemia (Cohort C).

Methods: Key eligibility criteria and study design are outlined in the Figure. Pts will receive etavopivat 400 mg once daily for 48 wks. Pts will provide written informed consent.

Baseline assessments will include medical, disease, transfusion and medication histories. Transfusions received during the study (every ~3-5 wks) will be recorded and include Hb values before and ≥15 min after transfusion, transfusion dates, number of RBC units, volume of packed RBCs and hematocrit of the transfused unit (if available). If a pt has an increase ≥1.0 g/dL in pre-transfusion Hb vs baseline, the investigator may delay transfusion 1 wk or reduce the number of RBC units transfused. RBC-exchange transfusions may also be performed in pts with SCD.

The primary endpoints are outlined in the Figure. Secondary and exploratory endpoints include the proportion of pts with a reduction in transfusions ≥33% and ≥50%, respectively, over 12 wks; reduction in transfusions over 12, 24 and 48 wks (Cohorts A/B); Hb response at Wks 24 and 48; and change from baseline in Hb over 12, 24 and 48 wks (Cohort C). Additional endpoints will be assessed in all cohorts: change from baseline in quality of life (using SF-36 and PROMIS); change from baseline in serum ferritin level at 12, 24 and 48 wks; liver iron at 48 wks; 2,3-DPG and
ATP; pharmacokinetics; and safety. Primary endpoints will be analyzed using a 1-sided test at $\alpha=0.025$.

**Results:** Results are not yet available for this trial in progress. Planned enrollment includes ≤20 pts (aged 12-65 y) in each of the 3 cohorts (Figure).

**Summary/Conclusion:** Etavopivat is a novel, investigational, once-daily, selective PKR activator with potential to improve RBC health and lifespan. This Phase 2 study will assess the safety of etavopivat and its impact on Hb levels and transfusion burden in pts (12-65 y) with SCD or thalassemia.
