Mitapivat (AG-348), an oral PK-R activator, in adults with non–transfusion-dependent thalassemia: A phase 2, open-label, multicenter study in progress

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BACKGROUND

Mitapivat sulfate (mitapivat; AG-348) is an orally available, small-molecule allosteric activator of wild-type (WT) and mutant PK-R.1

With a total of 17 patients enrolled, the study would have 80% power to reject a null hypothesis that mitapivat does not lead to a non-inferior mean change from baseline in Hb of 1.5 g/dL over 24 weeks.2

Patients will not receive dose escalation if:

• Reductions in spleen weight (≤50% of baseline) have occurred

Additional markers of erythropoietic activity: growth differentiation factor –15 and non–transfusion dependent, defined as having ≤5 units of RBC transfused during the 24-week period and achieving Hb response with an acceptable safety profile may continue mitapivat treatment for an additional 2 years in this extension period following confirmation by the sponsor’s medical monitor.

The study is currently enrolling at four sites in the US, Canada, and the UK.

Figure 1. Pyruvate kinase and the PK-R activator mitapivat

Figure 2. Hypothesis: Mitapivat may improve thalassemic RBC survival by increasing ATP production

Figure 3. Mitapivat improved red cell parameters in a mouse model of β-thalassemia

Figure 4. Mitapivat increases PK activity and ATP levels in human thalassemic RBCs ex vivo

Figure 5. Design of the phase 2, open-label, multicenter study

SUMMARY

Mitapivat is an oral, small-molecule allosteric activator of WT and mutant PK-R.

Thalassemic RBCs have reduced ATP levels.

Mitapivat increases ATP in RBCs by activating PK-R.

Mitapivat increased ATP and improved RBC parameters in a mouse model of β-thalassemia, and increased ATP levels and RBC survival in human β-thalassemic RBCs.

An ongoing, phase 2, open-label, multicenter study examines the effect of mitapivat on Hb in non–transfusion-dependent patients with thalassemia.

The study is currently enrolling at four sites in the US, Canada, and the UK.

Core period

• All eligible patients will receive an initial mitapivat dose of 50 mg BID.
• At Week 6, patients may receive dose escalation to mitapivat 100 mg BID on the basis of safety and Hb levels.
• Patients will not receive dose escalation if:
  • They have achieved an Hb increase from baseline to 12 g/dL (women) or 13 g/dL (men), and/or
  • They have experienced any grade 3 treatment-emergent adverse events (TEAEs) deemed related to study drug.

Extension period

• Patients who complete the 24-week core period and achieve Hb response with an acceptable safety profile may continue mitapivat treatment for an additional 2 years in this extension period following confirmation by the sponsor’s medical monitor.

Key study end points

Primary

• Hb response: ≥1.0 g/dL increase in Hb from baseline at least one assessment (Weeks 4–12)

Secondary

• Mean change from baseline Hb between Weeks 12 and 24.
• Sustained Hb response: ≥1.0 g/dL increase in Hb at two or more evaluable assessments (Weeks 12–24).
• For subjects who did not reach the primary endpoint, delayed Hb response of ≥1.0 g/dL increase at one or more assessments after Week 12.
• AE, serious AE, and AE leading to dose reduction, interruption, discontinuation.
• Markers of hemolysis: reticulocyte count, bilirubin, lactate dehydrogenase, and haptoglobin.
• Markers of erythropoietic activity: nucleated RBC, erythropoietin, and soluble transferrin receptor.

Exploratory

Additional markers of erythropoietic activity: growth differentiation factor –15 and –11, non–transferrin-bound iron, and erythroferrone (iron panel also includes: iron, serum ferritin, total iron binding capacity, transferrin saturation, hepcidin, and C-reactive protein).

Markers of oxidative stress: urinary 8-isoprostane, methylmalonic acid, and total homocysteine.

Pharmakodynamics/pharmacokinetics: ATP, 2,3-DPG, PK-R activity, PK-R protein levels, and PK-R flux assay.

Statistics

• With a total of 17 patients enrolled, the study would have 80% power to reject a 30% null response rate at a one-sided 0.05 type I error rate if the true response rate was 80%.

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