Mitapivat improves iron overload in patients with pyruvate kinase deficiency who are regularly transfused

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BACKGROUND

- Pyruvate kinase (PK) deficiency is a rare, hereditary disease resulting in chronic hemolytic anemia and serious complications, including iron overload[1–4]
- Iron overload can lead to further comorbidities including liver cirrhosis, cardiomyopathy, arrhythmia, sudden cardiac death, and endocrine dysfunction[5,6]
- Iron overload is highly prevalent in patients with PK deficiency regardless of transfusion status[3,4,7]
- Regular transfusions further add to the burden of iron overload, negatively impacting patients' quality of life and healthcare costs[8–11]
- Assessment of liver iron concentration (LIC) by magnetic resonance imaging (MRI) is considered the gold standard method to quantify the total iron burden[4,12–14]
  - LIC values >5 mg Fe/g dry weight (dw) have been independently associated with increased risk of morbidities in patients with non–transfusion-dependent thalassemia[6,15]
- 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,[16] and by the European Union European Medicines Agency[17] and the Medicines and Healthcare products Regulatory Agency in Great Britain[18] for the treatment of PK deficiency in adults
- Previously reported data from ACTIVATE (NCT03548220),[19] ACTIVATE-T (NCT03559699),[8] and their long-term extension (LTE; NCT03853798) showed that long-term treatment with mitapivat improved markers of iron overload in adults with PK deficiency regardless of transfusion status[20,21]

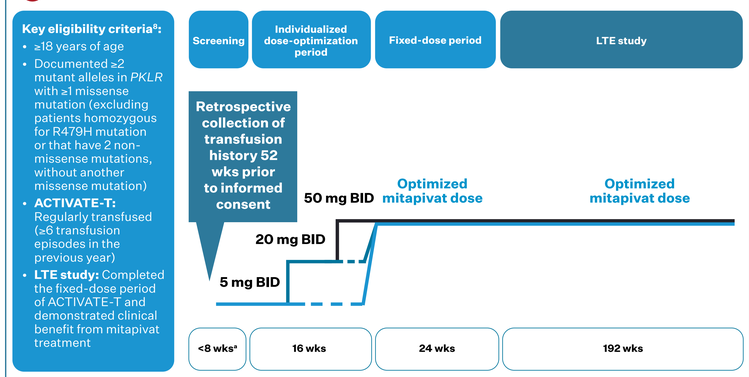
OBJECTIVE

- **To present longer-term data from ACTIVATE-T and its LTE on the impact of mitapivat treatment on iron overload, in patients with PK deficiency who were regularly transfused and classified as achieving a transfusion-reduction response (TRR) and transfusion-free status in ACTIVATE-T**

METHODS

- ACTIVATE-T was a phase 3, global, single-arm study of mitapivat in adult patients with PK deficiency who were regularly transfused (≥6 episodes in the previous year)[8]
- Patients who demonstrated a clinical benefit from mitapivat in the fixed-dose period of ACTIVATE-T, in the opinion of the investigator, were eligible to continue in the LTE **(Figure 1)**[8]
- Patients who achieved a TRR were defined as having a ≥33% reduction in red blood cell (RBC) units transfused during the fixed-dose period of ACTIVATE-T vs historical control
  - The subset of patients who achieved transfusion-free status were defined as those who were transfusion-free in the fixed-dose period of ACTIVATE-T

Figure 1. ACTIVATE-T/LTE trial design



[a]Screening may have been extended beyond 8 wks 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-T (NCT03559699); BID, twice daily; LTE, long-term extension; wks, weeks

Analyses

- Change from baseline (BL) in LIC by MRI was evaluated up to Week 136
  - BL was defined as the last assessment before start of treatment
- Changes in chelation therapy in the subset of patients who achieved transfusion-free status were also assessed up to Week 136
- Data are reported as of 27Mar2022

RESULTS

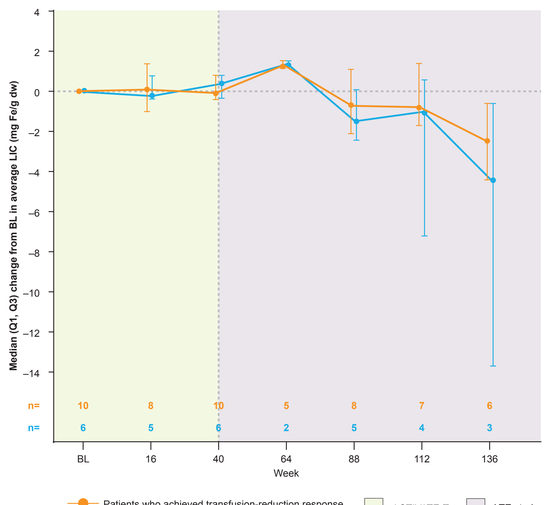
ACTIVATE-T/LTE population

- BL characteristics for patients in ACTIVATE-T/LTE have previously been reported[8]
- In ACTIVATE-T, 37% (10/27) of patients achieved a TRR, of which 6 patients achieved transfusion-free status[8]

Changes in LIC by MRI in patients who achieved a TRR and transfusion-free status

- Clinically meaningful improvements in LIC were observed in these patients up to Week 136 **(Figure 2)**
- Patients who achieved a TRR (n=10)
  - Median (Q1, Q3) LIC decrease from BL to Week 136 of mitapivat treatment was −2.5 (−4.4, −0.6) mg Fe/g dw
- Subset of TRR patients who achieved transfusion-free status (n=6)
  - Median (Q1, Q3) LIC decrease from BL to Week 136 of mitapivat treatment was −4.4 (−13.7, −0.6) mg Fe/g dw
- 4 patients who achieved a TRR had BL LIC ≥5 mg Fe/g dw; between Weeks 112 and 136, 3 of these patients had decreases to <5 mg Fe/g dw after treatment with mitapivat
  - 2 of the 4 patients who achieved a TRR and had BL LIC ≥5 mg Fe/g dw also achieved transfusion-free status; both (2/2) of these patients had decreases to <5 mg Fe/g dw after treatment with mitapivat between Weeks 112 and 136

Figure 2. Changes in LIC from BL[a] in patients treated with mitapivat who achieved a TRR[b] and transfusion-free status[c] in ACTIVATE-T and the LTE study

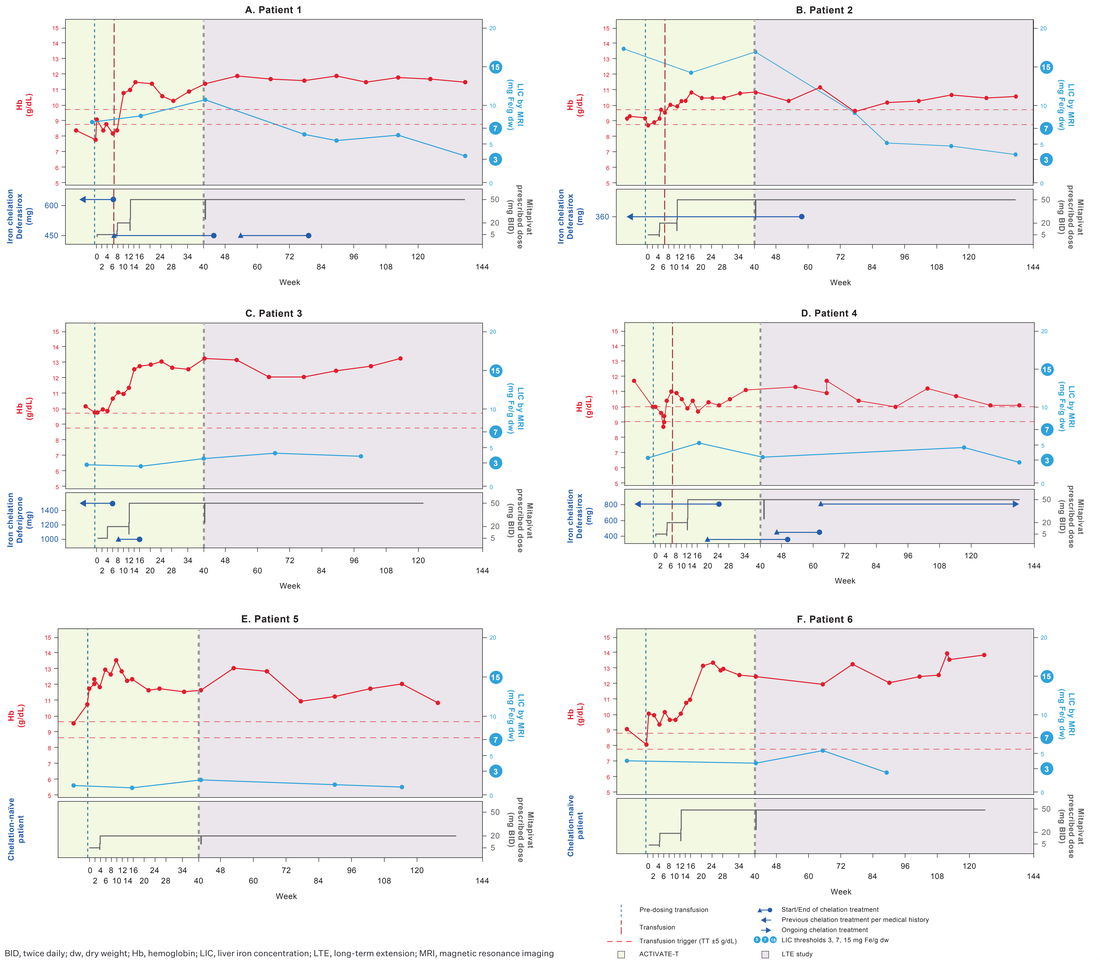


[a]BL is defined as the last assessment before start of study treatment; [b]Patients who achieved a TRR: patients who had ≥33% reduction in the number of RBC units transfused during the fixed-dose period standardized to 24 weeks compared with the historical number of RBC units transfused standardized to 24 weeks; [c]Patients who achieved transfusion-free status: patients who were transfusion-free in the fixed-dose period; BL, baseline; dw, dry weight; LIC, liver iron concentration; LTE, long-term extension; Q, quartile; RBC, red blood cell; TRR, transfusion-reduction response

Changes in chelation therapy in patients who achieved transfusion-free status

- 6 patients achieved transfusion-free status in ACTIVATE-T
  - 4 patients were receiving iron chelation at the start of mitapivat treatment **(Figure 3; A–D)**
    - Of these 4 patients, 3 discontinued chelation and 1 remained at a stable dose without increase
    - In 2 of the 3 patients who discontinued chelation, LIC continued to improve over time after chelation had been stopped
  - Furthermore, LIC also improved after starting mitapivat in both patients who did not receive chelation therapy **(Figure 3; E, F)**

Figure 3. LIC by MRI and chelation therapy over time in patients who achieved transfusion-free status in ACTIVATE-T and the LTE study



BID, twice daily; dw, dry weight; Hb, hemoglobin; LIC, liver iron concentration; LTE, long-term extension; MRI, magnetic resonance imaging

CONCLUSIONS

- **Treatment with mitapivat resulted in continued meaningful improvements in iron overload as measured via LIC by MRI, in adults with PK deficiency who are regularly transfused**
- **Importantly, patients that were chelation naïve, as well as patients that discontinued chelation while on mitapivat, continued to show meaningful improvements and stabilization in LIC, supporting that mitapivat's beneficial effects on iron overload may occur independently from chelation therapy**

Long-term continued treatment with mitapivat improves iron overload in adults with PK deficiency, and may therefore provide additional clinical benefits to those with this condition

Acknowledgments: We would like to thank the patients and study investigators for taking part in this study. Editorial assistance was provided by Nia Higgs, MPharm, Adelphi Communications, Macclesfield, UK, and supported by Agios Pharmaceuticals, Inc.

Disclosures: This study was funded by Agios Pharmaceuticals, Inc.

EJvB: Agios – advisory board member; Agios, Novartis, Pfizer, RR Mechatronics – research funding. **HA-S:** Agios, argenx, Forma, Moderna, Novartis, Pharmacosmos, Rigel, Sobi – consultancy; Agios, Amgen, Novartis, Sobi, Vaderis – research funding. **RFG:** Agios, Novartis, Sobi – research funding; Agios, Sanofi – consultancy. **WB:** Agios, Alexion, Novartis – honoraria; Agios – research funding; Bioverativ, Incyte – board membership or advisory committee. **AG:** Agios, bluebird bio, Bristol Myers Squibb, Novartis, Novo Nordisk, Pharmacosmos – consultancy/advisory board; Agios, Saniona, Sanofi – research support. **VB:** Agios – employee and shareholder. **MW-R:** Agios – employee and shareholder. **RX:** Agios – employee and shareholder. **MDB:** Agios – employee and shareholder. **PP:** Agios – employee and shareholder. **JBP:** Agios, bluebird bio, Celgene, La Jolla Pharmaceuticals, Protagonism, Silence Therapeutics, Vifor – honoraria; Agios, bluebird bio, Celgene – consultancy. **KHMK:** Agios, Alexion, Apellis, bluebird bio, Celgene, Novartis, Pfizer – consultancy; Alexion, Novartis – honoraria; Agios, Bioverativ – membership on an entity's Board of Directors or advisory committees; Agios, Pfizer – research funding.

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Presented at the 2023 European Hematology Association (EHA) Hybrid Congress, June 8–11, 2023, Frankfurt, Germany, and Virtual