Early-Onset Osteopenia and Osteoporosis in Patients With Pyruvate Kinase Deficiency

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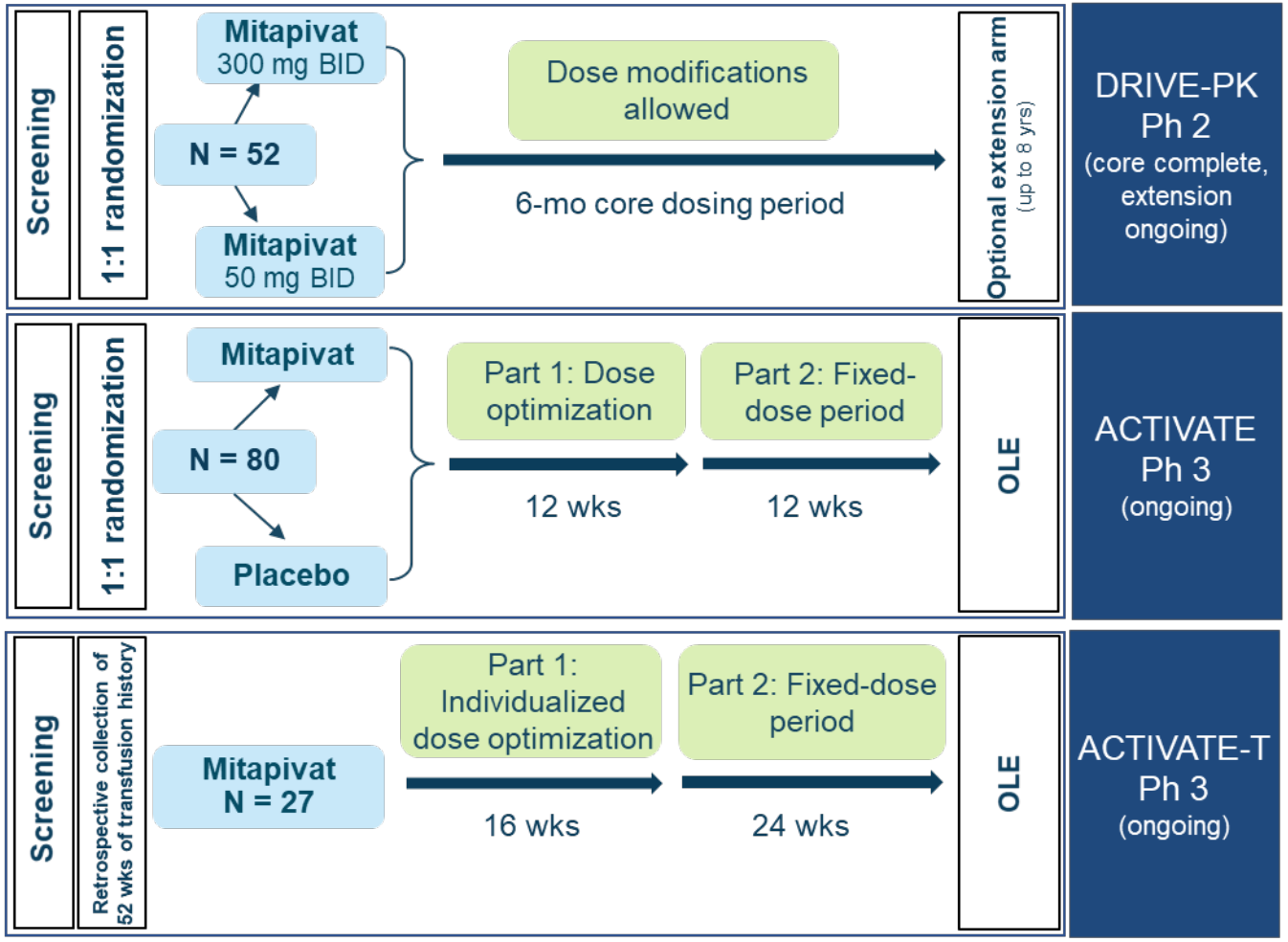
Background, objective, and methods

- 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
- To better characterize BMD in patients with PK deficiency, this study evaluated pooled pre-treatment baseline data from 3 clinical trials investigating mitapivat, an allosteric activator of PK, in patients with PK deficiency: DRIVE-PK, ACTIVATE, and ACTIVATE-T
- BMD was measured using dual-energy x-ray absorptiometry (DXA) scans at baseline
  - Scans were obtained locally for all 3 studies
  - Scans were interpreted locally for DRIVE-PK and centrally for ACTIVATE and ACTIVATE-T
- Osteopenia and osteoporosis were identified on DXA scanning according to standard definitions, and the prevalence of each was compared with the prevalence ascertained via medical history

Study designs



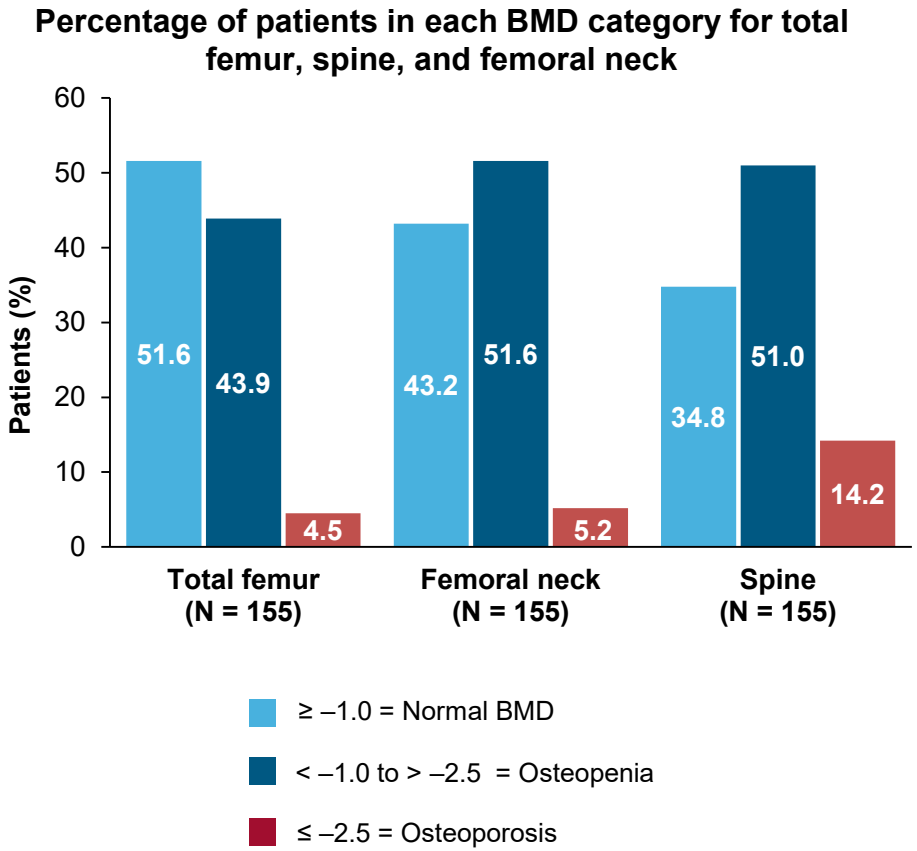
Key Inclusion Criteria

- Pts ≥ 18 yrs of age with diagnosed PK deficiency
- DRIVE-PK: not regularly transfused (≤ 3 units of red blood cells in prior 12 mo, no transfusions in prior 4 mo)
- ACTIVATE: not regularly transfused (≤ 4 transfusion episodes in previous yr, no transfusions in prior 3 mo)
- ACTIVATE-T: regularly transfused (≥ 6 transfusion episodes in previous yr)

DRIVE-PK: NCT02476916; ACTIVATE: NCT03548220; ACTIVATE-T: NCT03559699
Mo = months; BID = twice daily; OLE = open-label extension; Ph = phase; PK = pyruvate kinase; pts = patients; wks = weeks; yr = year

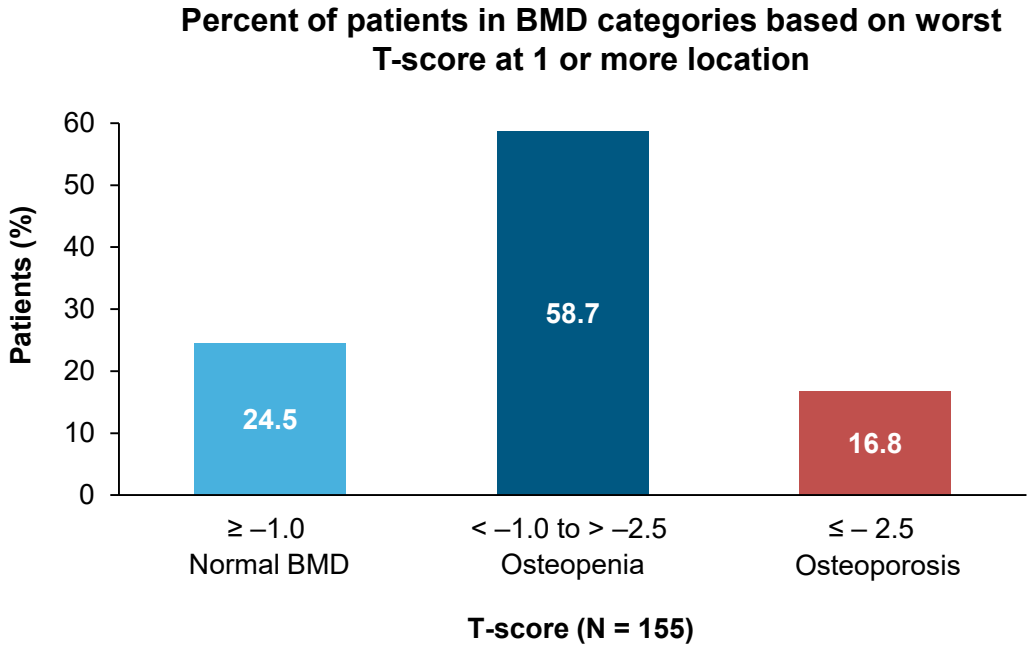
Demographics and baseline characteristics[a]

Characteristic	Total (N = 159)
Median age (range), year	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	106 (66.7)
Missense/non-missense	38 (23.9)
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 DRIVE-PK, ACTIVATE, and ACTIVATE-T clinical trials
BMD = bone mineral density; PK = pyruvate kinase; PKLR = pyruvate kinase L/R; SD = standard deviation

Prevalence of osteopenia and osteoporosis by medical history and DXA T-scores[a]



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

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

[a]Pooled population includes patients with PK deficiency from DRIVE-PK, ACTIVATE, and ACTIVATE-T clinical trials
BMD = bone mineral density; DXA = dual-energy X-ray absorptiometry; PK = pyruvate kinase; SD = standard deviation

Prevalence of osteopenia and osteoporosis by medical history or DXA T-scores[a] and 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), year	34 (18–78)
Not regularly transfused, n (%)	70 (90.6)
Regularly transfused, n (%)	15 (9.4)
Medical history of osteoporosis or DXA T-score ≤ –2.5[b], n (%)	**33 (20.8)**
Median age (range), year	41 (18–70)
Not regularly transfused, n (%)	28 (84.8)
Regularly transfused, n (%)	5 (15.2)

Out of 159 patients, 53.5% patients had osteopenia and 20.8% patients had osteoporosis based on medical history or DXA T-scores

[a]Pooled population includes patients with PK deficiency from DRIVE-PK, ACTIVATE, and ACTIVATE-T clinical trials
[b]Based on worst T-score at any one location
DXA = dual-energy x-ray absorptiometry; PK = pyruvate kinase

Summary

- 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 yrs), 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

DXA = dual-energy x-ray absorptiometry; PK = pyruvate kinase; yrs = years

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