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

Pyruvate kinase (PK) deficiency is a rare, hereditary, chronic hemolytic anemia that is associated with serious complications including reduced bone mineral density (BMD). A recent study revealed that low BMD is highly prevalent in patients with PK deficiency pretreatment. Here, we report the first large-cohort analysis to systematically evaluate BMD over time in patients with PK deficiency receiving long-term mitapivat treatment, using data from clinical studies (*clinicaltrials gov. Identifiers: NCT02476916, NCT03548220, NCT03559699, NCT03853798*). In our analysis, BMD remained stable or improved in the majority of patients for up to 5.9 years, regardless of age. Given our findings, mitapivat may halt bone loss by decreasing hemolysis, improving erythropoiesis, and stabilizing iron homeostasis in patients with PK deficiency.

PK deficiency is caused by mutations in the *PKLR* gene encoding the red blood cell (RBC)-specific form of the PK enzyme.[1] This results in impaired glycolysis, leading to reduced RBC membrane integrity and premature RBC destruction,[2] causing multiple complications including iron overload, jaundice, and pulmonary hypertension.[2] PK deficiency is also associated with increased risk of reduced BMD, leading to early onset osteopenia and osteoporosis, and bone fractures.[3] The rate of osteoporosis was significantly higher among patients with PK deficiency (n=122) than 1,220 age- and sex-matched individuals in the general population (15.6% *vs*. 0.0%, respectively).[4] Systematic dual-energy X-ray absorptiometry (DXA) scanning in a large, pooled-cohort analysis (159 adults) of phase II and III clinical trials of mitapivat treatment in patients with PK deficiency revealed that 43.3% had low or very low BMD at baseline, indicating that decreased BMD is highly prevalent in these patients, occurring to a greater extent than previously reported.[5]

Although the mechanisms leading to reduced BMD in PK deficiency are not well understood, they may include widening of marrow spaces due to erythroid hyperplasia, iron overload and its treatment, endocrine disruption, and genetic factors.[6,7]

Mitapivat is a first-in-class, oral allosteric activator of PK, approved by the Food and Drug Administration for the treatment of hemolytic anemia in adults with PK deficiency[8] and by the European Medicines Agency for the treatment of adults with PK deficiency.[9] Mitapivat has been shown to improve anemia, hemolysis, and erythropoiesis, and decrease transfusion burden.[10,11] Although mitapivat has mild aromatase inhibition effects that could potentially affect BMD,[12] it may positively influence BMD by reducing ineffective erythropoiesis.[10] This highlights the need to assess the impact of long-term mitapivat treatment on BMD.

We report BMD over time in patients (≥18 years old) with PK deficiency receiving long-term mitapivat (>12 months), using pooled data from the phase II DRIVE-PK[13] (*clinicaltrials gov. Identifier: NCT02476916*) study, phase III ACTIVATE[10] (*clinicaltrials gov. Identifier: NCT03548220*) and ACTIVATE-T[11] (*clinicaltrials gov. Identifier: NCT03559699*) studies, and long-term extension (LTE) study (*clinicaltrials gov. Identifier: NCT03853798*) (*Online Supplementary Figure S1*).

Baseline DXA scans were taken at screening for ACTIVATE and ACTIVATE-T, and at screening or up to 3 months before the first dose for DRIVE-PK. DXA scans were performed every 24 weeks during mitapivat and performed locally for all three studies. Interpretation of scans was conducted locally for DRIVE-PK and centrally for ACTIVATE, ACTIVATE-T, and the LTE.

T-scores and Z-scores, derived from DXA scans at three body locations (total hip, total lumbar spine, and femoral neck [DRIVE-PK]; and total femur [combined neck and total hip], femoral neck, and spine [ACTIVATE and ACTIVATE-T]), were used to classify patients into BMD categories according to standard definitions. T-scores are used to diagnose osteopenia and osteoporosis in men aged ≥50 years and women of non-childbearing potential by comparing BMD with that of an average healthy 30-year-old. Z-scores are used in men aged <50 years and women of childbearing potential and compare BMD with that of a person of the same age and sex. Mean changes from baseline in worst DXA T- and Z-scores to last assessment were assessed for patients receiving osteoporosis medications (started before or after the first dose of mitapivat), and those who did not receive these medications. Overall mean change in BMD over time was evaluated by assessing changes in DXA T- and Z-scores by each of the three body locations from baseline to last available assessment during treatment with mitapivat.

Patients with T-scores ≥-1.0 at all scan locations were categorized as having normal BMD, those with scores <-1.0 to >-2.5 at ≥1 location as having low BMD/osteopenia, and those with scores ≤-2.5 at ≥1 location as having very low BMD/osteoporosis; Z-scores of ≤-2.0 indicated low BMD; Z-scores >-2.0 indicated normal BMD (Figure 1).[14]

DXA scans from the last available time point were compared with baseline scans to determine if a patient's baseline DXA score had worsened (decreased from ≥-1.0 to <-1.0 or >-2.5 to ≤-2.5 [T-score] or from >-2.0 to ≤-2.0 [Z-score]), remained stable (stayed in the same T- or Z-score range as at baseline), or improved (increased from ≤-2.5 to >-2.5 or <-1.0 to ≥-1.0 [T-score] or from ≤-2.0 to >-2.0 [Z-score]) while on mitapivat. Proportions of patients with improved, stable, or worsened BMD who received long-term mitapivat

were calculated. At baseline and last assessment, worst DXA T- or Z-score was defined as the worst score across the three specified anatomic locations. All findings are summarized descriptively by age and childbearing status. Of 159 patients enrolled in the clinical studies, 107 received long-term mitapivat (>12 months). Overall, median duration of mitapivat treatment was 22.5 months (range, 12.3-70.7). Overall, 27.1% of patients (n=29) were men aged ≥50 years or women of non-childbearing potential and 72.9% (n=78) were men aged <50 years or women of childbearing potential. Median patient age was 36.0 years (range, 18-78); patient demographics and baseline characteristics are shown in *Online Supplementary Table S1*.

BMD DXA T- and Z-scores were stable for up to 5.9 years in the majority of patients in this analysis, regardless of age (Figure 2).

At last BMD assessment (data cutoff August 28, 2021 for DRIVE-PK and September 12, 2021 for ACTIVATE and ACTIVATE-T), the majority of patients remained within the same BMD category for worst DXA T-score or DXA Z-score as at baseline (Table 1). Overall, five of five patients with normal baseline DXA T-scores (≥-1.0) remained stable at last assessment with no worsening of BMD. Among 17 patients with baseline T-scores of >-2.5 to <-1.0 (osteopenia),

- BMD was measured using DXA scans of total femur (combined neck and total hip), femoral neck, and spine locations
- Scans were collected
  - DRIVE-PK: At BL, every 6 months through 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

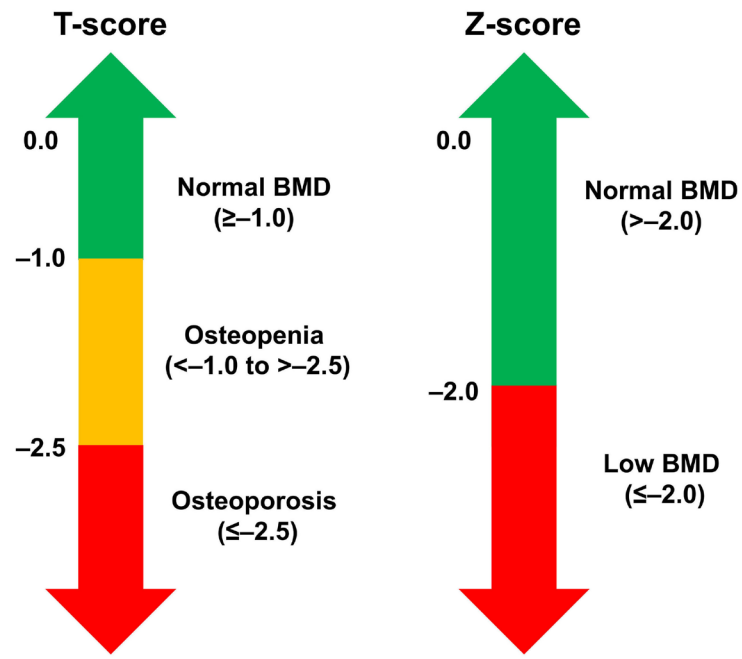


Figure 1. Dual-energy X-ray absorptiometry T- and Z-score assessments and classifications. BMD: bone mineral density; DXA: dual-energy X-ray absorptiometry; BL: baseline; LTE: long-term extension.

Table 1. Shift of worst DXA T-score category (in men aged ≥50 years and women of non-childbearing potential treated with mitapivat for >12 months [N=29][*,**]) and shift of worst DXA Z-score category (in men aged <50 years and women of childbearing potential treated with mitapivat for >12 months [N=77][*]) across body locations from baseline to the last assessment in a pooled analysis[*] of patients.

Baseline		T-score at last assessment N (%)		
Prior category[*]	Patients N (%)	Normal BMD ≥–1.0	Osteopenia >-2.5 to <-1.0	Osteoporosis ≤-2.5
Normal BMD ≥-1.0	5 (17.2)	5 (17.2)°	0[#]	0[#]
Osteopenia >-2.5 to <-1.0	17 (58.6)	2 (6.9)[†]	12 (41.4)°	3 (10.3)[#]
Osteoporosis ≤-2.5	6 (20.7)	0[†]	0[†]	6 (20.7)°
Baseline		**Z-score at last assessment N (%)**		
Prior category[*]	**Patients N (%)**	**Normal BMD >-2.0**		**Low BMD ≤-2.0**
Normal BMD >-2.0	51 (66.2)	46 (59.7)°		5 (6.5)[#]
Low BMD ≤-2.0	26 (33.8)	5 (6.5)[†]		21 (27.3)°

[*]Safety analysis set: patients who received mitapivat for >12 months (365 days); only patients with evaluable post-BL DXA T/Z-scores (as relevant) are included in the analysis. [**]BL DXA T-score was missing for 1 patient. [†]improved; °stable; [#]worsened. BSL: baseline; BMD: bone mineral density; DXA: dual-energy X-ray absorptiometry.

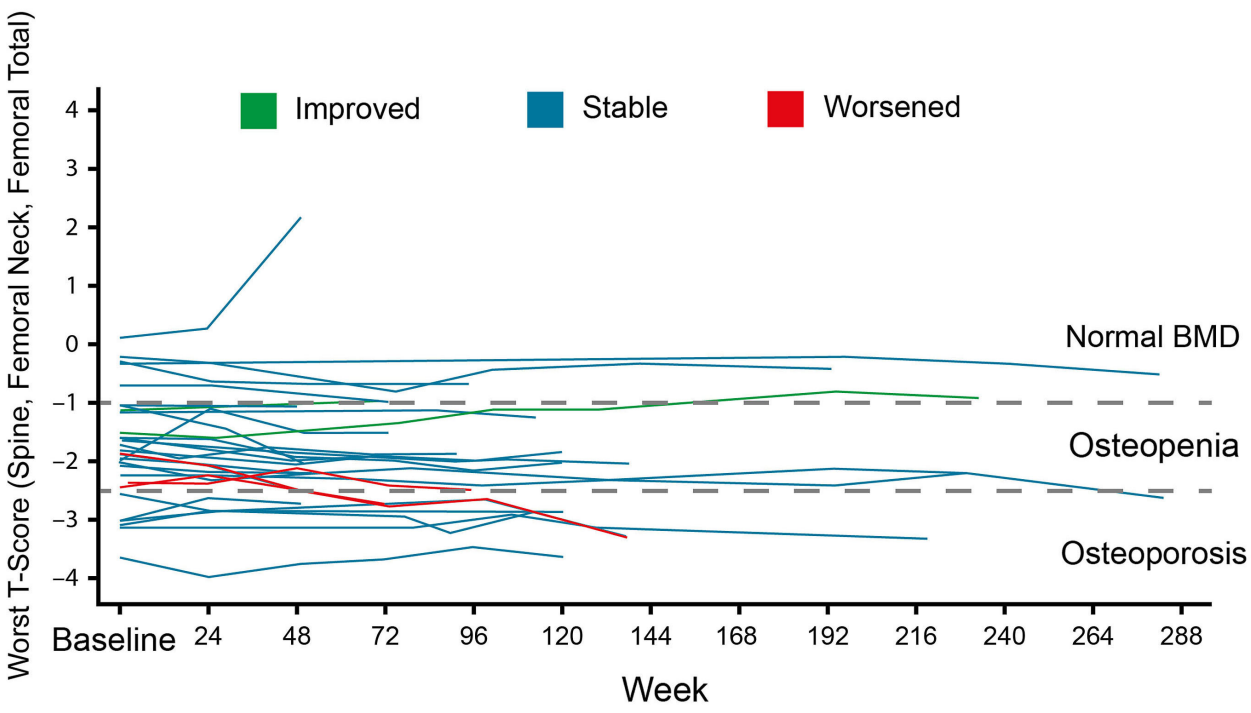
T-scores improved (indicating normal BMD) in two patients at last assessment; remained stable in 12; and worsened in three. All six patients with baseline T-scores of ≤-2.5 (osteoporosis) remained in this DXA T-score category at last assessment (Table 1).

Among 51 patients with normal baseline DXA Z-scores of >-2.0, Z-scores remained stable in 46 at last assessment and worsened in five. Of 26 patients with baseline Z-scores ≤-2.0 (low BMD), Z-scores improved in five and remained stable in 21 (Table 1).

Mean (standard deviation) changes in DXA T- and Z-scores from baseline to last assessment during treatment by body location are shown in *Online Supplementary Table S2*. Change from baseline in worst DXA T- and Z-scores by baseline BMD category to last assessment is shown in *Online Supplementary Table S2*. Ten patients (9.3%) received anti-osteoporosis medications during mitapivat treatment. The mean changes from baseline in worst DXA T- and Z-scores at the last assessment for patients receiving these medications and those who did not receive them were similar (*Online Supplementary Table S2*).

In summary, this pooled analysis showed that BMD remained stable or improved in the majority of patients with PK deficiency treated with long-term mitapivat for up to 5.9 years.

Limitations of this analysis include the lack of formal studies defining the optimal diagnostic methods for osteopenia and osteoporosis in patients with PK deficiency. Therefore, this analysis adhered to conventions broadly used in other populations (e.g., thalassemia). In addition, DXA scans for the DRIVE-PK study[13] were not read centrally so could be subject to inter-rater variability. Potential bias may result from the worst T- or Z-score analysis, which may not fully reflect the largest magnitude of change. Another limitation was that concomitant medication was not assessed over time, so potential contributory effects



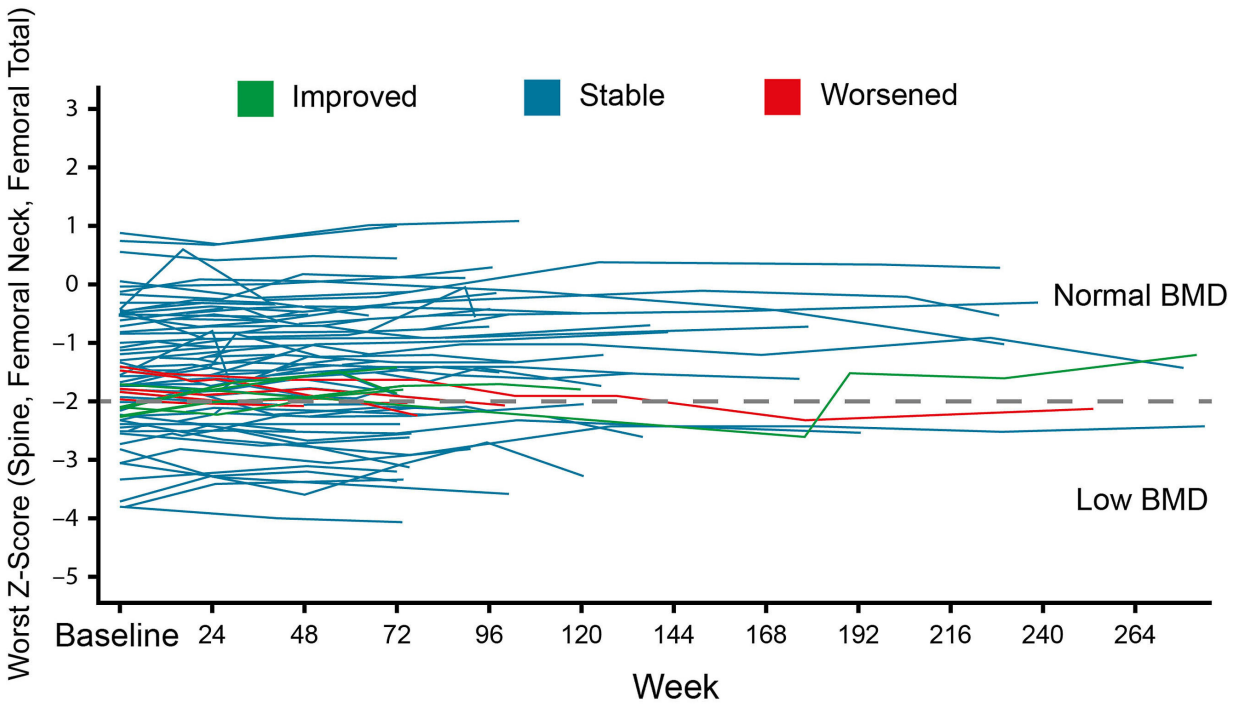


Figure 2. Individual longitudinal plots of worst dual-energy X-ray absorptiometry (DXA) T-score and worst DXA Z-score across body locations. (A) Worst DXA T-score across body locations in a pooled analysis* of patients (men aged ≥50 years and women of non-childbearing potential) treated with mitapivat for >12 months (N=29)**,***,**** and (B) worst DXA Z-score across body locations in a pooled analysis* of patients (men aged <50 years and women of childbearing potential) treated with mitapivat for >12 months (N=77).**,***** *Data pooled from DRIVE-PK (*clinicaltrials gov. Identifier: NCT02476916*), ACTIVATE (*clinicaltrials gov. Identifier: NCT03548220*), ACTIVATE-T (*clinicaltrials gov. Identifier: NCT03559699*), and the LTE (*clinicaltrials gov. Identifier: NCT03853798*) studies. **Safety analysis set: patients who received mitapivat for >12 months (365 days); only patients with evaluable post-baseline (BL) DXA T- and Z-scores are included in the analysis. ***BL DXA T-score was missing for 1 patient. ****Some patients have up to 12 months of mitapivat treatment but do not have DXA records beyond 24 weeks. BMD: bone mineral density; LTE: long-term extension; DXA: dual-energy X-ray absorptiometry.

on BMD are unknown. Finally, while patients were treated and followed up for up to 5 years, most were treated for a shorter period, and progression of BMD abnormalities usually occurs over years in the general population and in patients with thalassemia syndromes.[15,16] While the stability observed here suggests against any major negative impact of potential mitapivat-associated aromatase inhibition on BMD, this needs to be further investigated over a longer time period. BMD will continue to be monitored as part of the ongoing LTE study of mitapivat in adult patients with PK deficiency and is being assessed in two ongoing studies in children (<18 years) with PK deficiency (*clinicaltrials gov. Identifier: NCT05175105, NCT05144256*).

Given the low baseline BMD in patients with PK deficiency, it is hypothesized that mitapivat may halt bone loss through its mechanism of action by decreasing hemolysis, improving erythropoiesis, and stabilizing iron homeostasis. In support of this mechanism, findings from a study in patients with α- or β-non-transfusion-dependent thalassemia receiving mitapivat have also shown that BMD remains stable over time through 84 weeks.[17] BMD will continue to be monitored as part of the ongoing LTE study of mitapivat in adult patients with PK deficiency and is being assessed in two ongoing studies in children (<18 years) with PK deficiency (*clinicaltrials gov. Identifier: NCT05175105, NCT05144256*).

Authors

Hanny Al-Samkari,[1] Rachael F. Grace,[2] Andreas Glenthøj,[3] Oliver Andres,[4] Wilma Barcellini,[5] Frédéric Galacteros,[6] Kevin H. M. Kuo,[7] D. Mark Layton,[8] Marta Morado,[9] Vip Viprakasit,[10] Feng Tai,[11] Rolandas Urbstonaitis,[11] Jaime Morales,[11] Bryan McGee[11] and Eduard J. van Beers[12]

[1]Division of Hematology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [2]Dana-Farber/Boston Children's Cancer and Blood Disorder Center, Harvard Medical School, Boston, MA, USA; [3]Department of Hematology, Rigshospitalet, Copenhagen, Denmark; [4]Department of Pediatrics, University of Würzburg, Würzburg, Germany; [5] Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [6]Unité des Maladies Génétiques du Globule Rouge, CHU Henri-Mondor AP-HP, Créteil, France; [7]Division of Hematology, University of Toronto, Toronto, Ontario, Canada; [8]Department of Immunology and Inflammation, Hammersmith Hospital, Imperial College Healthcare NHS Foundation Trust, London, UK; [9]Hematology Department, Hospital Universitario La Paz, Madrid, Spain; [10]Department of Pediatrics, Siriaj Hospital, Mahidol University, Bangkok, Thailand; [11]Agios Pharmaceuticals, Inc., Cambridge, MA, USA and [12]Center for Benign Hematology, Thrombosis and Hemostasis, Van Creveldkliniek, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands

Correspondence:
H. AL-SAMKARI - hal-samkari@mgh.harvard.edu

https://doi.org/10.3324/haematol.2023.282884

Received: February 3, 2023.
Accepted: September 14, 2023.
Early view: September 21, 2023.

Disclosures

HAS has received consultancy fees from Agios, Argenx, Forma, Moderna, Novartis, Pharmacosmos, Rigel, and Sobi; and research funding from Agios, Amgen, Novartis, Sobi, and Vaderis. RFG has received research funding from Agios, Novartis, and Sobi; and consultancy fees from Agios and Sanofi. AG has received consultancy fees from and is an advisory board member for Agios, Bluebird Bio, Bristol Myers Squibb, Novartis, Novo Nordisk, and Pharmacosmos; and has received research support from Agios, Saniona, and Sanofi. OA has no conflicts of interest to disclose. WB has received honoraria from Agios, Alexion, and Novartis; has received research funding from Agios; and has a board membership or advisory committee for Bioverativ and Incyte. FG has a board membership or advisory committee for Addmedica, Agios, Novartis, Pfizer, and Vertex. KHMK has received consultancy fees from Agios, Alexion, Apellis, Bluebird Bio, Celgene, Novartis, and Pfizer; honoraria from Alexion and Novartis; discloses membership of an entity's board of directors or advisory committees for Agios and Bioverativ; and has received research funding from Agios and Pfizer. DML has received consultancy fees from Agios and Novartis; and discloses membership of an entity's board of directors or advisory committees for Agios, Cerus, and Novartis. MM has received honoraria and other grants from Sanofi Genzyme. VV has received consultancy fees, honoraria, research funding, and speaker's bureau from Bristol-Myers Squibb; and research funding and consultancy fees from Agios, Ionis Pharmaceuticals and La Jolla Pharmaceuticals. FT, RU, JM, and BM are employees of and shareholders in Agios. EJvanB is an advisory member for Agios; and has received research funding from Agios, Novartis, Pfizer and RR Mechatronics.

Contributions

HAS and EJvanB performed research, interpreted data, wrote, reviewed, and approved the paper. RFG, AG, OA, WB, FG, KHMK, DML, MM, and VV, all performed research, reviewed and approved the paper. FT analyzed data, reviewed and approved the paper. RU, JM, and BM interpreted data, reviewed and approved the paper.

Acknowledgments

The authors would like to thank the patients, their families, and all investigators involved in this study. Medical writing support, including assisting authors with the development of the outline and initial draft and incorporation of comments, was provided by Julie Gray, and editorial support, including figure preparation, formatting, proofreading, and submission, was provided by Thea Sheridon, both of Adelphi Communications Ltd, supported by Agios Pharmaceuticals, Inc. according to Good Publication Practice guidelines (https://www.acpjournals.org/doi/10.7326/M22-1460). The

Sponsor was involved in the study design, collection, analysis, and interpretation of data, as well as data checking of information provided in the manuscript. However, the authors assume ultimate responsibility for the opinions, conclusions, and data interpretation within the manuscript.

Funding
This study was funded by Agios Pharmaceuticals, Inc.

Data-sharing statement
Qualified researchers may request access to related clinical study documents. Please send your data-sharing requests to datasharing@agios.com. The following considerations will be taken into account as part of the review: ability for external researcher to re-identify trial participants such as those of small, rare disease trials or single-center trials; language used in data and requested documents (e.g., English or other); informed consent language with respect to allowance for data sharing; plan to re-evaluate safety or efficacy data summarized in the approved product labeling; potential conflict of interest or competitive risk (see http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html).

References

1. Kung C, Hixon J, Kosinski PA, et al. AG-348 enhances pyruvate kinase activity in red blood cells from patients with pyruvate kinase deficiency. Blood. 2017;130(11):1347-1356.
2. Bianchi P, Fermo E, Glader B, et al. Addressing the diagnostic gaps in pyruvate kinase deficiency: consensus recommendations on the diagnosis of pyruvate kinase deficiency. Am J Hematol. 2019;94(1):149-161.
3. Grace RF, Mark Layton D, Barcellini W. How we manage patients with pyruvate kinase deficiency. Br J Haematol. 2019;184(5):721-734.
4. Boscoe AN, Yan Y, Hedgeman E, et al. Comorbidities and complications in adults with pyruvate kinase deficiency. Eur J Haematol. 2021;106(4):484-492.
5. Al-Samkari H, Grace RF, Glenthøj A, et al. Early-onset reduced bone mineral density in patients with pyruvate kinase deficiency. Am J Hematol. 2023;98(3):e57-e60.
6. Basu S, Kumar A. Hair-on-end appearance in radiograph of skull and facial bones in a case of beta thalassaemia. Br J Haematol. 2009;144(6):807.
7. Rossi F, Perrotta S, Bellini G, et al. Iron overload causes osteoporosis in thalassemia major patients through interaction with transient receptor potential vanilloid type 1 (TRPV1) channels. Haematologica. 2014;99(12):1876-1884.
8. Pyrukynd. Prescribing information. Agios Pharmaceuticals Inc. 2022. Accessed November 21, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/216196s000lbl.pdf
9. Pyrukynd. Summary of product characteristics. Agios Pharmaceuticals Inc. 2022. Accessed November 21, 2022. https://www.agios.com/wp-content/uploads/2022/11/SmPC-EN.pdf
10. Al-Samkari H, Galacteros F, Glenthoj A, et al. Mitapivat versus placebo for pyruvate kinase deficiency. N Engl J Med. 2022;386(15):1432-1442.
11. Glenthøj A, Beers EJv, Al-Samkari H, et al. Mitapivat in adult patients with pyruvate kinase deficiency receiving regular transfusions (ACTIVATE-T): a multicentre, open-label, single-arm, phase 3 trial. Lancet Haematol. 2022;9(10):e724-e732.
12. Al-Samkari H, van Beers EJ. Mitapivat, a novel pyruvate kinase activator, for the treatment of hereditary hemolytic anemias. Ther Adv Hematol. 2021;12:1-11.
13. Grace RF, Rose C, Layton MD, et al. Safety and efficacy of mitapivat in pyruvate kinase deficiency. N Engl J Med. 2019;381(10):933-944.
14. Jeremiah MP, Unwin BK, Greenawald MH, et al. Diagnosis and management of osteoporosis. Am Fam Physician. 2015;92(4):261-268.
15. Lauretani F, Bandinelli S, Griswold ME, et al. Longitudinal changes in BMD and bone geometry in a population-based study. J Bone Miner Res. 2008;23(3):400-408.
16. Wong P, Fuller PJ, Gillespie MT, et al. Thalassemia bone disease: a 19-year longitudinal analysis. J Bone Miner Res. 2014;29(11):2468-2473.
17. Kuo KHM, Layton DM, Lal A, et al. Long-term efficacy and safety of the oral pyruvate kinase activator mitapivat in adults with non–transfusion-dependent alpha-or beta-thalassemia. Blood. 2021;138(Suppl 1):S576.