Long-term treatment with oral mitapivat is associated with normalization of hemoglobin levels in patients with pyruvate kinase deficiency

P1548

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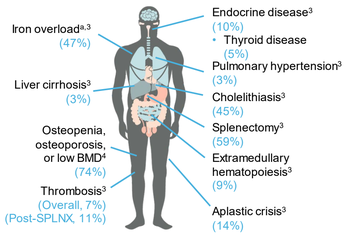
BACKGROUND

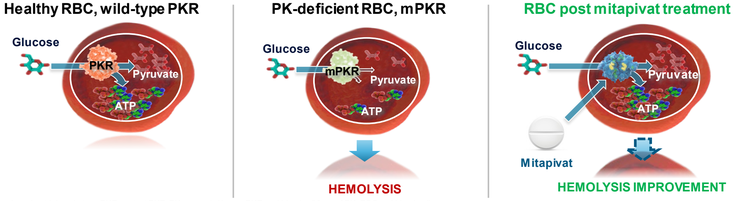
- Pyruvate kinase (PK) deficiency is a rare, hereditary, lifelong disorder, caused by mutations in the *PKLR* gene, which code the PK enzyme[1,2]
  - PK catalyzes the final step in the glycolytic pathway and maintains red blood cell (RBC) health
- Reduced PK activity results in chronic hemolytic anemia and serious complications (**Figure 1**)[3–7]
- Many patients with PK deficiency undergo splenectomy and/or receive RBC transfusions to increase hemoglobin (Hb) levels and improve anemia[8]
  - However, splenectomy is only partially effective at improving anemia and approximately 10% of patients remain transfusion dependent after splenectomy
  - Both therapies are associated with short- and long-term complications
- Mitapivat is an oral PK activator that has been approved by the US Food and Drug Administration for the treatment of hemolytic anemia in adults with PK deficiency (**Figure 2**)[9–11]

Figure 1. Comorbidities and long-term complications associated with PK deficiency[3,4]



[a]Iron overload is defined as a ferritin level of >1000 ng/mL or a liver iron concentration >3 mg Fe/g dry weight liver on T2* MRI in the 12 months prior to enrollment or had received chelation therapy in the 12 months before enrollment; BMD, bone mineral density; Fe, iron; MRI, magnetic resonance imaging; PK, pyruvate kinase; post-SPLNX, post-splenectomy

Figure 2. Mitapivat mechanism of action



ATP, adenosine triphosphate; mPKR, mutant PKR; PK, pyruvate kinase; PKR, red blood cell form of PK; RBC, red blood cell

- Pivotal phase 3 ACTIVATE and ACTIVATE-T studies met their primary endpoints and benefits were maintained in their long-term extension (LTE) study (**Figure 3**)

Figure 3. ACTIVATE, ACTIVATE-T and LTE studies

ACTIVATE[12] (NCT03548220, double-blind, placebo-controlled, N=80)

- **Primary endpoint met**: 16/40 patients (40%) randomized to mitapivat achieved a Hb increase of ≥1.5 g/dL at ≥2 scheduled assessments at Weeks 16, 20, and 24 during the fixed-dose period compared with 0 patients randomized to placebo (2-sided p<0.0001)
- **Secondary endpoints met**: Mitapivat showed significant improvements in markers of hemolysis and hematopoiesis, and PK deficiency-specific patient-reported outcome measures
- **Safety:** No new safety signals were reported

ACTIVATE-T[13] (NCT03548220, single-arm, open-label, N=27)

- **Primary endpoint met**: 10/27 patients (37%) achieved a ≥33% reduction in transfusion burden compared with individual historical transfusion burden standardized to 24 weeks (1-sided p=0.0002)
  - 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
- **Key secondary endpoint**: 6 patients (22%) achieved transfusion-free status (no transfusions during the 24-week fixed-dose period)
- **Safety:** No new safety signals were reported

LTE[14,15] (NCT03853798, open-label study of patients who completed ACTIVATE/ACTIVATE-T)

- **ACTIVATE/LTE**: Sustained improvements in Hb for up to 72 weeks
- **ACTIVATE-T/LTE**: All patients (n=6) who achieved transfusion-free status maintained this status in the LTE for up to 21.9 months

OBJECTIVE

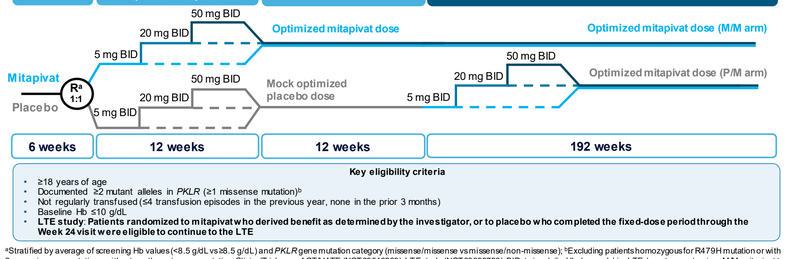
- **To assess the normalization of Hb levels in patients with PK deficiency, who were not regularly transfused and enrolled in ACTIVATE and its ongoing LTE study**

METHODS

Study design

- The randomized, double-blind, placebo-controlled ACTIVATE study consisted of a 12-week dose-optimization period (5/20/50 mg twice daily) and a 12-week fixed-dose period (**Figure 4**)
- 80 patients (≥18 years) with a diagnosis of PK deficiency who were not regularly transfused (≤4 transfusion episodes in prior year; none in the prior 3 months) were randomized 1:1 to receive mitapivat or placebo
- All patients randomized to placebo or mitapivat who completed the fixed-dose period of ACTIVATE through the Week 24 visit were eligible to continue in the LTE study, where all patients then received mitapivat

Figure 4. ACTIVATE/LTE study design



[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]Excluding patients homozygous for R479H mutation or with 2 non-missense mutations, without another missense mutation. ClinicalTrials.gov: ACTIVATE (NCT03548220); LTE study (NCT03853798); BID, twice daily; Hb, hemoglobin; LTE, long-term extension; M/M, mitapivat-to-mitapivat; P/M, placebo-to-mitapivat; R, randomized

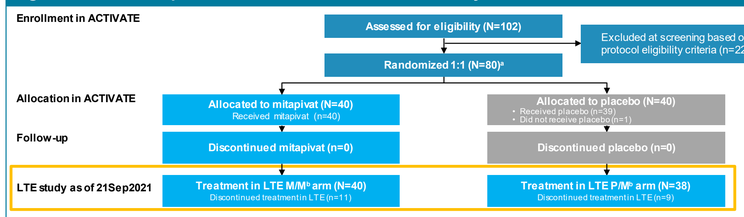
Endpoints and analyses

- ACTIVATE and LTE
  - Hb response, defined as ≥1.5 g/dL increase in Hb from baseline sustained at ≥2 scheduled assessments at:
    - Weeks 16, 20, and 24 in the fixed-dose period for patients randomized to mitapivat in ACTIVATE who continued to the LTE (mitapivat-to-mitapivat [M/M] arm)
    - Weeks 16, 20, and 24 of the LTE for patients randomized to placebo in ACTIVATE who switched to mitapivat in the LTE (placebo-to-mitapivat [P/M] arm)
- Normalization of Hb analysis (data cutoff 21Sept2021)
  - The proportions of ***all patients*** in the M/M arm, P/M arm, and total ACTIVATE/LTE population who achieved a normal Hb level at least once while receiving mitapivat
  - The proportions of ***Hb endpoint responders*** in the M/M arm, P/M arm, and total ACTIVATE/LTE population who achieved a normal Hb level at least once while receiving mitapivat
  - Normal Hb range defined according to central laboratory manual: females 11.5–15.5 g/dL and males 13.2–17.0 g/dL
    - Locally reported laboratory values were also included in this analysis, where definition of normal range may vary
- In ACTIVATE, Hb levels were collected every 2 weeks up to Week 12, then every 4 weeks up to Week 24
- In the LTE, Hb levels were collected as follows:
  - **M/M arm:** every 12 weeks up to Week 96, then every 24 weeks
  - **P/M arm:** every 2 weeks up to Week 12, then every 4 weeks up to Week 24, then every 12 weeks up to Week 96, then every 24 weeks
- Hb levels collected within 2 months (61 days) after an RBC transfusion were excluded from this analysis

RESULTS

- 80 patients were randomized in ACTIVATE (mitapivat N=40; placebo N=40)
- As of 21Sept2021, 40/40 ACTIVATE patients in the M/M arm and 38/40 ACTIVATE patients in the P/M arm continued treatment in the LTE (**Figure 5**)
  - Of these, 11/40 patients in the M/M arm and 9/38 patients in the P/M arm discontinued treatment during the LTE

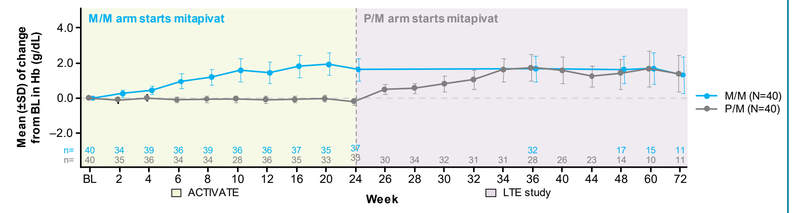
Figure 5. Patient disposition in ACTIVATE and its LTE study



[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; LTE, long-term extension; M/M, mitapivat-to-mitapivat; P/M, placebo-to-mitapivat

- Early improvement in mean Hb level was maintained with long-term mitapivat treatment in ACTIVATE and its LTE study (**Figure 5**)
- Across the ACTIVATE and LTE studies, 28/78 (35.9%) of all patients achieved a normal Hb level at least once during treatment with mitapivat (**Table 1**)
  - **M/M arm:** 15/40 (37.5%) achieved a normal Hb level at least once while on treatment with mitapivat
  - **P/M arm:** 13/38 (34.2%) achieved a normal Hb level at least once while on treatment with mitapivat
- Among Hb endpoint responders, 26/31 (83.9%) achieved a normal Hb level at least once while receiving treatment with mitapivat (**Table 1**, **Figure 6**)
  - **M/M arm:** 14/16 (87.5%) Hb endpoint responders achieved a normal Hb level at least once while on treatment with mitapivat
  - **P/M arm:** 12/15 (80.0%) Hb endpoint responders achieved a normal Hb at least once while on treatment with mitapivat

Figure 6. Mean change from baseline[a] in Hb over time in patients randomized to mitapivat or placebo in ACTIVATE who then continued in its LTE study on mitapivat[b,c]



[a]BL is defined as the average of all screening assessments within 45 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; RBC, red blood cell; SD, standard deviation

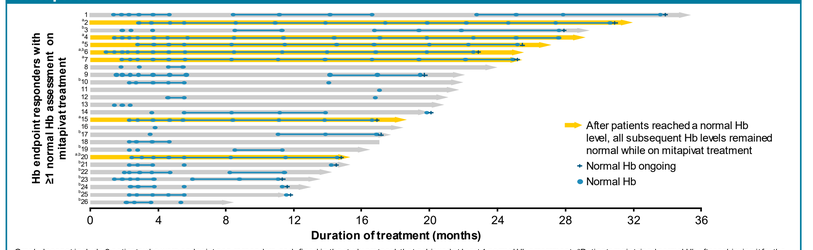
Table 1. Patients who achieved a normal Hb level at least once during mitapivat treatment in ACTIVATE and its LTE

	M/M arm	P/M arm	Total
All patients in ACTIVATE and its LTE, n	40	38	78
Hb at baseline, mean (SD) g/dL	8.6 (9.90)	8.4 (9.33)	8.5 (9.58)
Patients who achieved a normal Hb level at least once during mitapivat treatment[a], n (%)	15 (37.5)	13 (34.2)	28 (35.9)
Patients in ACTIVATE and its LTE who achieved a Hb response, n (%)	16 (40.0)	15 (39.5)	31 (39.7)
Hb endpoint responders who achieved a normal Hb level at least once during mitapivat treatment[a], n (%)	14 (87.5)	12 (80.0)	26 (83.9)

[a]2 months or more after an RBC transfusion; Hb, hemoglobin; LTE, long-term extension; M/M, mitapivat-to-mitapivat; P/M, placebo-to-mitapivat; RBC, red blood cell; SD, standard deviation

- The majority of patients in the M/M arm and all patients in the P/M arm who achieved a normal Hb level at least once in the ACTIVATE and LTE studies achieved their first normal Hb level within 4 months of treatment with mitapivat
- After reaching a normal Hb level, all subsequent Hb levels remained normal in 7 patients while on mitapivat treatment (**Figure 7**)

Figure 7. Hb endpoint responders who achieved normal Hb level at least once while receiving mitapivat



Graph does not include 2 patients who were endpoint non-responders, as defined in the study protocol, that achieved at least 1 normal Hb assessment; [a]Patients maintained normal Hb after achieving it for the first time within 4 months of treatment with mitapivat; [b]Patient was randomized to placebo in the ACTIVATE study and received mitapivat in the LTE study; Hb, hemoglobin; LTE, long-term extension

CONCLUSIONS

- Treatment with mitapivat was associated with early and robust Hb responses, with 36% of all study patients and 83.9% of Hb endpoint responders achieving a normal Hb level at least once while receiving mitapivat

These results add to previously reported data from ACTIVATE, ACTIVATE-T, and their LTE and provide additional evidence that mitapivat is an effective and disease-modifying therapy for patients with PK deficiency, irrespective of transfusion needs

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