Clinically relevant hemoglobin response in adults with pyruvate kinase deficiency treated with mitapivat – A sub-analysis of the ACTIVATE trial

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BACKGROUND

- Pyruvate kinase (PK) deficiency is a rare, inherited disease caused by mutations in the *PKLR* gene encoding the red blood cell-specific form of PK, which leads to chronic hemolytic anemia[1–4]
- PK deficiency is associated with a range of acute and long-term complications, including reduced health-related quality of life[3,5]
- 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,[6] and by the European Union European Medicines Agency[7] and the Medicines and Healthcare products Regulatory Agency in Great Britain,[8] for the treatment of PK deficiency in adults
- In the ACTIVATE trial (NCT03548220) and its long-term extension (LTE; NCT03853798), mitapivat demonstrated sustained improvements in hemoglobin (Hb) in adult patients who were not regularly transfused **(Figure 1)**[9,10]

Figure 1. Key findings from ACTIVATE and the LTE

ACTIVATE[9]
- 40% achieved Hb response on mitapivat vs 0% on placebo (2-sided p<0.0001)
  - Defined as ≥1.5 g/dL increase in Hb concentration from baseline (BL) sustained at ≥2 scheduled assessments at Weeks 16, 20, and 24 during fixed-dose period
- Significant improvements observed with mitapivat for secondary endpoints including average change from BL in markers of hemolysis and hematopoietic activity, and change from BL in patient-reported outcomes (PROs)
- The most common adverse events were nausea and headaches, occurring in 17.5% and 15.0% of patients in the mitapivat study arm, and 22.5% and 32.5% of patients in the placebo arm, respectively

ACTIVATE/LTE[10]
- Hb response was sustained with long-term mitapivat treatment, with responses ongoing up to 32.9 months as of 27Mar2022
- No new safety signals identified

- Studies in other hemolytic anemias, eg, thalassemia, have demonstrated that increases in Hb levels of ≥1.0 g/dL are independently associated with a decreased morbidity burden[11]
- Understanding Hb response using a clinically applicable definition of ≥1.0 g/dL improvement after mitapivat treatment may provide further insight into the beneficial effects of this medication

OBJECTIVE

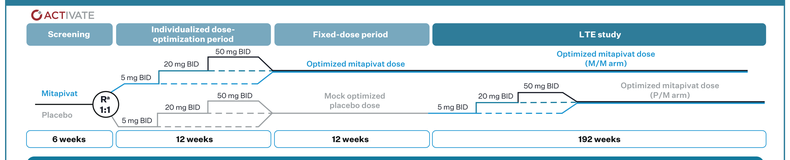
- **To examine Hb, hemolysis, and disease-specific PRO responses to mitapivat during ACTIVATE and/or the LTE in patients who had a ≥1.0 g/dL Hb increase**

METHODS

ACTIVATE and the LTE study design

- ACTIVATE was a phase 3, global, double-blind, placebo-controlled study of mitapivat in adult (≥18 years) patients with PK deficiency who were not regularly transfused
  - 80 patients were randomized 1:1 to receive mitapivat or placebo for a 12-week dose-optimization period (5/20/50 mg twice daily), followed by a 12-week fixed-dose period
- Patients who completed the trial were eligible to continue in the LTE, where all patients received mitapivat treatment **(Figure 2)**

Figure 2. ACTIVATE and the LTE study design



Key eligibility criteria:
- ≥18 years of age
- Documented ≥2 mutant alleles in *PKLR* with ≥1 missense mutation
- **ACTIVATE:** Not regularly transfused (≤4 transfusion episodes in the previous year); BL Hb ≤10 g/dL
- **LTE study:** Completed the fixed-dose period of ACTIVATE and, in the opinion of the Investigator, demonstrated clinical benefit from mitapivat treatment or were assigned to the placebo arm in ACTIVATE

[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);
BID, twice daily; BL, baseline; Hb, hemoglobin; LTE, long-term extension; M/M, mitapivat-to-mitapivat; P/M, placebo-to-mitapivat; R, randomized

Analysis

- This analysis included patients treated with mitapivat in ACTIVATE and/or the LTE who had a clinically relevant Hb response defined as ≥1.0 g/dL increase from BL for at least 2 timepoints after the start of the fixed-dose period
- Change from BL in Hb, hemolysis markers, and quality of life were evaluated up to Week 108
- Hemolysis markers assessed were indirect bilirubin and reticulocyte %
- Quality of life was evaluated using 2 PK deficiency-specific PRO measures: the PK Deficiency Diary (PKDD) and PK Deficiency Impact Assessment (PKDIA); for both, a lower score represents lower disease burden **(Supplemental Figure 1)**
  - The minimal clinically important change (MCIC) is defined as a reduction of 4.2 and 5.5 in PKDD and PKDIA scores, respectively[12]
- Data are reported as of 27Mar2022

RESULTS

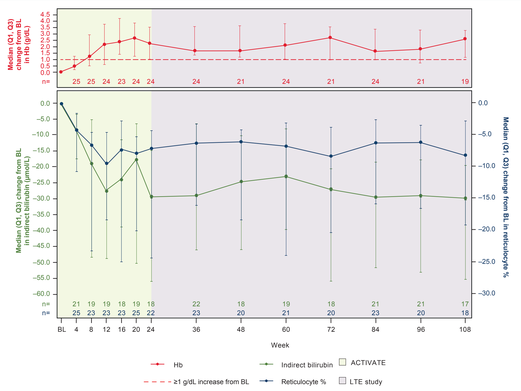
Hb response

- 25/40 (62.5%) patients originally randomized to mitapivat in ACTIVATE met the criteria for having a clinically relevant Hb response (≥1.0 g/dL), which occurred as early as 20 weeks and as late as 108 weeks of treatment
  - Hb improvement from BL to Week 108 was: mean (SD) 2.44 g/dL (1.73), median (Q1, Q3) 2.6 g/dL (1.17, 3.27; n=19) **(Figure 3)**
- 19/25 patients meeting the criteria for clinically relevant Hb response had a ≥1.5 g/dL Hb increase on ≥2 timepoints after the start of the fixed-dose period, of whom 16 achieved this by Week 24

Markers of hemolysis

- Improvements in hemolysis markers were observed in patients who met the criteria for having a clinically relevant Hb response (≥1.0 g/dL) **(Figure 3)**
  - Change from BL to Week 108 in indirect bilirubin was: mean (SD) −35.71 µmol/L (25.65), median (Q1, Q3) −30.1 µmol/L (−55.15, −19.20; n=17)
  - Change from BL to Week 108 in reticulocyte % was: mean (SD) −13.10% (12.84), median (Q1, Q3) −8.3% (−19.2%, −2.8%; n=18)

Figure 3. Change in Hb level and hemolysis markers over time for patients who had a clinically relevant Hb response (≥1.0 g/dL)

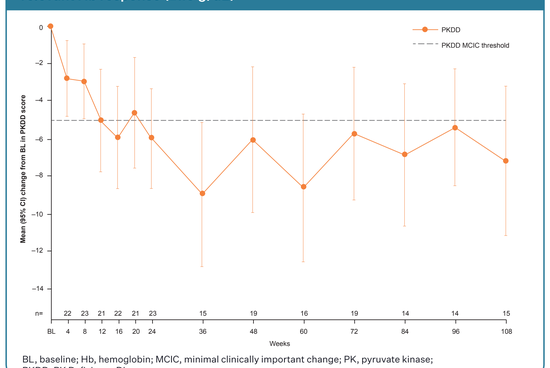


BL, baseline; Hb, hemoglobin; LTE, long-term extension; Q, quartile

Patient-reported outcomes

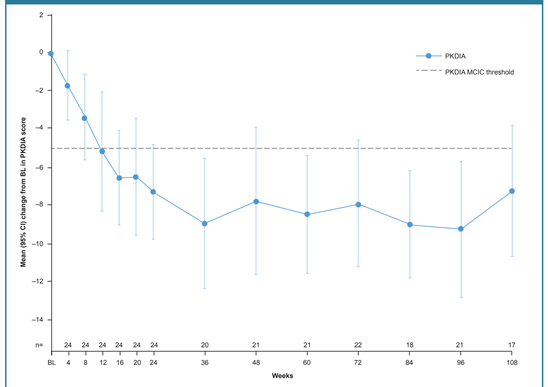
- Improvements in PROs were observed in patients who met the criteria for having a clinically relevant Hb response (≥1.0 g/dL) **(Figures 4** and **5)**
  - At Week 108, mean (95% CI) changes from BL in PKDD and PKDIA scores were −7.2 (−11.1, −3.2; n=15) and −7.3 (−10.8, −3.8; n=17), respectively

Figure 4. Change in PKDD score over time for patients who had a clinically relevant Hb response (≥1.0 g/dL)



BL, baseline; Hb, hemoglobin; MCIC, minimal clinically important change; PK, pyruvate kinase;
PKDD, PK Deficiency Diary

Figure 5. Change in PKDIA score over time for patients who had a clinically relevant Hb response (≥1.0 g/dL)



BL, baseline; Hb, hemoglobin; MCIC, minimal clinically. important change;
PK, pyruvate kinase; PKDIA, PK Deficiency Impact Assessment

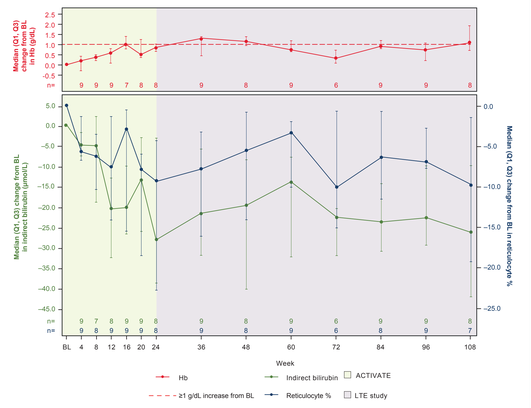
Subset of patients who did not meet the original protocol endpoint

- The 25 patients who met the criteria for having a clinically relevant Hb response (≥1.0 g/dL) included a subset of 9 patients who did not meet the original protocol endpoint (≥1.5 g/dL increase in Hb concentration from BL sustained at ≥2 scheduled assessments at Weeks 16, 20, and 24 during the fixed-dose period)

Hb response, hemolysis markers, and PROs in the subset of patients who did not meet the original protocol endpoint

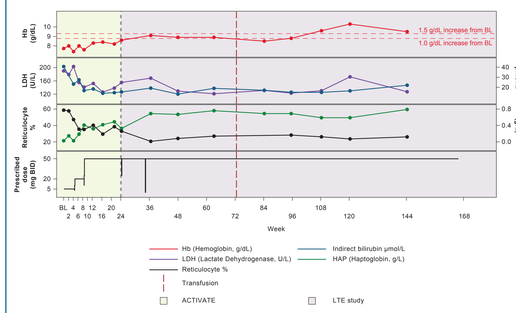
- Hb improvement from BL to Week 108 was: mean (SD) 1.24 g/dL (1.17), median (Q1, Q3) 1.07 g/dL (0.69, 1.92; n=8) **(Figure 6)**
  - 3 patients achieved ≥1.5 g/dL Hb improvement after Week 24 of treatment (as late as Week 120); one patient profile is shown in **Figure 7**
- Improvements in hemolysis markers were similar to the broader group:
  - Change from BL to Week 108 in indirect bilirubin was: mean (SD) −27.34 µmol/L (22.49), median (Q1, Q3) −26.03 µmol/L (−41.90, −9.78; n=8) **(Figure 6)**
  - Change from BL to Week 108 in reticulocyte % was: mean (SD) −11.71% (11.43), median (Q1, Q3) −9.8% (−19.2%, −1.5%; n=7) **(Figure 6)**
- Mean (95% CI) changes from BL in PKDD and PKDIA scores were −6.1 (−14.6, 2.3; n=4) and −6.2 (−15.5, 3.2; n=6), respectively

Figure 6. Change in Hb level and hemolysis markers over time for the subset of 9 patients who did not meet the original protocol endpoint



BL, baseline; Hb, hemoglobin; LTE, long-term extension; Q, quartile

Figure 7. Early improvements in markers of hemolysis in a patient with delayed Hb response



BID, twice daily; BL, baseline; HAP, haptoglobin; Hb, hemoglobin; LDH, lactate dehydrogenase;
LTE, long-term extension

CONCLUSIONS

- **A majority (62.5%) of patients treated with mitapivat in ACTIVATE and/or the LTE achieved a clinically relevant Hb response (defined as Hb increase of ≥1.0 g/dL), along with improvements in hemolysis and PROs**
- **Further, some Hb responses ≥1.0 g/dL occurred after 6 months of mitapivat treatment, indicating that patients may reach this threshold with continued treatment regardless of initial Hb response**

These data show that a clinically relevant improvement in Hb (≥1.0 g/dL) has beneficial effects in adult patients with PK deficiency treated with mitapivat, and that some patients may benefit from continued treatment irrespective of their initial Hb response; these findings may be highly applicable to a real-world setting

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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. **AG:** Agios, bluebird bio, Bristol Myers Squibb, Novartis, Novo Nordisk, Pharmacosmos – consultancy/advisory board; Agios, Saniona, Sanofi – research support. **WB:** Agios, Alexion, Novartis – honoraria; Agios – research funding; Biovarativ, Incyte – board membership or advisory committee. **MV:** Vertex – consultancy. **JAR:** Pfizer – consultancy; Agios, Novartis, Pfizer – honoraria; Agios, bluebird bio, Novartis, Pfizer – research funding. **MMA:** Sanofi Genzyme – honoraria and other grants. **DML:** Agios, Novartis – consultancy; Agios, Cerus, Novartis – membership on an entity's Board of Directors or advisory committees. **OA:** Agios – advisory board member. **FG:** Addmedica – board membership or advisory committee. **KO:** nothing to disclose. **SC:** Agios, Alexion, Global Blood Therapeutics, Novartis, Takeda – consultancy/research funding. **RX:** Agios – employee and shareholder. **BMG:** Agios – employee and shareholder. **MD:** Agios – employee and shareholder. **JM-A:** Agios – employee and shareholder. **EJvB:** Agios – advisory board member; Agios, Novartis, Pfizer, RR Mechatronics – research funding.

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