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CORRESPONDENCE

Clinically meaningful improvements in patient-reported outcomes in mitapivat-treated patients with pyruvate kinase deficiency

To the Editor:

Pyruvate kinase (PK) deficiency is a rare, hereditary hemolytic anemia caused by defects in the *PKLR* gene.[1] The disease is associated with acute and long-term complications, and clinical symptoms including jaundice, fatigue, and dyspnea,[1,2] resulting in a substantial disease burden and impact on health-related quality of life (HRQoL). Patients report both physical limitations, due to fatigue, that can restrict activities of daily living and lead to cognitive and emotional difficulties, and symptoms, such as jaundice, that can negatively affect self-esteem.[2] Currently used patient-reported outcome (PRO) instruments for assessing HRQoL are generic or cancer-specific and therefore insensitive to the unique complications of PK deficiency, for example, iron overload and jaundice, contributing to reduced HRQoL.[2] Development of reliable PK deficiency-specific PRO measures is therefore critically important to evaluate the impact of the disease and treatments on patients.

Two PK deficiency-specific PRO measures for adults have recently been developed and validated in a clinical trial setting. The Pyruvate Kinase Deficiency Diary (PKDD) is a daily instrument measuring the core signs and symptoms of PK deficiency, and the Pyruvate Kinase Deficiency Impact Assessment (PKDIA) is a weekly measure assessing impacts of PK deficiency on patients.[3]

Mitapivat, a first-in-class, oral activator of PK approved for adults with PK deficiency[4] has demonstrated improvements in anemia and transfusion burden in adults with PK deficiency in two phase 3 trials (ACTIVATE [NCT03548220] and ACTIVATE-T [NCT03559699]).[5,6] This study describes the impact of mitapivat on patient-reported symptoms and function, as measured by the PKDD and PKDIA in patients enrolled in these trials and the subsequent long-term extension (LTE; NCT03853798) study,[5,6] and assesses the proportion of patients who achieved the minimal clinically important change (MCIC) for these instruments.

The PKDD and PKDIA are two self-administered PK deficiency-specific instruments that capture and assess changes in symptom burden and disease impact (Figure S1). The responses to the PKDD and PKDIA each comprise a total score based on specific item measures. The range for total scores is 25–76 for PKDD and 30–76 for PKDIA,[3] with higher scores indicating higher disease burden.

The PKDD is a seven-item measure, designed as a daily diary to be completed in the evening, that assesses the core signs and symptoms of PK deficiency in adults, such as tiredness, jaundice, and shortness of breath. It has a 24 h recall period (constituting the same day as administration).[3] The PKDIA is a weekly, 12-item measure, of the daily life impact of PK deficiency (e.g., feeling bothered by appearance, as well as the impact on the ability to do household activities and on moderate physical activity), with a recall period constituting the past 7 days for all questions.[3] The psychometric validation of the PKDD and PKDIA[3] was conducted in ACTIVATE, and both instruments were assessed as valid, reliable, and responsive tools.

MCIC is defined as the minimal change that is clinically meaningful for patients. MCIC offers a standardized method for evaluating the effectiveness of a given treatment, and for describing patient satisfaction in reference to that treatment in clinical practice. MCIC thresholds were estimated with an anchor-based method (Patient Global Impression of Severity [PGIS] as the anchor) using data from ACTIVATE. MCIC was estimated to be a reduction of 4.2 and 5.5 in PKDD and PKDIA scores, respectively, from baseline, at Week 24 among patients achieving a 1-point improvement in PGIS.

Adults ≥18 years in ACTIVATE had not received regular red blood cell (RBC) transfusions (≤4 transfusion episodes in the previous year and no transfusions ≤3 months before randomization); adults in ACTIVATE-T received regular RBC transfusions (≥6 transfusions in the 52 weeks before enrollment). Patients in the ACTIVATE trial were randomized to mitapivat or placebo for 24 weeks, while all patients in the ACTIVATE-T trial received mitapivat for 40 weeks. Further study design details of ACTIVATE and ACTIVATE-T have been previously described.[5,6] Patients who completed the fixed-dose periods of ACTIVATE or ACTIVATE-T were eligible for inclusion in the LTE if they had demonstrated clinical benefit from mitapivat (as judged by investigators) or had received placebo in ACTIVATE. Patients enrolled in the LTE were assigned to one of the following cohorts: mitapivat-to-mitapivat (M/M), patients who received mitapivat in ACTIVATE and continued mitapivat in the LTE; placebo-to-mitapivat (P/M), patients who received placebo in ACTIVATE and started mitapivat in the LTE; mitapivat (M), patients from ACTIVATE-T who continued mitapivat in the LTE.

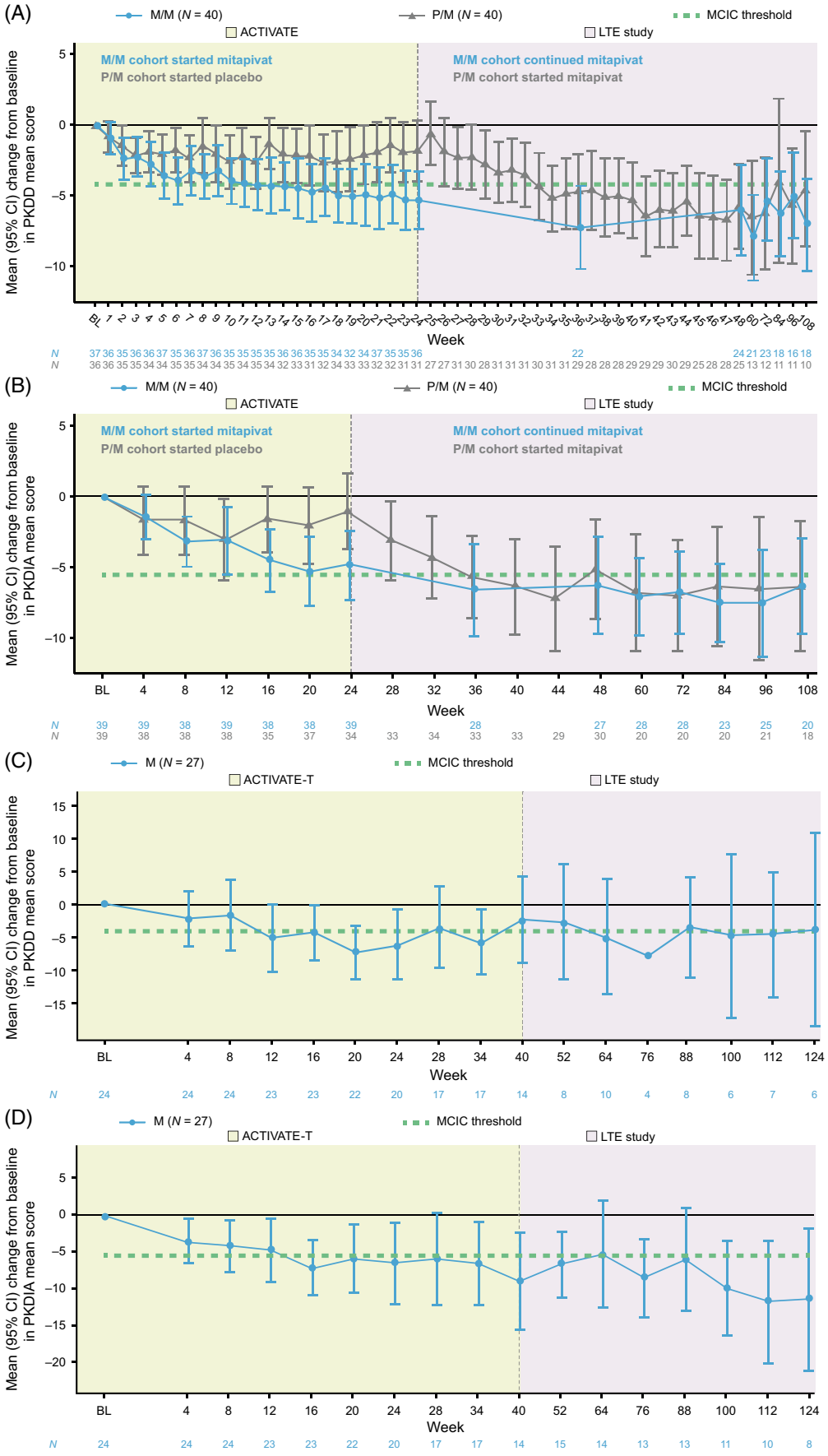

FIGURE 1 Legend on next page.

Changes from baseline in PKDD and PKDIA scores to the end of the core-study period for ACTIVATE (Week 24) and ACTIVATE-T (Week 40), and up to Week 84 of the LTE (data cutoff March 27, 2022) were summarized descriptively. The proportions of patients who achieved the MCIC at the end of the core-study periods of both trials, and at Week 84 of the LTE, were reported. A post hoc analysis was additionally conducted in the subset of patients in ACTIVATE who achieved the protocol-defined primary endpoint of hemoglobin (Hb) response at Week 24 (a ≥1.5 g/dL increase in Hb from baseline, sustained at ≥2 scheduled assessments at Weeks 16, 20, and 24).

Eighty patients were randomized 1:1 to receive mitapivat ($N = 40$) (5/20/50 mg twice daily) or placebo ($N = 40$) in ACTIVATE.[5] In ACTIVATE-T, 27 patients received mitapivat.[6] Patients in both studies had a high disease burden at baseline.[5,6] Further details on the patient baseline characteristics and study results from ACTIVATE and ACTIVATE-T are available in the primary publications.[5,6] Ninety patients from ACTIVATE and ACTIVATE-T enrolled in the LTE: 35 patients in the M/M cohort; 38 in the P/M cohort, and 17 in the M cohort.

In ACTIVATE, significant improvements in signs and symptoms (indicated by PKDD score) and disease impact (indicated by PKDIA score) over the core period were previously reported among patients who received mitapivat compared with placebo patients.[5,6] Throughout the LTE, sustained improvements in both PKDD and PKDIA mean scores were observed among M/M patients (Figure 1A,B). At Week 84 of the LTE, mean (±SD) change from baseline was −7.2 ± 6.7 in PKDD and −6.3 ± 7.1 in PKDIA scores (Table S1). Improvements were also observed among P/M patients after starting mitapivat in the LTE; such improvements were consistent with the initial improvements seen among patients treated with mitapivat in the core period (Figure 1A,B). At Week 84 of the LTE, mean (±SD) change from baseline was −4.0 ± 6.4 in PKDD and −5.3 ± 9.4 in PKDIA scores (Table S1). More than half of ACTIVATE patients receiving mitapivat (from the M/M and P/M cohorts) in the LTE had clinically meaningful improvements from baseline in both PKDD (57.1% achieved an MCIC) and PKDIA (55.3% achieved an MCIC) mean scores (Table S1).

The post hoc analysis included a subset of 16 ACTIVATE patients who achieved the protocol-defined primary endpoint at Week 24; all 16 patients were treated with mitapivat. The mean (±SD) reduction from baseline at Week 24 in PKDD was larger in this subset (−7.1 ± 7.0) than those in the overall mitapivat arm (−5.4 ± 6.0) and placebo arm (−1.9 ± 6.0). In addition, a larger proportion of patients in this subset (60.0%) achieved clinically meaningful improvements compared with the overall mitapivat arm (55.6%) and placebo arm (29.0%). For PKDIA, a larger mean (±SD) reduction (−8.1 ± 5.4 for the subset, −4.8 ± 7.3 for the mitapivat arm, and −1.1 ± 7.6 for the placebo arm) and a higher proportion of patients achieving clinically meaningful improvement (60.0%, 43.6%, and 26.5%, respectively) were also observed (Table S2). These improvements occurred early in treatment and were sustained throughout the core study period (Figure S2A,B).

In ACTIVATE-T, the improvements in PKDD and PKDIA mean scores observed over the core period were sustained over the LTE among patients who continued to receive mitapivat (M cohort; Figure 1C,D). At Week 84 of the LTE, mean (±SD) changes from baseline in PKDD and PKDIA scores were −3.9 ± 14.1 and −11.5 ± 11.5, respectively, and 50.0% and 75.0% of patients achieved an MCIC in PKDD and PKDIA scores, respectively (Table S1).

The PKDD and PKDIA are the first disease-specific PRO tools developed to evaluate the wide range of symptoms and impacts on daily living that patients with PK deficiency experience. Through evaluation of data from two phase 3 clinical trials and an LTE study, treatment with mitapivat showed durable and clinically meaningful impacts on patient HRQoL, irrespective of transfusion status. In addition to amelioration of chronic hemolytic anemia, mitapivat also showed improvements in disease symptoms such as jaundice, tiredness/fatigue, and shortness of breath (measured by the PKDD), and further contributed to patients' improved ability to participate in daily life activities (measured by the PKDIA).

Common symptoms of PK deficiency can negatively impact various aspects of patients' lives, such as their ability to perform physical and social activities, and activities of daily living, and their emotional and cognitive states.[2] Given the substantial disease burden of patients with PK deficiency, the development of the novel PKDD and PKDIA tools represents an important milestone in understanding how symptoms of PK deficiency affect patients' daily lives. These novel tools provide important insight into the impact of the disease on patient HRQoL and a greater appreciation of the challenges that patients with PK deficiency endure. Furthermore, the PK deficiency-specific PRO tools will enable measurement of patient-centered outcomes with treatment interventions in clinical trials.

FIGURE 1 Mean change from baseline in (A) PKDD mean score and (B) PKDIA mean score in patients with PK deficiency randomized to mitapivat or placebo in the ACTIVATE study who then continued in the LTE study receiving mitapivat. BL is defined as the last complete assessment (with no missing item in response) before randomization for subjects randomized and not dosed, or before start of study treatment for subjects randomized and dosed. In the LTE study, PKDD and PKDIA scores were assessed at 12-week intervals for the M/M cohort. Mean change from baseline in (C) PKDD mean score and (D) PKDIA mean score in patients with PK deficiency enrolled in the ACTIVATE-T study and receiving mitapivat who then continued mitapivat treatment in the LTE study. Baseline is defined as the last complete assessment (with no missing item in response) before start of study treatment. Not all patients included in ACTIVATE-T continued into the LTE study period, resulting in a small sample size for this analysis. Further, not all patients who entered the LTE were treated at Week 84 and beyond; of the patients who did receive treatment up to Week 84, data were unavailable for some individuals. BL, baseline; CI, confidence interval; LTE, long-term extension; M, mitapivat; MCIC, minimal clinically important change; M/M, mitapivat-to-mitapivat; PKDD, Pyruvate Kinase Deficiency Diary; PKDIA, Pyruvate Kinase Deficiency Impact Assessment, P/M, placebo-to-mitapivat.

The results highlight the importance for clinicians to consider the range of symptoms related to PK deficiency that can substantially impact patients' HRQoL (e.g., jaundice, fatigue, dyspnea). Our findings further emphasize the utility of assessing the various signs and symptoms that can negatively affect patients' overall wellbeing, which factor into decision-making in the therapeutic management of PK deficiency. We show that improvements with mitapivat ameliorate clinical symptoms of PK deficiency and provide clinically meaningful benefits to patients' daily HRQoL.

A limitation of this analysis was that, although the study population was large for this type of rare disease, there was a relatively small overall patient population assessed during the 84-week LTE. Another was because the PRO assessments were not always completed by each patient at every timepoint, the number of completed surveys was low at certain timepoints during the studies.

Treatment with mitapivat showed long-term, durable, and clinically meaningful improvements in signs, symptoms, and functional impacts of PK deficiency based on disease-specific PRO instruments, irrespective of transfusion status. Mitapivat may provide meaningful patient-centric benefits by improving these symptoms and life impacts.

AUTHOR CONTRIBUTIONS

Kevin H. M. Kuo, Rachael F. Grace, Eduard J. van Beers, Wilma Barcellini, Vanessa Beynon, Susan Morris, Parija Patel, Erin Zagadailov, and Hanny Al-Samkari performed research, interpreted data, wrote, reviewed, and approved the article. Junlong Li analyzed and interpreted data, wrote, reviewed, and approved the article. Andreas Glenthøj and Susanne Holzhauer interpreted data, reviewed and approved the article.

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CONFLICT OF INTEREST STATEMENT

Kevin H. M. Kuo has received consultancy fees from Agios, Alexion, Bristol Myers Squibb, Forma Therapeutics, NovoNordisk, Pfizer, Vertex Pharmaceuticals, membership of an entity's Board of Directors or advisory committees for Agios and Bioverativ/Sanofi/Sangamo, and research funding from Agios and Pfizer. Rachael F. Grace has received research funding from Agios, Novartis, and Sobi, and consultancy fees from Agios and Sanofi. Eduard J. van Beers is an advisory member for Agios, and has received research funding from Agios, Novartis, Pfizer, and RR Mechatronics. Wilma Barcellini has received honoraria from Agios, Alexion, and Novartis, has received research funding from Agios, and has a board membership or is on an advisory committee for Bioverativ and Incyte. Andreas Glenthøj has received consultancy fees 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, Novo Nordisk, Saniona, and Sanofi. Susanne Holzhauer, no relationships to disclose. Vanessa Beynon, Susan Morris, Junlong Li, and Parija Patel are employees of and shareholders in Agios. Erin Zagadailov was an employee and shareholder in Agios at the time of the study. Hanny Al-Samkari has received consultancy fees from Agios, Argenx, Forma, Moderna, Novartis, Pharmacosmos, Rigel, and Sobi, and research funding from Agios, Amgen, Novartis, Sobi, and Vaderis.

PATIENT CONSENT STATEMENT

All the patients who participated in the trials included in this study provided written informed consent.

DATA AVAILABILITY 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 considered as part of the review: (1) Ability for external researchers to re-identify trial participants such as small, rare disease trials or single-center trials. (2) Language used in data and requested documents (e.g., English or other). (3) Informed consent language with respect to allowance for data sharing. (4) Plan to re-evaluate safety or efficacy data summarized in the approved product labeling. (5) Potential conflict of interest or competitive risk.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.