Bone mineral density is stable in adults with pyruvate kinase deficiency receiving long-term treatment with mitapivat

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BACKGROUND

- Pyruvate kinase (PK) deficiency is characterized by lifelong hemolytic anemia that can lead to both acute and long-term comorbidities and complications
  - Among these is reduced bone mineral density (BMD), which can result in premature osteopenia, osteoporosis, and fractures[1]
    - A recent analysis of dual-energy X-ray absorptiometry (DXA) scans from 159 patients with PK deficiency showed that > 75% of adult patients had lower than normal BMD at a median age of 34 years[2]
- The mechanisms leading to BMD loss in PK deficiency are not well understood, but may involve:
  - Marrow expansion[3]
  - Genetic factors[4,5]
  - Endocrine dysfunction (eg, thyroid disease)[4,6]
  - Iron overload and its treatment[4,5]
- Mitapivat is an investigational, first-in-class, allosteric activator of PK
  - In the DRIVE-PK study, mitapivat was previously shown to improve hemoglobin (Hb) and other hemolysis markers for up to 42 months in patients with PK deficiency (data cutoff: March 27, 2019)[7–9]
  - Mitapivat has mild aromatase inhibition effects; however, it is not clear whether this carries a negative impact on BMD in patients with PK deficiency
  - Conversely, reducing hemolysis and improving ineffective erythropoiesis through PK activation may have a positive effect on BMD

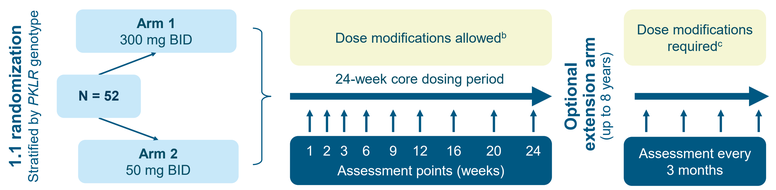
OBJECTIVE

- To report BMD over time in adult patients with PK deficiency receiving long-term treatment with mitapivat in the DRIVE-PK study (NCT02476916)

METHODS

- DRIVE-PK is a phase 2, randomized, open-label, dose-ranging study of mitapivat in adults with PK deficiency who were not receiving regular transfusions[a] (**Figure 1**)

Figure 1. DRIVE-PK study design



DRIVE-PK: NCT02476916; [a]≤ 3 units of RBCs in prior 12 months, no transfusions in prior 4 months. [b]Dose adjustments were allowed in the core period on the basis of safety, side-effect profile, and Hb response. [c]Protocol amendments required that patients who did not have an increase from baseline Hb of ≥ 1.0 g/dL for ≥ 3 of prior 4 measurements withdraw from the study; and that patients treated with mitapivat doses > 25 mg BID undergo a dose taper and continue on a dose that maintained their Hb level at no lower than 1.0 g/dL below their pre-taper Hb level.
BID = twice daily; Hb = hemoglobin; PK = pyruvate kinase; *PKLR* = gene encoding the PK liver and RBC isozymes; RBC = red blood cell.

Key eligibility criteria:

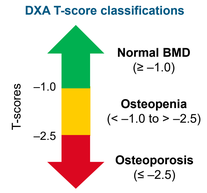
- Patients ≥ 18 years of age with diagnosed PK deficiency
- Not regularly transfused (≤ 3 units of red blood cells in prior 12 months, no transfusions in prior 4 months)
- Hb ≤ 12.0 g/dL (if male) or ≤ 11.0 g/dL (if female)

METHODS (CONTINUED)

- Patients who received mitapivat for > 12 months and had on-treatment DXA monitoring were included in this analysis (**Figure 2**)

Figure 2. DXA T-score assessment methods and classifications

- BMD was measured using DXA scans at baseline, every 6 months through month 30, and then annually
  - Scans captured hip, spine, and femoral neck
  - Scans were obtained and interpreted locally
- Decrease in BMD was identified on DXA scanning according to standard definitions
- Patients were classified as having normal BMD, osteopenia, or osteoporosis based on DXA T-scores
- DXA changes over time were assessed for patients receiving mitapivat > 12 months



BMD = bone mineral density; DXA = dual-energy X-ray absorptiometry.

RESULTS

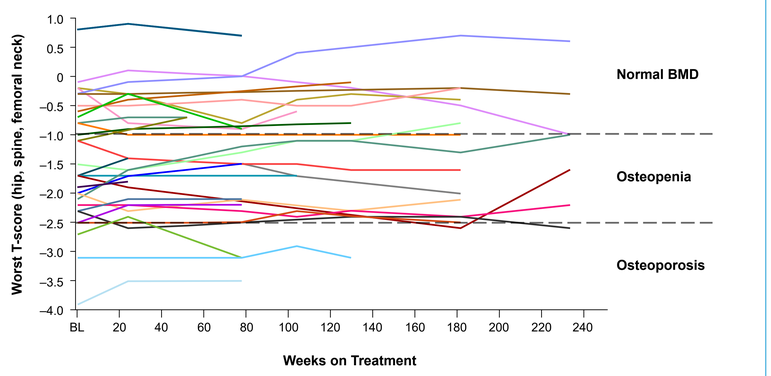
- Of 52 patients enrolled in DRIVE-PK, 31 met the criteria for this analysis (**Table 1**)

Table 1. Demographics and patient characteristics

Characteristic	Total (N = 31)
Median age at baseline (range), year	34 (19–61)
Sex, n (%)	
Female	10 (32)
Median Hb at baseline (range), g/dL	9.5 (7.3–12.3)
Median mitapivat treatment duration (range), year	3.8 (1.0–4.9)
Concomitant anti-osteoporosis medication, n (%)	2 (6.5)
Alendronic acid	1 (3.2)
Zoledronic acid	1 (3.2)

- T-scores remained mostly stable over time in this group of patients (**Figure 3**)

Figure 3. Individual longitudinal plot[a] of worst DXA T-score in patients treated with mitapivat for > 12 months[b,c]



[a]Each colored line represents an individual patient's longitudinal T-score results; [b]Patients who received mitapivat for > 12 months (365 days); only patients with evaluable post-basline DXA T-score are included in the analysis; [c]Two patients are included who were treated for > 12 months, but only have evaluable post-baseline T-score results up to 6 months; one patient is included who has no evaluable T-score results from baseline to 18 months.
BL = baseline; BMD = bone mineral density; DXA = dual-energy X-ray absorptiometry.

RESULTS (CONTINUED)

- The majority of patients remained within the same BMD category as they were at baseline (**Table 2**)

Table 2. Shift of worst DXA T-score category across hip, spine, or femoral neck from baseline to last study assessment

Baseline		T-score at last assessment, n (%)		
Prior category[a]	n (%)	Normal BMD ≥ –1.0	Osteopenia > –2.5 to < –1.0	Osteoporosis ≤ –2.5
Normal BMD ≥ –1.0	12 (38.7)	12 (38.7)	0	0
Osteopenia > –2.5 to < –1.0	13 (41.9)	3 (9.7)	9 (29.0)	1 (3.2)
Osteoporosis ≤ –2.5	5 (16.1)	0	1 (3.2)	4 (12.9)

= Stable = Improved = Worsened

[a]Patients who received mitapivat for > 12 months (365 days); only patients with evaluable post-baseline DXA T-score are included in the analysis.
Note: One patient did not have baseline DXA, so the table shows results for 30/31 patients.
BMD = bone mineral density; DXA = dual-energy X-ray absorptiometry.

CONCLUSIONS

- **DXA scanning revealed that BMD was mostly stable over time in adult patients with PK deficiency receiving long-term treatment with mitapivat for up to 56 months, despite a substantial degree of reduced BMD at baseline**
  - **No fractures were reported during the study period**
- **Mitapivat does not appear to promote progression of BMD abnormalities in these patients**
- **Longer-term BMD data will continue to be collected as part of this ongoing extension study**

By decreasing hemolysis and ineffective erythropoiesis, mitapivat may have the potential to halt the pathophysiologic process that leads to osteopenia and osteoporosis in patients with PK deficiency

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