RISE UP

A phase 2/3, double-blind, randomized, placebo-controlled, multicenter study to evaluate the efficacy and safety of mitapivat in patients with sickle cell disease[1]

KEY INCLUSION CRITERIA

- Age 16 years or older, with a documented diagnosis of sickle cell disease (HbSS, HbSC, HbS/β0 thalassemia, HbS/β+ thalassemia, or other sickle cell syndrome variants)
- At least 2 and no more than 10 sickle cell pain crises in the 12 months prior to informed consent
  - Defined as acute episodes of pain, acute chest syndrome, priapism, hepatic or splenic sequestration
- If taking hydroxyurea, the hydroxyurea dose must be stable for at least 90 days before randomization

KEY EXCLUSION CRITERIA

- Pregnant or breastfeeding
- Receiving regularly scheduled transfusions
- Hepatobiliary disorders, significant liver disease, gallbladder disease, or severe kidney disease
- Prior exposure to gene therapy or prior bone marrow or stem cell transplantation
- Currently receiving voxelotor, crizanlizumab, or L-glutamine
- Currently receiving treatment with hematopoietic-stimulating agents
- Taking strong CYP3A4/5 inhibitors or strong inducers or CYP3A4

Participants will be enrolled in either phase 2 or phase 3 of RISE UP. Once enrolled, participants cannot reenroll in a different phase.[1]

PHASE 2

- A 3-month, placebo-controlled, dose-finding study[1]
- Evaluate the safety and efficacy of 2 dose levels of mitapivat in the improvement of anemia in sickle cell disease and determine the recommended phase 3 dosage[1]

Screening Period
Up to 28 Days

During this time, doctors will confirm eligibility to take part in the clinical trial

Randomization
1:1:1 N=69

Participants will be assigned to 1 of 3 groups shown below

Double-blind Period
12 Weeks

- Mitapivat (50 mg BID)
- Mitapivat (100 mg BID)
- Placebo (BID)

Primary endpoints: Mitapivat safety as well as hemoglobin (Hb) response, defined as the percentage of participants who experience an average Hb increase of ≥1.0 g/dL by week 12 and to identify the selected dose to be used in phase 3.

Open-label Extension
216 Weeks

- Mitapivat (50 mg BID)
- Mitapivat (100 mg BID)

Safety Follow-up
~4 Weeks After Last Dose

End of Phase 2

PHASE 3

- A 52-week, placebo-controlled, efficacy and safety study[1]
- Determine the effect of mitapivat on anemia and pain crises in sickle cell disease[1]

Screening Period
Up to 28 Days

During this time, doctors will confirm eligibility to take part in the clinical trial

Randomization
2:1 N=198

Participants will be assigned to 1 of 2 groups shown below

Double-blind Period
52 Weeks

- Mitapivat
  Dosage determined in phase 2
- Placebo (BID)

Primary endpoint: Mitapivat efficacy, including Hb response (defined in phase 2), as well as the annualized rate of sickle cell pain crises by week 52.

Open-label Extension
216 Weeks

Mitapivat
(Selected Dosage)

Safety Follow-up
~4 Weeks After Last Dose

End of Phase 3

For additional details about Agios study AG-348-C-020 (RISE UP), including the study design, study sites, or other information, please visit **ClinicalTrials.gov** (Identifier: NCT05031780) or contact Agios Medical Affairs at:

medinfo@agios.com **1-833-228-8474**

BID=twice daily.

Reference: 1. Data on file. Agios Pharmaceuticals, Inc.

Mitapivat is a pyruvate kinase activator approved by the FDA for the treatment of hemolytic anemia in adults with pyruvate kinase (PK) deficiency. Mitapivat is not authorized for use by the EMA or any health authority outside the United States. The safety and efficacy of mitapivat in other indications are under investigation and have not been established. There is no guarantee that mitapivat will receive health authority approvals or become commercially available in any country for the uses under investigation.

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