The launch of a global, phase 2, open-label, multicenter, single-arm study of mitapivat in patients with sickle cell disease and nephropathy

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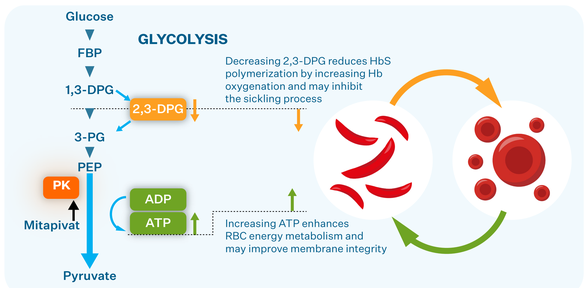
BACKGROUND

- Sickle cell nephropathy (SCN) causes significant mortality,[1] with approximately 10% of all sickle cell disease (SCD)-related deaths associated with kidney disease[2]
- It is estimated that approximately 30% of adults with SCD develop chronic kidney disease secondary to SCN[3]
- Albuminuria is a marker of kidney damage and predicts progressive decline in kidney function in children and adults with SCD[1]
- SCD treatment guidelines recommend screening for potential SCN in patients with SCD using urinary albumin-creatinine ratio (ACR),[4,5] a widely acceptable biomarker of kidney disease
- Mitapivat, a first-in-class, oral, small-molecule allosteric activator of pyruvate kinase (PK), including red blood cell-specific PK (PKR) and PK muscle isoenzyme 2 (PKM2) isoforms, is under investigation for the treatment of SCD[6–8] (**Figure 1**)
- In patients with SCD, mitapivat has demonstrated statistically significant and clinically meaningful improvement in hemoglobin (Hb) response compared with placebo, in addition to observed improvements in markers of hemolysis and erythropoiesis and reductions in annualized rates of sickle cell pain crises (SCPCs) (phase 2 portion of RISE UP [NCT05031780])[8]
  - Mitapivat was well tolerated, with an observed safety profile consistent with previously reported data on mitapivat in SCD and other hemolytic anemias[8]

Figure 1. PK activation in SCD may improve anemia and reduce sickling[9]



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

- In patients with SCN, improvement in anemia and reduction in sickling and hemolysis may reduce damage to the kidneys by improving blood perfusion, reducing sickling-related ischemia, and decreasing the toxicity caused by free heme in the kidneys
- Furthermore, PKM2 is highly expressed in kidney tubules,[10–12] and improved ATP production in the hypoxic, acidotic, and hyperosmolar environment of the tubules is a proposed mechanism by which mitapivat may benefit patients with renal disease in SCN[4,13,14]
- Studies are ongoing to investigate the role of PKM2 activation in improving renal fibrosis by reprogramming metabolism and decreasing collagen synthesis[15]
- There continue to be significant unmet needs for patients with SCN, and therapies that target end-organ damage in SCD, such as SCN, are needed

OBJECTIVE

- **To report the design of the phase 2, open-label, multicenter, global, single-arm study evaluating the efficacy and safety of mitapivat in patients with SCD and nephropathy (NCT06286046)[16]**

METHODS

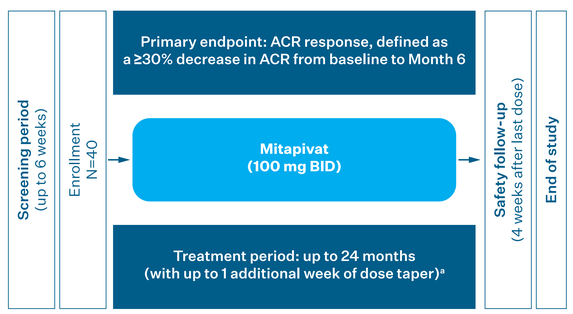
Study design

- This phase 2 study is designed to evaluate the efficacy and safety of mitapivat in patients with SCD and nephropathy, with the primary and key secondary objectives and endpoints displayed in **Tables 1 and 2**
- Patients with SCD and nephropathy will receive oral mitapivat 100 mg twice daily for up to 24 months (**Figure 2**)
- Treatment continuation past Month 6 will be at the discretion of the investigator and patient
- Duration of participation in the study is up to 2.2 years

Populations for analysis

- All patients who received at least 1 dose of mitapivat will be included in efficacy and safety analyses

Figure 2. Phase 2 study design



[a]Primary endpoint is assessed at 6 months; it is at the discretion of the Investigator and the patient whether to continue mitapivat treatment for up to 24 months
ACR, albumin-creatinine ratio; BID, twice daily

Key inclusion criteria

- Aged ≥16 years (≥18 years in France) at the time of providing informed consent/assent
- Documented SCD diagnosis (homozygous for sickle cell Hb or HbS/ß0-thalassemia)
- Hb level 5.5–10.5 g/dL during the screening period
- 2 urine ACR results[a] of ≥100 and <2000 mg/g collected during the screening period
- 1 ACR result >100 mg/g within 24 weeks before providing informed consent/assent
- If receiving hydroxyurea (HU), the dose must be stable for ≥90 days before starting mitapivat
- If taking angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy, the dose must be stable for ≥90 days before providing informed consent/assent
- Women of childbearing potential must be abstinent of activities that may induce pregnancy, or agree to use 2 forms of contraception, 1 of which must be considered highly effective

[a]1 result can be from an untimed urine sample; the other must be from the first (or second) morning void on a different day

Key exclusion criteria

- Pregnant, breastfeeding, or parturient
- Receiving regularly scheduled blood transfusions
  - Episodic transfusion in response to worsened anemia or vaso-occlusive crisis is permitted
- Received blood transfusion within 60 days of providing informed consent/assent or during the screening period
- Hospitalization[a] due to SCPCs or other vaso-occlusive event within 14 days of providing informed consent/assent or during the screening period
- >10 SCPCs in the 52 weeks prior to providing informed consent/assent
- Renal dysfunction (defined as estimated glomerular filtration rate [eGFR] <45 mL/min/1.73 m^2), renal disease due to another disorder unrelated to SCD, or evidence of acute kidney injury
- History of stroke, hepatobiliary disorders, or kidney transplantation at any time
- Currently undergoing renal replacement therapy (hemodialysis, peritoneal dialysis, hemofiltration, kidney transplantation)
- Individuals receiving treatment with disease-modifying SCD therapies other than HU, or hematopoietic stimulating agents (last dose of such therapies must have been administered ≥90 days prior to randomization)
- Poorly controlled hypertension[b] refractory to medical management

[a]Defined as an in-patient admission to a hospital that may or may not be preceded by an emergency room or outpatient clinic visit; [b]Defined as systolic blood pressure (BP) >150 mm Hg or diastolic BP >90 mm Hg

Table 1. Study primary objective and endpoint

Primary objective *To determine the effect of mitapivat on:*	**Primary endpoint** *Measured by:*
ACR response in patients with SCD and nephropathy	≥30% decrease in ACR[a] from baseline to Month 6

[a]Derived as the mean of the ACR results from 2 urine samples (1 untimed and 1 from a first or second morning void)
ACR, albumin-creatinine ratio; SCD, sickle cell disease

Table 2. Key secondary objectives and endpoints

Key secondary objectives *To determine the effect of mitapivat on:*	**Key secondary endpoints** *Measured by:*
Cystatin C and creatinine-based eGFR ($eGFR_{cr\text{-}cys}$)	Change from baseline in $eGFR_{cr\text{-}cys}$ • $eGFR_{cr\text{-}cys}$ will be calculated according to the 2021 Chronic Kidney Disease Epidemiology Collaboration creatinine-cystatin equation[17]
ACR	Change from baseline in ACR Stable ACR, defined as Month 6 ACR within ±20% of baseline ACR
Efficacy measures related to nephropathy	Annualized rate of visits to emergency room Annualized rate of days of hospitalizations
To evaluate the safety of mitapivat	Type, frequency, and severity of adverse events (AEs) and serious AEs and relationship to study drug

ACR, albumin-creatinine ratio; AE, adverse event; eGFR, estimated glomerular filtration rate; $eGFR_{cr\text{-}cys}$, cystatin C and creatinine-based estimated glomerular filtration rate

RESULTS

- Approximately 40 patients with SCD and nephropathy will be enrolled in this study
- 35 sites across 7 countries are planned for recruitment (**Figure 3**)

Figure 3. Study geographic distribution

CONCLUSION

- **This phase 2 study is designed to evaluate the efficacy and safety of mitapivat in patients with SCD and nephropathy**

Further trial information is available at www.clinicaltrials.gov (NCT06286046) and from medinfo@agios.com

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References and supplemental materials are available via the QR code

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