Mitapivat Improves Ineffective Erythropoiesis and Reduces Iron Overload in Patients with Pyruvate Kinase Deficiency

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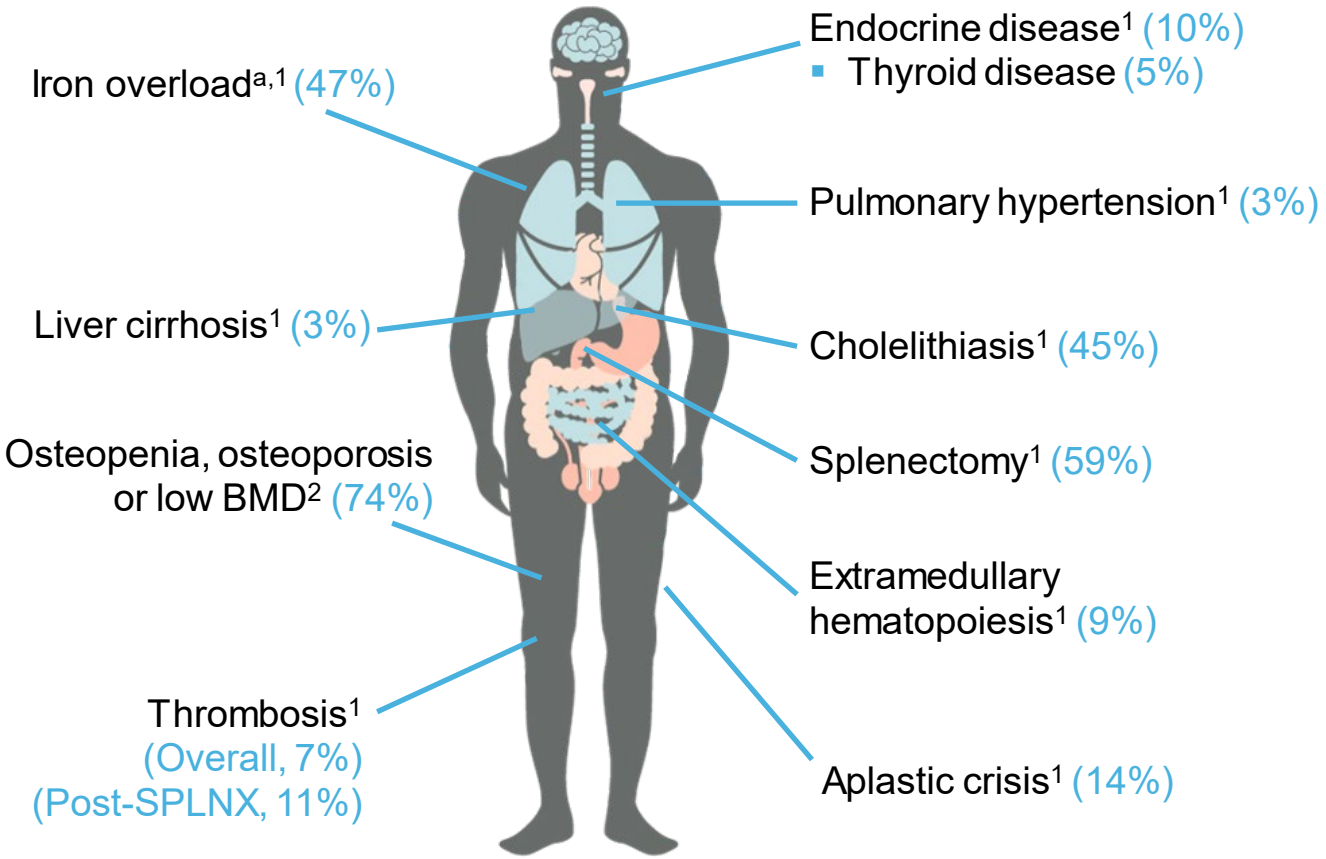
Pyruvate kinase (PK) deficiency is a rare, lifelong, hereditary anemia

Comorbidities and long-term complications are common and affect multiple organ systems[1,2]



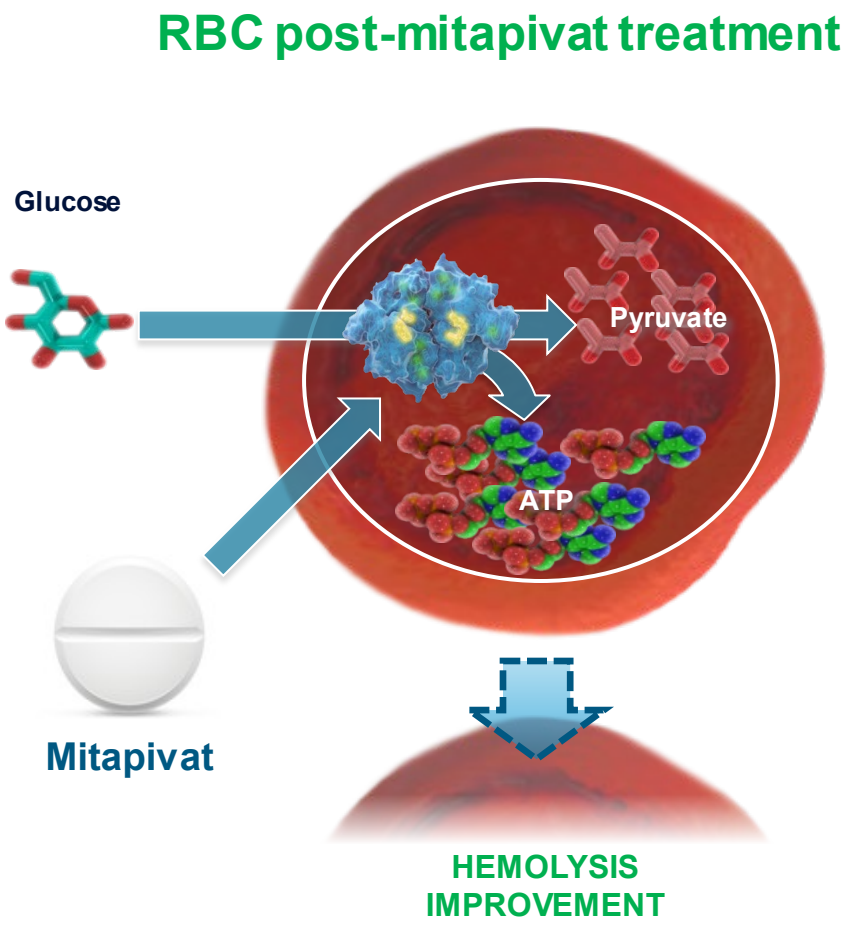
- Caused by mutations in the *PKLR* gene, encoding the red blood cell PK (PKR) enzyme[3,4]
- In patients with PK deficiency, iron overload is linked to chronic hemolysis and ineffective erythropoiesis,[5] occurs independent of transfusion requirements and can be further worsened by transfusions, and may require iron chelation therapy[6,7]
- Iron overload can lead to long-term complications including liver cirrhosis, cardiomyopathy, arrhythmia, sudden cardiac death, and endocrine dysfunction[8,9]
- There are no approved disease-modifying pharmacotherapies
- Available supportive therapies are associated with short- and long-term complications[7]

[a]Iron overload is defined as a ferritin level of > 1000 ng/mL or a liver iron concentration > 3 mg Fe/g dry weight liver on T2* MRI in the 12 months prior to enrolment or had received chelation therapy in the 12 months before enrolment. BMD = bone mineral density; MRI = magnetic resonance imaging; PK = pyruvate kinase; PKR = red blood cell-specific form of PK; post-SPLNX = post-splenectomy.

1. Grace RF et al. *Blood* 2018;131:2183–92. **2.**Al-Samkari H et al. *06/09/21;325452;EP692 EHA Library*. **3.** Grace RF et al. *Am J Hematol* 2015;90:825–30. **4.** Zanella A et al. *Br J Haematol* 2005;130:11–25. **5.** Grootendorst S et al. *Int J Mol Sci* 2021;22:2204. **6.** van Beers EJ et al. *Haematologica* 2019;104:e51–3. **7.** Grace RF et al. *Br J Haematol* 2019;184:721–34. **8.** Kohgo Y et al. *Int J Hematol*. 2008;88:7–15. **9.** Taher AT et al. Hematology *Am Soc Hematol Educ Program* 2017:2017:265–71.

Mitapivat, an investigational, first-in-class, oral allosteric activator

Mitapivat targets the **underlying enzymatic defect** that causes hemolysis in PK deficiency by **restoring PKR activity**[1,2]



- In phase 3 studies of adults with PK deficiency, mitapivat demonstrated:
  - Statistically significant improvements in hemoglobin (Hb), markers of hemolysis, and 2 PK deficiency-specific quality of life patient-reported outcome measures in non-regularly transfused patients (ACTIVATE, NCT03548220)[3]
  - A statistically significant reduction in transfusion burden in regularly transfused patients (ACTIVATE-T, NCT03559699)[4]

ATP = adenosine triphosphate; Hb = hemoglobin; PK = pyruvate kinase; PKR = red blood cell-specific form of pyruvate kinase.

1. Yang H et al. *Clin Pharmacol Drug Dev* 2019;8:246–59. **2.** Kung C et al. *Blood* 2017;130:1347–56. **3.** Al-Samkari H. *06/09/21;324678;S270 EHA Library*. **4.** Glenthøj A. *06/09/21;324679;S271 EHA Library*.

Objective

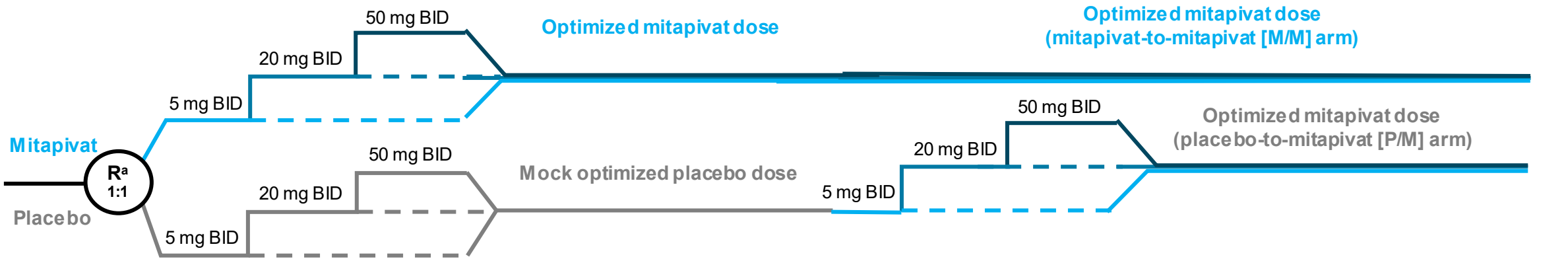
To assess the effect of mitapivat on markers of erythropoietic activity and iron overload in adult patients with PK deficiency enrolled in ACTIVATE, ACTIVATE-T, and their long-term extension (LTE) study (NCT03853798)

LTE = long-term extension; PK = pyruvate kinase.

ACTIVATE and the LTE study design

ACTIVATE

Screening	Individualized dose escalation period	Fixed-dose period	LTE study



6 wks	12 wks	12 wks	192 wks

Key eligibility criteria

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

[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. *ClinicalTrials.gov:* ACTIVATE (NCT03548220); LTE study (NCT03853798); BID = twice daily; BL = baseline; Hb = hemoglobin; LTE = long-term extension; M/M = mitapivat-to-mitapivat; P/M = placebo-to-mitapivat; R = randomized; Wks = weeks.

ACTIVATE-T and the LTE study design

ACTIVATE-T

Screening	Individualized dose-escalation period	Fixed-dose period	LTE study
< 8 wks[a]	16 wks	24 wks	192 wks

Key eligibility criteria

- ≥ 18 years of age
- Documented ≥ 2 mutant alleles in *PKLR* with ≥ 1 missense mutation (excluding patients homozygous for R479H mutation or have who have 2 non-missense mutations, without another missense mutation)
- Regularly transfused (≥ 6 transfusion episodes in previous year)
- LTE study: patients must have completed the fixed-dose period of ACTIVATE-T and demonstrated clinical benefit from mitapivat treatment

[a]Screening may have been extended beyond 8 wks 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. *ClinicalTrials.gov:* ACTIVATE-T (NCT03559699); LTE study (NCT03853798); BID = twice daily; LTE = long-term extension; Wks = weeks.

Methods

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

BL = baseline; EPO = erythropoietin; LIC = liver iron concentration; LTE = long-term extension; M/M = mitapivat-to-mitapivat; MRI = magnetic resonance imaging; P/M = placebo-to-mitapivat; TSAT = transferrin saturation; sTfR = soluble transferrin receptor.

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

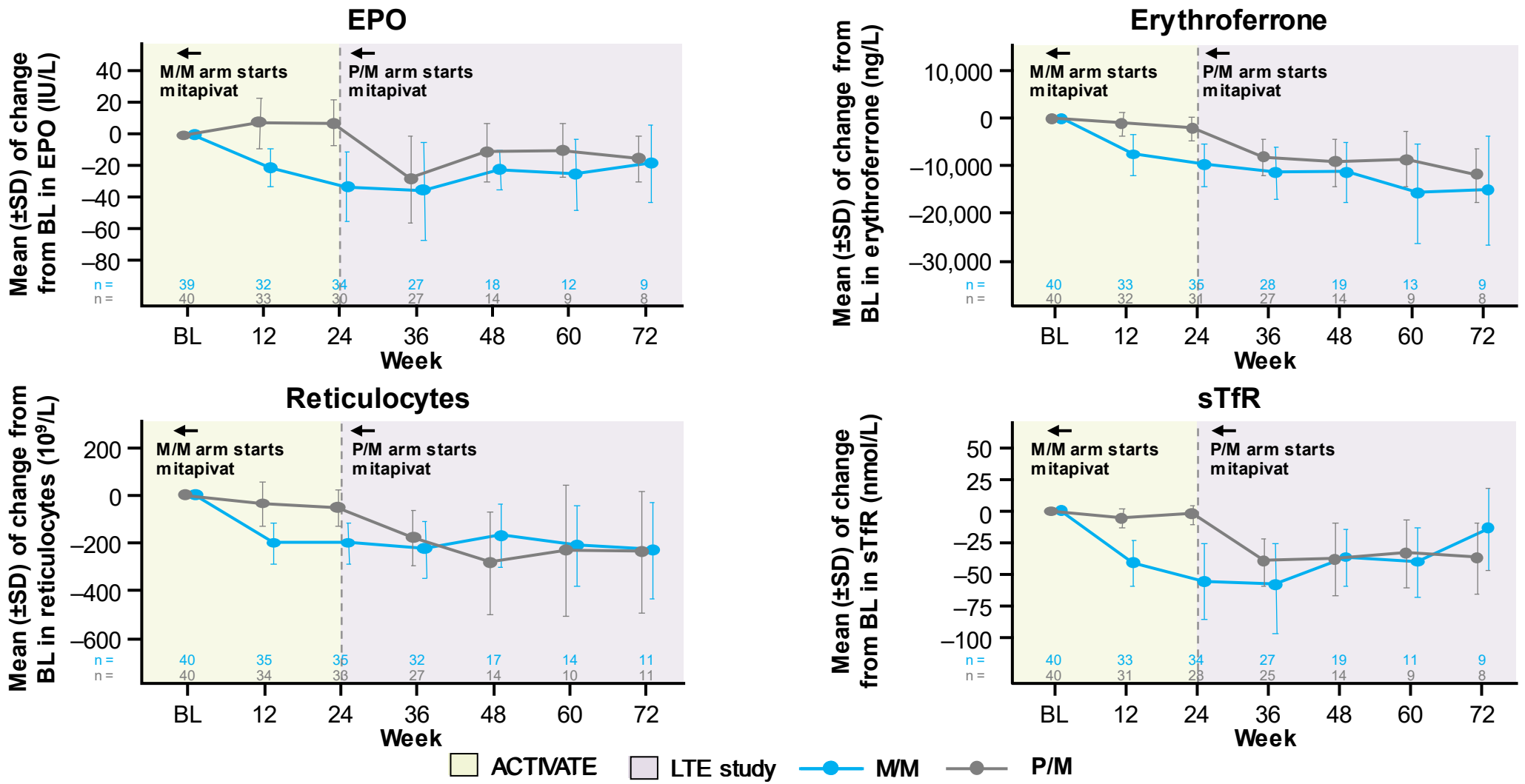
Marker	M/M	P/M
EPO, IU/L		
BL[a]	n = 39	n = 40
Mean (SD)	73.9 (59.85)	74.1 (57.01)
Wk 24 (change from BL)	n = 34	n = 30
Mean (SD)	–32.9 (62.47)	7.0 (38.18)
Wk 48 (change from BL)	n = 18	n = 14
Mean (SD)	–22.0 (24.43)	–11.6 (30.74)
Reticulocytes, 10^9/L		
BL[a]	n = 40	n = 40
Mean (SD)	817.8 (454.18)	901.7 (465.69)
Wk 24 (change from BL)	n = 35	n = 33
Mean (SD)	–202.0 (246.97)	–52.1 (210.68)
Wk 48 (change from BL)	n = 17	n = 14
Mean (SD)	–168.6 (257.34)	–283.7 (374.27)

Marker	M/M	P/M
Erythroferrone, ng/L		
BL[a]	n = 40	n = 40
Mean (SD)	21079.8 (16029.26)	20379.8 (13095.47)
Wk 24 (change from BL)	n = 35	n = 31
Mean (SD)	–9834.9 (13081.15)	–2132.9 (6278.41)
Wk 48 (change from BL)	n = 19	n = 14
Mean (SD)	–11341.8 (12556.80)	–9246.1 (8314.17)
sTfR, nmol/L		
BL[a]	n = 40	n = 40
Mean (SD)	187.0 (75.85)	174.3 (68.90)
Wk 24 (change from BL)	n = 34	n=28
Mean (SD)	–56.0 (82.57)	–2.1 (17.23)
Wk 48 (change from BL)	n = 19	n = 14
Mean (SD)	–36.9 (45.17)	–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 pts 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; Wk = week.

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



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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 (N = 40)	P/M (N = 40)
Hepcidin, ng/L		
BL[a] Mean (SD)	n = 40 25,920.0 (27899.90)	n = 40 29,988.8 (18,044.22)
Wk 24 (change from BL) Mean (SD)	n = 35 4770.0 (18,346.74)	n = 31 –3282.3 (14,735.06)
Wk 48 (change from BL) Mean (SD)	n = 19 2642.1 (27,623.45)	n = 14 15,875.0 (22,232.27)
Iron, µmol/L		
BL[a] Mean (SD)	n = 40 24.1 (9.78)	n = 40 26.6 (9.32)
Wk 24 (change from BL) Mean (SD)	n = 37 –0.8 (9.93)	n = 32 1.3 (8.94)
Wk 48 (change from BL) Mean (SD)	n = 20 –1.4 (10.98)	n = 14 –2.4 (13.38)
TSAT, fraction of 1[c]		
BL[a] Mean (SD)	n = 40 0.5 (0.22)	n = 40 0.5 (0.19)
Wk 24 (change from BL) Mean (SD)	n = 37 –0.01 (0.185)	n = 31 0.03 (0.205)
Wk 48 (change from BL) Mean (SD)	n = 19 –0.01 (0.196)	n = 14 –0.06 (0.257)

Marker	M/M (N = 40)	P/M (N = 40)
Ferritin, µg/L		
BL[a] Mean (SD)	n = 39 747.9 (1116.18)	n = 38 688.0 (605.25)
Wk 24 (change from BL) Mean (SD)	n = 36 39.3 (285.39)	n = 31 –50.2 (216.53)
Wk 48 (change from BL) Mean (SD)	n = 18 3.2 (374.93)	n = 14 –17.8 (206.08)
LIC assessment by MRI, mg Fe/g dw		
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)
Wk 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)
Wk 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)

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 (Wk 24) = – 1% (18.5%); M/M (Wk 48) = – 1% (19.6%); P/M (Wk 24) = 3% (20.5%); P/M (Wk 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; LIC = liver iron concentration; LTE = long-term extension study; M/M = mitapivat-to-mitapivat; MRI = magnetic resonance imaging; P/M = placebo-to-mitapivat; SD = standard deviation; TSAT = transferrin saturation; Wk = week.

ACTIVATE-T and the LTE study design

ACTIVATE-T

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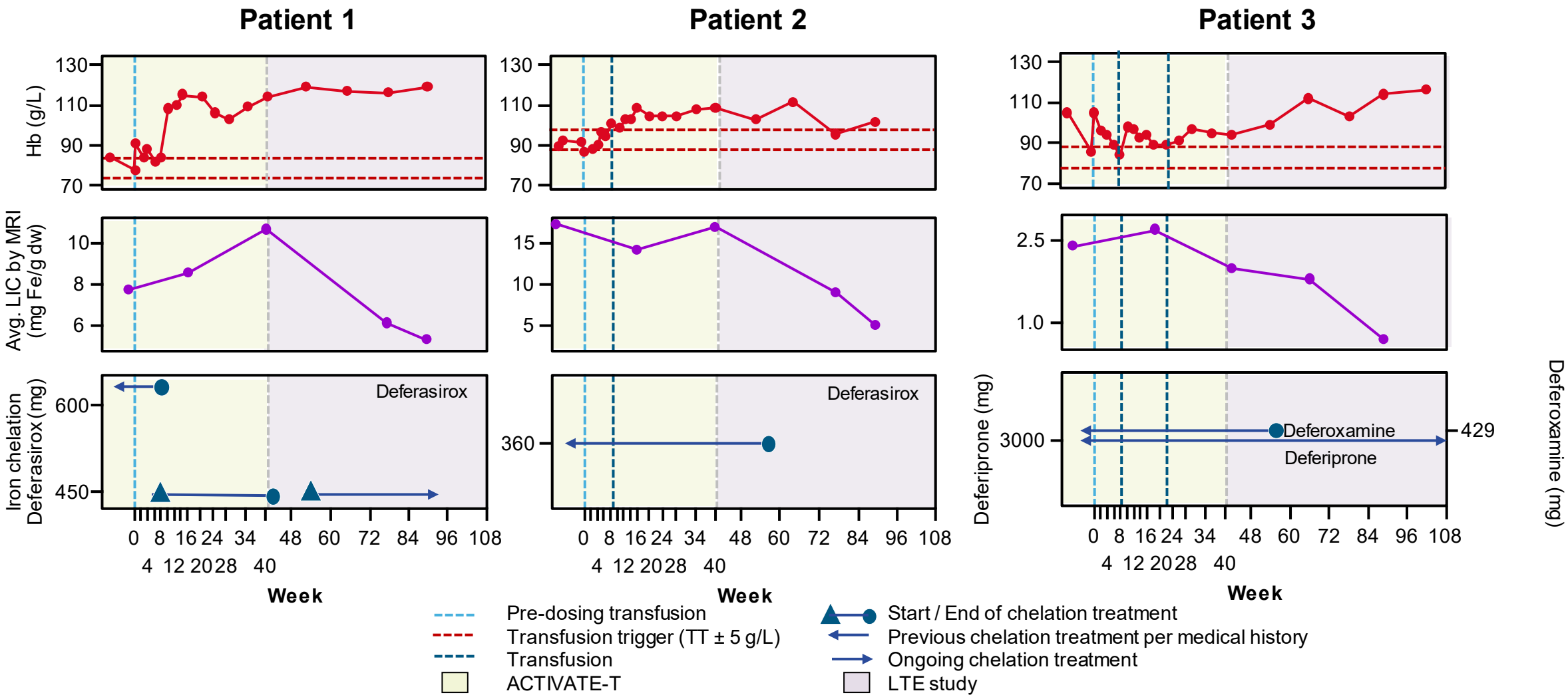
Results

- 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
- One 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

LTE = long-term extension study.

LIC by MRI and chelation over time in transfusion-free responders in ACTIVATE-T and the LTE study



Patients with LIC/MRI data available in the LTE period are shown. 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; Hb = hemoglobin; LIC = liver iron concentration; LTE = long-term extension; MRI = magnetic resonance imaging.

Conclusion

- Data from ACTIVATE, ACTIVATE-T, and the LTE study show that activation of PKR 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 has the potential to become the first approved therapy in patients with PK deficiency, with a beneficial effect on ineffective erythropoiesis and iron overload, independent of transfusion needs

LTE = long-term extension; PK = pyruvate kinase; PKR = red blood cell-specific form of PK.