Study design of the phase 3 portion of RISE UP: A phase 2/3, randomized, double-blind, placebo-controlled study of mitapivat in patients with sickle cell disease

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BACKGROUND

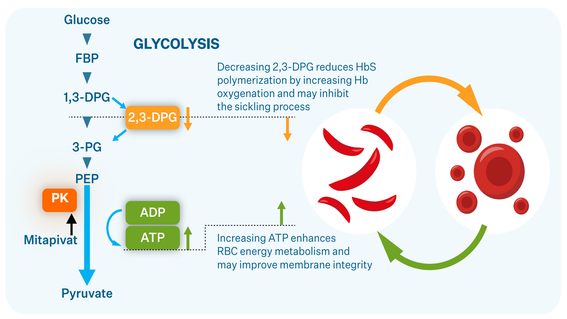
Introduction to sickle cell disease (SCD)

- SCD is a serious, inherited hemoglobin (Hb) disorder caused by a mutation in the ß-globin gene[1,2]
- Most patients with SCD are homozygous for sickle cell Hb (HbSS), but some individuals may have coinherited hemoglobin S (HbS) with another ß-globin chain variant, for example, HbS plus a hemoglobin C (HbC; HbSC) or ß-thalassemia gene variant[1,3]
- A recent analysis estimated that between 2000 and 2021, worldwide prevalence of SCD rose by 41.4% from 5.5 million to 7.7 million[4]
- Fatigue and pain from SCD have a high impact on health-related quality of life, limiting daily function, schooling, and employment[5]

Pathophysiology of SCD and role of pyruvate kinase (PK)

- Red blood cells (RBCs) in SCD are distorted and stiff, with increased adhesiveness, which causes impeded blood flow, vaso-occlusion, and pain[6,7]
- Distorted (sickled) RBCs also have shortened lifespans, resulting in hemolytic anemia and fatigue[2,7,8]
- Both vaso-occlusion and hemolysis contributes to vasculopathy and endothelial dysfunction[2,9]
- PK is a key enzyme in RBC metabolism and ATP production; its activity and stability are decreased in SCD[10] (**Figure 1**)
- The glycolytic intermediate 2,3-diphosphoglycerate (DPG) is increased, preferentially binding to and stabilizing deoxy-HbS[10–13]; ATP (a product of glycolysis) is decreased, leading to RBC dehydration[12,13]
  - Both factors promote HbS polymerization[11,13]
- In SCD, the activity and stability of PK and the ratio of ATP:2,3-DPG are decreased[10]

Figure 1. PK activation in SCD may improve anemia and reduce sickling[14]



ADP, adenosine diphosphate; DPG, diphosphoglycerate; FBP, fructose bisphosphate; Hb, hemoglobin; HbS, hemoglobin S; PEP, phosphoenolpyruvate; PG, phosphoglycerate; PK, pyruvate kinase; RBC, red blood cell; SCD, sickle cell disease

Mitapivat as a potential therapy for SCD

- Mitapivat, a first-in-class, oral, small-molecule allosteric activator of PK, including RBC-specific PK (PKR) and PK muscle isoenzyme 2 (PKM2) isoforms, is under investigation for the treatment of SCD[15–17] (**Figure 1**)
- In the phase 2, dose-finding portion of RISE UP (NCT05031780):
  - Treatment with mitapivat demonstrated statistically significant and clinically meaningful improvements in Hb response compared with placebo[17]
  - Reductions in annualized rates of sickle cell pain crises (SCPCs; defined by an acute pain episode, acute chest syndrome, priapism, hepatic sequestration, or splenic sequestration) and improvements in markers of hemolysis and erythropoiesis were observed[17]
- Mitapivat was well tolerated, with a safety profile consistent with previous studies[17]
- Mitapivat 100 mg twice daily (BID) was selected as the dose for the phase 3 portion of the phase 2/3 RISE UP trial, conducted in patients with SCD
- The primary and key secondary objectives and endpoints, and the safety objectives for the phase 3 portion of the RISE UP trial are displayed in **Tables 1–3**

OBJECTIVE

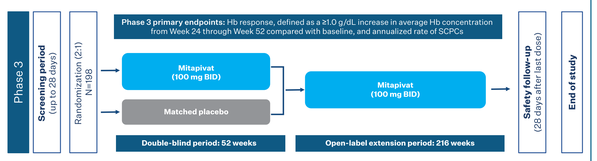
- **To report the design of the phase 3 portion of RISE UP, a global, phase 2/3, double-blind, randomized, placebo-controlled trial evaluating the efficacy and safety of mitapivat in patients with SCD**

METHODS

Study design

- In the double-blind, phase 3 portion of the RISE UP study, 198 patients (who did not participate in the phase 2 dose-finding portion) are being randomized 2:1 to receive mitapivat 100 mg BID or matched placebo for 52 weeks (**Figure 2**)
- Randomization will be stratified by the number of SCPCs in the prior year (<5, ≥5) and concomitant hydroxyurea use
- Patients who complete the double-blind period will be eligible to receive mitapivat for an additional 216 weeks in an open-label extension

Figure 2. RISE UP phase 3 study design



BID, twice daily; Hb, hemoglobin; SCPC, sickle cell pain crisis

Key inclusion criteria for phase 2/3 trial

- Aged ≥16 years (≥18 years in France and Germany)
- Confirmed SCD diagnosis (HbSS, HbSC, HbS/ß0-thalassemia, HbS/ß+-thalassemia, or other sickle cell syndrome variants)
- 2–10 SCPCs in the 12 months prior to providing informed consent (defined as acute pain needing medical contact and treatment, acute chest syndrome, priapism needing medical contact, or hepatic or splenic sequestration)
- Hb level of 5.5–10.5 g/dL (based on an average of ≥2 Hb concentration measurements separated by ≥7 days and collected during the screening period)
- Patients receiving concomitant hydroxyurea can participate; however, the dose must be stable for ≥90 days prior to randomization
- Women of childbearing potential must agree to be abstinent or use 2 forms of contraception

Key exclusion criteria for phase 2/3 trial

- Pregnant, breastfeeding, or parturient
- Individuals receiving scheduled RBC transfusions (episodic transfusions in response to worsened anemia or vaso-occlusive crises are permitted)
- Hospitalized for an SCPC or other vaso-occlusive event within 14 days prior to providing informed assent/consent or during the screening period
- Individuals receiving treatment with disease-modifying SCD therapies other than hydroxyurea, or hematopoietic stimulating agents (last dose of such therapies must have been administered ≥90 days prior to randomization)
- Severe kidney disease or hepatobiliary disorders

Table 1. RISE UP primary objectives and endpoints

Primary objectives *To determine the effect of mitapivat vs placebo on:*	Primary endpoints *Measured by:*
Anemia	Hb response; defined as a ≥1.0 g/dL increase in average Hb concentration from Week 24 through Week 52 compared with baseline
SCPCs	Annualized rate of SCPCs
If either of the primary endpoints is met, key secondary efficacy endpoints will be tested at the time of the primary analysis	

Hb, hemoglobin; SCPC, sickle cell pain crisis

Table 2. Key secondary objectives and endpoints

Key secondary objectives *To determine the effect of mitapivat vs placebo on:*	Key secondary endpoints *Measured by:*
Anemia	Average change from baseline Hb concentration from Week 24 through Week 52
Markers of hemolysis	Average change from baseline in indirect bilirubin from Week 24 through Week 52
Markers of erythropoiesis	Average change from baseline in percent reticulocytes from Week 24 through Week 52
Patient-reported fatigue	Average change from baseline in Patient-Reported Outcomes Measurement Information System® Fatigue 13a Short Form scores from Week 24 through Week 52
Additional clinical efficacy measures related to SCPCs	Annualized frequency of hospitalizations for SCPCs

Hb, hemoglobin; SCPC, sickle cell pain crisis

Table 3. RISE UP safety objective and endpoint

Safety objective *To determine the effect of mitapivat vs placebo on:*	Safety endpoint *Measured by:*
Safety	Type, severity, and relationship to study drug of AEs and serious AEs

AE, adverse event

RESULTS

Enrollment status

- Patients are currently being enrolled into the phase 3 portion of the RISE UP trial
- Recruitment is anticipated to take place across approximately 100 sites globally (**Figure 3**)

Figure 3. SCD phase 2/3 study geographic distribution[a]

[a]Countries with sites approved or under consideration
SCD, sickle cell disease

CONCLUSIONS

- **The phase 3 portion of RISE UP will assess the efficacy and safety of mitapivat compared with placebo in patients with SCD, at the dose identified in the phase 2 portion of the study (100 mg BID)**
- **Mitapivat, a small-molecule allosteric activator of PK, has the potential to be the first novel oral therapy approved to address both hemolytic anemia and SCPCs in patients with SCD**

Additional information on the RISE UP study can be found at ClinicalTrials.gov (NCT05031780) and from medinfo@agios.com

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References and downloadable poster are available via the QR code

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