Mitapivat improves iron overload in patients with pyruvate kinase deficiency

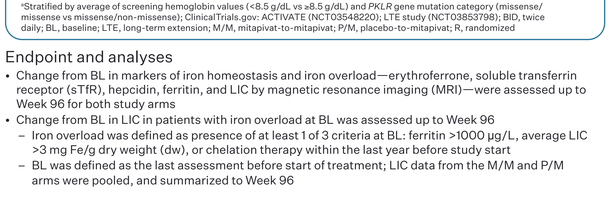
Eduard J van Beers, MD, PhD,[1] Hanny Al-Samkari, MD,[2] Rachael F Grace, MD,[3] Wilma Barcellini, MD,[4] Andreas Glenthøj, MD, PhD,[5] Melissa DiBacco, MD,[6] Penelope A Kosinski, MS,[6] Emily Xu, PhD,[6] Vanessa Beynon, MD,[6] Parija Patel, PharmD, MBA,[6] John B Porter, MD,[7] **Kevin HM Kuo, MD**[8]

[1]Benign Hematology Center, Van Creveldkliniek, University Medical Center Utrecht, University of Utrecht, Utrecht, The Netherlands; [2]Division of Hematology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [3]Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Harvard Medical School, Boston, MA, USA; [4]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [5]Department of Haematology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; [6]Agios Pharmaceuticals, Inc., Cambridge, MA, USA; [7]Haematology Department, University College London Hospitals, London, UK; [8]Division of Hematology, University of Toronto, Toronto, ON, Canada

BACKGROUND

- Pyruvate kinase (PK) deficiency is a rare, hereditary disease resulting in chronic hemolytic anemia and serious complications, including iron overload[1–4]
- Iron overload is highly prevalent in patients with PK deficiency regardless of transfusion requirements; dyserythropoietic features have been evidenced in PK deficiency[4–6]
- In patients with PK deficiency, ineffective erythropoiesis combined with chronic hemolysis contributes to the manifestation of iron overload (**Figure 1**)[5,7–11]
  - The erythroferrone-hepcidin axis seems to play a crucial role in the pathogenesis as erythroferrone produced by erythroblasts in response to erythropoietin acts by suppressing hepcidin, thereby increasing iron absorption and mobilization for erythropoiesis demand[7,8]
- Iron overload can lead to serious complications including liver cirrhosis, cardiomyopathy, arrhythmia, sudden cardiac death, and endocrine dysfunction[12,13]

Figure 1. Pathophysiology of iron overload in PK deficiency



EPO, erythropoietin; PK, pyruvate kinase; sTfR, soluble transferrin receptor

- Mitapivat (AG-348) is a first-in-class, oral, allosteric activator of the red blood cell wild-type and mutant PK enzyme (PKR) that is approved by the US FDA for the treatment of hemolytic anemia in adults with PK deficiency[14–17]
- In the phase 3 ACTIVATE study (NCT03548220)[17] and its long-term extension (LTE) (NCT03853798), mitapivat showed improvements in hemolysis and erythropoiesis and initial positive changes in markers of iron homeostasis in adults with PK deficiency[18]

OBJECTIVE

- **To provide longer-term data from ACTIVATE and its LTE study on the impact of mitapivat on iron homeostasis and iron overload, and assess liver iron concentration (LIC) changes in patients with iron overload at baseline (BL)**

METHODS

- ACTIVATE was a global, phase 3, double-blind, placebo-controlled study of mitapivat in adults with PK deficiency who were not regularly transfused (≤4 transfusion episodes in the prior year)[17]
- Patients who had demonstrated clinical benefit from mitapivat upon completion of the fixed-dose period for ACTIVATE (24 weeks), or who were assigned to the placebo arm in ACTIVATE, were eligible to continue in the LTE (**Figure 2**)
  - All patients enrolled in the LTE received mitapivat
  - Patients from ACTIVATE who continued in the LTE were categorized into the mitapivat-to-mitapivat (M/M) arm or the placebo-to-mitapivat (P/M) arm

Figure 2. ACTIVATE and LTE study designs

Key eligibility criteria:
- ≥18 years of age[17]
- 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)[17]
- **ACTIVATE:** Not regularly transfused (≤4 transfusion episodes in the previous year); BL hemoglobin ≤10 g/dL[17]
- **LTE study:** Completed the fixed-dose period of ACTIVATE 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 hemoglobin 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; LTE, long-term extension; M/M, mitapivat-to-mitapivat; P/M, placebo-to-mitapivat; R, randomized

Endpoint and analyses

- Change from BL in markers of iron homeostasis and iron overload—erythroferrone, soluble transferrin receptor (sTfR), hepcidin, ferritin, and LIC by magnetic resonance imaging (MRI)—were assessed up to Week 96 for both study arms
- Change from BL in LIC in patients with iron overload at BL was assessed up to Week 96
  - Iron overload was defined as presence of at least 1 of 3 criteria at BL: ferritin >1000 µg/L, average LIC >3 mg Fe/g dry weight (dw), or chelation therapy within the last year before study start
  - BL was defined as the last assessment before start of treatment; LIC data from the M/M and P/M arms were pooled, and summarized to Week 96

RESULTS

ACTIVATE/LTE study population

- 80 patients were included in the ACTIVATE/LTE analysis (M/M=40; P/M=40)[17]
  - Enrolled patients in both arms had a high disease burden at BL; BL characteristics for patients in ACTIVATE/LTE have previously been reported[17,18]
  - Patients in both arms had abnormal levels of BL markers that consistently contribute or are related to iron overload: hepcidin, erythroferrone, sTfR, and LIC

Markers of systemic iron homeostasis and iron overload

- Meaningful and continued improvements in mean hepcidin, erythroferrone, and sTfR, and median LIC by MRI results were observed with mitapivat up to Week 96 (**Table 1, Figure 3**)
  - M/M arm:
    - Improvements in all these markers from BL to Week 24 were observed with mitapivat treatment, and were sustained from Week 24 up to Week 96 in the LTE
  - P/M arm:
    - These markers remained relatively unchanged from BL to Week 24 while receiving placebo, but upon transitioning to mitapivat LTE, improvements similar to the M/M arm were observed from Week 24 up to Week 96
- Ferritin levels remained stable in the M/M and P/M groups (**Table 1**)

Table 1. Change from BL in markers of iron metabolism and iron overload at Week 24 and Week 96 in patients with PK deficiency in ACTIVATE and the LTE study

Marker	M/M (N=40)	P/M (N=40)
Hepcidin, ng/L		
BL[a]	n=40	n=40
Mean (SD)	25,920.0 (27,899.90)	29,988.8 (18,044.22)
Wk 24 (change from BL)	n=35	n=31
Mean (SD)	4770.0 (18,346.74)	−3282.3 (14,735.06)
Wk 96 (change from BL)	n=29	n=23
Mean (SD)	6008.6 (23,134.63)	9934.8 (23,579.96)
Erythroferrone, ng/L		
BL[a]	n=40	n=40
Mean (SD)	21,079.8 (16,029.26)	20,379.8 (13,095.47)
Wk 24 (change from BL)	n=35	n=31
Mean (SD)	−9834.9 (13,081.15)	−2132.9 (6278.41)
Wk 96 (change from BL)	n=29	n=23
Mean (SD)	−12,634.7 (13,019.11)	−10,720.2 (6729.34)
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 96 (change from BL)	n=28	n=25
Mean (SD)	−59.8 (84.69)	−30.5 (41.39)
Ferritin, µg/L		
BL[a]	n=39	n=38
Mean (SD)	747.9 (1116.18)	688.0 (605.25)
Wk 24 (change from BL)	n=36	n=31
Mean (SD)	39.3 (285.39)	−50.2 (216.53)
Wk 96 (change from BL)	n=28	n=26
Mean (SD)	24.9 (188.35)	58.6 (393.45)
LIC assessment by MRI, mg Fe/g dw		
BL[b]	n=38	n=39
Median (Q1, Q3)	3.05 (1.70, 6.50)	3.40 (2.00, 6.30)
Wk 24 (change from BL)	n=31	n=31
Median (Q1, Q3)	−0.40 (−1.10, 0.70)	0.30 (−0.30, 1.20)
Wk 96 (change from BL)	n=22	n=23
Median (Q1, Q3)	−0.85 (−1.90, −0.10)	−0.30 (−1.30, 0.70)

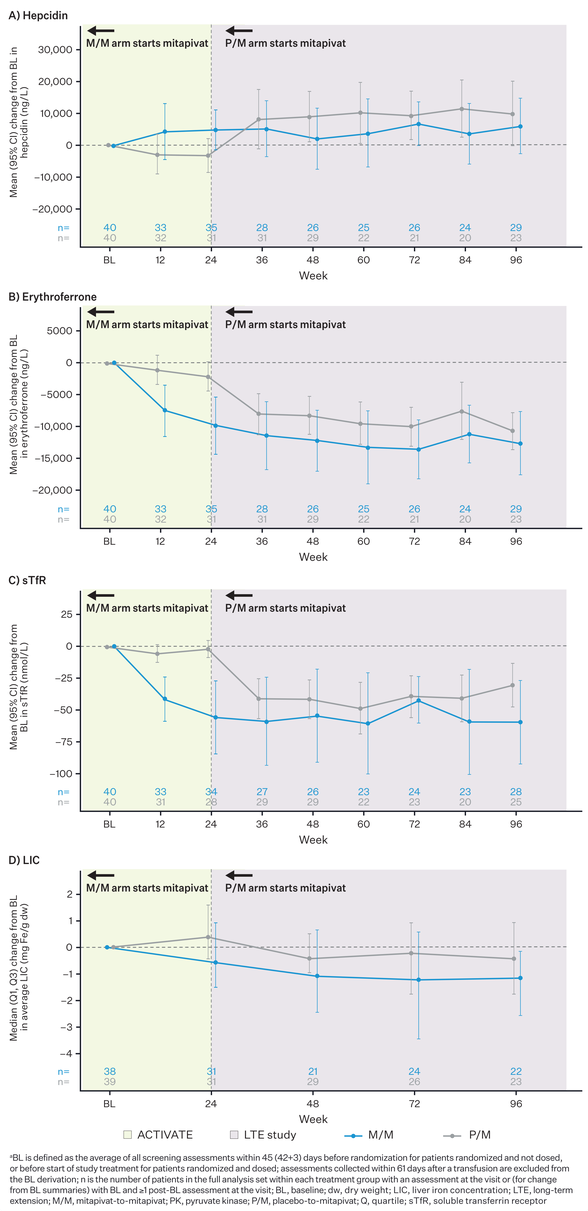
BL | Patients on mitapivat | Patients on placebo

[a]BL erythroferrone, sTfR, and hepcidin are defined as the average of all screening assessments within 45 (42+3) days before randomization for pts randomized and not dosed, or before start of study treatment for pts randomized and dosed. Assessments collected within 61 days after a transfusion are excluded from the BL derivation; [b]BL LIC is defined as the last assessment before randomization for pts randomized and not dosed or the last assessment before start of study treatment for pts randomized and dosed; 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 ≥1 post-BL assessment at the visit; pts in the M/M arm started mitapivat treatment at BL; pts in the P/M arm started mitapivat treatment at Wk 24; BL, baseline; dw, dry weight; LIC, liver iron concentration; LTE, long-term extension; M/M, mitapivat-to-mitapivat; MRI, magnetic resonance imaging; PK, pyruvate kinase; P/M, placebo-to-mitapivat; pt, patient; Q, quartile; sTfR, soluble transferrin receptor; Wk, Week

LIC changes over time (up to 96 weeks) in patients with evidence of iron overload at BL

- Among patients treated with mitapivat (N=78), 55.1% (n=43) met the criteria for iron overload at BL (**Table 2**)
- These patients showed clinically meaningful and continued improvements in iron overload over time as measured by LIC (median [Q1, Q3] decrease from BL to Week 96 of mitapivat treatment of −1.95 [−4.85, −0.70] mg Fe/g dw) (**Figure 4**)

Figure 3. Change from BL[a] over time in markers of erythropoiesis and iron overload in patients with PK deficiency in ACTIVATE and the LTE study



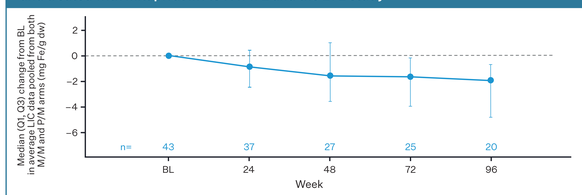
[a]BL is defined as the average of all screening assessments within 45 (42+3) days before randomization for patients randomized and not dosed, or before start of study treatment for patients randomized and dosed; assessments collected within 61 days after a transfusion are excluded from the BL derivation; 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 ≥1 post-BL assessment at the visit; BL, baseline; dw, dry weight; LIC, liver iron concentration; LTE, long-term extension; M/M, mitapivat-to-mitapivat; PK, pyruvate kinase; P/M, placebo-to-mitapivat; Q, quartile; sTfR, soluble transferrin receptor

Table 2. Mitapivat-treated patients meeting criteria for iron overload at BL

Criteria, n (%)	Mitapivat (N=78)
BL ferritin >1000 µg/L	
Yes	15 (19.2)
No	61 (78.2)
Missing	2 (2.6)
BL average LIC >3 mg Fe/g dw	
Yes	39 (50.0)
No	37 (47.4)
Missing	2 (2.6)
Prior chelation status[a]	
Yes	16 (20.5)
No	62 (79.5)
Iron overload at BL[b]	
Yes	**43 (55.1)**
No	35 (44.9)

The denominator used to calculate percentages is N, the number of subjects in the full analysis set; ferritin values reported as >1500 µg/L due to a laboratory dilution error were excluded; BL for ferritin 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 from the BL derivation; BL for average LIC is defined as the last assessment before start of treatment with mitapivat; [a]"Yes" if a subject has received chelation therapy within 52 weeks (364 days) before start of treatment with mitapivat; [b]"Yes" if subject meets at least 1 of 3 criteria: BL ferritin >1000 µg/L, BL average LIC >3 mg Fe/g dw, prior chelation status = Yes; BL, baseline; dw, dry weight; LIC, liver iron concentration; LTE, long-term extension

Figure 4. Change from BL[a] over time in LIC in patients with iron overload[b] at BL and treated with mitapivat in ACTIVATE and the LTE study



[a]BL is defined as the last assessment before start of treatment with mitapivat; [b]Patients were considered to have iron overload at BL if they met at least 1 of 3 criteria: BL ferritin >1000 µg/L, BL average LIC >3 mg Fe/g dw, or chelation therapy within the last year before study start; BL, baseline; dw, dry weight; LIC, liver iron concentration; LTE, long-term extension; M/M, mitapivat-to-mitapivat; P/M, placebo-to-mitapivat; Q, quartile

CONCLUSIONS

PK activation with mitapivat showed meaningful long-term improvements in key systemic regulators of iron homeostasis and measures of iron overload. Mitapivat is the first disease-modifying pharmacotherapy shown to have beneficial effects on iron overload in patients with PK deficiency

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