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

PK deficiency is a rare, congenital, hemolytic anemia (Figure 1). Following safety assessments the dose can be increased from 5 to 20 mg BID and subsequently from 20 to 50 mg BID.

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);

• Mitapivat sulfate (mitapivat) 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.1

Mitapivat PK deficiency

PK deficiency: disease overview

• Under-recognized hereditary disease

• Heterogeneous disease with variable severity among all ages

• Caused by mutations in the PKLR gene coding for red cell PK (PK-R), resulting in defective glycolysis and decreased red blood cell longevity (Figure 2).

• Life-threatening anemia

• Lethal hepatic, aseptic

• and other complications

• Infection and thrombosis risk post splenectomy

• PK-R enzyme activity and genetic testing

• Supportive treatments: transfusions, splenectomy, iron chelation

• PK-R activity

Non-missense/non-missense

• Homozygous for the R479H mutation or two non-missense mutations in PKLR

• ≥18 years of age

• ≤120 kg

• Hemoglobin (Hb) ≤12.0 g/dL (if male) or ≤11.0 g/dL (if female)

• Non-missense mutations in PKLR

• Hb ≥10.5 g/dL at baseline

• No major organ dysfunction

• ≤20% transfusion history

• ≤40% transfusion burden

• ≤10% transfusion rate of 10%, based on a two-sided Fisher’s exact test at a 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 a 0.05 significance level.

Key exclusion criteria

• Homozygous for the R479H mutation or two non-missense mutations in PKLR

• History of transfusion occurring, on average, more than once every 3 weeks

• Significant medical condition that could confound the interpretation of study results

Table 1: Active sites as of October 2019

<table>
<thead>
<tr>
<th>Country</th>
<th>Participating site</th>
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<tbody>
<tr>
<td>Canada</td>
<td>St. Michael’s Hospital, Toronto</td>
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<tr>
<td>Czech Republic</td>
<td>Ustav hematologie a hemorheologie, Prague</td>
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<td>Denmark</td>
<td>Herlev and Gentofte University Hospital</td>
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<td>France</td>
<td>AP-HP – Hôpital Henri Mondor, Créteil, AP-HP – Hôpital de la Tonnelle, Maisons-Alfort, CHU de Bordeaux – Hôpital Saint-Antoine, IUCT – Institut Universitaire du Cancer de Toulouse</td>
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<td>USA</td>
<td>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, San Francisco, CA</td>
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Figure 1. Pyruvate kinase (PK) deficiency and mitapivat, a PK-R activator

Figure 2. Change from baseline in Hb level, according to PKLR genotype, in the DRIVE PK study

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

Figure 4. ACTIVATE-T study sites

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 (NCT03556999; Figure 3).

• The 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).

Part 1: Baseline 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.

Table 1: Active sites as of October 2019

Part 2: Fixed-dose period

• Patients receive mitapivat at their optimized dose, with no planned adjustment for 24 weeks.

• Dose can be reduced if indicated or stopped 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 (NCT03853798).

• If patients are eligible, they will receive mitapivat and will receive MNU for up to 192 weeks.

• Objective: evaluate the long-term safety, tolerability, and efficacy of treatment with mitapivat in participants who have completed ACTIVATE-T in the companion study, ACTIVATE.

Part 2: Fixed-dose period

• Patients receive mitapivat at their optimized dose, with no planned adjustment for 24 weeks.

Other safety

• 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.

• Sample size is described by feasibility (up to 40 patients).

• If 19 of 52 patients do not receive a sufficient response (30% increase in Hb), the study will be closed.