LETTER TO THE EDITOR

Bone mineral density in adult patients with pyruvate kinase deficiency on long-term mitapivat treatment

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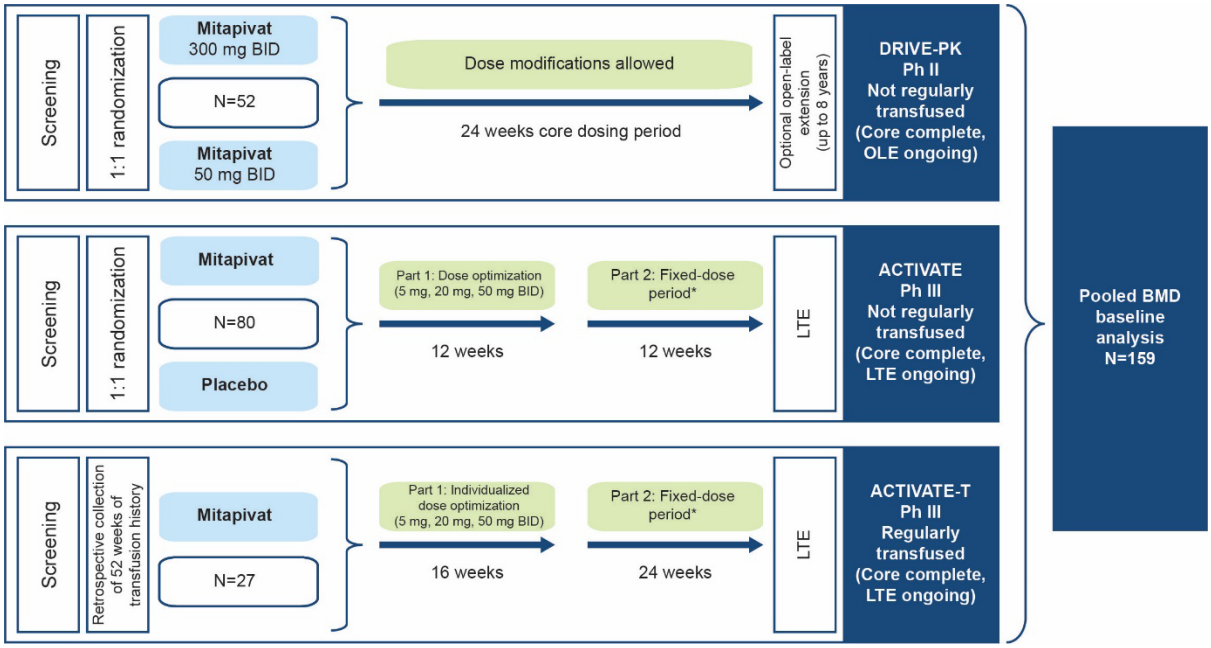
Supplemental data

Supplemental Figure S1. Study designs for the DRIVE-PK, ACTIVATE, ACTIVATE-T, and the LTE studies.



Key inclusion criteria: All: patients aged ≥18 years with diagnosed PK deficiency; DRIVE-PK: not regularly transfused, ≤3 units of red blood cells 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 previous year.

During the dose optimization period of the ACTIVATE and ACTIVATE-T studies, mitapivat or placebo was administered at an initial oral dose of 5 mg BID with two potential sequential steps to increase the dose (from 5 to 20 mg BID and from 20 to 50 mg BID) on the basis of safety and efficacy assessments. *The dose that patients were receiving at the Week 12 visit (ACTIVATE) or Week 16 visit (ACTIVATE-T) was maintained during the subsequent fixed-dose period.

BID: twice daily; BMD: bone mineral density; LTE: long-term extension of ACTIVATE and ACTIVATE-T; OLE: open-label extension of DRIVE-PK; Ph: phase; PK: pyruvate kinase.

Supplemental Table S1. Patient demographics and baseline characteristics*.

Characteristic	Men aged <50 years and women of childbearing potential (N=78)	Men aged ≥50 years and women of non-childbearing potential (N=29)	Total (N=107)
Median age (range), years	28.5 (18–50)	55.0 (34–78)	36.0 (18–78)
Sex, n (%)			
Male	42 (53.8)	9 (31.0)	51 (47.7)
Female	36 (46.2)	20 (69.0)	56 (52.3)
Hemoglobin at baseline, median (range), g/dL	88.0 (64.3–123.0)	91.0 (77.3–119.5)	89.0 (64.3–123.0)
Ferritin at baseline, median (range), ng/mL	601.0 (21.4–5890.3)	536.0 (45.4–3128.2)	566.4 (21.4–5890.3)
DXA scan T-score at BL, mean (SD)	n=77**	n=28**	n=105**
Total femur**	–0.82 (0.967)	–1.04 (1.028)	–0.88 (0.984)
Femoral neck	–1.01 (0.932)	–1.51 (0.872)	–1.14 (0.939)
Spine	–1.40 (1.146)	–1.20 (1.251)	–1.35 (1.172)
DXA scan Z-score at BL, mean (SD)	n=77**	n=28**	n=105**
Total femur***	–0.70 (0.947)	–0.44 (1.117)	–0.63 (0.996)
Femoral neck	–0.78 (0.877)	–0.57 (0.906)	–0.72 (0.886)
Spine	–1.31 (1.143)	–0.43 (1.345)	–1.08 (1.255)
Medical history, n (%)			
Prior cholecystectomy	58 (74.4)	23 (79.3)	81 (75.7)
Prior splenectomy	59 (75.6)	15 (51.7)	74 (69.2)
Prior chelation therapy	27 (34.6)	9 (31.0)	36 (33.6)
Prior fracture****	7 (9.0)	5 (17.2)	12 (11.2)
Iron overload	6 (7.7)	1 (3.4)	7 (6.5)
Concomitant anti-osteoporosis medication, n (%)			
Alendronic acid	2 (2.6)	2 (6.9)	4 (3.7)
Alendronate sodium	1 (1.3)	2 (6.9)	3 (2.8)
Minodronic acid	1 (1.3)	0	1 (0.9)
Risedronate sodium	1 (1.3)	0	1 (0.9)
Zoledronic acid	1 (1.3)	0	1 (0.9)

*Summarized using the safety analysis set within each treatment group (patients receiving mitapivat for >12 months). **One patient missing from each group. ***Combined neck and total hip. ****Medical history of fracture includes events with High-Level Group Term (terminology specified by MedDRA, whereby clinical terms are reported at the grouping level and are not intended to be a coding level) of “Fractures” or “Bone and joint injuries,” excluding events with Preferred Term of “Joint dislocation.”
BL: baseline; DXA: dual-energy X-ray absorptiometry; MedDRA; Medical Dictionary for Regulatory Activities; SD: standard deviation.

Supplemental Table S2. Mean change from baseline in DXA T-scores* and in DXA Z-scores** at last assessment by body location following treatment with mitapivat for >12 months, and change from baseline in worst DXA T-scores* and worst DXA Z-scores** across body locations and for patients receiving osteoporosis medications versus those not receiving these medications at last assessment following mitapivat for >12 months.

		Mean change from baseline in DXA T-scores at last assessment (SD) (N=29)	Mean change from baseline in DXA Z-scores at last assessment (SD) (N=78)
Body location			
Total femur* **		–0.13 (0.27)	0.01 (0.28)
Adjusted spine		–0.14 (0.38)	0.10 (0.37)
Femur neck		–0.10 (0.43)	0.01 (0.32)
Baseline		**Mean change from baseline in worst DXA T-scores at last assessment (SD)**	**Median change from baseline in worst DXA T-scores at last assessment (range)**
Prior category	**Patients, n**** **		
Normal BMD ≥–1.0	5	0.20 (1.04)	–0.20 (–0.35 to 2.06)
Osteopenia >–2.5 to <–1.0	17	–0.23 (0.43)	–0.25 (–1.15 to 0.60)
Osteoporosis ≤–2.5	6	–0.01 (0.31)	–0.09 (–0.30 to 0.42)
Osteoporosis medications use			
Patients using osteoporosis medications	2	–0.13 (0.21)	–0.13 (–0.27 to 0.02)
Patients not using osteoporosis medications	26	–0.10 (0.59)	–0.20 (–0.35 to –0.01)
Baseline		**Mean change from baseline in worst DXA Z-scores at last assessment (SD)**	**Median change from baseline in worst DXA Z-scores at last assessment (range)**
Prior category	**Patients, n***** **		
Normal BMD >–2.0	51	0.08 (0.35)	0.10 (–0.90 to 0.80)
Low BMD ≤–2.0	26	0.07 (0.34)	0.08 (–0.75 to 0.70)

Osteoporosis medications use			
Patients using osteoporosis medications	6	0.16 (0.25)	0.21 (0.13 to 0.30)
Patients not using osteoporosis medications	71	0.07 (0.35)	0.06 (–0.12 to 0.30)

*In men aged ≥50 years and women of non-childbearing potential. **In men aged <50 years and women of childbearing potential. ***Total hip was assessed in the DRIVE-PK study and combined neck and total hip was assessed in the ACTIVATE and ACTIVATE-T studies.

****BL DXA T-score was missing for one patient. *****BL DXA Z-score was missing for one patient.

BL: baseline; DXA: dual-energy X-ray absorptiometry; SD: standard deviation.