ACTIVATE-Kids: Mitapivat in children with pyruvate kinase deficiency who are not regularly transfused

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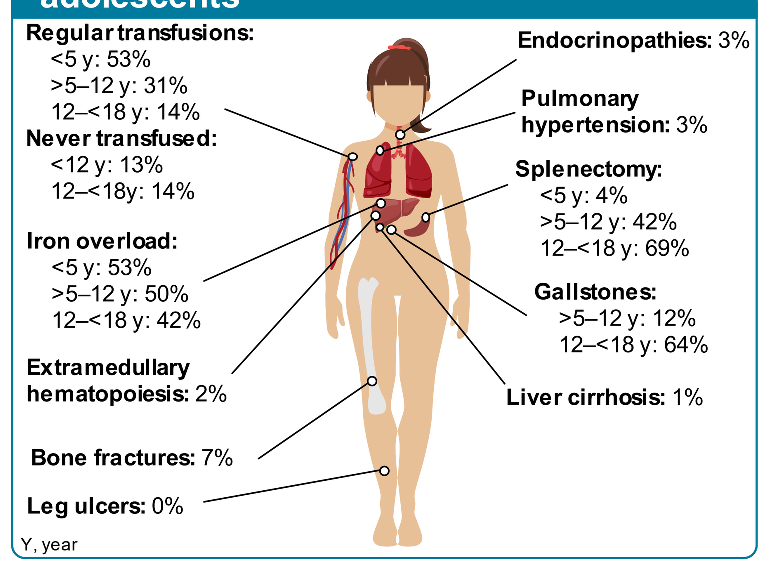
BACKGROUND

Figure 1. PK deficiency in children and adolescents[1]

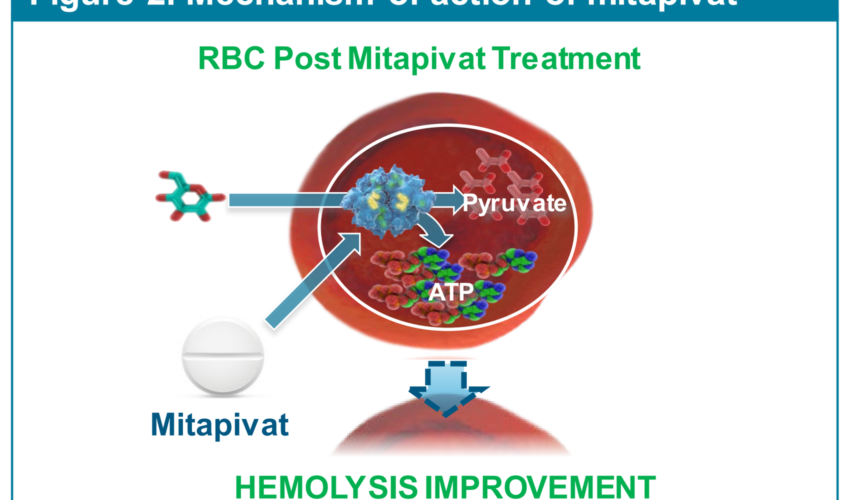


Y, year

- Pyruvate kinase (PK) deficiency is a rare, inherited disorder caused by mutations in the *PKLR* gene resulting in defects in the red blood cell (RBC) PK enzyme (PKR)[2,3]
- PK deficiency is primarily managed with RBC transfusions in children <5 years of age[1,4]
- Splenectomy is common in children who are ≥5 years of age to alleviate transfusion needs (**Figure 1**)[1,4]
  - However, splenectomy is associated with risk of sepsis and thrombosis and is only partially effective at improving anemia
- No pharmacotherapies are approved for the treatment of PK deficiency in children, and therapies targeting the underlying cause of hemolysis are needed[1]

- 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 (**Figure 2**)[5,6]
- Two clinical trials assessing efficacy and safety of mitapivat in adults with PK deficiency met their primary endpoints (**Figure 3**)[7,8]
- Findings from ACTIVATE[7] and ACTIVATE-T[8] support the evaluation of mitapivat in pediatric patients with PK deficiency, independent of transfusion needs
  - Two phase 3 studies will evaluate the efficacy and safety of mitapivat treatment in children with PK deficiency who are not regularly transfused (ACTIVATE-Kids; NCT05175105) and who are regularly transfused (ACTIVATE-KidsT; NCT05144256)

Figure 2. Mechanism of action of mitapivat



ATP, adenosine triphosphate; RBC, red blood cell

Figure 3. ACTIVATE and ACTIVATE-T pivotal phase 3 studies

ACTIVATE

- **Adult patients with PK deficiency who are not regularly transfused[7]**
- **Primary efficacy endpoint achieved:** Higher Hb response rate with mitapivat than placebo
  - 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 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 Hb concentration and in markers of hemolysis and hematopoietic activity, and change from BL in PROs
- **Safety profile:** No new safety signals reported

ACTIVATE-T

- **Adult patients with PK deficiency who are regularly transfused[8]**
- **Primary efficacy endpoint achieved:** Significant reduction in transfusion burden with mitapivat
  - 37% (95% CI 19.4–57.6; one-sided p=0.00017) of patients achieved per-protocol transfusion reduction response in fixed-dose period
    - Defined as ≥33% reduction in number of RBC units transfused during fixed-dose period, compared with patient's individual historical transfusion burden standardized to 24 weeks
    - 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
  - 22% of patients were transfusion-free and 11% of patients achieved normal Hb concentrations during the fixed-dose period
- Improvements in HRQoL observed based on PK deficiency-specific PROs
- **Safety profile:** No new safety signals reported

BL, baseline; Hb, hemoglobin; HRQoL, health-related quality of life; LTE, long-term extension; PK, pyruvate kinase; PRO, patient-reported outcome; RBC, red blood cells

OBJECTIVE

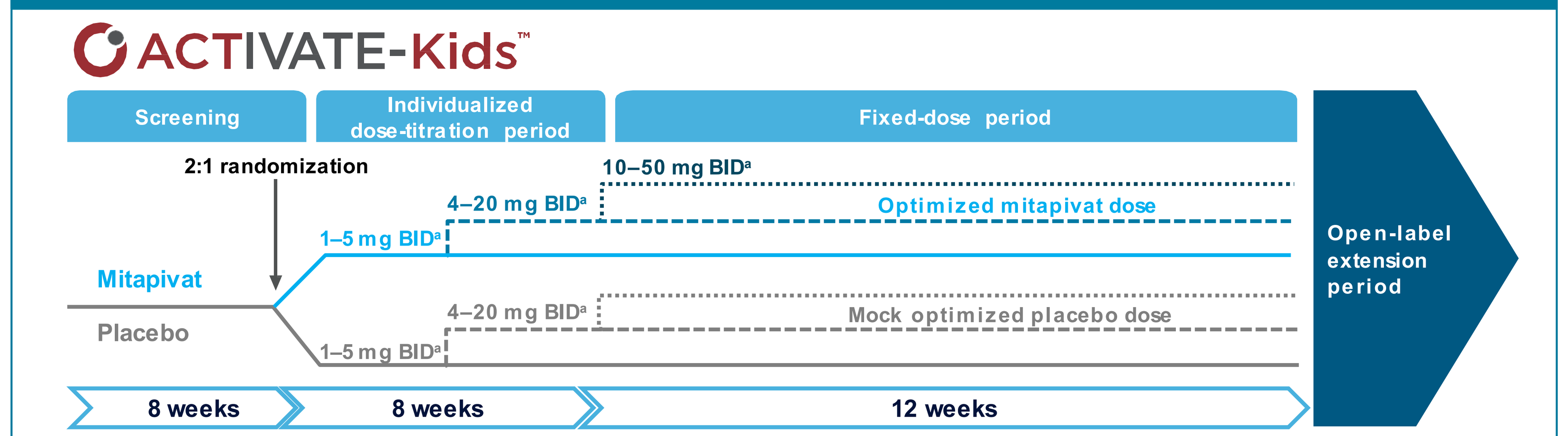
- **Report the design of the phase 3 ACTIVATE-Kids study, which will evaluate the efficacy and safety of mitapivat in children with PK deficiency who are not regularly transfused**

METHODS

Study design

- ACTIVATE-Kids is a global, phase 3, multicenter, randomized, double-blind, placebo-controlled study of children 1–<18 years of age with PK deficiency **who are not regularly transfused** (**Figure 4**)
- Following an 8-week screening period, patients will enter the double-blind period, consisting of an 8-week dose-titration period followed by a 12-week fixed-dose period
- Patients completing the double-blind period may receive mitapivat for up to 5 years in an open-label extension period

Figure 4. ACTIVATE-Kids study design



Key inclusion criteria

- 1 to <18 years of age with central laboratory confirmation of PK deficiency (presence of ≥2 mutant alleles in the *PKLR* gene, of which ≥1 is a missense mutation)
- Hb concentration ≤10 g/dL for patients 12 to <18 years of age or ≤9 g/dL for patients 1 to <12 years of age during the Screening Period
- ≤5 RBC transfusions in the 52 weeks prior to informed consent and no transfusions ≤12 weeks prior to first dose

Key exclusion criteria

- Homozygous for the R479H mutation or have 2 non-missense mutations, without presence of another missense mutation, in the *PKLR* gene
- Currently receiving hematopoietic stimulating agents; last dose must have been administered ≥28 days or a time equivalent to 5 half-lives (whichever is longer) before randomization
- Prior bone marrow or stem cell transplantation

[a]Dose of mitapivat or matched placebo based on patient's age and weight; BID, twice daily; Hb, hemoglobin; PK, pyruvate kinase; RBC, red blood cells

- Randomization: At least 30 children will be randomized
- Stratification factors: Age (1 to <6 years, 6 to <12 years, and 12 to <18 years)
- A minimum of 6 patients in each age group will then be randomized (2:1) to receive mitapivat or placebo at doses of 1–50 mg twice daily (BID)
- Study treatment
  - Drug will be administered orally (as granules taken with food or tablets swallowed whole) at a dose of 1–50 mg BID, depending on age and weight (**Table 1**)
    - Pediatric dosing is based on pharmacokinetic modeling and simulation such that the proposed doses in each age and weight group provide exposure similar to those in adult exposure at the same dose level (EHA PB2247)
  - To gradually increase Hb levels and maximize efficacy during the dose-titration period, study drug will be titrated with dose increases occurring approximately every 4 weeks
- Study endpoints are shown in **Table 2**; an amendment is in-progress, some endpoints may be updated

Table 1. Study drug dose levels

Age	Dose level 1[a] (mg, BID dosing)	Dose level 2 (mg, BID dosing)	Dose level 3 (mg, BID dosing)
1 to <2 years	1	4	10
2 to <12 years			
Weight <20 kg	1	5	15
Weight ≥20 to <40 kg	2	10	20
Weight ≥40 kg	5	20	50
12 to <18 years[b]	5	20	50

[a]Starting dose; [b]Dose to be administered only if patients 12 to <18 years of age weigh ≥40 kg; if patients 12 to <18 years of age weigh < 40 kg, dosing by weight as described for the 2 to <12 years of age category should be followed; BID, twice daily

Table 2. Study endpoints

Primary endpoint
• Hb response, defined as a ≥1.5 g/dL increase in Hb concentration from BL that is sustained at ≥2 scheduled assessments at Weeks 12, 16, and 20 in the double-blind period[a]
Secondary endpoints
• Average change from BL in Hb concentration at Weeks 12, 16, and 20
• Maximal Hb concentration increase from BL during the double-blind period
• Changes in safety assessments including measurement of sex hormones, sexual maturity rating (Tanner stage), development and assessment of ovarian cysts[b]
• Changes over time in height- and weight-for-age z-score, BMI-for-age z-score, and BMD z-score and bone age ratio
• Average change from BL in indirect bilirubin and LDH at Weeks 12, 16, and 20
• Change from BL in haptoglobin at Week 16
• Change from BL in reticulocytes
• Change from BL in markers of iron metabolism, and indicators of iron overload (serum iron, serum ferritin, total iron-binding capacity, hepcidin, transferrin/transferrin saturation)
• Change from BL in HRQoL assessments
• Pharmacokinetic parameters including, but not limited to, C_{max}, AUC, C_{ss}, and C_{trough}
Exploratory endpoints
• Change from baseline in biomarkers including additional markers of erythropoietic activity (eg, EPO) and iron overload (LIC)
• Change from BL in HRQoL PRO scores: PedsQL, Multidimensional Fatigue Scale, PedsQL Generic Core Scales
• PRO measures, efficacy parameters, markers of iron overload and metabolism, and exploratory biomarkers, during the OLE period
• Type, severity, and relationship to study drug of AEs and serious AEs during the OLE period
• Acceptability assessments of the age-appropriate solid dosage form

[a]The patient's Hb concentration at BL is defined as the average of all available Hb concentrations collected for that patient during the screening period up to the first dose of study drug; [b]Female patients only; AE, adverse event; AUC, area under the concentration-time curve; BL, baseline; BMD, bone mineral density; BMI, body mass index; C_{max}, maximum plasma concentration; C_{ss}, concentration at steady state; C_{trough}, trough concentration; EPO, erythropoietin; Hb, hemoglobin; HRQoL, health-related quality of life; LDH, lactate dehydrogenase; LIC, liver iron concentration; OLE, open-label extension; PedsQL, Pediatric Quality of Life; PRO, patient-reported outcomes

Statistics

- With a planned sample size of 30 randomized patients (mitapivat, N=20; placebo, N=10), and assuming an Hb response rate of 35% for mitapivat and 5% for placebo, there will be >80% probability that the lower bound of the 95% credible interval for the odds ratio of Hb response (mitapivat vs placebo), based on the Bayesian logistic regression model with weight ≥0.35, of a robust prior, will be >1
- The primary endpoint of Hb response will use a Bayesian logistic regression model, including Hb response status (yes, no) as the dependent variable and treatment as the independent variable

RESULTS

- Global site recruitment is in-progress; geographic distribution of planned study sites is shown in **Figure 5**
- A total of 20 sites are planned
- Support will be provided that may allow patients to travel to open sites to participate

Figure 5. ACTIVATE-Kids phase 3 study geographic distribution

CONCLUSIONS

- There are no pharmacotherapies approved in children that target the underlying cause of hemolytic anemia in PK deficiency, representing a global unmet need in this patient population
- ACTIVATE-Kids will be the first study to evaluate treatment with mitapivat, a disease-modifying pharmacotherapy, in children with PK deficiency who are not regularly transfused
  - A complementary study (ACTIVATE-KidsT; NCT03559699) will evaluate mitapivat in children with PK deficiency who are regularly transfused (EHA #P1546)
- Mitapivat has the potential to become the first approved pharmacotherapy that treats PK deficiency in children, including in pediatric patients who are not regularly transfused
- Enrollment in the ACTIVATE-Kids study (and ACTIVATE-KidsT) is planned to start in 2022

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References: 1. Grace RF et al. *Blood* 2020;136:1241–9. **2.** Grace RF et al. *Am J Hematol* 2015;90:825–30. **3** Zanella A et al. *Br J Haematol* 2005;130:11–25. **3.** Grootendorst S et al. *Int J Mol Sci* 2021;22:2204. **4.** Chonat S et al. *Pediatr Blood Cancer* 2021;68:e29148. **5.** Kung C et al. *Blood* 2017;130:1347–56. **6.** PYRUKYND® (mitapivat) [US prescribing information]. Cambridge, MA: Agios Pharmaceuticals, Inc.;2022. **7.** Al-Samkari H et al. *N Engl J Med* 2022;386:1432–42. **8.** Glenthøj A et al. *HemaSphere* 2021;5(S2):94, Abstract: S271.

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