Improvements in patient-reported outcomes in mitapivat-treated patients with pyruvate kinase deficiency: A descriptive analysis from the phase 3 ACTIVATE trial

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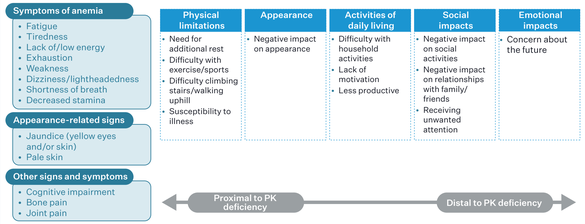
BACKGROUND

- Pyruvate kinase (PK) deficiency is a rare, congenital hemolytic anemia characterized by mutations in *PKLR* encoding the red blood cell (RBC)-specific form of PK (PKR)[1–4]
- PK deficiency is associated with acute and long-term complications, as well as a spectrum of signs and symptoms including jaundice, fatigue, and dyspnea, resulting in a profound, wide-ranging impact on health-related quality of life (HRQoL; **Figure 1**)[3,5]

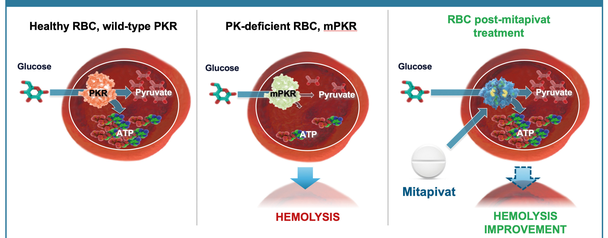
Figure 1. Conceptual model of the burden and impact of PK deficiency on HRQoL, based on the signs, symptoms, and impacts reported[a] by 21 adult patients with PK deficiency[b,5]



[a]1-hour interviews were conducted to better understand the burden of PK deficiency in terms of signs, symptoms, and impact of the disease on participants' HRQoL; [b]Participants were primarily recruited through the Pyruvate Kinase Natural History Study (NHS; NCT02053480) via a recruitment flyer distributed by NHS investigators. Participants were also recruited through a patient advisory board, a PK deficiency patient advocacy/support website, and a Facebook support page; HRQoL, health-related quality of life; NHS, Natural History Study; PK, pyruvate kinase

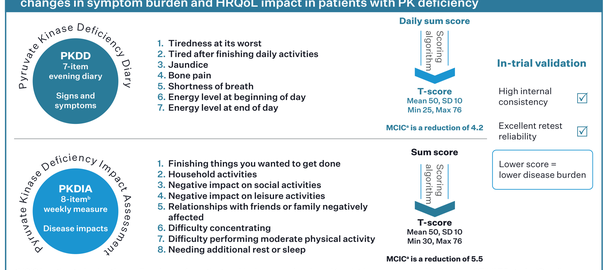
- Mitapivat is an oral PK activator that has been approved by the US FDA for the treatment of hemolytic anemia in adults with PK deficiency; it targets the underlying enzymatic defect that causes hemolysis in PK deficiency by restoring PKR activity (**Figure 2**)[6–8]
- Mitapivat was shown to improve hemoglobin (Hb), hemolysis, and hematopoiesis in a phase 3, randomized, placebo-controlled trial evaluating mitapivat in adults with PK deficiency who were not regularly transfused (ACTIVATE; NCT03548220)[9]
- In addition, significant improvements in patient-reported outcomes (PROs) (measured by validated, disease-specific PRO instruments: the PK deficiency diary [PKDD] and the PK deficiency impact assessment [PKDIA]; **Figure 3**) were demonstrated in patients receiving mitapivat compared with placebo[9–11]

Figure 2. Mitapivat mechanism of action in PK deficiency



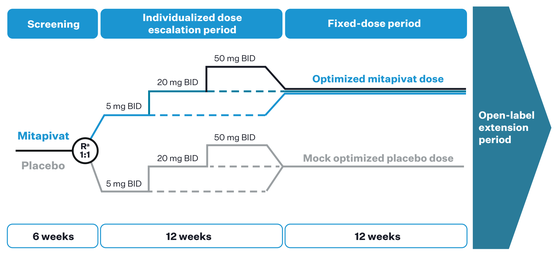
ATP, adenosine triphosphate; mPKR, mutant PKR; PK, pyruvate kinase; PKR, RBC-specific form of PK; RBC, red blood cell

Figure 3. The PKDD and PKDIA were developed as self-administered tools to assess and capture changes in symptom burden and HRQoL impact in patients with PK deficiency



[a]MCIC is estimated using the median change for patients achieving an anchor-based 1-point improvement in PGIS in the ACTIVATE study; [b]Baseline IRT modeling revealed that 4 of the original 12 items were less relevant to the ACTIVATE trial population or did not contribute unique information due to skewness or redundancy and were removed; HRQoL, health-related quality of life; IRT, item response theory; MCIC, minimal clinically important change; PGIS, Patient Global Impression of Severity; PK, pyruvate kinase; PKDD, PK deficiency diary; PKDIA, PK deficiency impact assessment; SD, standard deviation

Figure 4. ACTIVATE study design



Key eligibility criteria:

- ≥18 yrs 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; PK, pyruvate kinase; R, randomized; wks, weeks; yrs, years

OBJECTIVE

- **To describe PKDD and PKDIA outcomes for the subset of patients in the ACTIVATE trial who achieved the primary endpoint of Hb response**

METHODS

- ACTIVATE was a phase 3, randomized, double-blind, placebo-controlled study that evaluated the efficacy and safety of mitapivat in adult patients with PK deficiency who were not regularly transfused (**Figure 4**)
  - Primary endpoint: Hb response, defined as ≥1.5 g/dL increase in Hb concentration from baseline (BL) sustained at ≥2 scheduled assessments at Weeks (Wks) 16, 20, and 24 during fixed-dose period
  - Changes from BL at Wk 24 in PKDD and PKDIA scores were prespecified secondary endpoints
- In this post hoc analysis:
  - Changes from BL in PKDD weekly mean score and PKDIA score measured at scheduled visits (Wks 4, 8, 12, 16, 20, and 24) were summarized descriptively for patients in ACTIVATE who:
    - Achieved the primary endpoint of Hb response and
    - Were randomized to receive either mitapivat or placebo and dosed
  - Numbers of patients who achieved minimal clinically important change (MCIC) at Wk 24 in terms of PKDD and PKDIA assessments were also summarized
    - MCIC is considered as a reduction of 4.2 in PKDD score, and 5.5 in PKDIA score from BL; those threshold values were estimated via an anchor-based method using Patient Global Impression of Severity (PGIS) as the anchor

RESULTS

Population

- 80 patients were randomized 1:1 to receive mitapivat (N=40) (5/20/50 mg twice daily) or PBO (N=40) in the ACTIVATE trial
  - Baseline characteristics were well-balanced across mitapivat and placebo arms, and reflective of high disease burden; these data have been previously reported[9]
- 16 (40%) mitapivat-treated patients met the primary endpoint of Hb response in the core study period, compared with 0 placebo-treated patients
- These 16 mitapivat-treated patients who met this endpoint of Hb response were the focus population for this post hoc analysis

ACTIVATE study primary analyses

- Results from primary analyses of the ACTIVATE trial have previously been reported[9]

Post hoc analysis

- Greater improvements across both disease-specific PRO instruments were observed in the 16 mitapivat-treated patients who achieved the primary endpoint of Hb response (**Tables 1** and **2**)
- The majority of mitapivat-treated patients who achieved Hb response also achieved meaningful improvements in both PKDD and PKDIA scores above the MCIC threshold at Wk 24 (**Tables 1** and **2**)
- Mean change from baseline in PKDD weekly mean score was greatest in mitapivat-treated patients who achieved Hb response, indicating the most improved signs/symptoms in this group (**Table 1**)

Table 1. Summary of PKDD weekly mean score and change from baseline at Wk 24 for patients who achieved Hb response and overall

Visit	Mitapivat: Patients who achieved Hb response n=16	Mitapivat: All patients N=40	Placebo all patients N=40
Baseline			
n	15	37	36
Mean (SD)	50.08 (6.274)	50.47 (7.315)	47.04 (8.103)
Median (Q1, Q3)	48.86 (45.67, 52.14)	50.57 (48.00, 52.86)	48.77 (44.58, 51.46)
Min, Max	42.2, 61.0	27.0, 65.1	27.0, 58.1
Wk 24			
n	16	39	34
Mean (SD)	42.27 (6.985)	44.41 (7.587)	45.81 (7.669)
Median (Q1, Q3)	43.00 (38.29, 46.77)	45.00 (40.00, 49.67)	47.29 (42.86, 49.33)
Min, Max	29.4, 55.4	27.0, 61.0	27.0, 64.3
Wk 24 Change from baseline			
n	15	36	31
Mean (SD)	−7.12 (6.959)	−5.43 (6.009)	−1.86 (5.945)
Median (Q1, Q3)	−9.14 (−12.74, −0.30)	−6.36 (−9.62, −0.15)	−1.29 (−4.21, 1.14)
Min, Max	−16.0, 4.8	−16.0, 5.6	−17.6, 12.5
% of patients with reduction in score ≥MCIC threshold	60.0	55.6	29.0

Baseline of weekly mean score is defined as the average of daily scores collected within 7 days before randomization for patients randomized and not dosed or before start of study treatment for patients randomized and dosed. Patient-level weekly mean score at week is NA if there are less than 4 daily scores in that week. MCIC threshold estimation is calculated using the median change score in ΔPGIS = −1 group; Hb, hemoglobin; MCIC, minimal clinically important change; NA, not available; PGIS, Patient Global Impression of Severity; PKDD, pyruvate kinase deficiency diary; SD, standard deviation; Wk, Week

- Mean change from baseline in PKDIA score was greatest in mitapivat-treated patients who achieved Hb response, indicating the most benefit on disease impact in this population (**Table 2**)

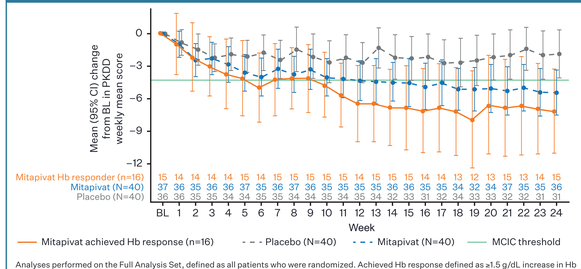
Table 2. Summary of PKDIA score and change from baseline at Wk 24 for patients who achieved Hb response and overall

Visit	Mitapivat: Patients who achieved Hb response n=16	Mitapivat: All patients N=40	Placebo all patients N=40
Baseline			
n	15	39	39
Mean (SD)	49.9 (6.85)	49.2 (9.00)	48.5 (9.15)
Median (Q1, Q3)	51.0 (43.0, 56.0)	51.0 (43.0, 56.0)	51.0 (39.0, 54.0)
Min, Max	39, 60	30, 66	30, 66
Wk 24			
n	16	40	34
Mean (SD)	41.7 (7.24)	44.3 (8.68)	47.5 (9.65)
Median (Q1, Q3)	39.5 (36.0, 44.5)	42.5 (37.0, 50.5)	48.0 (39.0, 55.0)
Min, Max	35, 59	30, 64	30, 62
Wk 24 Change from baseline			
n	15	39	34
Mean (SD)	−8.1 (5.39)	−4.8 (7.27)	−1.1 (7.58)
Median (Q1, Q3)	−9.0 (−12.0, −4.0)	−4.0 (−11.0, 0.0)	0.0 (−6.0, 3.0)
Min, Max	−16, 0	−21, 9	−18, 14
% of patients with reduction in score ≥MCIC threshold	60.0	43.6	26.5

Baseline is defined as the last complete assessment (with no missing item in response) before randomization for patients randomized and not dosed or before start of study treatment for patients randomized and dosed. MCIC threshold estimation is calculated using the median change score in ΔPGIS = −1 group; Hb, hemoglobin; MCIC, minimal clinically important change; PGIS, Patient Global Impression of Severity; PKDIA, pyruvate kinase deficiency impact assessment; SD, standard deviation; Wk, Week

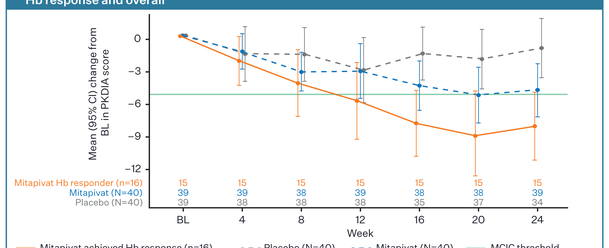
- Mitapivat led to early and sustained improvements in PKDD weekly mean score; improvements were even more pronounced in the 16 mitapivat-treated patients who achieved the primary endpoint of Hb response (**Figure 5**)
- Mitapivat led to early and sustained improvements in PKDIA score; improvements were even more pronounced in the 16 mitapivat-treated patients who achieved the primary endpoint of Hb response (**Figure 6**)

Figure 5. Mean (95% CI) change from baseline in PKDD weekly mean score for patients who achieved Hb response and overall



Analyses performed on the Full Analysis Set, defined as all patients who were randomized. Achieved Hb response defined as ≥1.5 g/dL increase in Hb from BL, sustained at ≥2 scheduled assessments at Wks 16, 20, and 24; BL, baseline; CI, confidence interval; Hb, hemoglobin; MCIC, minimal clinically important change; PKDD, pyruvate kinase deficiency diary; Wk, Week

Figure 6. Mean (95% CI) change from baseline in PKDIA score for patients who achieved Hb response and overall



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CONCLUSIONS

- **In the ACTIVATE trial, mitapivat-treated patients demonstrated significant improvements in signs, symptoms, and impacts based on PK deficiency-specific PRO instruments, compared with placebo**
- **This post hoc analysis further suggests that across both PRO instruments (the PKDD and PKDIA), improvements in HRQoL were even greater and were clinically meaningful in the subset of mitapivat-treated patients who achieved the protocol-defined primary endpoint of Hb response**

Mitapivat, a disease-modifying pharmacotherapy for patients with PK deficiency, improved HRQoL, indicating a potential for beneficial real-world impacts in patients with this condition

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