Mitapivat improves markers of hemolysis and erythropoiesis in patients with pyruvate kinase deficiency irrespective of hemoglobin response

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BACKGROUND

- Pyruvate kinase (PK) deficiency is a rare, hereditary disorder caused by mutations in the *PKLR* gene encoding the red blood cell-specific form of PK (PKR), which leads to chronic hemolytic anemia[1–4]
- PK deficiency is associated with serious acute and long-term complications, most of which occur as a consequence of chronic, ongoing hemolysis and ineffective erythropoiesis[3–6]
- Mitapivat (AG-348), a first-in-class, oral, allosteric activator of PKR, is approved by the US FDA for the treatment of hemolytic anemia in adults with PK deficiency[7–10]
- By activating PKR, mitapivat has been shown in the phase 3 ACTIVATE study (NCT03548220) to significantly improve hemoglobin (Hb) and markers of hemolysis and erythropoiesis in patients with PK deficiency who were not regularly transfused[11]
- To a lesser degree, induction of *UGT1A1* by mitapivat may also affect the metabolism of indirect bilirubin (one of the hemolysis markers studied), potentially contributing to decreased levels of this marker[9]
- The impact of mitapivat on markers of hemolysis specifically in patients who were not Hb responders as defined by the primary endpoint of ACTIVATE has not yet been reported

OBJECTIVE

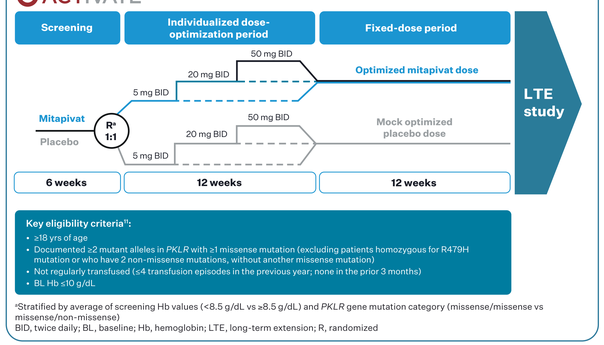
- **To assess changes in markers of hemolysis and erythropoiesis specifically in patients from the phase 3 ACTIVATE trial who did not achieve a Hb response as defined in the study protocol**

METHODS

ACTIVATE study design

- The randomized, double-blind, placebo-controlled ACTIVATE study consisted of a 12-week dose-optimization period (5/20/50 mg twice daily) and a 12-week fixed-dose period (**Figure 1**); details have been previously reported[11]

Figure 1. ACTIVATE study design



Key eligibility criteria[11]**:**
- ≥18 yrs of age
- Documented ≥2 mutant alleles in *PKLR* with ≥1 missense mutation (excluding patients homozygous for R479H mutation or who have 2 non-missense mutations, without another missense mutation)
- Not regularly transfused (≤4 transfusion episodes in the previous year; none in the prior 3 months)
- BL Hb ≤10 g/dL

*Stratified by average of screening Hb values (<8.5 g/dL vs ≥8.5 g/dL) and *PKLR* gene mutation category (missense/missense vs missense/non-missense)
BID, twice daily; BL, baseline; Hb, hemoglobin; LTE, long-term extension; R, randomized

- 80 adults (≥18 years) with PK deficiency who were not regularly transfused (≤4 transfusion episodes in the prior year; none in the prior 3 months) were randomized 1:1 to receive mitapivat or placebo

Analysis

- Results from primary analyses have been previously reported[11]
- This analysis compared hemolysis and erythropoiesis markers in patients treated with mitapivat who did not achieve the protocol-defined Hb response (defined as ≥1.5 g/dL increase in Hb from baseline [BL] sustained at ≥2 scheduled assessments at Weeks 16, 20, and 24 in the fixed-dose period) with those randomized to placebo

RESULTS

Baseline characteristics[11]

- 80 patients were randomized 1:1 to receive mitapivat (N=40) or placebo (N=40)
- Mean Hb at BL was 8.6 g/dL

Primary endpoint: Hb response[11]

- 16/40 patients (40%) in the mitapivat arm and 0/40 patients (0%) in the placebo arm achieved a Hb response (2-sided p<0.001)

Markers of hemolysis and erythropoiesis in protocol-defined non-responders

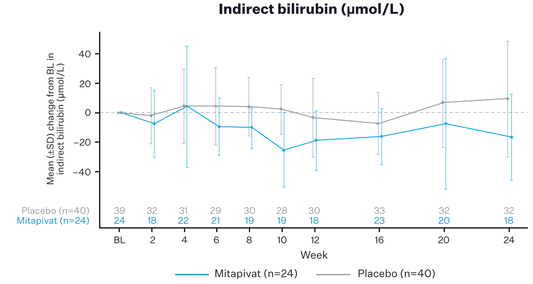
- Markers of hemolysis and erythropoiesis improved in patients randomized to mitapivat who did not achieve a protocol-defined Hb response, as shown by the average change from BL at Weeks 16, 20, and 24 (**Table 1, Figures 2–5**)
- Minimal or no average improvement from BL was seen in patients in the placebo arm at Weeks 16, 20, and 24 (**Table 1, Figures 2–5**)

Table 1. Average change from BL at Weeks 16, 20, and 24 in markers of hemolysis in protocol-defined non-responders in the ACTIVATE study

Marker	Mitapivat arm (n=24)	Placebo arm (n=40)
Indirect bilirubin, µmol/L		
BL mean (SD)	98.4 (68.4)	89.1 (61.8)
Mean change from BL (SD)	−12.7 (24.6)	3.0 (20.1)
Reticulocyte, %		
BL mean (SD)	0.48 (0.22)	0.40 (0.22)
Mean change from BL (SD)	−0.07 (0.07)	−0.00 (0.06)
LDH, U/L		
BL mean (SD)	292.8 (248.7)	260.0 (140.2)
Mean change from BL (SD)	−27.1 (106.5)	−8.7 (76.4)
Haptoglobin, g/L		
BL mean (SD)	0.10 (0.13)	0.08 (0.14)
Mean change from BL (SD)	0.05 (0.14)	0.01 (0.07)

BL, baseline; LDH, lactate dehydrogenase

Figure 2. Mean change from BL in indirect bilirubin in patients who did not achieve a protocol-defined Hb response compared with placebo



Analysis performed in the 24 patients with PK deficiency treated with mitapivat who did not achieve a protocol-defined Hb response and the 40 patients randomized to placebo (none of whom achieved a Hb response); a Hb response was defined as ≥1.5 g/dL increase in Hb from BL sustained at ≥2 scheduled assessments at Weeks 16, 20, and 24 in the fixed-dose period; BL is the average of all assessments within 45 (42+3) days before start of treatment with mitapivat. Assessments collected within 61 days after a transfusion are excluded; BL, baseline; Hb, hemoglobin; PK, pyruvate kinase

Figure 3. Mean change from BL in reticulocyte (%) in patients who did not achieve a protocol-defined Hb response compared with placebo

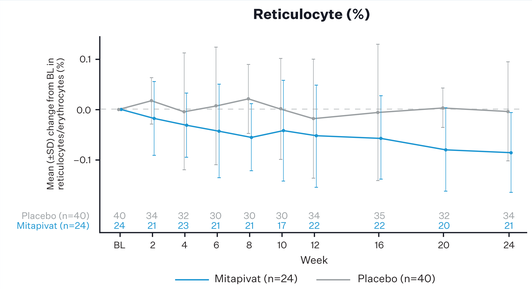


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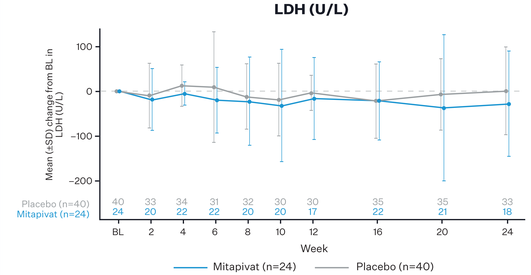
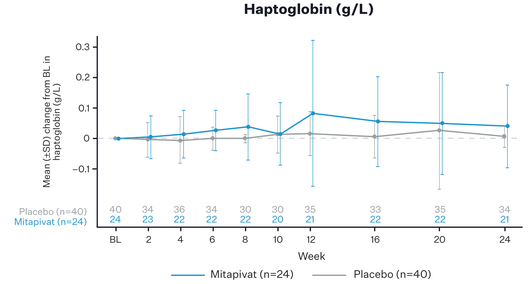
Figure 4. Mean change from BL in LDH in patients who did not achieve a protocol-defined Hb response compared with placebo



Analysis performed in the 24 patients with PK deficiency treated with mitapivat who did not achieve a protocol-defined Hb response and the 40 patients randomized to placebo (none of whom achieved a Hb response); a Hb response was defined as ≥1.5 g/dL increase in Hb from BL sustained at ≥2 scheduled assessments at Weeks 16, 20, and 24 in the fixed-dose period; BL is the average of all assessments within 45 (42+3) days before start of treatment with mitapivat. Assessments collected within 61 days after a transfusion are excluded; BL, baseline; Hb, hemoglobin; LDH, lactate dehydrogenase; PK, pyruvate kinase

Figure 5. Mean change from BL in haptoglobin in patients who did not achieve a protocol-defined Hb response compared with placebo



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CONCLUSIONS

- **Mitapivat directly targets the underlying pathophysiologic defect in PK deficiency by activating PKR**
- **In ACTIVATE, significant improvements in markers of hemolysis and erythropoiesis have been demonstrated for the overall patient population treated with mitapivat[11]**
- **This analysis shows that these improvements occur even in patients from the mitapivat arm who did not achieve the clinical trial definition of Hb response**

By improving markers of hemolysis and ineffective erythropoiesis, oral mitapivat is the first agent that has the potential to minimize long-term complications in patients with PK deficiency, even in those who do not meet the study-defined threshold for a Hb response

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