A Phase 3, Multicenter, Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Mitapivat in Pediatric Subjects With Pyruvate Kinase Deficiency Who Are Regularly Transfused, Followed by a 5-Year Open-label Extension Period

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This study has been transitioned to CTIS with ID 2024-515024-37-00 check the CTIS register for the current data. To determine the efficacy of treatment with mitapivat compared with placebo, as assessed by the reduction in transfusion burden in...

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

Summary

ID

NL-OMON53547

Source
ToetsingOnline

Brief title
AG348-C-022 (Activate-KidsT)

Condition

- Red blood cell disorders

Synonym
genetic red blood cell enzyme disorder, hemolytic anemia

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Mitapivat, Pediatric, Pyruvate Kinase Deficiency, Transfusion

Outcome measures

Primary outcome

Transfusion reduction response (TRR), defined as achievement of a >=33% reduction in the total red blood cell (RBC) transfusion volume from Week 9 through Week 32 of the Double-blind Period normalized by weight and actual study drug duration compared with the historical transfusion volume standardized by weight and to 24 weeks.

Secondary outcome

• Transfusion-free response, defined as achievement of 0 transfusions administered from Week 9 through Week 32 of the Double-blind Period

• Change in the number of transfusion episodes from Week 9 through Week 32 of the Double-blind Period compared with the historical number of transfusion episodes standardized to 24 weeks

• Percentage change in weight-normalized and study treatment duration-

normalized total transfusion volume from Week 9 through Week 32 of the Doubleblind Period compared with the historical transfusion volume standardized by weight and to 24 weeks

• Normal hemoglobin (Hb) response, defined as achievement of Hb concentrations in the normal range at least once, 8 weeks or more after a transfusion during Week 9 through Week 32 of the Double-blind Period

• Changes in safety assessments including measurement of sex hormones, sexual maturity rating with Tanner stage, development and the assessment of ovarian cysts (female subjects only)

• Changes over time in height-for-age z-score, weightfor-age z-score, and body mass index-for-age z-score

• Changes over time in bone mineral density z-score

• Change from baseline in markers of iron metabolism and indicators of iron overload (serum iron, serum ferritin, total iron-binding capacity, transferrin/transferrin saturation)

• Change from baseline in quality of life assessments: Pediatric Quality of Life (PedsQL) Multidimensional Fatigue Scale and PedsQL Generic Core Scale

• Pharmacokinetic parameters including, but not limited to, Cmax (maximum concentration), AUC (area under the concentration-time curve), Css (concentration at steady state), and Ctrough (trough concentration)

Study description

Background summary

2.1.1. Pyruvate Kinase Deficiency
Pyruvate kinase deficiency (PK deficiency) is a rare nonspherocytic chronic hemolytic anemia. It is an autosomal recessive disease that is caused by mutations in the PKLR gene that result in a defective red blood cell (RBC)-specific form of pyruvate kinase (PKR). Pyruvate kinase R, a key enzyme in the final step of glycolysis, catalyzes the conversion of phosphoenolpyruvate (PEP) and adenosine diphosphate (ADP) into pyruvate and adenosine triphosphate (ATP). Mature RBCs rely on the process of glycolysis to generate ATP; thus, PKR is a key enzyme for maintaining energy homeostasis in RBCs.
The presence of mutant PKR (mPKR) in patients with PK deficiency leads to a disruption in the glycolytic pathway, causing accumulation of PEP and 2,3-diphosphoglycerate and a reduction in ATP. This glycolytic defect and subsequent reduction in ATP lead to shortened reticulocyte and RBC life spans due to an inability to maintain the electrochemical gradient and membrane integrity of these cells, with patients experiencing chronic hemolysis as a consequence.
As with many rare genetic diseases, PK deficiency is underdiagnosed, and while the exact prevalence is unknown, it is estimated that the prevalence of clinically diagnosed PK deficiency is between 3.2 and 8.5 per million people in Western populations. The prevalence of both diagnosed and undiagnosed PK deficiency is estimated to be as high as 51 per million.
Diagnosis of PK deficiency is based on the exclusion of more common causes of hemolysis, which is typically followed by the demonstration of reduced pyruvate kinase enzymatic activity and the detection of mutations in the PKLR gene. Genotype distributions are similar in adults and children with PK deficiency, as would be expected for a congenital disease.

2.1.1.1. Disease Burden in Pediatric and Adult Patients With Pyruvate Kinase Deficiency
Pyruvate kinase deficiency is an autosomal recessive genetic condition that has a lifelong physical, mental, social, and economic impact on patients.
Real-world evidence suggests patients with PK deficiency may also have an increased risk of mortality when compared with age matched controls.
The clinical manifestations of PK deficiency are heterogeneous, of varying severity, and frequently appear within the first month of life, with common symptoms comprising jaundice and anemia. In infants and children, a low hemoglobin (Hb) concentration may result in poor feeding, growth, and energy levels, as well as irritability, while in older children and adolescents, low Hb concentration may result in poor focus in school, a persistent need for

naps, and low energy levels. Common symptoms and signs of lifelong hemolytic anemia are fatigue, shortness of breath, tachycardia, jaundice, and bone changes associated with extramedullary hematopoiesis. Patients may also experience episodes of severe acute hemolytic anemia as a result of increased hemolysis during infections, stress, aplastic crisis associated with parvovirus, and pregnancy (female patients of childbearing potential).
Patients with PK deficiency are at risk of long-term complications associated with hemolysis, such as gallstones (67.8% of patients), liver iron overload (62.3% of patients), osteoporosis (15.6% of patients), and pulmonary hypertension (4.6% of patients). If left untreated, these complications may result in high morbidity.
Overall, because PK deficiency is a chronic disease, the rate and number of complications, except for iron overload, are generally greater in adults compared with pediatric patients.

2.1.1.2. Management of Pediatric and Adult Patients With Pyruvate Kinase Deficiency
There is no approved therapeutic agent for the treatment of patients with PK deficiency. Patients* current treatment options are supportive, treating the symptoms of lifelong hemolytic anemia and associated complications, but do not target the underlying pathophysiology. These supportive care options (described below) may lead to additional complications and further compound existing complications. There are no standard guidelines for treating patients with PK deficiency. During the patient-focused drug development meeting hosted in September 2019 by the National Organization for Rare Disorders and the Foundation for Rare Blood Diseases, only 11% of patients reported feeling that their current supportive treatment options worked very well.
Pediatric patients are typically managed with RBC transfusions administered as needed, with 87% of patients younger than 18 years of age having received at least 1 transfusion in their lifetime. Data from the PK deficiency Natural History Study illustrate trends in the use of transfusions among different age groups: Among the youngest patients (<6 years of age), transfusions are commonly used to treat anemia, with 48% of patients in this age group having received >=6 transfusions per year (ie, being regularly transfused). This percentage dropped to 26% in children aged 6 to <12 years, reflecting the use of splenectomy at a median age of 5 years (detailed below). Acute stressors, such as viral infections, might result in intermittent transfusions; for some children, recurrent viral infections in early childhood may give the appearance of transfusion dependence due to frequent episodes of increased hemolysis. As children continue to grow, and their rates of viral infections and hemolytic triggers decrease, the frequency of transfusions continues to fall through adolescence to adulthood, with 14% of patients aged 12 to <18 years, and 11% of adults with PK deficiency receiving regular transfusions (defined as >=6 transfusions per year). In adults, the symptoms of anemia may increase with age and comorbidities, resulting in reinitiation of regular transfusions. There are no guidelines defining transfusion regimens in pediatric or adult patients with PK deficiency; the decision to transfuse a patient is based on each patient*s

tolerance of anemia, their lifestyle, and quality of life (QOL) considerations.
To reduce the need for transfusion and/or to increase Hb, patients with PK deficiency may undergo splenectomy. Splenectomy is typically delayed until after the age of 5 years, to decrease the risk of sepsis due to encapsulated organism bacteremia. Only 5% of patients who are diagnosed with PK deficiency undergo splenectomy at <5 years, with 70% of patients diagnosed with PK deficiency having undergone total or partial splenectomy by 18 years of age. Splenectomy may only partially ameliorate anemia or not fully alleviate the need for transfusions because hemolysis continues at other anatomical sites. In almost all patients, hemolysis and indirect hyperbilirubinemia persist postsplenectomy, and patients remain at risk for gallstones and jaundice. In addition, splenectomy increases the risk of infection, requiring patients to undergo prolonged prophylactic antibiotic therapy and maintain strict vaccination compliance, and increases the risk of thrombosis, pulmonary hypertension, and contributes to the risk of iron overload.
Iron overload is common in patients with PK deficiency and may lead to hepatic, cardiac, and endocrine complications. Approximately 50% of children aged <18 years have iron overload. The risk of iron loading does not appear to change with age. Iron chelation is commonly used to treat iron overload caused by hemolysis and/or other supportive care treatments, such as transfusion; however, compliance is often poor, limiting its benefit. Risks associated with iron chelation include impacted growth in children, visual and auditory toxicity, hepatic toxicity, renal toxicity, gastrointestinal hemorrhage, and neutropenia and agranulocytosis. The approach to chelation is similar between adult and pediatric patients with PK deficiency.
Gallstones are a frequent complication of PK deficiency and occur in a

Study objective

This study has been transitioned to CTIS with ID 2024-515024-37-00 check the CTIS register for the current data.

To determine the efficacy of treatment with mitapivat compared with placebo, as assessed by the reduction in transfusion burden in pediatric subjects with pyruvate kinase deficiency (PK deficiency) who are regularly transfused.

Study design

Study AG348-C-022 is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of mitapivat versus placebo in pediatric subjects with PK deficiency who are regularly transfused, followed by a 5-year OLE Period to evaluate long-term safety and efficacy.
The Double-blind Period comprises an 8-week Dose Titration Period followed by a 24-week Fixed-Dose Period. Subjects who have completed the Double-blind Period

will be eligible to receive mitapivat for up to 5 years in the OLE Period.
During the OLE Period, all subjects will receive mitapivat. To maintain the blinding of the subject*s treatment assignment during the Double-blind Period, all subjects entering the OLE Period will undergo a double-dummy Dose Titration Period in which all subjects will receive both mitapivat and placebo for 8 weeks.
Transfusions and other supportive care therapies are permitted as clinically indicated. Dose modifications are permitted for excessive Hb response and study drug-related AEs.

Intervention

The study is happening in two parts.
In the Core part of the study, some patients will receive the new medicine, mitapivat, and some patients will receive placebo, for 32 weeks (Double-Blind period). Patients will be randomly assigned in a 2:1 ratio to receive mitapivat or placebo
After the 32-week period, all patients will be given the option to receive mitapivat for an additional 5 years (Open-Label Extension Period [OLE]), in which all interested and eligible patients will receive mitapivat.

Study burden and risks

cf. ICF sections 6 and 7

Taking part in this study may or may not make your health better. There is no guarantee that your health will improve, and it is possible that your condition may get worse. Also, there are risks as mentioned in the side effects and risk section. We do know that the information from this study will help doctors learn more about mitapivat. This information could help other people who have a similar medical condition in the future.

Taking part in the study can have these disadvantages:
- You may experience the side effects or adverse effects of mitapivat, as described in Section 6.
- There may be some discomfort from the measurements during the study. For example: taking a blood sample can be a little painful. Or you could get a bruise as a result.
- Taking part in the study will cost you extra time.
- You have to comply with the study agreements.

Radiation
For DXA scan we use X-rays. In this study, you will get around 0.03 mSv of radiation in total. For comparison: the standard radiation that everyone in the Netherlands gets anyway, is about ~2.5 mSv per year. It is not dangerous if you have to have an examination or treatment with radiation for a medical reason.

• If you have other checks with radiation, you should discuss with the study doctor if it is wise for you to participate.
• The radiation we use during the study may cause damage to your health. But this is a small risk. We do, however, advise you not to take part in a medical study with radiation again in the near future.
It is possible that an accidental discovery is made during the study that is not directly related to the research, but does concern your health or that of your family members. If this happens, your own doctor or specialist will discuss with you what needs to happen next. However, we believe that the risks to you and your family are very low, because your samples will be coded and there are no plans to return the results of genetic testing to you or your personal physician.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Babies and toddlers (28 days-23 months)

Inclusion criteria

1. Written informed consent from the subject, or the subject*s legally authorized representative, parent(s), or legal guardian, and the subject*s assent, where applicable (informed consent/assent) must be obtained before any study-related procedures are conducted, and subjects must be willing to comply with all study procedures for the duration of the study.
2. Aged 1 to <18 years. Subjects between 12 and 24 months of age must weigh a minimum of 7 kg.
3. Clinical laboratory confirmation of PK deficiency, defined as documented presence of at least 2 mutant alleles in the PKLR gene, of which at least 1 is a missense mutation, as determined per the genotyping performed by the study central genotyping laboratory
4. Six to 26 transfusion episodes in the 52-week period before providing informed consent/assent
5. Have complete records of transfusion history for the 52 weeks before providing informed consent/assent, defined as having all the following available: (1) all the transfusion dates, (2) the RBC transfusion volume (milliliters and/or number of units) for all the transfusions, and (3) Hb concentrations within 1 week before transfusion for at least 80% of the transfusions
6. Receiving folic acid supplementation as part of routine clinical care for at least 21 days before administration of the first dose of study drug, to be continued during study participation
7. Female subjects who have attained menarche and/or breast development in Tanner Stage 2, must be abstinent of sexual activities that may induce 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 informed consent/assent, throughout the study, and for 28 days after the last dose of study drug (including the time required to dose taper). The second form of contraception can include an acceptable barrier method.

Exclusion criteria

1. Pregnant or breastfeeding
2. Homozygous for the R479H mutation or have 2 nonmissense mutations, without the presence of another missense mutation, in the PKLR gene as determined per the genotyping performed by the study central genotyping laboratory
3. History of malignancy
4. History of active and/or uncontrolled cardiac or pulmonary disease or clinically relevant QT prolongation within 6 months before providing informed consent/assent
5. Hepatobiliary disorders including but not limited to:

a. Liver disease with histopathological evidence of cirrhosis or severe fibrosis
b. Clinically symptomatic cholelithiasis or cholecystitis (subjects with prior cholecystectomy are eligible)
c. History of drug-induced cholestatic hepatitis
d. Aspartate aminotransferase >2.5× the upper limit of normal (ULN) (unless due to hemolysis and/or hepatic iron deposition) and alanine aminotransferase >2.5×ULN (unless due to hepatic iron deposition)
6. Renal dysfunction as defined by an estimated glomerular filtration rate <60 mL/min/1.73 m2 (bedside Schwartz equation)
7. Nonfasting triglycerides >440 mg/dL (5 mmol/L)
8. Active uncontrolled infection requiring systemic antimicrobial therapy
9. Subjects with known active hepatitis B or hepatitis C who subsequently test positive for hepatitis B antigen or hepatitis C virus antibody with signs of active hepatitis B or hepatitis C virus infection
10. Subjects with known HIV infection
11. History of major surgery (including splenectomy) <=6 months before providing informed consent/assent and/or planning on undergoing a major surgical procedure during the Screening or Double-blind Period
12. Current enrollment or past participation (within 90 days before 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 study drug or device
13. Prior exposure to gene therapy, or bone marrow or stem cell transplantation
14. Currently receiving hematopoietic stimulating agents; the last dose must have been administered at least 28 days or a time frame equivalent to 5 half-lives (whichever is longer) before randomization
15. Receiving products that are strong inhibitors of cytochrome P450 (CYP)3A4/5 that have not been stopped for >=5 days or a time frame equivalent to 5 half-lives (whichever is longer), or strong inducers of CYP3A4 that have not been stopped for >=28 days or a time frame equivalent to 5 half-lives (whichever is longer), before randomization
16. Receiving anabolic steroids, including testosterone preparations, that have not been stopped for at least 28 days before randomization
17. Known allergy, or other contraindication, to mitapivat or its excipients (microcrystalline cellulose, croscarmellose sodium, sodium stearyl fumarate, mannitol, Opadry® II Blue [hypromellose, titanium dioxide, lactose monohydrate, triacetin, and FD&C Blue #2], Opadry® II White [hypromellose, titanium dioxide, lactose monohydrate, and triacetin], and magnesium stearate)
18. Any medical, hematologic, 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 included are:
- Subjects who are institutionalized by regulatory or court order
- Subjects who 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)
19. Receiving a pyruvate kinase activator that has not been stopped for >=52 weeks before providing informed consent/assent.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	09-05-2023
Enrollment:	6
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO

Date:	11-10-2022
Application type:	First submission

Review commission:	METC NedMec
Approved WMO Date:	07-03-2023
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	26-03-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-04-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-11-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-01-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-02-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-04-2024
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	CTIS2024-515024-37-00
EudraCT	EUCTR2021-003265-36-NL
CCMO	NL80412.041.22