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

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This study has been transitioned to CTIS with ID 2024-515569-32-00 check the CTIS register for the current data. To study the safety and efficacy of mitapivat in the treatment of adult subjects with sickle cell disease.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Red blood cell disorders
Study type	Interventional

Summary

ID

NL-OMON54689

Source
ToetsingOnline

Brief title
ESTIMATE

Condition

- Red blood cell disorders

Synonym
sickle cell anemia, Sickle cell disease

Research involving
Human

Sponsors and support

Primary sponsor: Julius Clinical
Source(s) of monetary or material Support: Agios Pharmaceuticals Inc.

Intervention

Keyword: Efficacy, Mitapivat, Safety, Sickle cell disease

Outcome measures

Primary outcome

- To assess (maximum) efficacy of treatment with mitapivat on sickling as evaluated by change in Point of Sicking (PoS, expressed in mmHg), as quantified by the Oxygenscan. During the Dose Finding Period the maximum efficacy is defined as the lowest PoS measured during the treatment period relative (%) to the mean PoS during the Screening Period (Day -50 to Day -1) and D0. During the Fixed Dose Extension Period, the efficacy of treatment with mitapivat is evaluated by mean PoS during this treatment period relative (%) to the mean PoS during the Screening Period (Day -50 to Day -1) and D0.

- To evaluate safety of AG-348 (including the type, incidence, severity and relationship of AG-348 to AE and SAE; number of medication discontinuations due to AE; physical examination findings, vital signs and 12-lead electrocardiogram (ECG) data).

Secondary outcome

Secondary:

- To evaluate the effect of mitapivat on changes in hemoglobin (Hb) an 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), C-reactive protein (CRP), LDH/HbCO).

- To evaluate the effect of mitapivat on RBC deformability using the Osmoscan (osmotic gradient ektacytometry).

- To evaluate the effect of mitapivat on clinical characteristics quality of life (questionnaires EQ-5D-5L and SF-12), fatigue (questionnaire PROMIS fatigue short form), questionnaire dyspnea (MRC dyspnea) and movement behaviour (accelerometer Activ8).

Exploratory:

- 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 AG-348 on the relation between these parameters.

- To evaluate changes in metabolomics

- To evaluate changes in additional urinary parameters and markers of sickle cell nephropathy

Study description

Background summary

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 our laboratory 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. Mitapivat has been shown to lower 2,3-DPG levels in healthy subjects and ex-vivo treated red blood cells of PKD patients. Therefore mitapivat represents an investigational agent that may offer clinical benefit for SCD patients as well.

Based on the results of mitapivat in healthy subjects and PKD patients, there is reason to believe that treatment of SCD patients with mitapivat 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, 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 brain-type natriuretic peptide (NT-proBNP)).

Study objective

This study has been transitioned to CTIS with ID 2024-515569-32-00 check the CTIS register for the current data.

To study the safety and efficacy of mitapivat in the treatment of adult subjects with sickle cell disease.

Study design

Prospective exploratory monocenter pilot study.

Intervention

During the 8-week Dose Finding Period, subjects will be treated with an initial dose of 20 mg mitapivat 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. Subjects who safely tolerate mitapivat 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 mitapivat. During the Fixed Dose Extension Period, the dose may not exceed the maximum doses that was used during Dose Finding Period. Hereafter, subjects may continue in the Prolonged Fixed Dose Extension for a period of 24 months.
After this period, patients will be given the opportunity to participate in the 'extended period' which will take 36 months. Long-term safety and efficacy data will be collected in this period.

Study burden and risks

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 mitapivat established in clinical trials to date is favorable. Mitapivat 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 and adult subjects with PK deficiency, although aromatase inhibition has been observed in both subject populations. Adverse drug reactions also included decreased bone mineral density, withdrawal hemolysis, insomnia, gastrointestinal disturbances, triglyceride increase and hot flushes. Taken together the risk benefit ratio for mitapivat in SCD is positive.

Contacts

Public
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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (16-17 years)
Adults (18-64 years)

Inclusion criteria

1. Male or female with homozygous sickle cell anemia (HbSS) or HbS/beta(0 or +)-thallassemia). 2. Documented history of VOCs, and number of days admitted in hospital for acute sickle cell related complications during 24 months before inclusion. 3. SCD with at least one of the following conditions: I. Had at least 1 (but no more than 10) VOC in the past 12 months prior to the first day of study treatment. II. any sickle cell related hospital admission in the past 12 months prior to the first day of study treatment; III. any history of sickle cell related complications (such as osteonecrosis, osteoporosis, nephropathy, retinopathy, leg ulcer, acute chest syndrome, acute hemolytic crisis); IV. presence of any clinical biomarkers associated with increased mortality in SCD prior to the first day of study treatment (NT-proBNP >160 pg/mL, LDH/HbCO ratio >1,200, tricuspid regurgitant jet velocity =2.5 m/s). 4. Age 16 years and older, inclusive; subjects age 16 or 17 years must be documented Tanner Stage 5. 5. Hemoglobin <=6.9 mmol/L (approx 11.1 g/dL) and >2.5 mmol/L (approx 4.0 g/dL). 6. For subjects on hydroxyurea: the dose must have been stable for at least 3 months prior the 1st day of study treatment. 7. Subjects must start or continue taking at least the equivalent of daily 0.7 mg oral folic acid for the duration of the study. 8. Have adequate organ function based on ALT, AST, billirubin, creatinine, neutrophil and platelet count and INR. 9. Willing and able to give written informed consent and comply to all study procedures. 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 at screening. 12. For (fertile men of) women of reproductive potential: Agree to use double anticonception during the study plus 90 days (for males) or 28 days (for females) after the last dose of the study drug.

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 to the first day of study treatment (rescreening is allowed).
3. Have a point of sickling (PoS) <=24.6 mmHg as quantified by the Oxygenscan during screening to exclude subjects with no clinical relevant detectable sickling.
4. Subjects age 16 or 17 years who are documented Tanner stage 1-4 (see Appendix II).
5. Receiving regularly scheduled (red blood cell) transfusion, defined as more than 4 transfusions in the 12 months prior 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.
6. Have a significant medical condition that confers an unacceptable risk to participation in the study, and/or that could confound interpretation of the study data (such as poorly controlled hypertension, cardiac diseases, cholelithiasis, cholecystitis, cholestatis hepatitis, iron overload that could result in cardiac/hepatic/pancreatic dysfunction, have diagnosis of other congenital or acquired blood disorder, active hepatitis B or C infection or antibodies, HIV-1 of HIV-2 antibodies, active infections, poorly controlled diabetes mellitus, history of primary malignancy (except for non-melanomatous skin cancer, curatively treated cervical or breast carcinoma in situ with no known active disease present and no treatment administered during the last 3 years, unstable extramedullary hematopoiesis that could pose a risk of imminent neurologic compromise, severe hepatic fibrosis/cirrhosis or NASH, current or recent history of psychiatric disorder that could compromise the ability of the subject to cooperate with study visits and procedures.
7. 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.
8. Have exposure to any investigational drug, device, or procedure within 3 months prior to the first dose of study treatment.
9. Have had any prior treatment with a pyruvate kinase activator.
10. Have a prior bone marrow or stem cell transplant.
11. Are currently pregnant or breastfeeding, or planning to become pregnant during the course of the study.
12. Have a history of major surgery within 6 months of signing informed consent. Note that procedures such as laparoscopic gallbladder surgery are not considered major in this context.
13. 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.
14. 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.
15. 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.
16. For men and women of reproductive potential: unwillingness to use double anticonception during the trial period.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	24-09-2020
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	AG-348 sulfate hydrate
Generic name:	Mitapivat sulfate

Ethics review

Approved WMO

Date:	28-04-2020
Application type:	First submission
Review commission:	METC NedMec

Approved WMO

Date:	14-05-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	06-10-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-10-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-03-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-04-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-11-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-12-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-03-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-03-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	01-05-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-07-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-08-2023
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2024-515569-32-00
EudraCT	EUCTR2019-003438-18-NL
CCMO	NL71253.041.20
Other	NL8517 (NTR)