



## Evaluation of safety and efficacy of mitapivat sulfate in adult patients with sickle cell disease

**Short title:** ESTIMATE study

**Principal investigator:** Dr. E.J. van Beers

**Sponsor:** Julius Clinical Research B.V.

**EudraCT nr.:** 2019-003438-18

**Patient population:** sickle cell anemia patients, aged 18 years and older

**Required no. of patients (if applicable):** 10

**Type of study:** Prospective exploratory monocenter pilot study

### Study objectives:

#### Primary objectives:

- To assess (maximum) efficacy of treatment with mitapivat (AG-348) on sickling as evaluated by change in Point of Sickling (PoS, expressed in mmHg), as quantified by the Oxygenscan.
- To evaluate safety of mitapivat (including the type, incidence, severity and relationship of mitapivat to AE and SAE; number of medication discontinuations due to AE; physical examination findings, vital signs and 12-lead electrocardiogram (ECG) data).

#### Secondary objectives:

- To evaluate the effect of mitapivat on changes in hemoglobin (Hb) and other hematological parameters, lactate dehydrogenase (LDH), bilirubin, carboxy hemoglobin (HbCO), red cell 2,3-DPG and ATP levels.
- To evaluate the effect of mitapivat on changes of surrogate markers of mortality and organ damage in SCD (NT-proBNP, urinary albumin to creatinine ratio (ACR), CRP, HbCO/LDH).
- To evaluate the effect of mitapivat on RBC deformability using the Osmoscan (osmotic gradient ektacytometry)
- To evaluate the effect of mitapivat on clinical characteristics: Health Related Quality of Life (HRQoL) (EQ-5D-5L, SF-36), movement behaviour (accelerometer Activ8), dyspnea (MRC dyspnea) and fatigue (PROMIS fatigue short form)

#### Exploratory objectives:

- To evaluate the number of VOCs (per 365 days) during study drug compliant period.
- To evaluate the number of days admitted in hospital for acute sickle cell related complications (per 365 days) during study drug compliant period.
- To evaluate PK activity and thermostability in relation to PoS, red cell ATP and 2,3-DPG levels and the effect of mitapivat on the relation between these parameters.
- To evaluate changes in metabolomics by mitapivat.
- To evaluate changes in additional urinary parameters and biomarkers of sickle cell nephropathy.

## Subject eligibility criteria:

### *Inclusion criteria:*

1. Male or female with documented homozygous sickle cell anemia (HbSS or HbS/beta(0)-thalassemia).
2. Documented history of VOCs, and number of days admitted in hospital for acute sickle cell related complications during 24 months before inclusion.
3. Had at least 1 (but no more than 10) VOC in the past 12 months prior to the first day of study treatment.
4. Age  $\geq 18$  years.
5. Hemoglobin (Hb)  $\leq 6.5$  mmol/L (approx. 10.4 g/dL) and  $> 3.8$  mmol/L (approx. 6.0 g/dL) during screening.
6. For subjects taking hydroxyurea (HU), the dose of HU (mg/kg) must have been stable for at least 3 months prior to the first day of study treatment.
7. Subjects must start or continue taking at least the equivalent of daily 0.8 mg oral folic acid for the duration of the study.
8. Have adequate organ function, as defined by:
  - a. Serum aspartate aminotransferase (AST)  $\leq 2.5 \times$  ULN (unless the increased AST is assessed by the Investigator as due to hemolysis and/or hepatic iron deposition) and alanine aminotransferase (ALT)  $\leq 2.5 \times$  ULN.
  - b. Normal or elevated levels of serum bilirubin. In subjects with serum bilirubin  $>$  ULN, the elevation must be attributed to hemolysis with or without Gilbert's syndrome and must not be associated with choledocholithiasis, cholecystitis, biliary obstruction, or hepatocellular disease. Elevated bilirubin attributed to hemolysis with or without Gilbert's syndrome is not exclusionary.
  - c. Serum creatinine  $\leq 1.25 \times$  ULN. If serum creatinine is  $> 1.25 \times$  ULN, then glomerular filtration rate, estimated by 24-hour measured or calculated (Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)) creatinine clearance, must be  $\geq 60$  mL/min/1.73 m<sup>2</sup>.
  - d. Absolute neutrophil count  $\geq 1.0 \times 10^9$ /L during screening.
  - e. Platelet count  $\geq 100 \times 10^9$ /L during screening.
  - f. Activated partial thromboplastin time and international normalized ratio  $\leq 1.25 \times$  ULN, unless the subject is receiving therapeutic anticoagulants.
9. Be willing and able to give written informed consent and to comply to all study procedures for the duration of the study.
10. Patients with increased albumin to creatinine ratio are prioritized above patients with a normal albumin to creatinine ratio. Both are eligible.
11. For women of reproductive potential, have a negative urine and serum pregnancy test during the Screening Period (D-50 to D-1). Women of reproductive potential are defined as sexually mature women who have not undergone a hysterectomy, bilateral oophorectomy or tubal occlusion; or who have not been naturally postmenopausal (i.e., who have not menstruated at all for at least the preceding 12 months prior to signing informed consent).
12. For (fertile men of) women of reproductive potential, agree to use double contraception during the trial period plus 90 days (for male subjects) or 28 days (for female subjects) after the last dose of AG-348.

*Exclusion criteria:*

1. More than 10 VOCs within the past 12 months.
2. Hospitalized for sickle cell crisis or other vaso-occlusive event within 14 days prior the first day of study treatment. Subjects who may get hospitalized during the Screening Period are allowed to be rescreened 14 days after discharge.
3. Receiving regularly scheduled blood (RBC) transfusion therapy (also termed chronic, prophylactic or preventive transfusion), defined as more than 4 transfusion episodes in the 12-month period up to the first day of study treatment, and/or have received a transfusion within the past 3 months prior to the first day of study treatment.
4. Have a significant medical condition that confers an unacceptable risk to participating in the study, and/or that could confound interpretation of the study data. Such significant medical conditions include, but are not limited to:
  - a) Poorly controlled hypertension (defined as systolic blood pressure >150 mmHg or diastolic blood pressure >90 mmHg) refractory to medical management.
  - b) Any history of congestive heart failure; myocardial infarction or unstable angina pectoris; hemorrhagic, embolic, or thrombotic stroke; or recent (< 6 months prior to signing informed consent) deep venous thrombosis, or pulmonary or arterial embolism.
  - c) Cardiac dysrhythmias judged as clinically significant by the Investigator.
  - d) Heart-rate corrected QT interval (QTc) by Fridericia's method >450 msec with the exception of subjects with right or left bundle branch block.
  - e) Clinically symptomatic cholelithiasis or cholecystitis. Prior cholecystectomy is not exclusionary. Subjects with symptomatic cholelithiasis or cholecystitis may be rescreened once the disorder has been treated and clinical symptoms have resolved.
  - f) History of drug-induced cholestatic hepatitis.
  - g) Iron overload sufficiently severe to result in a clinical diagnosis by the Investigator of cardiac (eg, clinically significant impaired left ventricular ejection fraction), hepatic (eg, fibrosis, cirrhosis), or pancreatic (eg, diabetes) dysfunction.
  - h) Have a diagnosis of any other congenital or acquired blood disorder or any other hemolytic process, except mild allo-immunization, as a consequence of transfusion therapy.
  - i) Positive test for HBsAg or HCVAb with signs of active hepatitis B or C virus infection. Subjects with hepatitis C may be rescreened after receiving appropriate hepatitis C treatment.
  - j) Positive test for HIV-1 or -2 antibodies.
  - k) Active infection requiring the use of parenteral antimicrobial agents or Grade  $\geq 3$  in severity (per NCI CTCAE) within 2 months prior to the first dose of study treatment.
  - l) Diabetes mellitus judged to be under poor control by the Investigator or requiring >3 antidiabetic agents, including insulin (all insulins are considered 1 agent); use of insulin per se is not exclusionary.
  - m) History of any primary malignancy, with the exception of: curatively treated non-melanomatous skin cancer; curatively treated cervical or breast carcinoma in situ; or other primary tumor treated with curative intent, no known active disease present, and no treatment administered during the last 3 years.
  - n) Unstable extramedullary hematopoiesis that could pose a risk of imminent neurologic compromise.
  - o) Severe hepatic issues such as liver fibrosis (F3 or worse), significant cirrhosis or non-alcoholic steatohepatitis.



- p) Current or recent history of psychiatric disorder that, in the opinion of the Investigator, could compromise the ability of the subject to cooperate with study visits and procedures.
5. Are currently enrolled in another therapeutic clinical trial involving ongoing therapy with any investigational or marketed product or placebo. Participation in registry studies is allowed.
  6. Have exposure to any investigational drug, device, or procedure within 3 months prior to the first dose of study treatment.
  7. Have had any prior treatment with a pyruvate kinase activator.
  8. Have a prior bone marrow or stem cell transplant.
  9. Are currently pregnant or breastfeeding, or planning to become pregnant during the course of the study.
  10. Have a history of major surgery within 6 months prior to signing informed consent. Note that procedures such as laparoscopic gallbladder surgery are not considered major in this context.
  11. Are currently receiving medications that are strong inhibitors of CYP3A4 or strong inducers of CYP3A4 that have not been stopped for a duration of at least 5 days or a timeframe equivalent to 5 half-lives (whichever is longer) prior to the first dose of study treatment.
  12. Are currently receiving hematopoietic stimulating agents (eg, erythropoietins, granulocyte colony stimulating factors, thrombopoietins) that have not been stopped for a duration of at least 28 days prior to the first dose of study treatment.
  13. Known allergy to mitapivat or its excipients (microcrystalline cellulose, croscarmellose sodium, sodium stearyl fumarate, and mannitol) or history of acute allergic reaction to drugs characterized by acute hemolytic anemia, drug-induced liver injury, anaphylaxis, rash of erythema multiforme type or Stevens-Johnson syndrome, cholestatic hepatitis, or other serious clinical manifestations.
  14. For men and women of reproductive potential: unwillingness to use double contraception during the trial period.

**Status:** open for inclusion

**Participating sites:** University Medical Center Utrecht

**Contact for more information:**

Dr. E.J. van Beers  
Van Creveldkliniek, University Medical Center Utrecht  
Heidelberglaan 100, PO Box 85500, 3508 GA Utrecht, The Netherlands  
e.j.vanbeers-3@umcutrecht.nl; tel: +31 88 755 8450

**Summary (optional):**

**Rationale:** The number one cause of years lost to disability by anemia in Western Europe and North America is Sickle Cell Disease (SCD). Patients with SCD have severe anemia and experience extremely painful events called vaso-occlusive crises (VOC). The intracellular level of 2,3-diphosphoglycerate (2,3-DPG, a glycolytic metabolite) is high in sickled red blood cells and associated with high Point of Sickling (PoS) and disease severity. Preliminary results from Laboratory for Clinical Chemistry and Hematology, University Medical Center (UMC) Utrecht, suggest that high 2,3-DPG levels in SCD patients may result from decreased pyruvate kinase (PK) (thermo-)stability.

Mitapivat sulfate (AG-348, mitapivat) is a drug currently in clinical development for the treatment of hereditary PK deficiency (PKD). PKD, like SCD, is associated with high 2,3-DPG levels. AG-348 has been shown to lower 2,3-DPG levels in healthy subjects and ex-vivo treated red blood cells of PKD patients. Therefore AG-348 represents an investigational agent that may offer clinical benefit for SCD patients as well.

Based on the results of AG-348 in healthy subjects and PKD patients, there is reason to believe that treatment of SCD patients with AG-348 may result in the same improvement in PoS as ex vivo treatment has shown. Subsequently, this may also result in associated improvement of erythrocyte parameters (erythrocyte count, hemoglobin (Hb), hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), red cell distribution width (RDW), reticulocyte parameters (reticulocyte count, immature reticulocyte fraction (IRF), reticulocyte hemoglobin concentration (CHCr)) and surrogate markers of mortality risk in SCD such as C-reactive protein (CRP) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP).

Objective: To study the safety and efficacy of AG-348 in the treatment of adult subjects with sickle cell disease

Study design: Prospective exploratory monocenter pilot study.

Study population: Ten sickle cell anemia patients, aged 18 years and older.

Intervention: During the 8-week Dose Finding Period, subjects will be treated with an initial dose of 20 mg AG-348 twice daily (BID). Depending on safety and Hb changes, dosing may be increased in two steps, i.e. from 20 mg BID to 50 mg BID at week 2, and subsequently from 50 mg BID to 100 mg BID for week 4 through 8. Subjects who remain on 20 mg BID through week 4 may be increased to 50 mg BID (but not 100 mg BID) for week 4 through 8, or remain on 20 mg BID. Subjects who safely tolerate AG-348 and show evidence of clinical activity, may be eligible to continue a 52-week follow-up period (Fixed Dose Extension Period), allowing patients to remain on their optimal dose of AG-348. During the Fixed Dose Extension Period, the dose may not exceed the maximum doses that was used during Dose Finding Period.

Main endpoints:

Safety and efficacy of AG-348 in SCD are the main endpoints in this study. Safety will be evaluated by analysis of adverse events, medication, physical examination findings and ECG. The primary efficacy measure will be the effect of AG-348 on sickling, evaluated by change in PoS (expressed in mmHg), as quantified by the Oxygenscan. Other efficacy measures include the percentage of patients that has an improvement in hemoglobin level of at least 1g/dL at any time point during the Dose Finding Period compared to baseline (mean Hb level during Screening Period (Day (D)-50 to D-1) and D0), and increase in mean hemoglobin level during the Fixed Dose Extension Period compared to baseline (mean Hb level during Screening Period (D-50 to D-1) and D0). Lastly, effect on clinical complication rate during Fixed Dose Extension Period will be compared to historical rates of patients during the 2 years prior to screening.



Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Besides anemia, SCD patients are confronted with extremely painful events called vaso-occlusive crises, chronic pain and a shortened life expectancy; half of the SCD patients in high income western society will have died before reaching the age of sixty. The safety profile of AG-348 established in clinical trials to date is favorable. AG-348 has been generally well tolerated in both healthy adult subjects at single doses up to 2500 mg and multiple doses up to 70 mg BID in healthy subjects and adult subjects with PK deficiency, although aromatase inhibition and transaminase increases have been observed in both subject populations. Adverse drug reactions also included decreased bone mineral density, withdrawal hemolysis, insomnia, gastrointestinal disturbances and triglyceride increase. Taken together the risk benefit ratio for AG-348 in SCD is positive.