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

- 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 (PK)1,2
- PK deficiency is primarily managed with RBC transfusions in children <6 years of age.3–5
- Splenectomy is common in children who are ≥5 years of age to alleviate transfusion needs (Figure 1) 6 – 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.7–9

OBJECTIVE

- To findings from ACTIVATE10,11
- Mitapivat is an oral, allosteric activator of PK that is independent of transfusion needs
- Two phase 3 studies—phase 1 (ACTIVATE-Kids; NCT03310505) and phase 2 (ACTIVATE-T; NCT03310505) with children who are not regularly transfused (ACTIVATE-KidsT; NCT03446268)

RESULTS

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

Figure 2. Mechanism of action of mitapivat

- Mechanism of action of mitapivat: Mitapivat is an oral, allosteric activator of PK that is independent of transfusion needs.
- PK deficiency in children is caused by mutations in the PKLR gene, which results in a decrease in PK activity. Mitapivat binds to the allosteric site of PK, which leads to an increase in PK activity.

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

- ACTIVATE: A randomized, double-blind, placebo-controlled study in children with PK deficiency who are not regularly transfused.
- ACTIVATE-T: A phase 3 extension study of mitapivat in children with PK deficiency who are not regularly transfused.

Figure 4. ACTIVATE-Kids study design

- Study design: Open-label, single-arm, Phase 3 study in children (ages <18 years) with PK deficiency who are not regularly transfused.
- Mitapivat is titrated in a dose-titration period, followed by a 12-week maintenance period.
- Primary outcome measure: Defined as ≥33% reduction in number of RBC units transfused across the double-blind period.

Figure 5. ACTIVATE-Kids phase 3 geographic distribution

- ACTIVATE-Kids phase 3 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 in children with PK deficiency who are not regularly transfused

Table 1. Study drug dose levels

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Table 2. Study endpoints

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