Long-term hemoglobin response and reduction in transfusion burden are maintained in patients with pyruvate kinase deficiency treated with mitapivat

Rachael F Grace, MD,[1] Andreas Glenthøj, MD,[2] Wilma Barcellini, MD,[3] Madeleine Verhovsek, MD,[4] Jennifer A Rothman, MD,[5] Marta Morado Arias, MD,[6] D Mark Layton, MB, BS,[7] Oliver Andres, MD,[8] Frédéric Galactéros, MD, PhD,[9] Eduard J van Beers, MD,[10] Koichi Onodera, MD,[11] Vip Viprakasit, MD, PhD,[12] Satheesh Chonat, MD,[13] Malia P Judge, BS,[14] Penelope A Kosinski, MS,[14] Peter Hawkins, PhD,[14] Sarah Gheuens, MD, PhD,[14] Emily Xu, PhD,[14] Bryan McGee, PharmD,[14] Vanessa Beynon, MD,[14] Hanny Al-Samkari, MD[15]

[1]Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA, USA; [2]Department of Haematology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; [3]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [4]McMaster University, Hamilton, ON, Canada; [5]Duke University Medical Center, Durham, NC, USA; [6]Hematology Department, Hospital Universitario La Paz, Madrid, Spain; [7]Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK; [8]Department of Paediatrics, University of Würzburg, Germany; [9]Unité des Maladies Génétiques du Globule Rouge, CHU Henri Mondor, Creteil, France; [10]Benign Hematology Center, Van Creveldkliniek, University Medical Center Utrecht, University of Utrecht, Utrecht, The Netherlands; [11]Tohoku University Hospital, Sendai, Japan; [12]Siriraj Hospital, Mahidol University, Bangkok, Thailand; [13]Aflac Cancer and Blood Disorders Center, Children's Healthcare of Atlanta and Department of Pediatrics, Emory University, Atlanta, GA, USA; [14]Agios Pharmaceuticals, Inc., Cambridge, MA, USA; [15]Division of Hematology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

BACKGROUND

- Pyruvate kinase (PK) deficiency is a rare, lifelong, hereditary hemolytic anemia caused by mutations in the *PKLR* gene, encoding the red blood cell (RBC)-specific form of PK (PKR)[1,2]
- Defects in PKR lead to chronic hemolysis and anemia, which are associated with serious complications, regardless of transfusion status, including iron overload, pulmonary hypertension, and osteoporosis[3–6]
- The disease also negatively impacts patient health-related quality of life[5]
- Until recently, there were no disease-modifying pharmacotherapies approved for PK deficiency; available supportive therapies are associated with short- and long-term complications[7]
- Mitapivat (AG-348) is a first-in-class, oral, allosteric activator of PKR that is approved by the US Food and Drug Administration for the treatment of hemolytic anemia in adults with PK deficiency[8–10]
- Mitapivat demonstrated significant improvements in hemoglobin (Hb) in adult patients who were not regularly transfused (ACTIVATE, NCT03548220)[11] and a significant reduction in transfusion burden in adult patients with PK deficiency who were regularly transfused (ACTIVATE-T, NCT03559699)[12]
- Mitapivat was well tolerated, and the safety profile was generally consistent across all reported studies (**Supplemental tables 1–3** [QR code])[11–14]

OBJECTIVE

- **To assess the long-term effects of mitapivat on Hb response and transfusion burden reduction in patients with PK deficiency in ACTIVATE, ACTIVATE-T, and their long-term extension (LTE) study**

METHODS

Study designs for ACTIVATE, ACTIVATE-T, and the LTE study

- ACTIVATE was a phase 3, global, double-blind, placebo-controlled study of mitapivat in adult patients with PK deficiency who were not regularly transfused[11]
- ACTIVATE-T was a phase 3, global, open-label, single-arm study of mitapivat in adult patients with PK deficiency who were regularly transfused[12]
- Patients who completed either trial were eligible to continue in the LTE where all patients received mitapivat treatment (**Figure 1**)

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

Key eligibility criteria:

- ≥18 years of age
- Documented ≥2 mutant alleles in *PKLR* with ≥1 missense mutation (excluding patients homozygous for R479H mutation or that have 2 non-missense mutations, without another missense mutation)
- **ACTIVATE:** Not regularly transfused (≤4 transfusion episodes in the previous year); BL Hb ≤10 g/dL
- **ACTIVATE-T:** Regularly transfused (≥6 transfusion episodes in the previous year)
- **LTE study:** Completed the fixed-dose period of ACTIVATE or ACTIVATE-T and demonstrated clinical benefit from mitapivat treatment or were assigned to the placebo arm in ACTIVATE and elected to continue to the LTE study

[a]Stratified by average of screening Hb values (<8.5 g/dL vs ≥8.5 g/dL) and *PKLR* gene mutation category (missense/missense vs missense/non-missense); [b]Screening may have been extended beyond 8 weeks if there was a delay in obtaining a patient's complete transfusion history or to ensure that the first dose of study drug could be administered 2–7 days after the most recent transfusion; ClinicalTrials.gov: ACTIVATE (NCT03548220); ACTIVATE-T (NCT03559699); LTE study (NCT03853798); BID, twice daily; BL, baseline; Hb, hemoglobin; LTE, long-term extension; M/M, mitapivat-to-mitapivat; P/M, placebo-to-mitapivat; R, randomized

Endpoints and analyses

- The **ACTIVATE/LTE** study analysis assessed:
  - Duration of Hb response (defined as the time from the date a patient first achieved an increase in Hb ≥1.5 g/dL from baseline [BL] to the date of the last Hb assessment where the next Hb assessment had change from BL <1.5 g/dL) in 2 cohorts
    - **Mitapivat-to-mitapivat (M/M) arm**: patients who received mitapivat and achieved a Hb response in ACTIVATE (defined as a ≥1.5 g/dL increase in Hb from BL sustained at ≥2 scheduled assessments at Weeks 16, 20, and 24 in ACTIVATE) and maintained it in the LTE study
    - **Placebo-to-mitapivat (P/M) arm**: patients who received placebo in ACTIVATE and switched to mitapivat in the LTE study and then achieved a Hb response (defined as a ≥1.5 g/dL increase in Hb from BL sustained at ≥2 scheduled assessments at Weeks 16, 20, and 24 in the LTE) and maintained in the LTE study
- The **ACTIVATE-T/LTE** study analysis assessed:
  - Duration of transfusion reduction response (TRR) among patients in ACTIVATE-T who achieved ≥33% reduction in number of RBC units transfused during the fixed-dose period in ACTIVATE-T, compared with the patient's individual historic transfusion burden standardized to 24 weeks
    - Duration of TRR is the time from the start of the fixed-dose period in ACTIVATE-T to the day before a transfusion in the LTE study where the transfusion burden reduction becomes <33%
  - Transfusion-free duration among patients in ACTIVATE-T who achieved transfusion-free status
    - Defined as a period of no transfusions received during ACTIVATE-T and the LTE study

RESULTS

Patient disposition in ACTIVATE, ACTIVATE-T, and the LTE study

- 80 patients were randomized in ACTIVATE (mitapivat N=40; placebo N=40); as of 27March2022, 35/40 patients continued from ACTIVATE to the LTE in the M/M arm and 38/40 patients continued to the LTE in the P/M arm (**Figure 2a**)
- 27 patients were treated with mitapivat in ACTIVATE-T; as of 27March2022, 17 patients continued from ACTIVATE-T to the LTE on mitapivat (**Figure 2b**)

Figure 2a. Patient disposition in ACTIVATE and the LTE study

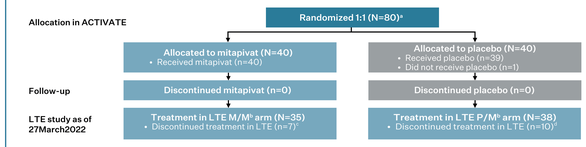


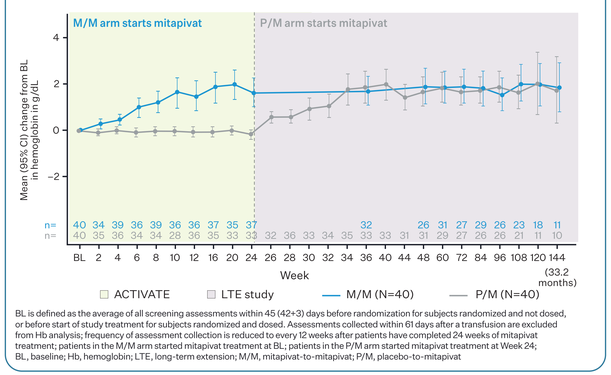
Figure 2b. Patient disposition in ACTIVATE-T and the LTE study

[a]Disposition for end of randomization reflects the disposition after randomization but before the start of study treatment; [b]LTE study is ongoing; 0 patients have completed treatment; [c]Reasons for discontinuation, withdrawal n=4, adverse event n=1, accidental death unrelated to treatment n=1, other n=1; [d]Reasons for discontinuation, withdrawal n=5, lack of efficacy n=2, physician decision n=1, adverse event n=1, other n=1; [e]Reasons for discontinuation, withdrawal n=3, lack of efficacy n=1, physician decision n=1, other n=1; LTE, long-term extension; M/M, mitapivat-to-mitapivat; P/M, placebo-to-mitapivat

Improvements in Hb concentrations with long-term mitapivat treatment in ACTIVATE and the LTE study

- An early increase in the mean Hb concentration from BL was observed in the M/M arm, with similar early improvements seen in the P/M arm following the switch to mitapivat in the LTE (**Figure 3**)
  - These improvements were sustained with continued treatment up to 33.2 months

Figure 3. Change from BL in Hb over time in patients randomized to mitapivat or placebo in ACTIVATE and continued in the LTE on mitapivat



BL is defined as the average of all screening assessments within 45 (42×3) days before randomization for subjects randomized and not dosed, or before start of study treatment for subjects randomized and dosed. Assessments collected within 61 days after a transfusion are excluded from Hb analysis; frequency of assessment collection is reduced to every 12 weeks after patients have completed 24 weeks of mitapivat treatment; patients in the M/M arm started mitapivat treatment at BL; patients in the P/M arm started mitapivat treatment at Week 24; BL, baseline; Hb, hemoglobin; LTE, long-term extension; M/M, mitapivat-to-mitapivat; P/M, placebo-to-mitapivat

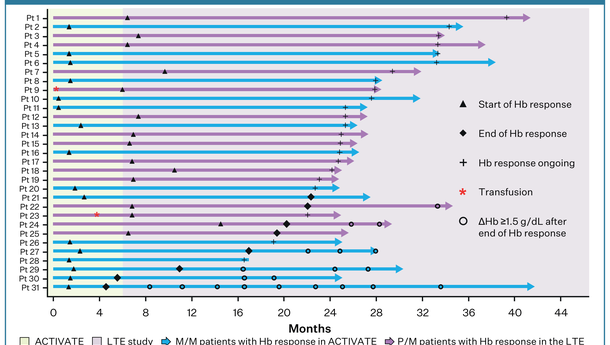
Greater Hb response rates in patients treated with mitapivat vs placebo in ACTIVATE and the LTE study

- In ACTIVATE, 40% (16/40) of patients treated with mitapivat achieved a Hb response by 24 weeks[11]
- None of the patients assigned to placebo in ACTIVATE (N=40) achieved a Hb response during ACTIVATE; in the LTE, 39.5% (15/38) of patients randomized to placebo in ACTIVATE showed a Hb response by 24 weeks after switching to mitapivat

Hb response was sustained with long-term mitapivat treatment in ACTIVATE and the LTE study

- As of 27March2022, the median duration of Hb response among the 31 Hb responders from ACTIVATE and the LTE study was 18.3 months, with responses ongoing up to 32.9 months (**Figure 4**)
- 8 patients from ACTIVATE and the LTE study fell below the 1.5 g/dL response threshold; however, 6/8 returned to a change from BL ≥1.5 g/dL, showing continued benefit from mitapivat treatment (**Figure 4**)

Figure 4. Duration of Hb response among all patients who achieved a Hb response in ACTIVATE and the LTE study

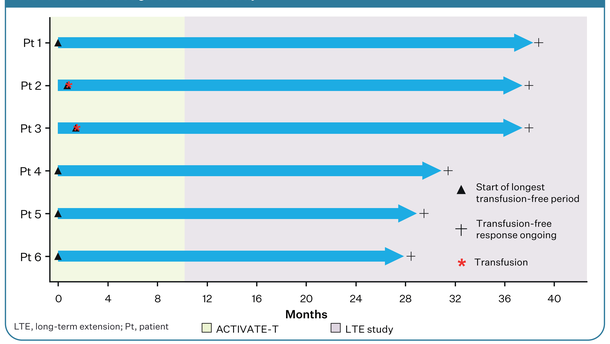


Hb response is defined as post-BL change from BL in Hb ≥15 g/L (1.5 g/dL) that is sustained at 2 or more assessments at Weeks 16, 20, and 24 in the fixed-dose period, excluding those within 61 days after a transfusion. Duration of Hb response was defined as the time from the date a patient first achieved an increase in Hb ≥1.5 g/dL from BL to the date of the last Hb assessment where the next Hb assessment had change from BL <1.5 g/dL; BL, baseline; Hb, hemoglobin; LTE, long-term extension; M/M, mitapivat-to-mitapivat; P/M, placebo-to-mitapivat; Pt, patient

Transfusion reduction and transfusion-free status of patients from ACTIVATE-T were maintained in the LTE study

- In ACTIVATE-T, 37% (10/27) of patients achieved a TRR and 22% (6 patients) achieved transfusion-free status[12]
- Among the 10 patients who achieved a TRR in ACTIVATE-T, the response was maintained in the LTE up to 37.1 months
- All 6 patients who achieved transfusion-free status in ACTIVATE-T maintained the status in the LTE up to 38.3 months (**Figure 5**)
  - The median duration of transfusion-free status was 33.4 months
  - 1 additional patient achieved TRR, but was not transfusion-free in ACTIVATE-T, and did not receive any transfusions in the LTE

Figure 5. Duration of transfusion-free response among transfusion-free patients from ACTIVATE-T through to the LTE study



LTE, long-term extension; Pt, patient

Long-term safety data

- As of 27March2022, mitapivat showed a consistent safety profile over the long-term duration of treatment (**Table 1**)
- No new safety findings were observed in subjects (N=90) treated in the LTE study
- The most common treatment-emergent adverse events (TEAEs) were headache (26 patients [28.9%]) and pyrexia (17 patients [18.9%])
- The majority of TEAEs were grade 1 or 2 in severity
- Two grade ≥3 treatment-related TEAEs were reported
  - ACTIVATE/LTE M/M arm: arthralgia (n=1)
  - ACTIVATE/LTE P/M arm: gastroenteritis (n=1)

Table 1. Summary of TEAEs in the LTE study

	ACTIVATE/LTE		ACTIVATE-T/ LTE	Total
	M/M (N=35) n (%)	P/M (N=38) n (%)	(N=17) n (%)	(N=90) n (%)
Any TEAEs	29 (82.9)	37 (97.4)	14 (82.4)	80 (88.9)
Grade ≥3 TEAEs	8 (22.9)	13 (34.2)	1 (5.9)	22 (24.4)
Treatment-related TEAEs	14 (40.0)	21 (55.3)	2 (11.8)	37 (41.1)
Grade ≥3 treatment-related TEAEs	1 (2.9)	1 (2.6)	0	2 (2.2)
Serious TEAEs	5 (14.3)	9 (23.7)	1 (5.9)	15 (16.7)
Serious treatment-related TEAEs	0	2 (5.3)	0	2 (2.2)
TEAEs leading to discontinuation of study drug	1 (2.9)	1 (2.6)	0	2 (2.2)
TEAEs leading to dose reduction of study drug	2 (5.7)	2 (5.3)	0	4 (4.4)
TEAEs leading to interruption of study drug	2 (5.7)	2 (5.3)	0	4 (4.4)
TEAEs leading to death[a]	1 (2.9)	0	0	1 (1.1)
Treatment-related TEAEs leading to death	0	0	0	0

[a]Accidental death, unrelated to treatment; LTE, long-term extension; M/M, mitapivat-to-mitapivat; P/M, placebo-to-mitapivat; TEAE, treatment-emergent adverse event

CONCLUSIONS

- **In patients with PK deficiency, treatment with mitapivat continues to show long-term and durable improvements in Hb and reduction in transfusion burden over several years**
- **Extended treatment duration in the LTE study shows no new safety findings and is consistent with previous studies**

These data continue to support the long-term use of mitapivat as the first disease-modifying drug therapy approved for adults with PK deficiency and its clear potential for real-word benefits in these patients

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