Mitapivat decreases the need for transfusions secondary to poorly tolerated anemia and acute events compared to placebo in patients with pyruvate kinase deficiency who are not regularly transfused

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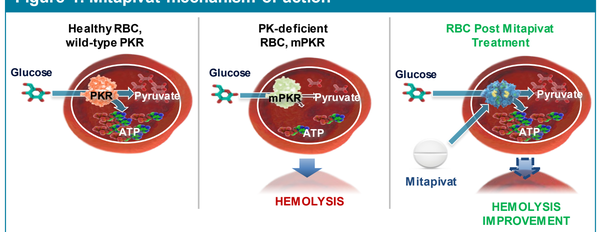
BACKGROUND

- Pyruvate kinase (PK) deficiency is a rare, hereditary, chronic hemolytic anemia characterized by mutations in the *PKLR* gene leading to reduced activity of the red blood cell (RBC) PK enzyme (PKR)[1,2]
  - Serious lifelong complications associated with PK deficiency include gallstones, iron overload, osteoporosis, liver cirrhosis, and pulmonary hypertension[3–5]
- Traditional management strategies for PK deficiency have been supportive only and include RBC transfusions and splenectomy; many patients continue to require transfusions even after splenectomy[6]
  - A subset of these patients require regular transfusions; however, intermittent transfusions may be needed in patients who are not regularly transfused due to hemolytic crisis, infections, and other acute events[6]
- Although transfusions can temporarily increase hemoglobin (Hb), they are associated with acute and chronic complications and can have a negative impact on health-related quality of life[7,8]
  - Transfusions can exacerbate iron overload, resulting in serious complications including hepatic cirrhosis, cardiomyopathy, and endocrinopathy, if left untreated[7,8]
  - Iron chelation therapy is used to treat iron overload; however, it is associated with side effects and poor compliance[8]

Mitapivat

- Mitapivat is an oral, allosteric activator of PK (**Figure 1**) that is approved by the US Food and Drug Administration for the treatment of hemolytic anemia in adults with PK deficiency[9–11]

Figure 1. Mitapivat mechanism of action



ATP, adenosine triphosphate; mPKR, mutant PKR; PK, pyruvate kinase; PKR, red blood cell form of PK; RBC, red blood cell

Pivotal phase 3 studies and their long-term extension study (LTE)

- In ACTIVATE (NCT03548220; N=80), a phase 3 double-blind, placebo-controlled study of adults with PK deficiency who were not regularly transfused, 16 mitapivat-treated patients (40%) demonstrated a significant increase (≥1.5 g/dL) in Hb from baseline sustained at ≥2 scheduled assessments at Weeks 16, 20, and 24 during the fixed-dose period compared with 0 placebo-treated patients (2-sided p<0.0001)[12]
  - Mitapivat also showed improvements in markers of hemolysis, hematopoiesis, and iron metabolism, all of which were maintained over time in ACTIVATE's LTE (NCT03853798)[12–14]
- In ACTIVATE-T (NCT03559699; N=27), a phase 3 single arm, open-label study of adults with PK deficiency who were regularly transfused, 10 patients (37%) achieved a significant reduction in transfusion burden, defined as a ≥33% reduction in the number of RBC units transfused compared to their individual historical transfusion burden standardized to 24 weeks (1-sided p=0.0002)[15]
  - P-value associated with the test of H0: transfusion reduction response rate ≤10% vs H1: transfusion reduction response rate >10%
  - All patients (n=6) who achieved transfusion-free status (no transfusions in the 24-week fixed-dose period of ACTIVATE-T), maintained this status in ACTIVATE-T's LTE (NCT03853798)[13,15]

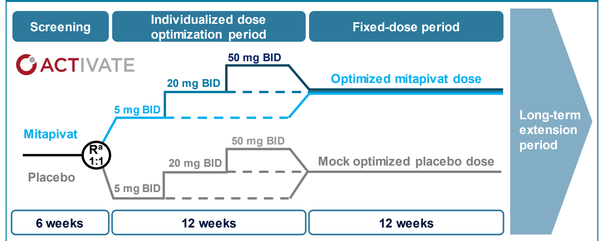
OBJECTIVE

- **To determine the effect of the PK activator, mitapivat, on the number of transfusion episodes and RBC units transfused in patients with PK deficiency who were not regularly transfused in the ACTIVATE study**

METHODS

- ACTIVATE was a phase 3, global, randomized, double-blind, placebo-controlled study of mitapivat in adults with PK deficiency who were not regularly transfused (≤4 transfusion episodes in the previous year, none in the prior 3 months) (**Figure 2**)
- Patients were randomized 1:1 to receive mitapivat or placebo and 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)
- ACTIVATE consisted of a 6-week screening period, followed by a 12-week dose optimization period (5 mg twice daily [BID], 20 mg BID, 50 mg BID) and a 12-week fixed-dose period

Figure 2. ACTIVATE study design and key eligibility criteria



Key eligibility criteria:
- ≥18 years of age
- Documented ≥2 mutant alleles in *PKLR* (≥1 missense mutation)
- Not regularly transfused (≤4 transfusion episodes in previous year)
- Baseline Hb ≤10 g/dL
- Adequate organ function

Key exclusion criteria:
- Homozygous for R479H mutation or have 2 non-missense mutations, without another missense mutation, in *PKLR*
- Splenectomy during study, or within 12 months of enrollment
- Prior bone marrow or stem cell transplant

[a]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; Hb, hemoglobin; R, randomized

Primary endpoint

- Hb response, defined as ≥1.5 g/dL increase in Hb concentration from baseline sustained at ≥2 scheduled assessments at Weeks 16, 20, and 24 during the fixed-dose period

Key secondary endpoint

- Average change from baseline in Hb concentration at Weeks 16, 20, and 24

Reported here are results from an exploratory endpoint

- Proportion of patients requiring transfusions and the total number of RBC units transfused during the 24-week study period

RESULTS

Patient demographics and baseline characteristics

- The population was balanced between the mitapivat (N=40) and placebo (N=40) arms (**Table 1**)
- Patients had evidence of high disease burden with high rates of prior splenectomy and cholecystectomy, elevated ferritin and liver iron concentration by magnetic resonance imaging levels, and decreased bone mineral density as measured by dual-energy X-ray absorptiometry scans[12]
- 11 patients in the mitapivat arm and 10 patients in the placebo arm received transfusions within the 52-weeks prior to study treatment

Table 1. Patient demographics and baseline characteristics[a]

Baseline demographics		Mitapivat (N=40)	Placebo (N=40)
Age (years)	Mean (SD)	36.0 (15.2)	37.2 (15.9)
	Range	18–70	19–78
Sex, n (%)	Male	16 (40.0)	16 (40.0)
	Female	24 (60.0)	24 (60.0)
Geographic region, n (%)	Western Europe	19 (47.5)	20 (50.0)
	North America	15 (37.5)	16 (40.0)
	Asia	5 (12.5)	3 (7.5)
	Middle East	0	1 (2.5)
	Latin America	1 (2.5)	0
Baseline characteristics			
Hb (g/dL), mean (SD)		8.6 (0.99)	8.5 (0.85)
Ferritin (µg/L), mean (SD)		748 (1116.2)	688 (605.2)
LIC by MRI (mg Fe/g dw)[b], mean (SD)		7.6 (10.78)	6.1 (8.01)
Patients with transfusion episodes in the 52 weeks prior to study treatment, n (%)	0 transfusion episodes	29 (72.5)	30 (75.0)
	Any number of transfusion episodes	11 (27.5)	10 (25.0)
	1 transfusion episode	8 (20.0)	7 (17.5)
	2 transfusion episodes	0	1 (2.5)
	3 transfusion episodes	3 (7.5)	1 (2.5)
	≥4 transfusion episodes	0	1 (2.5)
Prior splenectomy, n (%)		28 (70.0)	30 (75.0)
Prior cholecystectomy, n (%)		28 (70.0)	30 (75.0)
Patients with chelation therapy in the 52 weeks prior to study treatment, n (%)[b]		5 (12.5)	10 (25.0)
DXA T-Score, mean (SD)	Femoral total[c]	–1.12 (1.081)	–0.79 (1.098)
	Adjusted spine	–1.78 (1.104)	–1.14 (1.153)
***PKLR* mutation category**	Missense/missense	28 (70.0)	27 (67.5)
	Missense/non-missense	12 (30.0)	13 (32.5)

From N Engl J Med, Hanny Al-Samkari et al., *Mitapivat versus Placebo for Pyruvate Kinase Deficiency*, 386, 1432–1442, Copyright © 2022, Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society [a]Summarized based on full analysis set (all patients who were randomized to treatment); [b]Baseline LIC by MRI results were available for 38 patients in the mitapivat arm and 39 patients in the placebo arm; [c]Femoral neck and total hip combined; Dw, dry weight; DXA, dual-energy x-ray absorptiometry; Fe, iron; Hb, hemoglobin; LIC, liver iron concentration; MRI, magnetic resonance imaging; SD, standard deviation

Frequency of on-study transfusion episodes

- 1 out of 11 patients (9.0%) in the mitapivat arm and 6 out of 10 patients (60.0%) in the placebo arm who received a transfusion in the 52 weeks prior to study treatment required an on-study transfusion
- In the mitapivat arm (N=40), 2 patients (5.0%) required transfusions during the 24-week study period (**Table 2**)
  - 1 patient experienced 1 transfusion episode and 1 patient experienced 4 transfusion episodes
  - Both patients (5.0%) received transfusions due to clinically significant or poorly controlled anemia
  - 0 patients received transfusions due to an adverse event
- In the placebo arm (N=39), 7 patients (17.9%) required transfusions during the 24-week study (**Table 2**)
  - 5 patients experienced 1 transfusion episode each, 1 patient experienced 2 transfusion episodes, and 1 patient experienced 3 transfusion episodes
  - 5 patients (12.8%) received transfusions due to clinically significant or poorly controlled anemia
  - 4 patients (10.8%) received transfusions due to an adverse event
    - 2 patients received transfusions due to both clinically significant or poorly controlled anemia and an adverse event

Table 2. Summary of on-treatment transfusion episodes[a]

Transfusion episodes		Mitapivat (N=40)	Placebo (N=39)
Patients with on-treatment transfusion episodes, n (%)	0 transfusion episodes	38 (95.0)	32 (82.1)
	Any number of transfusion episodes	2 (5.0)	7 (17.9)
	1 transfusion episode	1 (2.5)	5 (12.8)
	2 transfusion episodes	0	1 (2.6)
	3 transfusion episodes	0	1 (2.6)
	4 transfusion episodes	1 (2.5)	0
Reason for transfusion[b], n (%)	Adverse event	0	4 (10.3)
	Clinically significant or poorly tolerated anemia	2 (5.0)	5 (12.8)

[a]Summarized based on safety analysis set (all patients who were received at least 1 treatment dose; [b]2 patients received transfusions due to both an adverse event and clinically significant or poorly tolerated anemia

Number of on-study RBC units received

- Among patients who experienced transfusion episodes due to clinically significant or poorly tolerated anemia (**Table 3**)
  - In the mitapivat arm, 1 patient experienced 1 episode with 2 RBC units transfused and 1 patient experienced 4 episodes with 1 RBC unit transfused per episode
  - In the placebo arm, 1 patient experienced 1 episode with 1 RBC unit transfused and 3 patients experienced 1 episode each with 2 RBC units transfused per episode and 1 patient experienced 2 episodes with 1 RBC unit transfused per episode
- Among patients who experienced transfusion episodes due to an adverse event (**Table 3**)
  - In the mitapivat arm, 0 patients experienced transfusion episodes due to an adverse event
  - In the placebo arm, 4 patients experienced 1 episode each with 1–2 RBC units transfused per episode
    - The adverse events that led to transfusions were viral upper respiratory tract infection, dyspnea, fatigue, and presyncope

Table 3. Number of transfusion episodes, number of units transfused, and reason for transfusion among the 9 patients who received transfusions during ACTIVATE

Mitapivat or placebo arm	Patient	Number of transfusion episodes per patient	Number of units transfused	Reason for transfusion
Mitapivat (n=2)	1	1	2	Clinically significant or poorly tolerated anemia
	2	4	4	Clinically significant or poorly tolerated anemia
Placebo (n=7)	3	1	2	Clinically significant or poorly tolerated anemia
	4	1	2	Clinically significant or poorly tolerated anemia
	5	1	2	Adverse event (viral upper respiratory tract infection)
	6	2[a]	1	Clinically significant or poorly tolerated anemia
			2	Adverse event (dyspnea)
	7	1	2	Clinically significant or poorly tolerated anemia
	8	1	N/A	Adverse event (fatigue)
	9	3[a]	2	Clinically significant or poorly tolerated anemia
			1	Adverse event (presyncope)

[a]Patient received transfusion due to both an adverse event and clinically significant or poorly tolerated anemia; N/A, not available

Safety results

- Mitapivat was well-tolerated, and its safety profile was consistent across all previously reported studies[12] (**Table 4**)

Table 4. Most frequently reported (≥10%) treatment-emergent adverse events in ACTIVATE[a]

Preferred term[b]	Mitapivat (N=40)	Placebo (N=39)
Patients with events, n (%)	35 (87.5)	35 (89.7)
Nausea	7 (17.5)	9 (23.1)
Headache	6 (15.0)	13 (33.3)
Nasopharyngitis	5 (12.5)	6 (15.4)
Fatigue	5 (12.5)	4 (10.3)
Back pain	5 (12.5)	3 (7.7)
Diarrhea	4 (10.0)	7 (17.9)
Dizziness	4 (10.0)	3 (7.7)
Abdominal pain	4 (10.0)	2 (5.1)
Arthralgia	4 (10.0)	2 (5.1)
Dyspnea	3 (7.5)	4 (10.3)
Alanine aminotransferase increased	1 (2.5)	6 (15.4)
Initial insomnia	1 (2.5)	4 (10.3)
Upper respiratory tract infection	0	4 (10.3)

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CONCLUSIONS

- These data support that mitapivat, a disease modifying pharmacotherapy, has the potential to decrease transfusion needs secondary to poorly tolerated anemia and acute events in patients with PK deficiency who are not regularly transfused
  - This finding is consistent with the decrease in transfusion burden previously shown with mitapivat treatment in adults with PK deficiency who were regularly transfused[14]

Given that RBC transfusions are associated with exacerbation of iron overload in patients with PK deficiency, a reduction in transfusion burden with the use of the oral agent mitapivat may have a beneficial effect on iron overload, long-term disease burden, and quality of life of patients with PK deficiency who are not regularly or regularly transfused

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