Mitapivat (AG-348) in adults with pyruvate kinase deficiency who are regularly transfused: A phase 3, open-label, multicenter study (ACTIVATE-T) in progress

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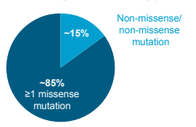
BACKGROUND

Figure 1. Pyruvate kinase (PK) deficiency and mitapivat, a PK-R activator

PK deficiency: disease overview[1-3]

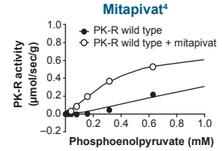
Description	• Under-recognized hereditary disease • Heterogeneous disease with variable severity among all ages
Etiology	• Caused by mutations in the *PKLR* gene coding for red cell PK (PK-R), resulting in defective glycolysis and decreased red blood cell lifespan
Disease burden	• Lifelong hemolytic anemia • Iron overload, jaundice, and other complications • Infection and thrombosis risk post splenectomy
Diagnosis and treatment	• PK-R enzyme activity and genetic testing • Supportive treatment: transfusions, splenectomy, iron chelation

PK deficiency: mutation type[3]



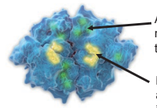
Types of *PKLR* mutations found in 193 **unrelated** cases in the PK deficiency natural history study

Mitapivat[4]



Mitapivat binding enhances the affinity of PK-R for its substrate, phosphoenolpyruvate (recombinant enzyme data shown)

PK-R tetramer[4]



Active PK-R is a tetramer; mutations (green) decrease the enzyme activity

Mitapivat (yellow) binds at the PK-R dimer-dimer interface, away from the active site and the most common mutations

Pyruvate kinase (PK) deficiency

- PK deficiency is a rare, congenital, hemolytic anemia (**Figure 1**).
- Mitapivat sulfate (mitapivat; AG-348) is a novel, first-in-class, small-molecule allosteric activator of red-cell PK (PK-R). It is being developed as a potential treatment for PK deficiency and has been tested in phase 1 and 2 (DRIVE PK) studies.[5,6]

Mitapivat in PK deficiency

DRIVE PK study

- Phase 2, open-label, dose-ranging study in adult patients with PK deficiency who are not regularly transfused (NCT02476916); hemoglobin (Hb) ≤12.0 g/dL (if male) or ≤11.0 g/dL (if female)[6]:
  - Primary endpoint: safety and side-effect profile of mitapivat
  - Secondary endpoints: Hb, markers of hemolysis, pharmacokinetics, and pharmacodynamics
  - Patients (N=52) were randomized to an initial mitapivat dose of 50 mg twice daily (BID) or 300 mg BID; subsequent dose changes were permitted on the basis of safety, tolerability, and Hb response
  - Core period (first 6 months) completed; extension period is ongoing (see Poster 3512 for extension study data).

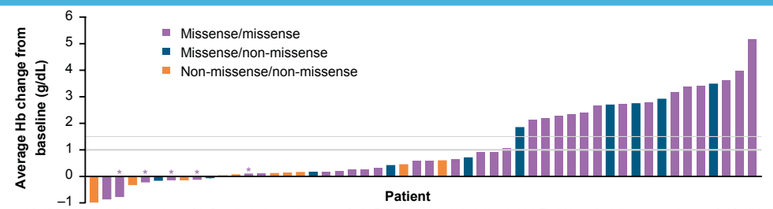
Cumulative safety summary

- Mitapivat was generally well tolerated during the core study and an ongoing extension as of data cutoff (August 31, 2018; median treatment duration of 16.4 months [range, 3–35]).[6]
  - All patients experienced at least one adverse event (AE), of which the majority were grade 1 or 2; 19 of 52 patients (37%) experienced a grade 3 or 4 AE.
  - Six treatment-related AEs led to discontinuation (an increase in alanine aminotransferase level plus nonalcoholic steatohepatitis, hemolytic anemia, nausea plus pharyngitis, hypertriglyceridemia, left renal-cell carcinoma, and pleural effusion).
  - There were 18 serious AEs in 15 patients.

Efficacy (core study)

- 26 of 52 patients (50%) had a maximum Hb increase from baseline of >1.0 g/dL.
  - Among these patients, the mean maximum increase in Hb was 3.4 g/dL (range, 1.1–5.8).
  - Median time until first observed Hb increase of >1.0 g/dL was 10 days (range, 7–187).
  - All patients who had a mean Hb increase from baseline of >1.0 g/dL had at least one missense mutation (**Figure 2**).

Figure 2. Change from baseline in Hb level, according to *PKLR* genotype, in the DRIVE-PK study[6]



A mean increase >1.0 g/dL in the Hb level did not occur in any of the five patients who were homozygous for the R479H mutation (as indicated by asterisks). The thick gray line indicates a mean increase of >1.0 g/dL in the Hb level and the thin gray line indicates a mean increase of ≥1.5 g/dL.
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ACTIVATE-T STUDY (PHASE 3)

Summary

- ACTIVATE-T is a global, multicenter, open-label study to evaluate the efficacy and safety of mitapivat in adult patients with PK deficiency who are regularly transfused (NCT03559699; **Figure 3**).

Current status

- This phase 3 study in adult patients with PK deficiency is enrolling patients at sites in North America, Europe, and Asia (**Figure 4** and **Table 1**).

Figure 3. Design of the ACTIVATE-T study and open-label extension (N, up to 40)

Key inclusion criteria

- ≥18 years of age
- Documented presence of at least two mutant alleles in *PKLR*, of which at least one is a missense mutation (based on genotype–Hb response correlations in DRIVE PK; see **Figure 2**)
- Six or more transfusion episodes in the past 52 weeks
- Adequate organ function

Key exclusion criteria

- Homozygous for the R479H mutation or two non-missense mutations in *PKLR*
- History of transfusions occurring, on average, more frequently than once every 3 weeks in the past 52 weeks
- Significant medical condition that confers an unacceptable risk to participating in the study, and/or that could confound the interpretation of data

Table 1. Active sites as of October 2019

Country	Participating site
Canada	Toronto General Hospital, ON
Czech Republic	Ústav Hematologie a Krevní Transfuze, Prague
Denmark	Herlev and Gentofte University Hospital
France	AP-HP – Hôpital Henri Mondor, Créteil; AP-HM – Hôpital de la Timone, Marseille; CHU de Bordeaux – Hôpital Saint-Andre; IUCT – Institut Universitaire du Cancer de Toulouse
Ireland	St James's Hospital, Dublin
Italy	Ospedali Galliera di Genova; IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano; A.O.U. Seconda Università Degli Studi di Napoli; Azienda Ospedaliera di Rilievo Nazionale Antonio Cardarelli, Napoli
Netherlands	University Medical Center Utrecht
Spain	Hospital Universitari Germans Trias i Pujol, Barcelona
Switzerland	Centre Hospitalier Universitaire Vaudois, Lausanne
Thailand	Faculty of Medicine Siriraj Hospital – Mahidol University, Bangkok
UK	Imperial College Healthcare NHS Trust, London; University College London Hospitals NHS Foundation Trust; Addenbrooke's Hospital, Cambridge; Manchester Royal Infirmary
USA	Massachusetts General Hospital, Boston, MA; Children's Healthcare of Atlanta/Emory University, Atlanta, GA; University of Washington, Seattle, WA; University of California San Francisco Benioff Children's Hospital

Screening

- Transfusion history information used to:
  - Calculate mean transfusion frequency
  - Calculate individual transfusion trigger: mean (±0.5 g/dL or ±0.31 mmol/L) of a patient's collected historical pretransfusion Hb values
  - Calculate mean number of blood units (MNU) transfused per transfusion
  - Function as historical control data for the analysis.

Part 1: Individualized dose optimization period

- All patients start on 5 mg BID mitapivat.
- Following safety assessments the dose can be increased from 5 to 20 mg BID and subsequently from 20 to 50 mg BID.
- Maximal Hb increases are sought while maintaining an acceptable safety profile.

Part 2: Fixed-dose period

- Patients receive mitapivat at their optimized dose, with no planned adjustment for 24 weeks.
- Doses can be reduced or suspended for safety reasons at any time during the study.
- Patients are transfused with their MNU when their Hb reaches their individual transfusion trigger.

Extension study

- Patients completing the study may have the opportunity to enroll in an ongoing open-label extension study (AG348-C-011; EudraCT 2018-003459-39 and NCT03853798) in which all participants will receive mitapivat for up to 192 weeks.
  - Objective: evaluate the long-term safety, tolerability, and efficacy of treatment with mitapivat in participants who were previously enrolled in ACTIVATE-T or its companion study, ACTIVATE.

Key endpoints

Primary

- Reduction in transfusion burden, defined as a reduction of ≥33% in the number of red blood cell units transfused during the 24 weeks of the fixed-dose period compared with the historical transfusion burden standardized to 24 weeks.

Key secondary

- Number of red blood cell units transfused during the study.
- Number of transfusion episodes during part 2.
- Proportion of patients who become transfusion free.
- Proportion of patients who achieve Hb levels in the normal range in part 2.

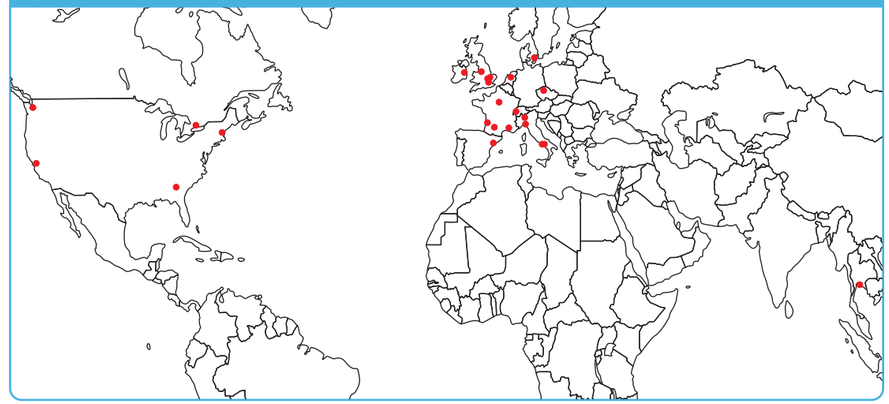
Other secondary

- The type, incidence, severity, and relationship to study treatment of AEs and serious AEs.
- Change from baseline in patient-reported, health-related quality-of-life scores.
- AEs leading to treatment dose reduction, treatment interruption, and treatment discontinuation.
- Pharmacokinetic parameters of mitapivat.

Statistics

- Sample size is driven by feasibility (up to 40 patients).
- With a sample size of 20, the power of the study will be 58% to detect a response rate of 30% compared with a null rate of 10%, based on a two-sided Fisher's exact test at the 0.05 significance level.

Figure 4. ACTIVATE-T study sites



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