Durability of hemoglobin response and reduction in transfusion burden is maintained over time in patients with pyruvate kinase deficiency treated with mitapivat in a long-term extension study

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BACKGROUND

- Pyruvate kinase (PK) deficiency is a rare, lifelong, hereditary anemia caused by mutations in the *PKLR* gene, encoding the red blood cell (RBC) PK enzyme[1,2]
- Defects in RBC PK (PKR) enzyme lead to chronic hemolytic anemia, which is associated with both acute and long-term complications – independent of transfusion needs – including iron overload, pulmonary hypertension, and osteoporosis;[3–6] the disease negatively impacts patient health-related quality of life (HRQoL)[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 in PK deficiency

- Mitapivat is an oral, allosteric activator of PK that is approved by the US Food and Drug Administration for the treatment of hemolytic anemia in adults with PK deficiency[8–10]
- In ACTIVATE, a phase 3 study in patients with PK deficiency who were not regularly transfused, 40% of patients achieved a hemoglobin (Hb) response on mitapivat compared with 0% on placebo (2-sided p<0.0001); significant improvements in markers of hemolysis and hematopoiesis were observed, along with a change from baseline in 2 PK deficiency specific HRQoL patient reported outcome measures[11]
- In ACTIVATE-T, a phase 3 study in patients with PK deficiency who were regularly transfused, mitapivat demonstrated a significant transfusion reduction response (37%, 1-sided p=0.0002)[12]
  - Calculation of the p-value was based on the binomial exact test of H0: transfusion reduction response rate ≤10% vs H1: transfusion reduction response rate >10% at a 1-sided α=0.025
- These results are consistent with the DRIVE-PK phase 2 study in which mitapivat showed early and significant increases in Hb concentration in patients with PK deficiency who were not regularly transfused, which were sustained for up to 42 months[13]
- Mitapivat was well-tolerated, and the safety profile was generally consistent across all reported studies[11–13]

OBJECTIVE

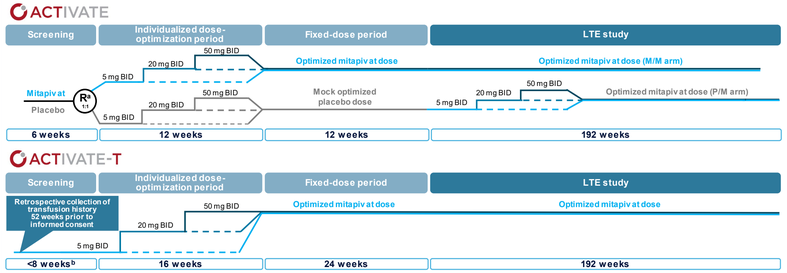
- **To assess the duration of effects of mitapivat on Hb response and transfusion burden reduction in patients with PK deficiency in ACTIVATE, ACTIVATE-T, and their long-term extension (LTE) study**

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
- ACTIVATE-T was a phase 3, global, open-label, single-arm study of mitapivat in adult patients with PK deficiency who were regularly transfused
- 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



[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; Hb, hemoglobin; LTE, long-term extension study; 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 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 baseline 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 baseline sustained at ≥2 scheduled assessments at Weeks 16, 20, or 24 in the LTE) and maintained in the LTE study
- The **ACTIVATE-T/LTE** study analysis assessed:
  - Transfusion burden reduction response in ACTIVATE-T and the LTE study
    - Defined as ≥33% reduction in number of RBC units transfused during the fixed-dose period in ACTIVATE-T and the LTE study standardized to 24 weeks, compared with the patient's individual historical transfusion burden standardized to 24 weeks
  - Transfusion-free duration among patients from ACTIVATE-T who achieved transfusion-free status
    - Defined as no transfusions in the fixed-dose period of ACTIVATE-T

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 12Nov2020, 35/40 patients continued from ACTIVATE to the LTE in the M/M arm and 36/40 patients continued to the LTE in the P/M arm (**Figure 2a**)
- 27 patients were treated with mitapivat in ACTIVATE-T; as of 12Nov2020, 17 patients continued from ACTIVATE-T to the LTE on mitapivat (**Figure 2b**)

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

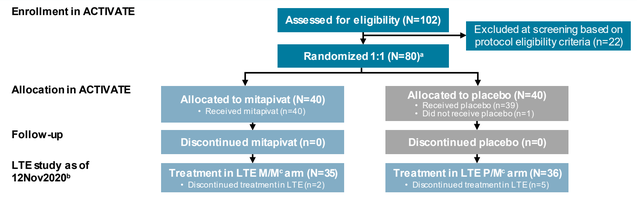
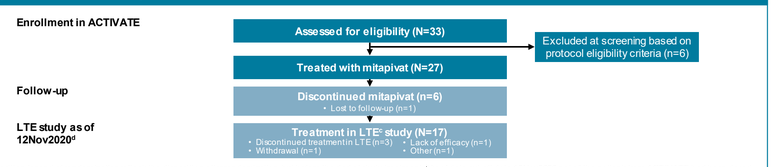


Figure 2b. Patient disposition in ACTIVATE-T and the LTE study

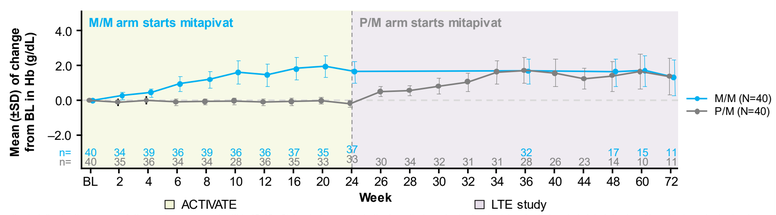


[a]Disposition for end of randomization reflects the disposition after randomization, but before the start of study treatment; [b]As of data cut-off date 12Nov2020 not all the patients from ACTIVATE had been dosed for the LTE study; [c]LTE study is ongoing; 0 patients have completed treatment; [a]As of data cut-off 12Nov2020, not all the patients from ACTIVATE-T had been dosed for the LTE study; LTE, long-term extension; M/M, mitapivat-to-mitapivat; P/M, placebo-to-mitapivat

Mean improvement in Hb concentrations maintained with long-term mitapivat treatment in ACTIVATE and the LTE study

- In ACTIVATE, 40% of patients treated with mitapivat (N=40) achieved an early Hb response
- In the LTE, patients who were randomized to placebo in ACTIVATE showed similar early improvements in Hb concentrations after switching to mitapivat
- In both cohorts, these improvements in Hb concentrations were sustained with continued treatment over time (**Figure 3**)

Figure 3. Mean change from BL[a] in Hb over time in patients randomized to mitapivat or placebo in ACTIVATE who then continued in the LTE study on mitapivat[b,c]

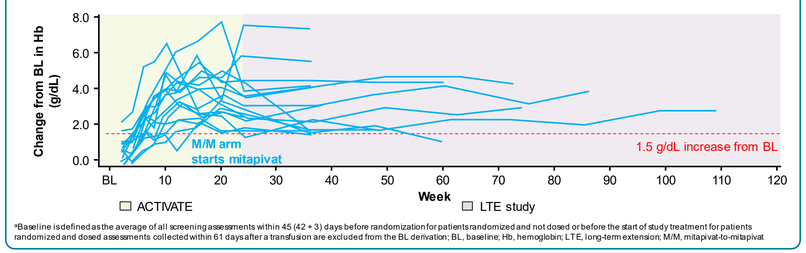


[a]Baseline is defined as the average of all screening assessments within 45 (42 + 3) days before randomization for patients randomized and not dosed or before start of study treatment for patients randomized and dosed. Assessments collected within 61 days after a transfusion are excluded from the baseline derivation; [b]Patients in the M/M arm were assessed every 12 weeks after the completion of the fixed-dose period in ACTIVATE (Week 24) and up to Week 48 of the LTE; [c]Data are shown up to 72 weeks, which is the timepoint where each arm has >5 patients; BL, baseline; Hb, hemoglobin; LTE, long-term extension; M/M, mitapivat-to-mitapivat; P/M, placebo-to-mitapivat; SD, standard deviation

Hb response was sustained in M/M patients in the ACTIVATE and the LTE studies

- All 16 patients assigned to mitapivat in ACTIVATE who achieved Hb responses continued to the LTE; as of the cut-off-date (12Nov2020) 15 M/M patients were evaluable for Hb assessment in the LTE
- At all Hb assessments, 86.7% (13/15) of M/M patients with a Hb response in ACTIVATE and evaluable timepoints in the LTE maintained increases in Hb concentration from baseline above the response threshold of ≥1.5 g/dL up to 19.5 months (**Figure 4**)

Figure 4. Change from BL[a] in Hb over time among patients treated with mitapivat in ACTIVATE who achieved an Hb response in the fixed-dose period and received ongoing treatment in the LTE

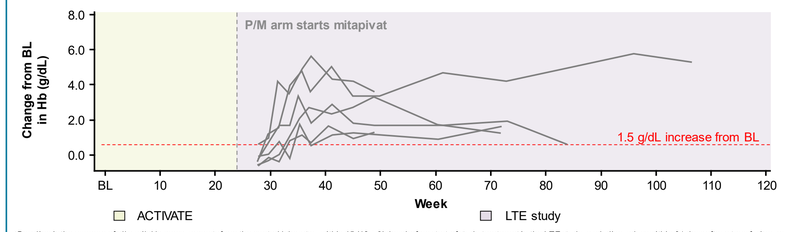


[a]Baseline is defined as the average of all screening assessments within 45 (42 + 3) days before randomization for patients randomized and not dosed or before the start of study treatment for patients randomized and dosed assessments collected within 61 days after a transfusion are excluded from the BL derivation; BL, baseline; Hb, hemoglobin; LTE, long-term extension; M/M, mitapivat-to-mitapivat

Hb response was achieved and sustained in P/M patients in the LTE study

- None of the patients assigned to placebo in ACTIVATE (N=40) had a Hb response during ACTIVATE
- 17 P/M patients had sufficient time (24 weeks of treatment) in the LTE for Hb response assessment as of 12Nov2020
- 35% (6/17) of P/M patients achieved Hb responses in the LTE, and all maintained Hb responses for the duration of follow-up (**Figure 5**)

Figure 5. Change from BL[a] in Hb over time among patients randomized to placebo in ACTIVATE and who started mitapivat treatment in the LTE study and achieved a Hb response

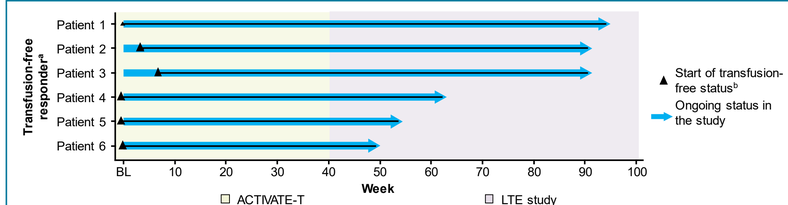


[a]Baseline is the average of all available measurements from the central laboratory within 45 (42 + 3) days before start of study treatment in the LTE study, excluding values within 61 days after a transfusion, or the BL value from the ACTIVATE study if no assessment was available; BL, baseline; Hb, hemoglobin; LTE, long-term extension study; P/M, placebo-to-mitapivat

Transfusion reduction response and duration of transfusion-free status of patients in the ACTIVATE-T and LTE studies

- In ACTIVATE-T (N=27), 10 patients (37.0%) achieved a transfusion reduction response and 6 patients (22.2%) achieved transfusion-free status
- As of 12Nov2020, 9 patients (33.3%) in the LTE study met the criteria for a transfusion reduction response
- All 6 patients who achieved transfusion-free status in ACTIVATE-T maintained the status in the LTE study for up to 21.9 months (**Figure 6**)

Figure 6. Transfusion-free duration among transfusion-free responders from ACTIVATE-T through the LTE study



[a]Patient received no transfusions in the fixed-dose period of ACTIVATE-T; [b]The start of transfusion-free responder status was from 1 day after the last transfusion date LTE, long-term extension

CONCLUSIONS

- PK deficiency is a lifelong serious hemolytic anemia; until recently there were no approved pharmacotherapies
- Patients who were not regularly transfused and randomized to mitapivat in ACTIVATE showed maintenance of Hb response through the LTE study for up to 19.5 months
  - Similarly, 35% of ACTIVATE patients who switched from placebo to mitapivat in the LTE study achieved a Hb response, which was maintained for the duration of follow-up
- All patients who were regularly transfused and who achieved transfusion-free status in ACTIVATE-T with mitapivat treatment maintained the status through the LTE study for up to 21.9 months

Mitapivat improved Hb and reduced transfusion burden in patients with PK deficiency over time, demonstrating the consistency and long-term durability of treatment response with this agent

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