P1548 LONG-TERM TREATMENT WITH ORAL MITAPIVAT IS ASSOCIATED WITH NORMALIZATION OF HEMOGLOBIN LEVELS IN PATIENTS WITH PYRUVATE KINASE DEFICIENCY

**Topic:** 28. Enzymopathies, membranopathies and other anemias

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**Background:** Pyruvate kinase (PK) deficiency is a rare hereditary anemia caused by mutations in the *PKLR* gene encoding the red blood cell PK enzyme (PKR). Defects in PKR lead to chronic hemolytic anemia, which is associated with serious complications regardless of transfusion status. Mitapivat (AG-348), a first-in-class, oral, allosteric activator of PKR, has been shown in a placebo (PBO)-controlled, phase 3 clinical trial (ACTIVATE, NCT03548220) to significantly improve hemoglobin (Hb) concentration and markers of hemolysis and hematopoiesis in patients (pts) with PK deficiency who were not regularly transfused. These improvements were sustained in a long-term extension (LTE, NCT03853798) study that included pts who completed the fixed-dose period of the ACTIVATE study.

**Aims:** This analysis focuses on normalization of Hb levels in pts treated in the ACTIVATE and ongoing LTE studies.

**Methods:** The randomized, double-blind, PBO-controlled ACTIVATE study consisted of a 12-week dose-optimization period (5/20/50 mg twice daily) and a 12-week fixed-dose period. Eighty pts (≥18 years) with a diagnosis of PK deficiency who were not regularly transfused (≤4 transfusion episodes in prior year; none in the prior 3 months) were randomized 1:1 to receive mitapivat or PBO. The primary endpoint was Hb response, defined as ≥1.5 g/dL increase in Hb from baseline sustained at ≥2 scheduled assessments at weeks 16, 20, and 24 in the fixed-dose period. Pts who completed the fixed-dose period of ACTIVATE were eligible to continue in the LTE study, where all pts received mitapivat treatment with serious complications regardless of transfusion status. Mitapivat (AG-348), a first-in-class, oral, allosteric activator of PKR, has been shown in a placebo (PBO)-controlled, phase 3 clinical trial (ACTIVATE, NCT03548220) to significantly improve hemoglobin (Hb) concentration and markers of hemolysis and hematopoiesis in patients (pts) with PK deficiency who were not regularly transfused. These improvements were sustained in a long-term extension (LTE, NCT03853798) study that included pts who completed the fixed-dose period of the ACTIVATE study.

**Results:** In ACTIVATE, 16 of the 40 pts (40%) treated with mitapivat and none of the 40 patients randomized to PBO achieved an Hb response as defined in the study protocol. Across the ACTIVATE and LTE studies, 28/78 (35.9%) pts achieved a normal Hb level at least once during treatment with mitapivat. Among pts treated with mitapivat in both the ACTIVATE and LTE studies (M/M arm, mean Hb at baseline 8.66 g/dL), 15/40 (37.5%) achieved a normal Hb level at least once during treatment, the majority within the first few months. Similarly, among patients randomized to PBO in the ACTIVATE study and treated with mitapivat in the LTE study (P/M arm, mean Hb at baseline 8.47 g/dL), 13/38 (34.2%) achieved a normal Hb level at least once during the LTE, all within the first 4 months of treatment with mitapivat. Of the 16 M/M pts who achieved Hb response, 14 (87.5%) achieved a normal Hb level at least once during treatment with mitapivat either in the ACTIVATE study or the LTE; of the 15 P/M pts who achieved a protocol-defined Hb response during mitapivat treatment in the LTE, 12 (80.0%) achieved a normal Hb at least once. Seven pts had normal hemoglobin measurements at each time point assessed while on mitapivat treatment (Figure).

**Image:**

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Summary/Conclusion: In this study, treatment with mitapivat was associated with early and robust Hb responses with approximately one-third of pts achieving normal Hb levels at least once. These results add to the evolving data demonstrating potential real-world benefits of mitapivat for patients with PK deficiency and supports mitapivat as an effective and disease-modifying therapy for this condition.