Mitapivat efficacy in adults with pyruvate kinase deficiency and baseline hemoglobin levels >10 g/dL

P1477

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BACKGROUND

- Pyruvate kinase (PK) deficiency is a chronic, hereditary disorder, characterized by hemolysis, ineffective erythropoiesis, and varying degrees of anemia[1–4]
- Patients with PK deficiency have a wide range of hemoglobin (Hb) levels,[1–3] yet those with less pronounced anemia (Hb >10 g/dL) may still experience complications, including iron overload, gallbladder disease, and osteopenia[3]
- Mitapivat, a first-in-class, oral, allosteric activator of PK **(Figure 1)**, is approved by the United States Food and Drug Administration for the treatment of hemolytic anemia in adults with PK deficiency,[5] and by the European Union European Medicines Agency[6] and the Medicines and Healthcare Products Regulatory Agency in Great Britain[7], for the treatment of PK deficiency in adults
- Mitapivat improved Hb levels during the phase 2 DRIVE-PK[8] (NCT02476916) study, and the global, phase 3, randomized, placebo-controlled ACTIVATE[9] trial and its long-term extension[10] (LTE) (NCT03548220/NCT03853798) study
  - Trial designs for DRIVE-PK and ACTIVATE/LTE are illustrated in **Figure 2**

Figure 1. Mechanism of action of mitapivat

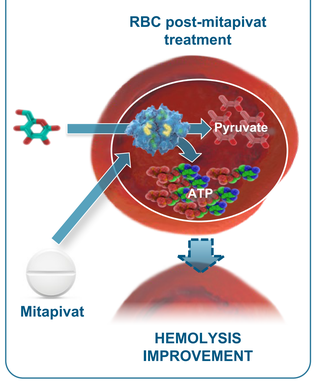
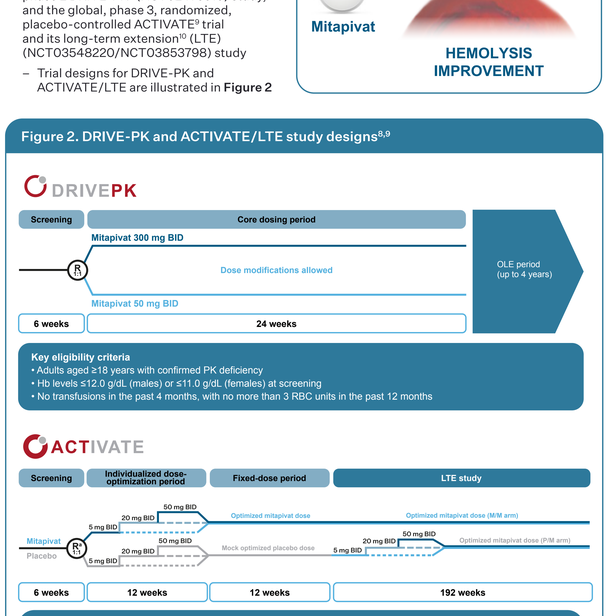


Figure 2. DRIVE-PK and ACTIVATE/LTE study designs[8,9]



[a]Excluding patients homozygous for R479H mutation or with 2 non–missense mutations, without another missense mutation. BID, twice daily; BL, baseline; Hb, hemoglobin; LTE, long-term extension; M/M, mitapivat/mitapivat; OLE, open-label extension; PK, pyruvate kinase; P/M, placebo/mitapivat; R, randomization; RBC, red blood cell

Efficacy and safety data

- DRIVE-PK:
  - Of 52 patients, 26 (50.0%) achieved an increase of >1 g/dL from baseline (BL) in Hb, with a mean (range) increase of 3.4 g/dL (1.1–5.8)[8]
  - Improvements in Hb levels achieved during the core period were sustained for up to 42 months in the extension period[11]
  - The most common adverse events were headache and insomnia, occurring in 44.2% and 40.4% of patients, respectively[8]
- ACTIVATE/LTE:
  - 40.0% of patients (16/40) treated with mitapivat in the ACTIVATE study achieved the primary endpoint of a Hb increase from BL of ≥1.5 g/dL at ≥2 scheduled assessments at Weeks 16, 20, and 24, compared with 0.0% of patients in the placebo arm[9]
  - The most common adverse events were nausea and headaches, occurring in 17.5% and 15.0% of patients treated with mitapivat, and 22.5% and 32.5% of patients within the placebo arm, respectively[9]
  - As of 27Mar2022, the median duration of response for the 31 patients from ACTIVATE and the LTE study who achieved Hb increase from BL of ≥1.5 g/dL at ≥2 scheduled assessments was 18.3 months, up to a longest duration of 32.9 months[10]

OBJECTIVE

- **To evaluate changes in Hb and hemolysis after mitapivat treatment in adult patients with PK deficiency and BL Hb >10 g/dL who were not regularly transfused and enrolled in the DRIVE-PK and ACTIVATE/LTE studies**

METHODS

- This analysis included adult (≥18 years at enrollment) patients with BL Hb >10 g/dL, who received mitapivat 50 mg twice daily in the DRIVE-PK or ACTIVATE/LTE studies
  - Data as of 28Aug2021 for patients in DRIVE-PK and 12Sep2021 for patients in ACTIVATE/LTE were included
  - BL Hb is the average of all screening assessments within 45 (42+3) days before the start of study treatment (including assessments on the date of the start of study treatment)
  - The change in Hb from BL and the proportion of patients with increases in Hb from BL ≥1.0 g/dL and ≥1.5 g/dL were evaluated through Week 48 (the latest timepoint with Hb data available for all patients)
  - All Hb data collected ≤61 days post-transfusion were considered ineligible
- Changes from BL in markers of hemolysis were also measured through Week 48:
  - Reticulocyte percentage
  - Indirect bilirubin
  - Lactate dehydrogenase (LDH)

RESULTS

BL characteristics

- 6 patients from DRIVE-PK and 4 patients from ACTIVATE/LTE had a BL Hb >10 g/dL, with ranges of 10.2–12.3 g/dL and 10.1–10.2 g/dL, respectively
- The average age at enrollment from both studies was 32 years, and 30% were female **(Table 1)**

Medical history

- 70% of patients had a prior splenectomy, at a median (range) age of 22 years (19–55) **(Table 1)**
- Iron overload and gallstones had been experienced by 30% and 40% of patients, respectively
- 20% of patients had previously received chelation therapy **(Table 1)**

Table 1. BL characteristics and medical history of patients with BL Hb >10 g/dL from both the DRIVE-PK and the ACTIVATE/LTE studies

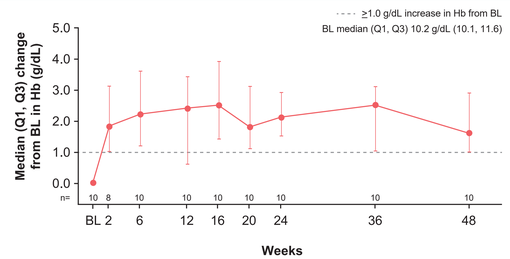
	All patients with BL Hb >10 g/dL
	N=10
BL characteristics	
Age at enrollment, median (range), years	32 (19–57)
Female, n (%)	3 (30)
Hb, g/dL, median (Q1, Q3)	10.2 (10.1–11.6)
Medical history	
Prior splenectomy, n (%)	7 (70)
Age at splenectomy, median (range), years	22 (19–55)
Iron overload[a], n (%)	3 (30)
Prior chelation therapy[b], n (%)	2 (20)
Gallstones, n (%)	4 (40)
Osteopenia[c], n (%)	0 (0)

[a]Iron overload defined as meeting ≥1 of 3 criteria: baseline ferritin >1000 µg/L, baseline average LIC >3 mg Fe/g dw, prior chelation status = Yes. [b]Prior chelation status was established as part of medical history, to distinguish from assessment of chelation on-treatment; "Yes" if a subject has received chelation therapy within 52 weeks (364 days) before start of treatment with mitapivat. [c]Defined as bone mineral density dual-energy X-ray absorptiometry scores >−2.5 to <−1.0. Range represents the minimum and maximum values within the group; BL, baseline; Hb, hemoglobin; LTE, long-term extension; Q, quartile

Hb

- Median (Q1, Q3) change from BL to Week 48 for Hb is displayed in **Figure 3**
  - At Week 48, median (Q1, Q3) change from BL was 1.6 g/dL (1.0, 2.9)
  - Mean (SD) Hb change from BL to Week 48 was 1.8 g/dL (1.8)
- The majority of patients (8/10, 80%) achieved a Hb improvement of ≥1.0 g/dL from baseline at Week 48
- 5/10 patients (50%) achieved a Hb improvement of ≥1.5 g/dL from baseline at Week 48
  - All 5 of these patients sustained improvements ≥1.5 g/dL from Week 6 through to Week 48

Figure 3. Median (Q1, Q3) change from BL in Hb in patients with BL Hb >10 g/dL from the DRIVE-PK and the ACTIVATE/LTE studies



Data are presented to Week 48, the latest timepoint at which all patients had available Hb data. In DRIVE-PK, timepoints after Week 24 were reported in months, while the ACTIVATE/LTE were reported in weeks. To pool timepoints, months were converted to weeks using the yearly mean of 30.4375 days per month. After conversion, timepoints within 1 month were pooled; BL, baseline; Hb, hemoglobin; LTE, long-term extension; Q, quartile

Markers of hemolysis

- The median changes from BL (Q1, Q3) for indirect bilirubin, reticulocyte percentage, and LDH are shown in **Figure 4A–C**, respectively
- At Week 48, median (Q1, Q3) changes from BL were:
  - Indirect bilirubin −35.1 µmol (−45.8, −31.6)
    - Indirect bilirubin levels were reduced from BL in 9/10 (90%) patients (data missing for 1 patient), with a mean (SD) change from BL of −43.2 µmol (27.4) at Week 48
  - Reticulocyte percentage −5.5% (−14.1, −2.0)
    - Reticulocyte percentage was reduced from BL in 9/10 (90%) patients, with a mean (SD) change from BL of −8.5% (8.3) at Week 48
  - LDH −28 U/L (−51, −5)
    - LDH levels were reduced from BL in 8/10 (80%) patients (data missing for 1 patient), with a mean (SD) change from BL of −46 U/L (84) at Week 48

Figure 4A. Median (Q1, Q3) change from BL in indirect bilirubin in patients with BL Hb >10 g/dL from the DRIVE-PK and the ACTIVATE/LTE studies

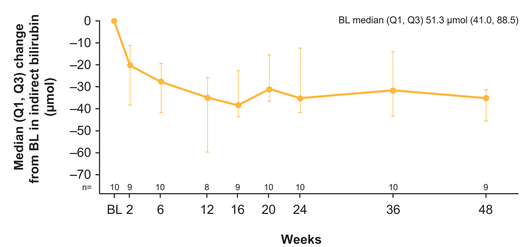


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Figure 4B. Median (Q1, Q3) change from BL in reticulocyte percentage in patients with BL Hb >10 g/dL from the DRIVE-PK and the ACTIVATE/LTE studies

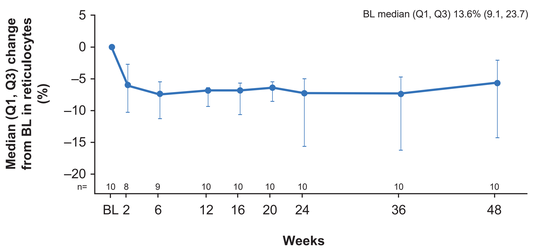

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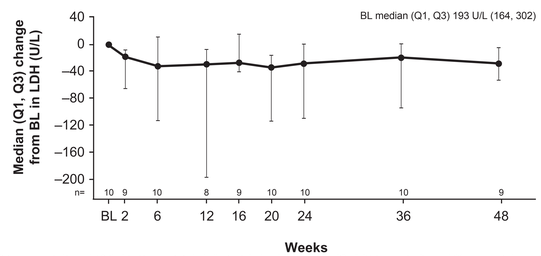
Figure 4C. Median (Q1, Q3) change from BL in LDH in patients with BL Hb >10 g/dL from the DRIVE-PK and the ACTIVATE/LTE studies



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CONCLUSIONS

- **This analysis shows that mitapivat improved Hb levels in adults with PK deficiency and BL Hb >10 g/dL who were not regularly transfused, supporting a therapeutic benefit of mitapivat for this subset of patients**
- **These patients also experienced a reduction in markers of hemolysis, suggesting that this treatment improves the underlying pathophysiology of PK deficiency**

Mitapivat treatment in patients with PK deficiency and BL Hb >10 g/dL improved anemia and hemolysis, thereby improving red blood cell health, and may in turn decrease the likelihood of complications within this patient subset

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