Mitapivat treatment reduces levels of interference in work/school activity for adult patients with pyruvate kinase deficiency

Jennifer A Rothman, MD[1], Parija Patel, PharmD, MBA[2], Jing Zhao, PhD[2], Susan Morris, PhD[2], Junlong Li, PhD[2], Hanny Al-Samkari, MD[3]

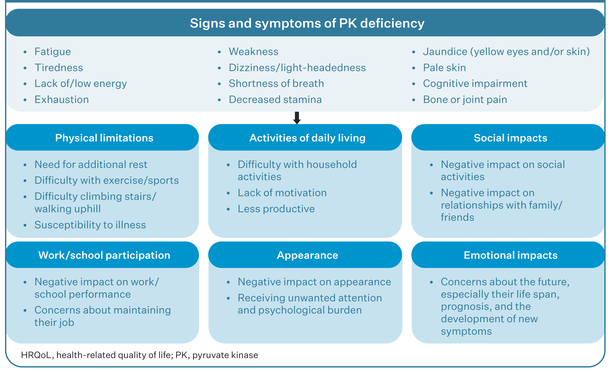
[1]Duke University Medical Center, Durham, NC, USA; [2]Agios Pharmaceuticals, Inc., Cambridge, MA, USA; [3]Division of Hematology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

2365

BACKGROUND

- Pyruvate kinase (PK) deficiency is a rare, hereditary disease resulting in chronic hemolytic anemia[1–4]
- It is associated with a range of acute and long-term complications, as well as a spectrum of disease signs and symptoms including jaundice, fatigue, and dyspnea that have a profound, wide-ranging impact on health-related quality of life (HRQoL)[5,6]
- Patients with PK deficiency report daily social and physical limitations that negatively affect various aspects of their lives (**Figure 1**)[6,7]
- While rare diseases in general have been shown to negatively impact work and school participation, this topic has not been elucidated and is under-recognized specifically in PK deficiency[8,9]
- Understanding the disease impact on work or school interference is paramount to increasing knowledge of the factors that negatively contribute to HRQoL and the health economic outcomes for patients with rare diseases such as PK deficiency

Figure 1. Burden and impact of PK deficiency on HRQoL[6,7]



HRQoL, health-related quality of life; PK, pyruvate kinase

- Mitapivat is a first-in-class, oral, allosteric activator of PK, approved by the United States Food and Drug Administration for the treatment of hemolytic anemia in adults with PK deficiency,[10] and in the European Union by the European Medicines Agency[11] and the Medicines and Healthcare products Regulatory Agency in Great Britain[12] for the treatment of PK deficiency in adults (**Supplemental Figure 1 [via QR code]**)
- Sustained and clinically meaningful improvements in the disease impact of PK deficiency were observed in adult patients who were not receiving regular transfusions in the pivotal ACTIVATE trial (NCT03548220) and its long-term extension (LTE) study (NCT03853798)[13,14]
  - Impact of PK deficiency was measured by 2 disease-specific patient-reported outcome instruments: PK Deficiency Impact Assessment (PKDIA) and PK Deficiency Diary (PKDD)

OBJECTIVE

- **To describe the impact of PK deficiency on work or school performance, and evaluate the effect of mitapivat treatment vs placebo (PBO) over time, in adult patients from the ACTIVATE/LTE studies**

METHODS

Study design

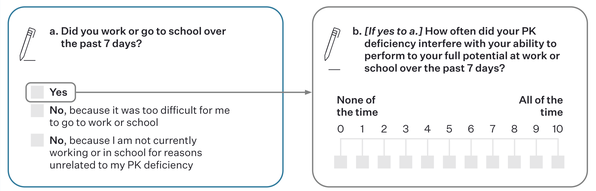
- ACTIVATE was a global, phase 3, double-blind, placebo-controlled study of mitapivat in adults with PK deficiency who were not receiving regular transfusions in the previous year[a,14]
- Patients who had demonstrated clinical benefit from mitapivat upon completion of ACTIVATE (24 weeks), or who were assigned to the PBO arm in ACTIVATE, were eligible to continue to the LTE where all patients received mitapivat (**Supplemental Figure 2 [via QR code]**)[14]
  - Patients from ACTIVATE who continued to the LTE were categorized into the mitapivat-to-mitapivat (M/M) cohort or the placebo-to-mitapivat (P/M) cohort
- This post hoc analysis used data from ACTIVATE and its LTE study

[a]Patients with PK deficiency who were not receiving regular transfusions were defined as having had no more than 4 transfusion episodes in the 12-month period up to the first day of study treatment and no transfusions in the 3 months prior to the first day of study treatment

Data collection

- As part of the PKDIA questionnaire, patients were asked at scheduled visits if they had attended work/school over the prior 7 days; patients who answered '*Yes*' were then asked to rate how often their PK deficiency interfered with their ability to perform to their full potential at work or school (**Figure 2**)
  - Scheduled visits: baseline (BL), Weeks 4, 8, 12, 16, 20, and 24 during ACTIVATE, and up to Week 60 of the LTE (Week 84 overall)
  - Patient rating was presented as work/school interference score ranging from 0 (none of the time) to 10 (all of the time); a higher score indicates a greater disease burden

Figure 2. Work/school interference item of the PKDIA



PK, pyruvate kinase; PKDIA, PK Deficiency Impact Assessment

Statistical analyses

- The work/school interference score and the corresponding change from BL over time were summarized descriptively by treatment arm in ACTIVATE and up to Week 60 of the LTE study (84 weeks overall)
  - BL was defined as the last complete assessment before start of study treatment in ACTIVATE
- A meaningful change analysis was performed to aid the interpretation of the score change
  - A distribution-based method was implemented, where the meaningful change threshold was estimated as half the SD of the BL interference score among all patients[15]

RESULTS

ACTIVATE population

- 80 adult patients with PK deficiency who were not receiving regular transfusions in the previous year[a] were included in this analysis (mitapivat arm N=40; PBO arm N=40)
  - Demographic and BL characteristics for these patients were similar between the mitapivat and PBO arms (**Table 1**)

[a]Patients with PK deficiency who were not receiving regular transfusions were defined as having had no more than 4 transfusion episodes in the 12-month period up to the first day of study treatment and no transfusions in the 3 months prior to the first day of study treatment

Table 1. BL patient demographics and characteristics

	Mitapivat arm N=40	PBO arm N=40	Total N=80
Age (years), mean (SD)	36.0 (15.18)	37.2 (15.92)	36.6 (15.47)
Sex, n (%)			
Male	16 (40.0)	16 (40.0)	32 (40.0)
Female	24 (60.0)	24 (60.0)	48 (60.0)
Baseline Hb (g/dL)			
n	40	40	80
Mean (SD)	8.6 (0.99)	8.5 (0.85)	8.6 (0.92)
Indirect bilirubin (µmol/L)			
n	37	39	76
Mean (SD)	81.8 (61.32)	89.1 (61.79)	85.6 (61.26)
Baseline ferritin (µg/L)			
n	39	38	77
Mean (SD)	747.9 (1116.18)	688.0 (605.25)	718.3 (895.64)
Prior transfusions, n (%)			
0	29 (72.5)	30 (75.0)	59 (73.8)
1	8 (20.0)	7 (17.5)	15 (18.8)
2	0	1 (2.5)	1 (1.3)
3	3 (7.5)	1 (2.5)	4 (5.0)
≥4	0	1 (2.5)	1 (1.3)

BL, baseline; Hb, hemoglobin; PBO, placebo

Work/school attendance at BL

- At BL, 54 (67.5%) patients with PK deficiency attended work/school over the past 7 days; 28 patients were randomized to mitapivat and 26 patients to PBO (**Table 2**)

Table 2. Work/school attendance at BL

BL	Mitapivat arm N=40	PBO arm N=40	Total N=80
Patients with PK deficiency who attended work/school in the past 7 days, n (%)	28 (70.0)	26 (65.0)	54 (67.5)
Patients who found it too difficult to attend work/school due to their PK deficiency, n (%)	0	3 (7.5)	3 (3.8)
Patients not attending work/school for reasons unrelated to PK deficiency, n (%)	11 (27.5)	10 (25.0)	21 (26.3)
Missing, n (%)	1 (2.5)	1 (2.5)	2 (2.5)

BL, baseline; PBO, placebo; PK, pyruvate kinase

Work/school interference in ACTIVATE

- Mean (SD) work/school interference scores for the 54 patients at BL were similar for the mitapivat (4.2 [2.42]) and PBO (3.9 [2.61]) arms (**Table 3**)
- Among the 54 patients with BL work/school interference scores, 33 had a score at Week 24, whereas, 2 found it too difficult to attend at Week 24, 17 did not attend at Week 24 for reasons unrelated to their PK deficiency, and data were unavailable for 2 patients
- In the 33 patients who attended work/school at both BL and Week 24 (**Table 3**):
  - A reduction in work/school interference score was observed in mitapivat-treated patients
    - Mean (SD) change from BL to Week 24: −1.5 (1.74)
  - Marginal worsening was observed among patients receiving PBO
    - Mean (SD) change from BL to Week 24: 0.1 (2.41)
- Meaningful reductions in work/school interference score at Week 24 were observed in mitapivat-treated patients
  - Mean (95% CI) difference in change from BL at Week 24 between mitapivat and PBO arms was −1.6 (−0.1, −3.1), while the estimated meaningful reduction threshold was −1.2

Table 3. Work/school interference scores in ACTIVATE

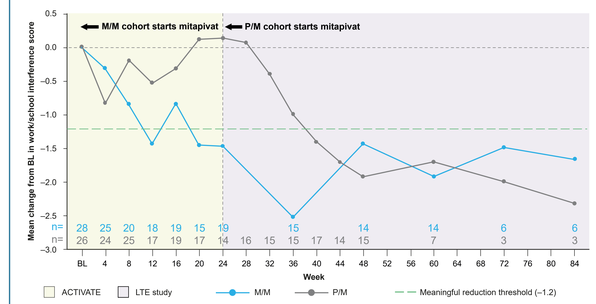
Work/school interference score (among patients with PK deficiency who attended work/school)[a]	Mitapivat arm N=40	PBO arm N=40
BL		
n	28	26
Mean (SD)	4.2 (2.42)	3.9 (2.61)
Min, max	[0, 8]	[0, 8]
Week 24		
n	22	15
Mean (SD)	2.5 (2.28)	3.8 (3.10)
Min, max	[0, 7]	[0, 10]
Change in work/school interference score from BL at Week 24[b]		
n	19	14
Mean (SD)	−1.5 (1.74)	0.1 (2.41)
Min, max	[−4.0, 2.0]	[−5.0, 5.0]

[a]Work/school interference score: patients who worked or went to school over the 7 days prior to a scheduled visit were asked to rate how often their PK deficiency interfered with their ability to perform to their full potential at work or school, using an 11-point numeric rating scale (work/school interference score; ranging from 0 [none of the time] to 10 [all of the time]); [b]This analysis includes patients who worked or attended school at both BL and Week 24; BL, baseline; PBO, placebo; PK, pyruvate kinase

Work/school interference in the LTE study

- Sustained improvements in the work/school interference score among patients in the M/M cohort were observed up to Week 60 of the LTE (84 weeks overall) (**Figure 3**)
  - Mean change from BL to Week 84 in the M/M cohort: −1.7
- Furthermore, a reduction in the work/school interference score was observed in patients in the P/M cohort after starting mitapivat treatment in the LTE period, consistent with the improvements seen in mitapivat-treated patients during ACTIVATE (**Figure 3**)
  - Mean change from BL to Week 84 in the P/M cohort: −2.3

Figure 3. Change from BL[a] in work/school interference score[b] in ACTIVATE and the LTE study



[a]BL is defined as the last complete assessment before start of study treatment in ACTIVATE; [b]Work/school interference score: patients who worked or went to school over the 7 days prior to a scheduled visit were asked to rate how often their PK deficiency interfered with their ability to perform to their full potential at work or school, using an 11-point numeric rating scale (work/school interference score; ranging from 0 [none of the time] to 10 [all of the time]). This analysis includes only patients who worked or attended school at BL, and who had available data for comparison through Week 84; BL, baseline; LTE, long-term extension; M/M, mitapivat-to-mitapivat; PK, pyruvate kinase; P/M, placebo-to-mitapivat

LIMITATIONS

- This is a single-item, post hoc analysis conducted within the sub sample of patients who participated in work or school
- The work/school interference item lacked the ability to provide the reasoning for those patients specifically selecting '*No, because I am not currently working or in school for reasons unrelated to my PK deficiency*' as part of the PKDIA questionnaire, making it difficult to extrapolate the multiple factors contributing to patients' inability to attend work/school; events, such as the COVID-19 pandemic, or other potential complications of the disease assessed as unrelated by the patient may have interfered with their ability to attend work/school

CONCLUSIONS

- **Interference in work or school performance was observed at BL in adult patients with PK deficiency**
- **In this post hoc analysis, sustained and meaningful improvements in work or school performance over time were observed among mitapivat-treated patients who attended work/school in ACTIVATE**

These data continue to support the potential for mitapivat to provide long-term benefits and reduced interference in work or school performance in adult patients with PK deficiency

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