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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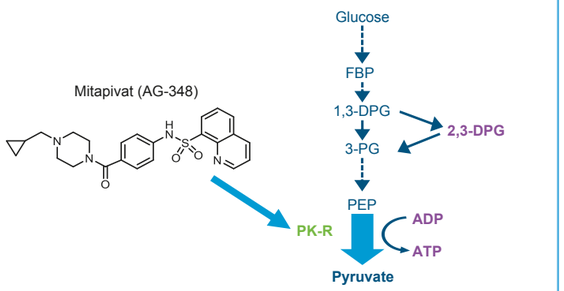
BACKGROUND



ADP = adenosine diphosphate; ATP = adenosine triphosphate; DPG = diphosphoglycerate; FBP = fructose 1,6-bisphosphate; PEP = phosphoenolpyruvate; PG = phosphoglycerate ; PK-R = red cell pyruvate kinase

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

- Pyruvate kinase (PK) is a key regulatory enzyme of glycolysis.
- PK catalyzes the conversion of phosphoenolpyruvate to pyruvate and generates two adenosine triphosphate (ATP) molecules per molecule of glucose (**Figure 1**).[1]
- PK-R is the form of PK present in red blood cells (RBC), where glycolysis is the primary energy production pathway.[1]
- Mitapivat sulfate (mitapivat; AG-348) is an orally available, small-molecule allosteric activator of wild-type (WT) and mutant PK-R.[2]
- In a phase 1 study in healthy volunteers, mitapivat increased blood ATP levels.[3]
- In a phase 2 study in adult patients with PK deficiency who were not regularly transfused, oral mitapivat was well tolerated and induced rapid, sustained hemoglobin (Hb) increases.[4]

HYPOTHESIS

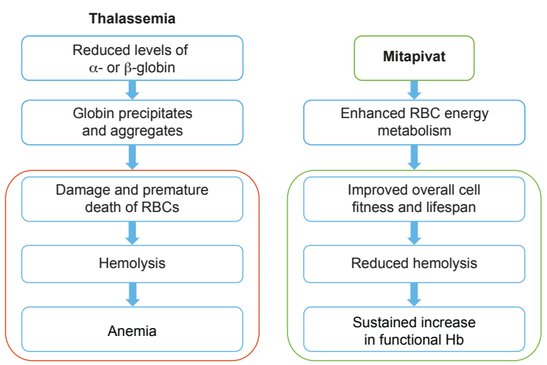
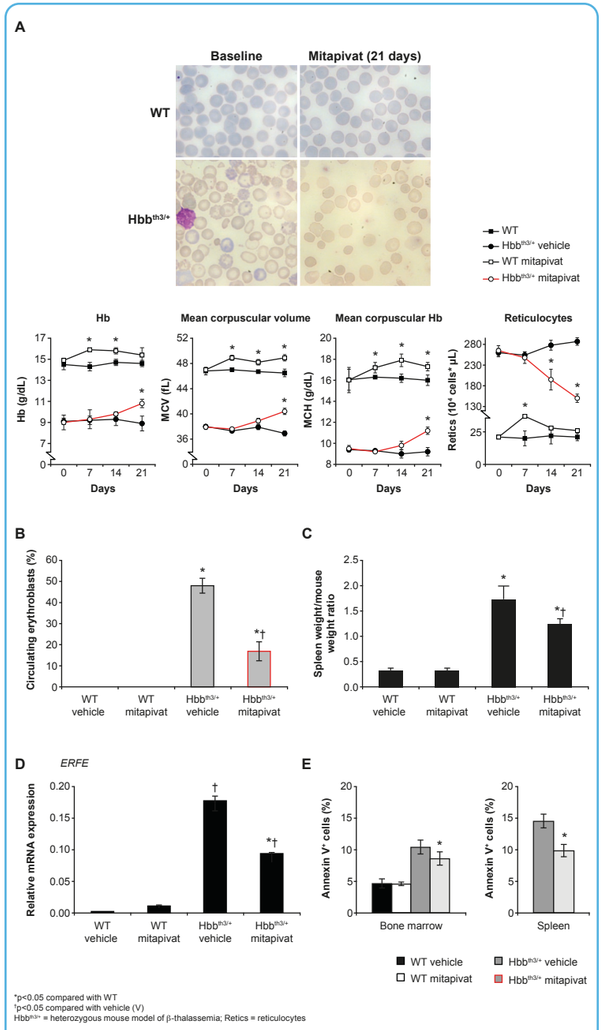


Figure 2. Hypothesis: Mitapivat may improve thalassemic RBC survival by increasing ATP production

- Owing to imbalanced globin chain production, thalassemic RBCs have increased ATP demand to maintain cell fitness (**Figure 2**).[5-8]
- Activation of WT PK-R in thalassemic RBCs may enhance glycolysis and increase RBC ATP levels, leading to improved cell fitness and survival.

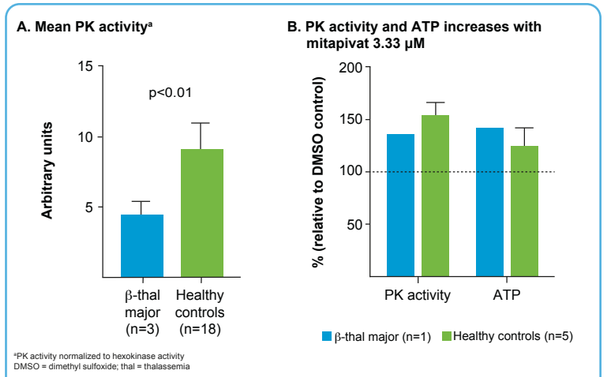
SUPPORTING DATA



*p<0.05 compared with WT
†p<0.05 compared with vehicle (V)
Hbb^th3/+ = heterozygous mouse model of β-thalassemia; Retics = reticulocytes

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

- β-thalassemic mice (Hbb$^{th3/+}$) treated with mitapivat for up to 2 months showed (**Figure 3**)[9]:
  - Improvements in Hb and other hematological parameters (**A**)
  - Reduction in circulating erythroblasts, suggesting improvements in ineffective erythropoiesis (**B**)
  - Reductions in spleen weight (**C**), *ERFE* expression (**D**), and markers of apoptosis (**E**).

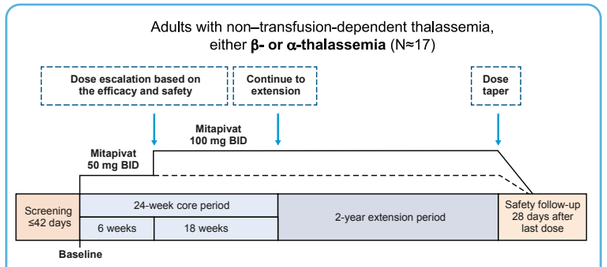


[a]PK activity normalized to hexokinase activity
DMSO = dimethyl sulfoxide; thal = thalassemia

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

- In RBCs from regularly transfused patients with β-thalassemia, PK activity was decreased compared with RBCs from healthy controls (**Figure 4A**).[10]
- *Ex vivo* treatment with mitapivat increased PK activity and ATP levels in RBCs from healthy controls and patients with β-thalassemia (**Figure 4B**).[10]

PHASE 2 TRIAL DESIGN



Major inclusion criteria

- Adults (≥18 years of age) with known medical history of thalassemia, including:
  - β-thalassemia (with or without α-globin gene mutation), Hb E/β-thalassemia, or Hb H disease
- Hb ≤10 g/dL
- Non–transfusion dependent, defined as having ≤5 units of RBC transfused during the 24-week period up to the first day of study drug.

Major exclusion criteria

- Hb S or Hb C
- Osteoporosis, defined as a T-score of −2.5 or lower at the lumbar spine, femur neck, or total hip
- Iron overload sufficiently severe to result in a clinical diagnosis of cardiac, hepatic, or pancreatic dysfunction.

EudraCT 2018-002217-35; ClinicalTrials.gov NCT03692052
EudraCT = European Union Drug Regulating Authorities Clinical Trials Database
BID = twice daily

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

- A phase 2, open-label, multicenter study is ongoing to assess the efficacy, safety, pharmacokinetics, and pharmacodynamics of mitapivat in non–transfusion-dependent thalassemia (NCT03692052; **Figure 5**).
- 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 (AEs) 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 the extension period following confirmation by the sponsor's medical monitor.

Key study endpoints

Primary

- **Hb response:** ≥1.0 g/dL increase in Hb from baseline in 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.
- **AEs**, **serious AEs**, and AEs leading to dose reduction, interruption, or 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.
- Pharmacokinetics/pharmacodynamics: 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 were 60%.

SUMMARY

- Mitapivat is an oral, small-molecule allosteric activator of WT and mutant PK-R.
- Thalassemic RBCs have reduced ATP levels.
- Mitapivat may improve RBC survival in thalassemia by increasing ATP production.
- Mitapivat increased ATP and improved RBC parameters in a mouse model of β-thalassemia, and increased ATP levels *ex vivo* in human β-thalassemia 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.

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Disclosures
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