A Phase 2/3, Randomized, Double-Blind, Placebo-Controlled Study of Mitapivat in Patients with Sickle Cell Disease

Poster #3109

Joanna Howard, MB BChir[1], Kevin H.M. Kuo, MD[2], Abdulafeez Oluyadi, PharmD[3], Hui Shao, PhD[3], Susan Morris, PhD[3], Ahmar U. Zaidi, MD[3], Eduard J. van Beers, MD[4], Swee Lay Thein, MBBS[5]

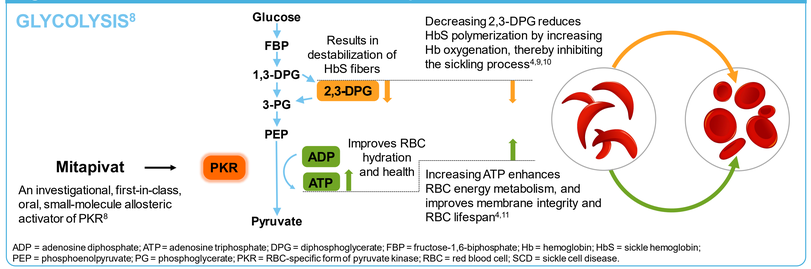
[1]Department of Hematology, Guy's and St Thomas' NHS Foundation Trust, London, UK; [2]Division of Hematology, University of Toronto, Toronto, ON, Canada; [3]Agios Pharmaceuticals, Inc., Cambridge, MA, USA; [4]Van Creveldkliniek, Department of Internal Medicine, University Medical Center Utrecht, Utrecht, Netherlands; [5]Sickle Cell Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, USA

RISE UP

BACKGROUND

- Sickle cell disease (SCD) is a life-threatening, hereditary hemoglobin (Hb) disorder characterized by chronic hemolytic anemia, pain, end-organ damage, and poor quality of life (QoL)[1–3]
- The key pathology is red blood cell (RBC) sickling due to polymerization of deoxygenated sickle Hb (HbS), which can be exacerbated by increased levels of the glycolytic metabolite 2,3-diphosphoglycerate (2,3-DPG), and decreased ATP[3,4]
- Sickled RBCs are rigid, not deformable, and fragile, which results in vaso-occlusion that triggers pain and chronic hemolysis[5–7]
- SCD treatment options are limited, with an unmet need for safe and effective therapies to improve anemia and reduce pain
- Activation of RBC-specific form of pyruvate kinase (PKR; a key enzyme in glycolysis) decreases 2,3-DPG and increases ATP (**Figure 1**), which may reduce HbS polymerization, RBC sickling, and hemolysis in SCD[4,8–10]

Figure 1. Potential dual mechanism of action of mitapivat in SCD



ADP = adenosine diphosphate; ATP = adenosine triphosphate; DPG = diphosphoglycerate; FBP = fructose-1,6-biphosphate; Hb = hemoglobin; HbS = sickle hemoglobin; PEP = phosphoenolpyruvate; PG = phosphoglycerate; PKR = RBC-specific form of pyruvate kinase; RBC = red blood cell; SCD = sickle cell disease.

- Activation of PKR has a potential application in the treatment of hemolytic anemias; mitapivat is currently being studied in a variety of hemolytic anemias including SCD, thalassemia, and pyruvate kinase deficiency
- Data from the phase 1 National Institutes of Health (NIH) multiple ascending dose study of up to 100 mg of mitapivat twice daily (BID) in patients with SCD (NCT04000165) showed that mitapivat:[9,12]
  - Demonstrated an acceptable safety and tolerability profile
  - Increased ATP and decreased 2,3-DPG levels in a dose-dependent manner
  - Improved Hb levels and reduced hemolytic markers
- Results from the dose-finding period of the ongoing phase 2 study (ESTIMATE, Utrecht) in SCD showed that mitapivat:[13]
  - Demonstrated an adequate safety profile
  - Decreased point of sickling
  - Improved ATP and decreased 2,3-DPG levels
  - Increased Hb levels and decreased hemolytic markers
- Data from the phase 1 NIH study (abstract #10) and the ESTIMATE study (abstract #2005) are presented at ASH 2021[12,13]
- A phase 2/3 study investigating the efficacy and safety of mitapivat in patients with SCD is planned, which will evaluate both anemia and sickle cell pain crises

OBJECTIVE

- To present the operationally seamless study design of a phase 2/3 study that will evaluate the efficacy and safety of mitapivat vs placebo in patients with SCD (RISE UP; NCT05031780; EudraCT: 2021-001674-34)

METHODS

Study design

- This is a phase 2/3, double-blind, randomized, placebo-controlled, global, multicenter study with an operationally seamless design (**Figure 2**)

Phase 2

- Patients will be randomized (1:1:1) to receive 50 mg BID mitapivat, 100 mg BID mitapivat, or matched placebo for 12 weeks (n = 69)

Phase 3

- Patients will be randomized (2:1) to receive the recommended phase 3 dose of mitapivat or placebo, BID, for 52 weeks (n = 198)
  - Patients who participate in the phase 2 study will not be eligible to participate in the phase 3 study
  - Patients are eligible to participate in the open-label extension period in each phase

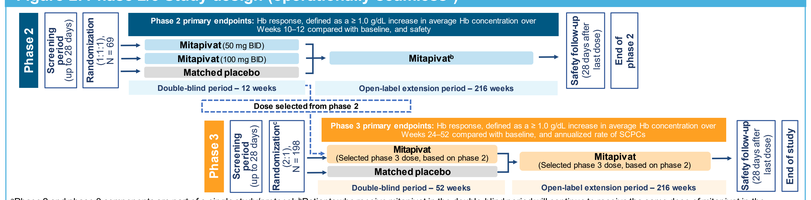
Phase 3 stratification

- Number of sickle cell pain crises (SCPCs) in the prior year (< 5, ≥ 5)
- Hydroxyurea (HU) use (yes, no)

Phase 3 dose selection

- The dose of mitapivat that will be evaluated in the phase 3 portion of the study (either 50 mg or 100 mg) will be based on the results of the phase 2 dose finding study

Figure 2. Phase 2/3 Study design (operationally seamless[a])



[a]Phase 2 and phase 3 components are part of a single study/protocol; [b]Patients who receive mitapivat in the double-blind period will continue to receive the same dose of mitapivat in the open-label extension period, patients who receive placebo will be randomized 1:1 to mitapivat 50 mg BID or 100 mg BID; [c]Randomization stratification factors: Number of SCPCs in the prior year (< 5, ≥ 5), hydroxyurea use (yes, no). BID = twice daily; Hb = hemoglobin; SCPC = sickle cell pain crises.

Study population

Key inclusion criteria

- ≥ 16 years of age; subjects who are 16 or 17 years of age must be documented Tanner Stage 5
- Documented SCD (HbSS, HbSC, HbSβ0/HbSβ+ thalassemia, other SCD variants)
- Recurrent vaso-occlusive crises (VOCs) – defined as the occurrence of 2–10 SCPCs (acute pain needing medical contact, acute chest syndrome, priapism, hepatic or splenic sequestration) in the prior 12 months
- Anemia – defined as a Hb level of 5.5–10.5 g/dL
- If taking HU, the dose must be stable for ≥ 90 days before starting study drug

Key exclusion criteria

- Receiving regularly scheduled RBC transfusions
- Severe kidney disease or hepatobiliary disorders
- Currently receiving treatment with SCD therapies (excluding HU)
- Prior exposure to gene therapy, or prior bone marrow or stem cell transplantation

- The criteria for anemia and recurrent VOCs will identify a study population with an unmet need for effective treatment
- Patients who are regularly-transfused will be excluded given the potentially confounding effect of transfusions on Hb assessments and other laboratory measurements

Objectives

Phase 2

Primary objectives

- To determine the recommended phase 3 dose of mitapivat by evaluating the effect of 2 dose levels of mitapivat vs placebo on anemia in patients with SCD, and safety

Secondary objectives

- To evaluate the effect of 2 doses of mitapivat vs placebo on anemia, markers of hemolysis and erythropoiesis, patient-reported fatigue, and SCPCs
- To evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) effects of mitapivat

Phase 3

Primary objectives

- To determine the effect of mitapivat vs placebo on anemia and SCPCs in patients with SCD

Key secondary objectives

- To evaluate the effect of mitapivat vs placebo on anemia in patients with SCD, markers of hemolysis and erythropoiesis, patient-reported fatigue, and additional clinical efficacy measures related to SCPC

Other secondary objectives

- To evaluate the effect of mitapivat on additional markers of hemolysis and erythropoiesis, additional clinical efficacy measures related to SCPC, additional patient-reported measures of fatigue and pain, physical activity, safety
- To evaluate the PK/PD effects of mitapivat

Endpoints

Phase 2 primary endpoints

- **Hb response, defined as a ≥ 1.0 g/dL increase in average Hb concentration over Weeks 10–12 compared with baseline (BL)**
- **Type, severity, and relationship to study drug of adverse events (AEs) and serious AEs (SAEs)**

Phase 2 secondary endpoints

Anemia
• Average change from BL in Hb concentration over Weeks 10–12

Hemolysis
• Average change from BL in markers of hemolysis, including indirect bilirubin and lactate dehydrogenase (LDH), over Weeks 10–12

Erythropoiesis
• Average change from BL in markers of erythropoiesis, including absolute reticulocyte count, percent reticulocyte, and erythropoietin, over Weeks 10–12

Patient-reported fatigue
• Average change from BL in Patient-Reported Outcomes Measurement Information System® (PROMIS) Fatigue 13a Short Form (SF) score over Weeks 10–12

SCPCs
• Annualized rate of SCPC

PK/PD
• Exposure response (or PK/PD) relationship between relevant PK parameters and endpoints that are indicators of clinical activity and safety
• Change in mitapivat concentration over time and derived mitapivat PK parameters (including area under the concentration × time curve and maximum [peak] concentration)

Phase 3 primary endpoints

- **Hb response, defined as a ≥ 1.0 g/dL increase in average Hb concentration over Weeks 24–52 compared with BL**
- **Annualized rate of SCPCs**

Phase 3 key secondary endpoints

Anemia
• Average change from BL in Hb concentration over Weeks 24–52

Hemolysis
• Average change from BL in indirect bilirubin over Weeks 24–52

Erythropoiesis
• Average change from BL in percent reticulocyte over Weeks 24–52

Patient-reported fatigue
• Average Change from BL in PROMIS Fatigue 13a SF score over Weeks 24–52

SCPCs
• Annualized frequency of hospitalizations for SCPC

Phase 3 other secondary endpoints

Hemolysis (additional markers)
• Average change from BL in LDH concentration over Weeks 24–52

Erythropoiesis (additional markers)
• Average change from BL in absolute reticulocytes and erythropoietin over Weeks 24–52

Patient-reported fatigue (additional measures)
• Improvement on the Patient Global Impression of Severity (PGIS) of fatigue by at least 1 category at Weeks 24, 28, 40, and 52 from BL, or remain stable if none or mild fatigue at BL
• Improvement on the Patient Global Impression of Change (PGIC) of fatigue at Weeks 24, 28, 40, and 52 from BL, or "no change" if none or mild fatigue at BL

SCPCs (additional measures)
• Time to first SCPC • Time to second SCPC • Annualized rate of hospitalization days for SCPC • Annualized rate of Emergency Room visits for SCPC

Physical activity
• Change from BL in 6-minute walk test at Week 52

Patient-reported pain
• Change from BL in PROMIS Pain Intensity 1a, Worst Pain Numeric Rating Scale and Adult Sickle Cell QoL Measurement Information System (ASCQ-Me) Pain Impact average scores at Week 24 and at Week 52
• PGIC of pain and change from BL in PGIS of pain at Week 52

Safety
• Type, severity, and relationship to study drug of AEs and SAEs

PK/PD
• Exposure response (or PK/PD) relationship between relevant PK parameters and endpoints that are indicators of clinical activity and safety
• Change in mitapivat concentration over time and derived mitapivat PK parameters (including area under the concentration × time curve and maximum [peak] concentration)

Statistics

Phase 2

- With the planned sample size (n = 69), for each statistical test (mitapivat 50 mg vs placebo; and 100 mg vs placebo) there will be 83% power to detect an increase in Hb response rate from 10% in the placebo arm to 51% in the mitapivat arm based on a 2-sided significance level of 0.05
- If the study meets the primary endpoint of Hb response for 1, or both mitapivat arms, the study will proceed to phase 3. There is no multiplicity adjustment between the 2 hypothesis tests

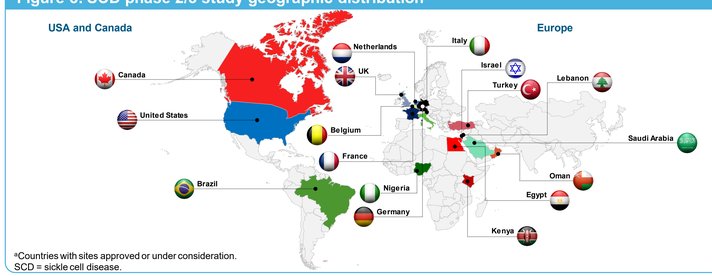
Phase 3

- With a planned sample size of 198 subjects (66 randomized to placebo and 132 randomized to mitapivat) there will be 91% power to detect an increase in Hb response rate from 10% in the placebo arm to 33% in the mitapivat arm based on a 2-sided significance level of 0.02
- The sample size will also provide 90% power to detect a decrease in the annualized SCPC rate of 3 in the placebo arm to 1.95 in the mitapivat arm at a 2-sided significance level of 0.03, assuming a dropout rate of 35% with an average of 0.55-years follow-up in the double-blind period, and a shape parameter of 0.2
- The key secondary endpoints will be tested using the Hochberg procedure only if at least one of the primary endpoints is statistically significant

Planned sites

- Geographic distribution of planned study sites (**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

- An unmet need exists for therapies that address both anemia and vaso-occlusion in SCD
- Activation of PKR by mitapivat may address anemia and vaso-occlusion by decreasing 2,3-DPG and increasing ATP, which may reduce HbS polymerization, RBC sickling, and hemolysis
- This phase 2/3 double-blind, randomized, placebo-controlled, global, multicenter study will utilize an operationally seamless design and clinically relevant endpoints to investigate the efficacy and safety of mitapivat, an investigational, first-in-class, oral, small-molecule allosteric activator of PKR, in patients ≥ 16 years of age with SCD
- Enrollment is currently ongoing

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Disclosures

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