Bone mineral density remains stable in pyruvate kinase deficiency patients receiving long-term treatment with mitapivat

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BACKGROUND

- Hereditary pyruvate kinase (PK) deficiency is an underrecognized, lifelong, hemolytic anemia characterized by mutations in the *PKLR* gene encoding the red blood cell PK (PKR) enzyme[1,2]
- Defective PKR causes chronic hemolysis and ineffective erythropoiesis which is associated with serious complications including reduced bone mineral density (BMD)[3]
- The mechanisms leading to reduced BMD in PK deficiency are not well understood, but may involve marrow expansion[4], iron overload and its treatment,[5,6] endocrine disruptions,[5,7] and genetic factors[7,8]
- Reduced BMD may lead to early onset osteopenia, osteoporosis, and bone fractures[3]
- In the PK Deficiency Natural History Study, the rates of bone fracture and bone deformities were 17% and 9%, respectively,[7] and the prevalence of osteoporosis was significantly higher among patients with PK deficiency compared to age- and sex-matched individuals in the general population (15.6% vs 0%)[9]
- Systematic dual-energy X-ray absorptiometry (DXA) scanning in a large pooled baseline (BL) analysis (N=159) of adults with PK deficiency revealed that over 75% of patients had low BMD or a medical history of osteopenia or osteoporosis at a median age of 34 years, regardless of transfusion status[10]
- Mitapivat is an oral, allosteric activator of PKR that has been shown to improve anemia and hemolysis, and decrease transfusion burden in patients with PK deficiency[11–14]
- Mitapivat has mild aromatase inhibition effects; however, a study of 30 non-regularly transfused patients with PK deficiency showed that mitapivat did not appear to promote progression of BMD abnormalities for up to 56 months[15]

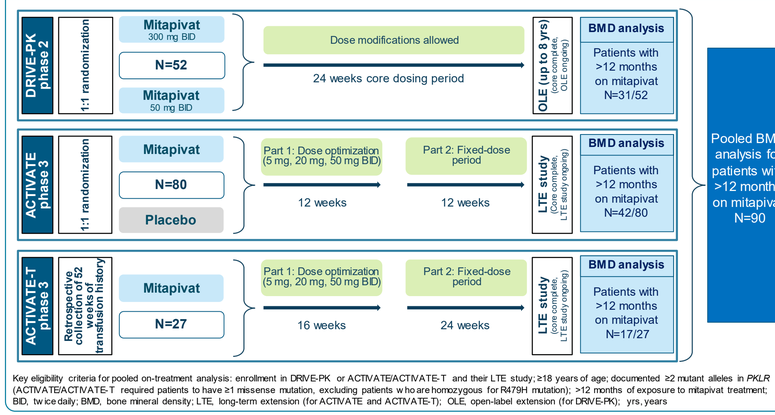
OBJECTIVE

- **To report BMD over time in a broad population of non-regularly transfused and regularly transfused patients with PK deficiency receiving long-term treatment with mitapivat in a large pooled analysis of the DRIVE-PK (NCT02476916), ACTIVATE (NCT03548220), ACTIVATE-T (NCT03559699), and the phase 3 long-term extension (LTE) study (NCT03853798)**

METHODS

- **DRIVE-PK** was a phase 2, global, randomized, open-label, dose-ranging (50 mg vs 300 mg twice daily) study of mitapivat in adults with PK deficiency who were not regularly transfused (≤3 transfusion episodes in previous year; none in prior 4 months)
- **ACTIVATE** was a phase 3, global, double-blind, placebo-controlled study of mitapivat in adults with PK deficiency who were not regularly transfused (≤4 transfusion episodes in previous year; none in prior 3 months)
- **ACTIVATE-T** was a phase 3, global, open-label, single-arm study of mitapivat in adults with PK deficiency who were regularly transfused (≥6 transfusion episodes in previous year)
- Patients who completed the DRIVE-PK core dosing period were eligible to continue on mitapivat for up to 8 years on an open-label extension study; patients who completed the ACTIVATE and ACTIVATE-T fixed-dose periods were eligible to continue to the **LTE study** where all patients received mitapivat treatment (**Figure 1**)

Figure 1. DRIVE-PK, ACTIVATE, ACTIVATE-T, and the LTE study designs

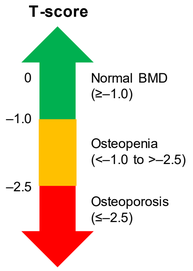


Key eligibility criteria for pooled on-treatment analysis: enrollment in DRIVE-PK or ACTIVATE/ACTIVATE-T and their LTE study; ≥18 years of age; documented ≥2 mutant alleles in *PKLR* (ACTIVATE/ACTIVATE-T required patients to have ≥1 missense mutation, excluding patients who are homozygous for R479H mutation); >12 months of exposure to mitapivat treatment; BID, twice daily; BMD, bone mineral density; LTE, long-term extension (for ACTIVATE and ACTIVATE-T); OLE, open-label extension (for DRIVE-PK); yrs, years

- Osteopenia (T-score <–1.0 to >–2.5) and osteoporosis (T-score ≤–2.5) were classified based on DXA scanning according to standard definitions (**Figure 2**)
- DXA scans at last assessment were compared to DXA scans at BL to assess if a patient's DXA T-score had **worsened** (decreased from ≥–1.0 to <–1.0 or >–2.5 to ≤–2.5), remained **stable** (stayed in the same T-score range as BL), or **improved** (increased from ≤–2.5 to >–2.5 or <–1.0 to ≥–1.0)

Figure 2. DXA T-score assessments and classifications

- BMD was measured using DXA scans of total femur (combined femoral neck and total hip), femoral neck, and spine locations
- Scans were collected
  - DRIVE-PK: at BL, every 6 months through to month 30, and then annually
  - ACTIVATE: at BL and Week 24
  - ACTIVATE-T: at BL, Week 16, and Week 40
  - LTE study: at BL, every 24 weeks through to Week 96, then every 48 weeks
- Scans were obtained locally for all studies, and interpreted locally for DRIVE-PK and centrally for ACTIVATE, ACTIVATE-T, and the LTE study



BL, baseline; BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry, LTE, long-term extension

RESULTS

- Of the 159 patients enrolled in DRIVE-PK, ACTIVATE, ACTIVATE-T, and the LTE study, 90 patients met inclusion criteria for this analysis (**Table 1**)

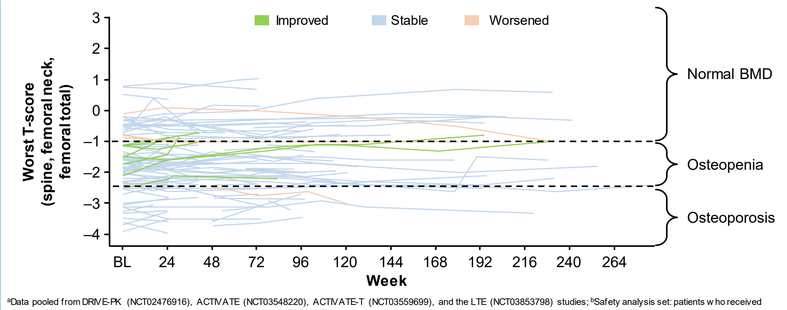
Table 1. Patient demographics and characteristics[a]

Characteristic	Total (N=90)
Median age (range), year	34.5 (18–71)
Sex, n (%)	
Female	45 (50)
Race, n (%)	
White	73 (81.1)
Asian, Native Hawaiian, or Pacific Islander	8 (8.9)
Other or not reported	9 (10.0)
Hemoglobin at BL, median (range), g/dL	9.0 (6.4–12.3)
Prior medical history of fracture[b], n (%)	8 (8.9)
DXA scan T-score at BL, mean (SD) (n=88)	
Total femur[c]	–0.9 (1.00)
Femoral neck	–1.1 (0.98)
Spine	–1.4 (1.14)
Median mitapivat treatment duration (range), months	20 (12.2–64.9)
Concomitant anti-osteoporosis medication, n (%)	8 (8.9)
Alendronic acid	4 (4.4)
Alendronate sodium	2 (2.2)
Minodronic acid	1 (1.1)
Risedronate sodium	1 (1.1)
Zoledronic acid	1 (1.1)

[a]Summarized using the safety analysis set within each treatment group; [b]There were 5 reported fractures during the study period; all were unrelated to the study treatment; [c]Combined neck and total hip; BL, baseline; DXA, dual-energy X-ray absorptiometry; LTE, long-term extension; SD, standard deviation

- BMD DXA T-scores were stable up to ~5.5 years in the majority of patients in this pooled analysis (**Figure 3**)
  - BL BMD DXA T-scores were collected for 88 of 90 patients
  - At last BMD assessment (data cut-off 04Mar2021), DXA T-scores for 76 of 88 patients (86.4%) remained stable, 7 patients (8.0%) improved, and 5 patients (5.7%) worsened

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



[a]Data pooled from DRIVE-PK (NCT02476916), ACTIVATE (NCT03548220), ACTIVATE-T (NCT03559699), and the LTE (NCT03853798) studies; [b]Safety analysis set: patients who received mitapivat for >12 months (365 days); only patients with evaluable post-BL DXA T-scores are included in the analysis; [c]BL DXA T-scores are missing for 2 (2.2%) patients; both patients were classified in the osteopenia category >–2.5 to <–1.0 at last assessment; [d]Some patients have up to 12 months of mitapivat treatment, but do not have DXA records beyond 24 weeks
BL, baseline; BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; LTE, long-term extension

- The majority of patients remained within the same BMD category as they were at BL (**Table 2**)
  - Among 24 patients with BL T-scores ≥–1.0, 21 patients remained stable, and 3 patients showed worsening BMD
  - Of 48 patients with BL T-scores >–2.5 to <–1.0, 6 patients improved to a T-score indicating normal BMD, 40 patients remained stable, and 2 patients worsened
  - Of 16 patients with BL T-scores ≤–2.5, 1 patient improved to a T-score of >–2.5 to <–1.0

Table 2. Shift of worst DXA T-score category from BL to the last assessment in a pooled analysis[a] of patients treated with mitapivat >12 months[a,b]

Baseline		T-score at last assessment, n (%)		
Prior category[a]	Patients, n (%)	Normal BMD ≥–1.0	Osteopenia >–2.5 to <–1.0	Osteoporosis ≤–2.5
Normal BMD ≥–1.0	24 (26.7)	21 (23.3)	3 (3.3)	0
Osteopenia >–2.5 to <–1.0	48 (53.3)	6 (6.7)	40 (44.4)	2 (2.2)
Osteoporosis ≤–2.5	16 (17.8)	0	1 (1.1)	15 (16.7)

Improved Stable Worsened

[a]Safety analysis set: patients who received mitapivat for >12 months (365 days); only patients with evaluable post-BL DXA T-scores are included in the analysis; [b]BL DXA T-scores are missing for 2 (2.2%) patients; both patients were classified in the osteopenia category >–2.5 to <–1.0 at last assessment; BL, baseline; BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry

CONCLUSIONS

- 71% of patients had low BMD at baseline, which for the vast majority remained stable or improved while being exposed to mitapivat
- Given the low BL BMD in these patients, it is hypothesized that mitapivat may halt bone loss in patients with PK deficiency via its mechanism of action by decreasing hemolysis, improving ineffective erythropoiesis, and stabilizing iron homeostasis
- BMD data will continue to be monitored as part of the ongoing LTE study

This large pooled analysis showed that BMD remained largely stable over time in adult patients with PK deficiency receiving long-term treatment with mitapivat for up to ~5.5 years

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