Early-onset osteopenia and osteoporosis in patients with pyruvate kinase deficiency

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BACKGROUND

- Pyruvate kinase (PK) deficiency is a rare, underrecognized, hereditary non-spherocytic hemolytic anemia[1,2]
  - It is caused by mutations in the *PKLR* gene that encodes red blood cell (RBC) PK (known as PKR), which is critical for maintaining RBC energy levels and morphology[1,2]
- PK deficiency is associated with serious complications, including reduced bone mineral density (BMD) which can result in premature osteopenia, osteoporosis, and fractures[3,4]
  - The mechanisms leading to BMD loss in PK deficiency are not well understood, but may involve marrow expansion, iron overload and its treatment, increased bone turnover, and hormone deficiencies[5]
  - In the PK Deficiency Natural History Study, the rates of bone fracture and bone deformities were found to be 17% and 9%, respectively[6]

OBJECTIVE

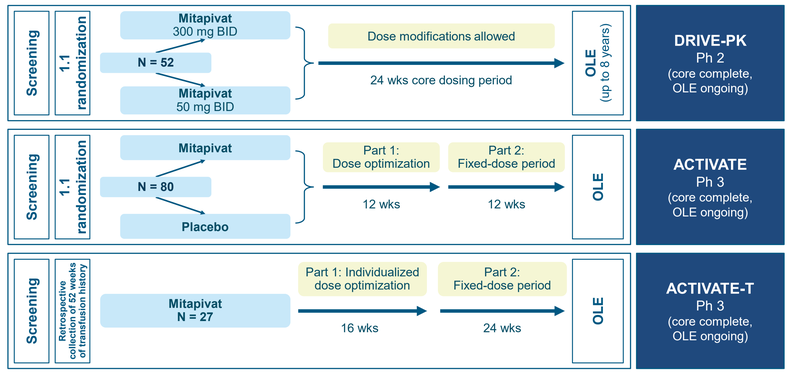
- To better characterize BMD abnormalities in patients with PK deficiency by evaluating pooled, pre-treatment baseline data from three clinical trials investigating mitapivat, an allosteric activator of PK, in patients with PK deficiency

METHODS

Study design

- DRIVE-PK (NCT02476916) is a phase 2, global, randomized, open-label study; ACTIVATE (NCT03548220) is a phase 3, global, randomized, double-blind, placebo-controlled study; ACTIVATE-T (NCT03559699) is a phase 3, global, open-label, single-arm study (**Figure 1**)

Figure 1. Study designs of DRIVE-PK, ACTIVATE, and ACTIVATE-T



BID = twice daily; mo = month; OLE = open-label extension; Ph = phase; wks = weeks.

Key eligibility criteria

- **All studies:** ≥ 18 years of age with diagnosed PK deficiency
- **DRIVE-PK:** Not regularly transfused (≤ 3 units of RBCs in prior 12 months, no transfusions in prior 4 months)
- **ACTIVATE:** Not regularly transfused (≤ 4 transfusion episodes in previous year, no transfusions in prior 3 months)
- **ACTIVATE-T:** Regularly transfused (≥ 6 transfusion episodes in prior 1 year)

Analysis

- BMD was measured using dual-energy x-ray absorptiometry (DXA) scans at baseline
  - Scans were obtained locally for all three studies
  - Scans were interpreted locally for DRIVE-PK and centrally for ACTIVATE and ACTIVATE-T
- DXA T-scores were classified as osteopenia or osteoporosis according to standard definitions, and the prevalence of each was compared with the prevalence ascertained via medical history

RESULTS

- Demographics and characteristics of patients at baseline are shown in **Table 1**
- Of 159 patients evaluated (DRIVE-PK, N = 52; ACTIVATE, N = 80; ACTIVATE-T, N = 27), the median age was 34 years and 55.3% were female

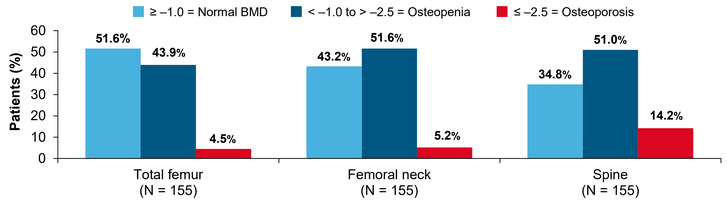
Table 1. Demographics and baseline characteristics[a]

Characteristic	Total (N = 159)
Median age (range), years	34 (18–78)
Sex, n (%)	
Female	88 (55.3)
Race, n (%)	
White	124 (78.0)
Asian	14 (8.8)
Other	5 (3.1)
Not reported	16 (10.1)
PKLR mutation type, n (%)	
Missense/missense	107 (67.3)
Missense/non-missense	42 (26.4)
Non-missense/non-missense	10 (6.3)
Median hemoglobin (range), g/dL	8.7 (6.4–12.3)
Median ferritin (range), ng/mL	648.2 (21.4–7258.8)
T-score total femur, mean (SD)	**–0.88 (0.99)**
T-score femoral neck, mean (SD)	**–1.12 (0.92)**
T-score spine, mean (SD)	**–1.39 (1.15)**

[a]Pooled population includes patients with PK deficiency from the DRIVE-PK, ACTIVATE, and ACTIVATE-T clinical trials.
PK = pyruvate kinase; *PKLR* = gene encoding the pyruvate kinase liver and red blood cell isozymes; SD = standard deviation.

- The proportion of patients in each T-score range for each of the three locations is shown in **Figure 2**

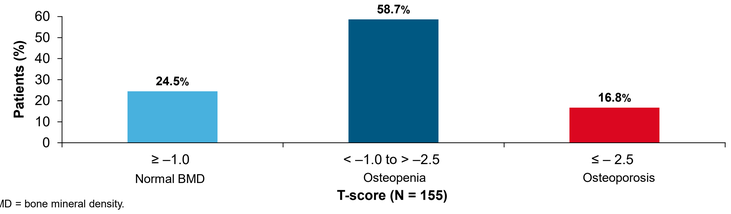
Figure 2. Percentage of patients in each BMD category for total femur, femoral neck, and spine



BMD = bone mineral density.

- The proportion of patients in each T-score range based on worst T-score at one or more locations is shown in **Figure 3**
- Of 155 patients who had baseline T-scores for total femur, spine, and femoral neck:
  - 38 (24.5%) had a T-score of ≥ –1.0 at all locations, indicating normal BMD
  - 91 (58.7%) had a worst T-score of < –1.0 to > –2.5 at one or more locations, indicating osteopenia
  - 26 (16.8%) had a worst T-score of ≤ –2.5 at one or more locations, indicating osteoporosis

Figure 3. Percentage of patients in BMD category based on worst T-score at one or more location



BMD = bone mineral density.

RESULTS (CONTINUED)

- In contrast to the DXA scan findings, only 28 (17.6%) and 23 (14.5%) patients had a known medical history of osteopenia or osteoporosis, respectively (**Table 2**)

Table 2. Prevalence of patient characteristics, including osteopenia and osteoporosis, by medical history[a]

Characteristic	Total (N = 159)
Medical history, n (%)	
Splenectomy	118 (74.2)
Chelation therapy	53 (33.3)
Iron overload	54 (34.0)
Vitamin D deficiency	15 (9.4)
Osteopenia	**28 (17.6)**
Osteoporosis	**23 (14.5)**

[a]Pooled population includes patients with PK deficiency from the DRIVE-PK, ACTIVATE, and ACTIVATE-T clinical trials.
PK = pyruvate kinase.

- Out of 159 patients, 85 (53.5%) patients had osteopenia and 33 (20.8%) had osteoporosis based on medical history or DXA T-scores (**Table 3**)

Table 3. Prevalence of osteopenia and osteoporosis by medical history or DXA T-scores,[a] stratified by transfusion status

Characteristic	Total (N = 159)
Medical history of osteopenia or DXA T-score < –1.0 to > –2.5,[b] n (%)	**85 (53.5)**
Median age (range), years	34 (18–78)
Regularly transfused, n (%)	15 (9.4)
Not regularly transfused, n (%)	70 (90.6)
Medical history of osteoporosis or DXA T-score ≤ –2.5[b], n (%)	**33 (20.8)**
Median age (range), years	41 (18–70)
Regularly transfused, n (%)	5 (15.2)[c]
Not regularly transfused, n (%)	28 (84.8)[c]

[a]Pooled population includes patients with PK deficiency from the DRIVE-PK, ACTIVATE, and ACTIVATE-T clinical trials.
[b]Based on worst T-score at any one location.
[c]Calculated as a percentage of patients with medical history of osteoporosis or DXA T-score ≤ –2.5, n = 33.
DXA = dual-energy x-ray absorptiometry.

CONCLUSIONS

This is the first large PK deficiency cohort in which DXA scores were systematically assessed and reported

DXA scanning revealed that over three-quarters of adults with PK deficiency had osteopenia or osteoporosis, irrespective of transfusion requirements

Given the young median age of the cohort (34 years), these findings have considerable implications for the screening and care of patients with PK deficiency

Early monitoring with DXA scans may be warranted in order to ensure a prompt diagnosis and treatment of bone density abnormalities

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