Mitapivat improves ineffective erythropoiesis and reduces iron overload in patients with pyruvate kinase deficiency

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BACKGROUND

- Pyruvate kinase (PK) deficiency is a rare, lifelong, hereditary anemia caused by mutations in the *PKLR* gene, encoding the red blood cell PK (PKR) enzyme, and which can result in chronic hemolytic anemia and serious complications including iron overload[1–4]
- In patients with PK deficiency, iron overload is linked to chronic hemolysis and ineffective erythropoiesis,[5] occurs independent of transfusion requirements and can be further worsened by transfusions, and may require iron chelation therapy[4,6]
- Iron overload can lead to long-term complications including liver cirrhosis, cardiomyopathy, arrhythmia, sudden cardiac death, and endocrine dysfunction[7,8]
- Available supportive therapies are associated with short- and long-term complications[6]

Mitapivat in PK deficiency

- Mitapivat is an oral, allosteric activator of PK that is approved by the US Food and Drug Administration for the treatment of hemolytic anemia in adults with PK; it targets the underlying enzymatic defect causing hemolysis in PK deficiency by restoring PKR activity[9–11]
- In phase 3 studies of adults with PK deficiency, mitapivat demonstrated:
  - Statistically significant improvements in hemoglobin (Hb), markers of hemolysis, and PK deficiency-specific quality of life patient-reported outcome measures in patients who were not regularly transfused (ACTIVATE, NCT03548220)[12]
  - A statistically significant reduction in transfusion burden in patients who were regularly transfused (ACTIVATE-T, NCT03559699)[13]

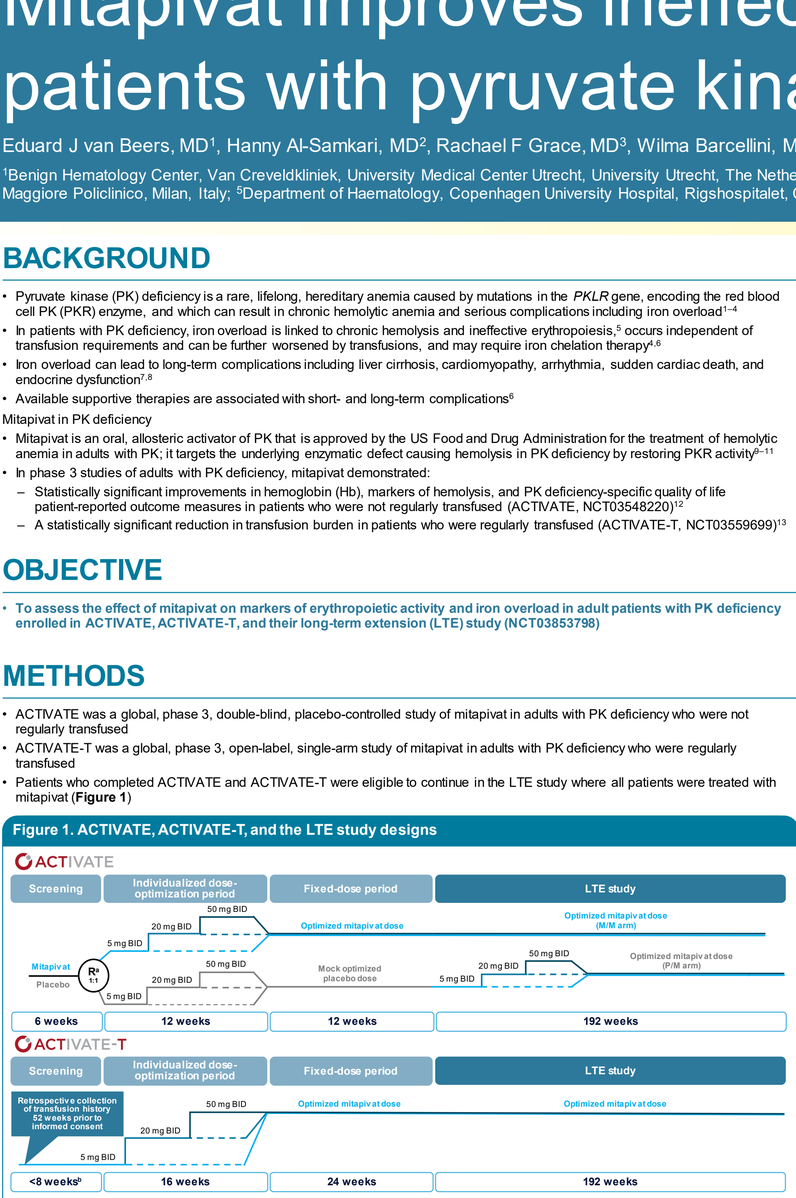
OBJECTIVE

- **To assess the effect of mitapivat on markers of erythropoietic activity and iron overload in adult patients with PK deficiency enrolled in ACTIVATE, ACTIVATE-T, and their long-term extension (LTE) study (NCT03853798)**

METHODS

- ACTIVATE was a global, phase 3, double-blind, placebo-controlled study of mitapivat in adults with PK deficiency who were not regularly transfused
- ACTIVATE-T was a global, phase 3, open-label, single-arm study of mitapivat in adults with PK deficiency who were regularly transfused
- Patients who completed ACTIVATE and ACTIVATE-T were eligible to continue in the LTE study where all patients were treated with mitapivat (**Figure 1**)

Figure 1. ACTIVATE, ACTIVATE-T, and the LTE study designs



Key eligibility criteria:

- ≥18 years of age
- Documented ≥2 mutant alleles in *PKLR* with ≥1 missense mutation (excluding patients homozygous for R479H mutation or that have 2 non-missense mutations, without another missense mutation)
- **ACTIVATE**: Not regularly transfused (≤4 transfusion episodes in previous year); baseline (BL) Hb ≤10 g/dL
- **ACTIVATE-T**: Regularly transfused (≥6 transfusion episodes in previous year)
- **LTE study**: patients must have completed the fixed-dose period of ACTIVATE or ACTVATE-T and demonstrated clinical benefit from mitapivat treatment or were assigned to the placebo arm in ACTIVATE and elected to continue to the LTE study

[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); [b]Screening may have been extended beyond 8 weeks if there was a delay in obtaining a patient's complete transfusion history or to ensure that the first dose of study drug could be administered 2–7 days after the most recent transfusion; BID, twice daily; Hb, hemoglobin; LTE, long-term extension study; M/M, mitapivat-to-mitapivat; P/M, placebo-to-mitapivat; R, randomized

Endpoints and analyses

- **Markers of erythropoietic activity** – erythropoietin (EPO), erythroferrone, reticulocytes, and soluble transferrin receptor (sTfR)
- **Markers of iron metabolism and indicators of iron overload** – hepcidin, iron, transferrin saturation (TSAT), ferritin, total iron binding capacity, and liver iron concentration (LIC) by magnetic resonance imaging (MRI)
- In the ACTIVATE/LTE study, patients assigned mitapivat in ACTIVATE were categorized into the mitapivat-to-mitapivat (M/M) arm and patients assigned placebo in ACTIVATE were categorized into the placebo-to-mitapivat (P/M) arm; the analysis assessed change in markers from BL over time in both study arms
- The ACTIVATE-T/LTE study analysis was descriptive and limited to patients who achieved transfusion-free status in the fixed-dose period of ACTIVATE-T to mitigate the confounding effect of transfusions on markers of erythropoietic activity, iron metabolism, and iron overload

RESULTS

- 80 patients were randomized in ACTIVATE to mitapivat (N=40) or placebo (N=40); as of the data cut-off date (12Nov2020), 71 patients (35 M/M; 36 P/M) continued to the LTE and received mitapivat treatment
- Mean EPO, erythroferrone, reticulocytes, and sTfR results are shown in **Table 1** and **Figure 2**
  - **M/M arm**
    - BL to Week 24
      - Improved on mitapivat
  - **P/M arm**
    - BL to Week 24
      - Remained stable while on placebo
    - Week 24 to Week 48 (LTE)
      - Improved to a level comparable to the M/M arm after starting mitapivat

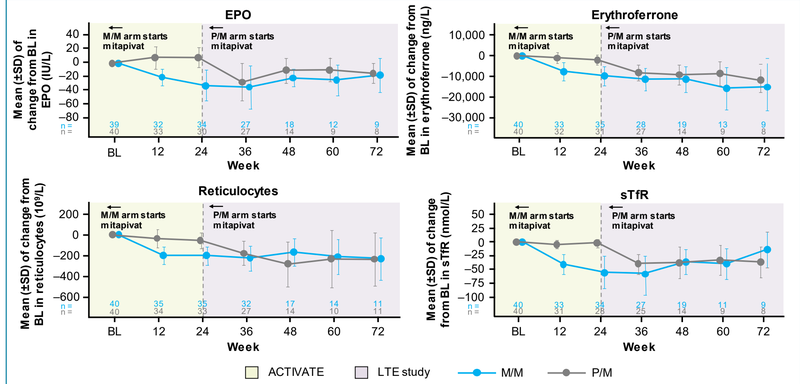
Table 1. Decreases in markers of erythropoietic activity in M/M and P/M arms with mitapivat treatment in ACTIVATE and the LTE study

Marker	M/M	P/M	Marker	M/M	P/M
EPO, IU/L			**Erythroferrone, ng/L**		
BL[a] Mean (SD)	n=39 73.9 (59.85)	n=40 74.1 (57.01)	**BL**[a] Mean (SD)	n=40 21,079.8 (16029.26)	n=40 20,379.8 (13095.47)
Week 24 (change from BL) Mean (SD)	n=34 −32.9 (62.47)	n=30 7.0 (38.18)	**Week 24 (change from BL)** Mean (SD)	n=35 −9834.9 (13081.15)	n=31 −2132.9 (6278.41)
Week 48 (change from BL) Mean (SD)	n=18 −22.0 (24.43)	n=14 −11.6 (30.74)	**Week 48 (change from BL)** Mean (SD)	n=19 −11,341.8 (12556.80)	n=14 −9246.1 (8314.17)
Reticulocytes, 10^9/L			**sTfR, nmol/L**		
BL[a] Mean (SD)	n=40 817.8 (454.18)	n=40 901.7 (465.69)	**BL**[a] Mean (SD)	n=40 187.0 (75.85)	n=40 174.3 (68.90)
Week 24 (change from BL) Mean (SD)	n=35 −202.0 (246.97)	n=33 −52.1 (210.68)	**Week 24 (change from BL)** Mean (SD)	n=34 −56.0 (82.57)	n=28 −2.1 (17.23)
Week 48 (change from BL) Mean (SD)	n=17 −168.6 (257.34)	n=14 −283.7 (374.27)	**Week 48 (change from BL)** Mean (SD)	n=19 −36.9 (45.17)	n=14 −38.7 (48.37)

BL Patients on mitapivat Patients on placebo

[a]BL is defined as the average of all screening assessments within 45 (42 + 3) days before randomization for patients randomized and not dosed or before start of study treatment for patients randomized and dosed; assessments collected within 61 days after a transfusion are excluded from the BL derivation; n is the number of patients in the full analysis set within each treatment group with an assessment at the visit or (for change from BL summaries) with BL and at least 1 post-BL assessment at the visit. BL, baseline; EPO, erythropoietin; LTE, long-term extension study; M/M, mitapivat-to-mitapivat; P/M, placebo-to-mitapivat; SD, standard deviation; sTfR, soluble transferrin receptor

Figure 2. Decreases in markers of erythropoietic activity in M/M and P/M arms with mitapivat treatment in ACTIVATE and the LTE study



BL is defined as the average of all screening assessments within 45 (42 + 3) days before randomization for patients randomized and not dosed, or before start of study treatment for patients randomized and dosed; assessments collected within 61 days after a transfusion are excluded from the BL derivation; n is the number of patients in the full analysis set within each treatment group with an assessment at the visit or (for change from BL summaries) with BL and ≥1 post-BL assessment at the visit; BL, baseline; EPO, erythropoietin; LTE, long-term extension study; M/M, mitapivat-to-mitapivat; P/M, placebo-to-mitapivat; SD, standard deviation; sTfR, soluble transferrin receptor

- Improvements in hepcidin, iron, TSAT, and LIC by MRI were observed with mitapivat treatment in the ACTIVATE/LTE study; ferritin remained stable (**Table 2**)
  - **M/M arm**
    - BL to Week 24
      - Hepcidin, iron, TSAT, and LIC by MRI improved on mitapivat
  - **P/M arm**
    - BL to Week 24
      - Hepcidin, iron, TSAT, and LIC by MRI worsened on placebo
    - Week 24 to Week 48 (LTE)
      - Hepcidin, iron, TSAT, and LIC by MRI improved after starting mitapivat

Table 2. Improvements in markers of iron metabolism and overload in M/M and P/M arms with mitapivat treatment in ACTIVATE and the LTE study

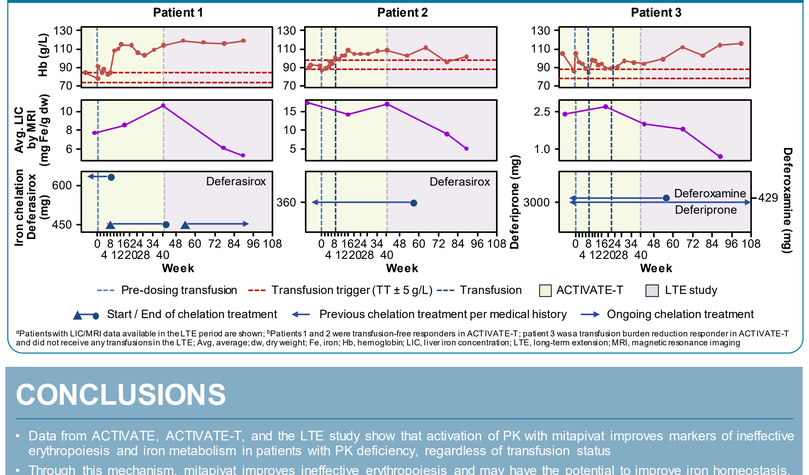
Marker	M/M	P/M	Marker	M/M	P/M
Hepcidin, ng/L			**Ferritin, µg/L**		
BL[a] Mean (SD)	n=40 25,920.0 (27899.90)	n=40 29,988.8 (18,044.22)	**BL**[a] Mean (SD)	n=39 747.9 (1116.18)	n=38 688.0 (605.25)
Week 24 (change from BL) Mean (SD)	n=35 4770.0 (18,346.74)	n=31 −3282.3 (14,735.06)	**Week 24 (change from BL)** Mean (SD)	n=36 39.3 (285.39)	n=31 −50.2 (216.53)
Week 48 (change from BL) Mean (SD)	n=19 2642.1 (27,623.45)	n=14 15,875.0 (22,232.27)	**Week 48 (change from BL)** Mean (SD)	n=18 3.2 (374.93)	n=14 −17.8 (206.08)
Iron, µmol/L			**LIC assessment by MRI, mg Fe/g dw**		
BL[a] Mean (SD)	n=40 24.1 (9.78)	n=40 26.6 (9.32)	**BL**[b] Mean (SD) Median (Q1, Q3)	n=38 7.6 (10.78) 3.05 (1.70, 6.50)	n=39 6.1 (8.01) 3.40 (2.00, 6.30)
Week 24 (change from BL) Mean (SD)	n=37 −0.8 (9.93)	n=32 1.3 (8.94)	**Week 24 (change from BL)** Mean (SD) Median (Q1, Q3)	n=31 1.7 (15.75) −0.40 (−1.10, 0.70)	n=31 1.4 (12.38) 0.30 (−0.30, 1.20)
Week 48 (change from BL) Mean (SD)	n=20 −1.4 (10.98)	n=14 −2.4 (13.38)	**Week 48 (change from BL)** Mean (SD) Median (Q1, Q3)	n=15 −1.6 (5.79) −1.80 (−2.80, −0.20)	n=16 −2.7 (6.08) −0.10 (−2.40, 0.45)
TSAT, fraction of 1[c]					
BL[a] Mean (SD)	n=40 0.5 (0.22)	n=40 0.5 (0.19)			
Week 24 (change from BL) Mean (SD)	n=37 −0.01 (0.185)	n=31 0.03 (0.205)			
Week 48 (change from BL) Mean (SD)	n=19 −0.01 (0.196)	n=14 −0.06 (0.257)			

BL Patients on mitapivat Patients on placebo

[a]BL is defined as the average of all screening assessments within 45 (42 + 3) days before randomization for patients randomized and not dosed, or before start of study treatment for patients randomized and dosed; assessments collected within 61 days after a transfusion are excluded from the BL derivation; [b]BL LIC by MRI is defined as the last assessment before randomization for patients randomized and not dosed or the last assessment before start of study treatment for patients randomized and dosed; [c]Mean (SD) TSAT may also be reported as a percentage: M/M (Week 24) = −1% (18.5%); M/M (Week 48) = −1% (19.6%); P/M (Week 24) = 3% (20.5%); P/M (Week 48) = −6% (25.7%). n is the number of patients in the full analysis set within each treatment group with an assessment at the visit or (for change from BL summaries) with BL and ≥1 post-BL assessment at the visit; BL, baseline; dw, dry weight; Fe, iron; LIC, liver iron concentration; LTE, long-term extension; M/M, mitapivat-to-mitapivat; MRI, magnetic resonance imaging; P/M, placebo-to-mitapivat; SD, standard deviation; TSAT, transferrin saturation

- Transfusion-free responders from ACTIVATE-T (n=6) experienced improvements in markers of erythropoietic activity and iron overload in the LTE study
- None of the transfusion-free responders had a dose increase in iron chelation, 1 patient had an iron chelation dose reduction, and 2 patients discontinued iron chelation completely
- 1 additional patient, who was a transfusion burden reduction responder in ACTIVATE-T, did not receive any transfusions after the start of the LTE and had an iron chelation dose reduction
- **Figure 3** shows LIC by MRI and iron chelation over time among the 3 transfusion-free responders with sufficient follow-up time in the LTE

Figure 3. LIC by MRI and chelation over time in transfusion-free responders[a,b] in ACTIVATE-T and the LTE study



[a]Patients with LIC/MRI data available in the LTE period are shown; [b]Patients 1 and 2 were transfusion-free responders in ACTIVATE-T; patient 3 was a transfusion burden reduction responder in ACTIVATE-T and did not receive any transfusions in the LTE; Avg, average; dw, dry weight; Fe, iron; Hb, hemoglobin; LIC, liver iron concentration; LTE, long-term extension; MRI, magnetic resonance imaging

CONCLUSIONS

- Data from ACTIVATE, ACTIVATE-T, and the LTE study show that activation of PK with mitapivat improves markers of ineffective erythropoiesis and iron metabolism in patients with PK deficiency, regardless of transfusion status
- Through this mechanism, mitapivat improves ineffective erythropoiesis and may have the potential to improve iron homeostasis, thereby reducing iron overload

Mitapivat may have the potential to improve iron metabolism and reduce iron overload in pts with PK deficiency, independent of transfusion needs

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References: 1. Grace RF et al. *Am J Hematol* 2015;90:825–30. **2.** Zanella A et al. *Br J Haematol* 2005;130:11–25. **3.** Boscoe AN et al. *Haematologica* 2019;104:e51–3. **5.** Grootendorst S et al. *Int J Mol Sci* 2021;22:2204. **6.** Grace RF et al. *Br J Haematol* 2019;184:721–34. **7.** Kohgo Y et al. *Int J Hematol* 2008;88:7–15. **8.** Taher AT et al. *Hematology Am Soc Hematol Educ Program* 2017:2017:265–71. **9.** Yang H et al. *Clin Pharmacol Drug Dev* 2019;8:246–59. **10.** Kung C et al. *Blood* 2017;130:1347–56. **11.** PYRUKYND® (mitapivat) [US prescribing information]. Cambridge, MA: Agios Pharmaceuticals, Inc.; 2022. **12.** Al-Samkari H et al. *N Engl J Med* 2022;386:1432–42. **13.** Glenthøj A, et al. Abstract: S271. *HemaSphere* 2021;5(S2):94.

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