ACTIVATE-KidsT: Mitapivat in children with pyruvate kinase deficiency who are regularly transfused

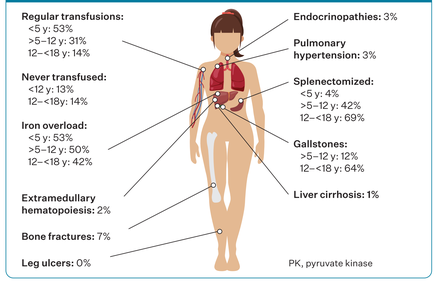
Rachael F Grace, MD,[1] Patrick D Tyler, MD,[2] Meredith Little, MPH,[2] Penelope A Kosinski, MS,[2] Vanessa Beynon, MD[2]

[1]Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Harvard Medical School, Boston, MA, USA; [2]Agios Pharmaceuticals, Inc., Cambridge, MA, USA

2330

BACKGROUND

Figure 1. PK deficiency in children and adolescents[3]

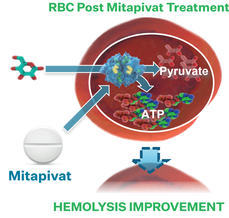


PK, pyruvate kinase

- 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)[1,2]
- PK deficiency is primarily managed with RBC transfusions in children <5 years of age[3,4]
- Splenectomy is common in children who are ≥5 years of age to alleviate transfusion needs (**Figure 1**)[3,4]
  - 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[3]

- 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 phase 3 clinical trials assessing the 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 are in-progress to 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 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
  - 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 cell

OBJECTIVE

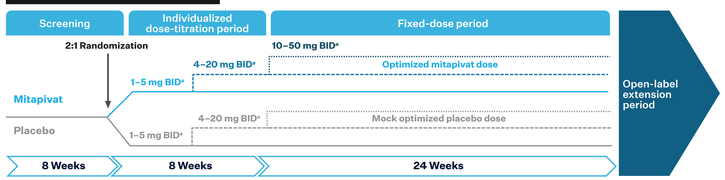
- **Report the design of the phase 3 ACTIVATE-KidsT study, evaluating the efficacy and safety of mitapivat in children with PK deficiency who are regularly transfused**

METHODS

Study design

- ACTIVATE-KidsT is a global, phase 3, multicenter, randomized, double-blind, placebo-controlled study of children 1–<18 years of age with PK deficiency **who are 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 24-week fixed-dose period
- Patients who complete the double-blind period will be eligible to receive mitapivat for up to 5 years in an open-label extension period

Figure 4. ACTIVATE-KidsT study design



[a]Dose of mitapivat or matched placebo based on patient's age and weight

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)
- 6–26 transfusion episodes in the 52-week period before providing informed consent
- Have complete records of transfusion history for the 52 weeks before informed consent

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

BID, twice daily; PK, pyruvate kinase; *PKLR*, gene encoding the pyruvate kinase liver and red blood cell isozymes

- Randomization: At least 45 children will be randomized
- Stratification factors: Age (1 to <6 years, 6 to <12 years, and 12 to <18 years) and Splenectomy status (yes, no)
- 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, within each age and weight category, the proposed dose provides exposure similar to that in adults at the same dose level
  - To gradually increase hemoglobin (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**

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
• Transfusion reduction response, defined as a ≥33% reduction in the total RBC transfusion volume during the fixed-dose period, normalized by weight and actual study drug duration, compared with the historical transfusion volume standardized by weight and to 24 weeks
Secondary endpoint
• Transfusion-free response • Change in the number of transfusion episodes during the fixed-dose period compared with the historical number of transfusion episodes standardized to 24 weeks • Percentage change in total transfusion volume during the fixed-dose period compared with the historical transfusion volume normalized to weight and duration of treatment • Normal Hb response (Hb concentrations in the normal range at least once, 8 weeks or more after a transfusion during the fixed-dose period)
• Changes in safety assessments including measurement of sex hormones, sexual maturity rating (Tanner stage), development and assessment of ovarian cysts[a] • Changes over time in height- and weight-for-age z-score, BMI-for-age z-score, and BMD z-score and bone age ratio
• 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 endpoint
• Change from baseline in biomarkers including markers of hemolysis (eg, indirect bilirubin, LDH, and haptoglobin), erythropoietic activity (eg, reticulocytes, erythropoietin), iron overload (eg,liver iron concentration), and level of PKR protein
• Change from BL in HRQoL PRO scores: PedsQL, Multidimensional Fatigue Scale, PedsQL Generic Core Scales
• Change from baseline in transfusion burden, PRO measures, 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]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; Hb, hemoglobin; HRQoL, health-related quality of life; LDH, lactate dehydrogenase; OLE, open-label extension; PedsQL, Pediatric Quality of Life; PK, pyruvate kinase; PKR, red blood cell PK enzyme; PRO, patient-reported outcome; RBC, red blood cell

Statistics

- With a planned sample size of 45 randomized patients (mitapivat, N=30; placebo, N=15), and assuming a transfusion reduction response (TRR) 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 TRR rate (mitapivat vs placebo), based on the Bayesian logistic regression model with weight ≥0.1 of a robust prior, will be >1
- Analysis of the primary endpoint, TRR, will use a Bayesian logistic regression model, including TRR status (yes, no) as the dependent variable and treatment arm as the independent variable, adjusting for splenectomy status

RESULTS

- Global site recruitment is in-progress; geographic distribution of planned study sites is shown in **Figure 5**
- A total of 27 sites are planned
- Support will be provided that may allow patients to travel to open sites to participate
- Patient enrollment has also begun, with the first patient enrolled in July 2022

Figure 5. ACTIVATE-KidsT phase 3 study geographic distribution

CONCLUSIONS

- **There are no disease-modifying pharmacotherapies approved for the treatment of PK deficiency in children, representing a global unmet need in this patient population**
- **ACTIVATE-KidsT is the first study to evaluate treatment with mitapivat, a pharmacotherapy that ameliorates hemolysis by treating the underlying enzymatic defect in PKR, in children with PK deficiency who are regularly transfused**
  - **A complementary study (ACTIVATE-Kids; NCT05175105) will evaluate mitapivat in children with PK deficiency who are not regularly transfused**
- **Mitapivat has the potential to become the first pharmacotherapy for PK deficiency in children, including in pediatric patients who are regularly transfused**
- **Enrollment in the ACTIVATE-KidsT study (and ACTIVATE-Kids) is in-progress**

Acknowledgments: Editorial assistance was provided by Kate Collins, MPharm, Adelphi Communications, Macclesfield, UK, and supported by Agios Pharmaceuticals, Inc.

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

RF Grace: Agios, Novartis, Dova – research funding; Principia, Agios – consulting; **PD Tyler:** employee and shareholder; **M Little:** employee and shareholder; **PA Kosinski:** Agios – consultancy and shareholder; **V Beynon:** Agios – employee and shareholder

References: 1. Grace RF et al. *Am J Hematol* 2015;90:825–30. **2.** Zanella A et al. *Br J Haematol* 2005;130:11–25. **3.** Grace RF et al. *Blood* 2020;136:1241–9. **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. *Lancet Haematol* 2022;S2352–3026(22)00214–9.

Presented at the 64th American Society of Hematology (ASH) Annual Meeting and Exposition, December 10–13, 2022, New Orleans, LA, USA, and Virtual