A Phase 3, Double-blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Efficacy and Safety of Mitapivat in Subjects With Non-Transfusion-Dependent Alpha- or Beta-Thalassemia (ENERGIZE)

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This study has been transitioned to CTIS with ID 2024-512745-16-00 check the CTIS register for the current data. Study AG348-C-017 is a Phase 3, double-blind, randomized, placebo-controlled, multicenter study designed to demonstrate the clinical...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON56352

Source
ToetsingOnline

Brief title
AG348-C-017 (ENERGIZE)

Condition

- Other condition
- Red blood cell disorders

Synonym
&alfa;- or β- non-transfusion-dependent thalassemia

Health condition

&alfa;- of β- niet-transfusie-afhankelijke thalassemie (NTDT)

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Double-blind, Efficacy and Safety, Placebo-Controlled, Randomized

Outcome measures

Primary outcome

The primary objective is to compare the effect of mitapivat versus placebo on anemia in subjects with α- or β non-transfusion-dependent thalassemia. The primary endpoint is Hemoglobin (Hb) response, defined as a >=1.0 g/dL increase in average Hb concentration from Week 12 through Week 24 compared with baseline.

Secondary outcome

The key secondary objectives are to compare the effect of mitapivat versus placebo on fatigue and to compare the effect of mitapivat versus placebo on additional measures of anemia.

Other secondary objectives are to evaluate the effect of mitapivat versus placebo on anemia and markers of hemolysis and erythropoiesis, to evaluate the effect of mitapivat versus placebo on anemia and markers of hemolysis and erythropoiesis, to evaluate the effect of mitapivat versus placebo on physical

activity, to evaluate the effect of mitapivat versus placebo on iron metabolism, to evaluate the safety of mitapivat and to evaluate the pharmacokinetic and pharmacodynamic effects of mitapivat.

Study description

Background summary

In thalassemia, the imbalance in globin chain synthesis imposes metabolic stress on the RBCs, specifically in the form of excess generation of reactive oxygen species and an increased demand on adenosine triphosphate (ATP)-dependent proteolytic mechanisms to clear excess globin chains. In thalassemic RBCs, ATP supply appears to be insufficient to maintain RBC membrane fitness and clearance of globin precipitates, leading to early and increased death of RBC precursors in the bone marrow and in extramedullary sites.
These pathophysiological changes lead to the hallmarks of the disease: ineffective erythropoiesis, peripheral hemolysis, and subsequent anemia. Clinical implications of the α- and β-globin imbalance include lack of sufficient RBCs and Hb for effective oxygen transport, and ineffective erythropoiesis and hemolysis, which can lead to splenomegaly, bone marrow expansion (extramedullary hematopoiesis), concomitant bone deformities, and iron overload.
Alpha- and β-thalassemias are genetically heterogeneous and vary by phenotype and severity.
Clinical management with RBC transfusions is an essential factor in classifying thalassemias as either transfusion-dependent thalassemia (TDT) or non-transfusion dependent thalassemia (NTDT). Patients with TDT need life-long regular transfusions for survival. Patients with NTDT do not need life-long regular transfusions for survival; however, they may require transfusions during times of erythroid stress such as infection, pregnancy, surgery, or aplastic crisis, and may transition to requiring regular transfusions and becoming transfusion-dependent later in life.
The investigational drug mitapivat (also known as mitapivat sulfate and AG-348) is a first in class, orally bioavailable, potent, allosteric activator of wild-type RBC-specific form of pyruvate kinase (PKR) and a range of PKR mutant enzymes. The RBC specific form of pyruvate kinase is 1 of 4 pyruvate kinase isoenzymes expressed in human tissues from 2 separate genes, liver specific form of pyruvate kinase (PKL) and pyruvate kinase muscle isozyme (PKM). Both PKR and PKL are splice isoforms of the PKLR gene, while PKM1 and PKM2 are both expressed from the PKM gene. Mitapivat is an allosteric activator of the PKR, PKL, and PKM2 isoenzymes, with similar potency against each.

Mitapivat acts by allosterically binding to the PKR tetramer and enhancing its affinity for phosphoenolpyruvate (PEP), thereby increasing the conversion of PEP + adenosine diphosphate to pyruvate + ATP.

Although recently approved therapies offer new options for patients with β-TDT, there are no approved treatments for patients with α-thalassemia or for patients with NTDT, indicating the unmet medical need for these patients. Mitapivat has the potential to treat anemia and improve how patients feel and function in a broader portion of the population of patients with thalassemia, while providing the option of oral administration.

Study objective

This study has been transitioned to CTIS with ID 2024-512745-16-00 check the CTIS register for the current data.

Study AG348-C-017 is a Phase 3, double-blind, randomized, placebo-controlled, multicenter study designed to demonstrate the clinical efficacy and safety of mitapivat in subjects with α- or β NTDT. The primary objective of the study is to compare the effect of mitapivat versus placebo on anemia (ie, Hb response), supported by patient-reported outcome (FACIT-Fatigue) and performance outcome (6MWT) measures evaluating how subjects feel and function, and hemolytic and erythropoietic parameters and iron metabolism.

Study design

This is a Phase 3, double-blind, randomized, placebo-controlled, multicenter study evaluating the efficacy and safety of mitapivat versus placebo in adult subjects with α- or β-NTDT followed by an Open-label Extension Period. Approximately 171 subjects are planned to be randomized in this study. This multicenter study will be conducted internationally

Intervention

Subjects will receive 100 mg BID (twice daily) mitapivat or matched-placebo for oral administration. Tablets are to be swallowed whole with water and may be taken with or without food.
Subjects who discontinue study drug should undergo the recommended dose taper and be monitored as clinically indicated for signs and symptoms of acute hemolysis and worsening anemia. If immediate or abrupt study drug discontinuation is required for an AE or medical emergency, subjects should be monitored as clinically indicated for signs of acute hemolysis or worsening anemia.

Study burden and risks

Mitapivat has been generally well tolerated in both healthy adult subjects and adult subjects with hemolytic anemias, although aromatase inhibition and transaminase increases have been observed. The doses of mitapivat planned for future clinical studies will not exceed a 200 mg total daily dose, which is expected to reduce the risks associated with potential liver toxicity.
Liver function tests will be monitored in clinical studies of mitapivat, and transaminase increased of more than 2.5× patient individual baseline or to Grade 2 will be reported as an AESI. Moreover, data available at this time also indicate that mitapivat does not have a significant QT/QTc prolongation effect.
Based on currently available data, reported benefits of treatment with mitapivat outweigh the observed risks of treatment.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. >=18 years of age at the time of providing informed consent.
2. Documented diagnosis of thalassemia (β-thalassemia with or without α-globin gene mutations, HbE/β-thalassemia, or α-thalassemia/HbH disease) based on Hb electrophoresis, Hb high-performance liquid chromatography, and/or DNA analysis from the subject*s medical record. If this information is not available from the subject*s medical record, the test(s) can be performed by a local laboratory during the Screening Period. If a local laboratory is unable to perform the test(s), results from the comprehensive α- and β-globin genotyping performed by the study central laboratory can be used.
3. Hb concentration <=10.0 g/dL (100.0 g/L), based on an average of at least 2 Hb concentration measurements (separated by >=7 days) collected during the Screening Period.
4. Non-transfusion dependent, defined as <=5 red blood cell (RBC) units during the 24-week period before randomization, and no RBC transfusions <=8 weeks before providing informed consent and no RBC transfusions during the Screening Period.
5. If taking hydroxyurea, the hydroxyurea dose must be stable for >=16 weeks before randomization.
6. Women of childbearing potential (WOCBP) must be abstinent of sexual activities that may result in pregnancy as part of their usual lifestyle or agree to use 2 forms of contraception, 1 of which must be considered highly effective, from the time of providing informed consent, throughout the study, and for 28 days after the last dose of study drug. The second form of contraception can be an acceptable barrier method.
7. Written informed consent before any study-related procedures are conducted and willing to comply with all study procedures for the duration of the study.

Exclusion criteria

1. Pregnant, breastfeeding or parturient.
2. Documented history of homozygous or heterozygous HbS or HbC.
3. Prior exposure to gene therapy or prior bone marrow or stem cell transplantation.
4. Currently receiving treatment with luspatercept; the last dose must have been administered >=18 weeks before randomisatie.
5. Currently receiving treatment with hematopoietic stimulating agents; the last dose must have been administered >=18 weeks before randomisatie.
6. History of malignancy (active or treated) <=5 years before providing informed consent, except for nonmelanomatous skin cancer in situ, cervical carcinoma in situ, or breast carcinoma in situ.
7. History of active and/or uncontrolled cardiac or pulmonary disease <=6 months before providing informed consent, including but not limited to:

a. New York Heart Association Class III or IV heart failure or clinically significant dysrhythmia
b. Myocardial infarction or unstable angina pectoris; hemorrhagic, embolic, or thrombotic stroke; deep venous thrombosis; or pulmonary or arterial embolism
c. Heart rate-corrected QT interval using Fridericia*s method >=450 milliseconds (males) or >=470 milliseconds (females), except for right or left bundle branch block
d. Severe pulmonary fibrosis as defined by severe hypoxia, evidence of right-sided heart failure, and radiographic pulmonary fibrosis >50%
e. Severe pulmonary hypertension as defined by severe symptoms associated with hypoxia, right-sided heart failure, and oxygen indicated
8. Hepatobiliary disorders, including but not limited to:
a. Liver disease with histopathological evidence of cirrhosis or severe fibrosis
b. Clinically symptomatic cholelithiasis or cholecystitis (prior cholecystectomy is not exclusionary)
c. History of drug-induced cholestatic hepatitis
d. Aspartate aminotransferase >2.5 × upper limit of normal (ULN); unless due to hemolysis and hepatic iron deposition) and alanine aminotransferase >2.5 × ULN (unless due to hepatic iron deposition)
9. Estimated glomerular filtration rate <45 mL/min/1.73 m2 by Chronic Kidney Disease Epidemiology Collaboration creatinine equation.
10. Nonfasting triglycerides >440 mg/dL (5 mmol/L)
11. Active infection requiring systemic antimicrobial therapy at the time of providing informed consent. If antimicrobial therapy is required during the Screening Period, screening procedures should not be performed while antimicrobial therapy is being administered, and the last dose of antimicrobial therapy must be administered >=7 days before randomization.
12. Positive test for hepatitis C virus (HCV) antibody (Ab) with evidence of active HCV infection, or positive test for hepatitis B surface antigen.
13. Positive test for HIV-1 Ab or HIV-2 Ab.
14. History of major surgery (including splenectomy) <=16 weeks before providing informed consent and/or a major surgical procedure planned during the study.
15. Current enrollment or past participation (<=12 weeks before administration of the first dose of study drug or a time frame equivalent to 5 half-lives of the investigational study drug, whichever is longer) in any other clinical study involving an investigational treatment or device.
16. Receiving strong cytochrome P450 (CYP)3A4/5 inhibitors that have not been stopped for >=5 days or a time frame equivalent to 5 half-lives (whichever is longer), or strong CYP3A4 inducers that have not been stopped for >=4 weeks or a time frame equivalent to 5 half-lives (whichever is longer), before randomisation.
17. Receiving anabolic steroids that have not been stopped for at least 4 weeks before
randomization. Testosterone replacement therapy to treat hypogonadism is allowed; the
testosterone dose and preparation must be stable for >=10 weeks before randomization.

18. Known allergy, or other contraindication to mitapivat or its excipients (microcrystalline cellulose, croscarmellose sodium, sodium stearyl fumarate, mannitol, and magnesium stearate), Opadry ® II Blue [hypromellose, titanium dioxide, lactose monohydrate, triacetin, and FD&C Blue #2]).
19. Any medical, hematological, psychological, or behavioral condition(s) or prior or current therapy that, in the opinion of the Investigator, may confer an unacceptable risk to participating in the study and/or could confound the interpretation of the study data. Also excluded are:
-Subjects who are institutionalized by regulatory or court order
-Subjects with any condition(s) that could create undue influence (including but not limited to incarceration, involuntary psychiatric confinement, and financial or familial affiliation with the Investigator or Sponsor)

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	03-10-2022
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Mitapivat, PYRUKYND
Generic name:	Mitapivat
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	29-11-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	19-05-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	04-01-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-03-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-04-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-09-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-10-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-04-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-05-2024

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	CTIS2024-512745-16-00
EudraCT	EUCTR2021-000211-23-NL
CCMO	NL77081.041.21