A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AG-348 in Not Regularly Transfused Adult Subjects With Pyruvate Kinase Deficiency

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Primary:• To evaluate the efficacy of treatment with AG-348 compared with placebo in increasing hemoglobin (Hb) concentrationsSecondary:• To evaluate the safety of AG-348• To determine the effect of the study treatment regimens on markers of...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON48591

Source
ToetsingOnline

Brief title
AG348-C-006

Condition

- Other condition
- Red blood cell disorders

Synonym
Pyruvate Kinase Defeciency

Health condition

Lack of Pyruvate Kinase enzyme

Research involving
Human

Sponsors and support

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

Intervention

Keyword: AG-348, Double-Blind, Not Regularly Transfused, Phase 3

Outcome measures

Primary outcome

The primary endpoint is the hemoglobin response (HR), defined as a >=1.5 g/dL (0.93 mmol/L) increase in Hb concentration from baseline that is sustained at 2 or more scheduled assessments at Weeks 16, 20, and 24 during the Fixed Dose Period. The individual subject*s baseline Hb concentration is defined as the average of all available Hb concentrations from the central laboratory for that subject during the Screening Period up to the first dose of study treatment.

Secondary outcome

Key Secondary Endpoint:

• Average change from baseline in Hb concentration at Weeks 16, 20, and 24

Other Secondary Endpoints:

• Maximal Hb concentration increase from baseline

• Time to first achieve an increase in Hb concentration of 1.5 g/dL (0.93 mmol/L) or more from baseline

• Average change from baseline at Weeks 16, 20, and 24 in markers of hemolysis: bilirubin, lactate dehydrogenase, and haptoglobin levels

• Average change from baseline at Weeks 16, 20, and 24 in markers of hematopoietic activity: reticulocyte percentages

• Change from baseline in HRQoL PRO scores: Pyruvate Kinase Deficiency Diary and Pyruvate Kinase Deficiency Impact Assessment

• Safety endpoints, including: the type, incidence, severity, and relationship to study treatment of AEs and serious adverse events (SAEs); number of discontinuations due to AEs; results of clinical laboratory tests over time (eg, serum chemistry, liver function test, hematology, lipids, sex steroids, urinalysis, coagulation); physical examination findings; dual-energy x-ray absorption (DXA) scans, vital signs; 12-lead electrocardiogram (ECG) data

• Pharmacokinetic endpoints, including plasma concentrations over time and pharmacokinetic parameters of AG-348 (eg, area under the concentration × time curve [AUC], maximum [peak] concentration [Cmax], others as applicable)

• Exposure-response relationship between safety parameters and AG-348 concentration and relevant AG-348 pharmacokinetic parameters

Study description

Background summary

Mitapivat sulfate is an orally available, potent, broad-spectrum activator of PKR with demonstrated activity against both WT and mPKR enzymes in vitro. Mitapivat sulfate acts by directly binding to the PKR tetramer and allosterically enhancing its affinity for PEP. Pharmacology studies have confirmed the potency of Mitapivat sulfate in activating wide-type (WT) PKR enzyme activity and modulating ATP and 2,3 DPG levels in healthy adult subjects. Mitapivat sulfate has also been shown to have acceptable absorption, distribution, metabolism, and excretion (ADME) and toxicology profiles. Treatment with Mitapivat sulfate has the potential to correct the underlying pathology of PK deficiency by activating PKR and inducing metabolic changes,

leading to increased glycolytic pathway activity in RBCs and providing a clinical benefit to patients with PK deficiency.

As described in Section 2.1.1.2 of the Investigator's Brochure, the activity of the glycolytic pathway is disrupted in patients with PK deficiency. This disruption results in significantly reduced RBC lifespan and manifests clinically as nonspherocytic hemolytic anemia. In patients with PK deficiency, RBCs and their progenitors are characterized by changes in metabolism associated with defective glycolysis, including a buildup of PEP and the intermediate 2,3-DPG, and lowered levels of ATP. It is hypothesized that AG-348 restores the ability of RBCs to convert PEP + ADP to pyruvate + ATP and thereby normalizes RBC metabolism in patients with PK deficiency. AG-348 also has the potential to modify the underlying pathology of thalassemia by enhancing the energy metabolism of RBCs, leading to improved overall cell fitness and lifespan, reduction of hemolysis, and a functional and sustained increase in hemoglobin.
AG-348 is currently under clinical development.
(See IB section 2.2)

Study objective

Primary:
• To evaluate the efficacy of treatment with AG-348 compared with placebo in increasing hemoglobin (Hb) concentrations
Secondary:
• To evaluate the safety of AG-348
• To determine the effect of the study treatment regimens on markers of hemolysis, hematopoietic activity, and other indicators of clinical activity
• To determine the effect of the study treatment regimens on health-related quality of life (HRQoL), as determined using patient-reported outcomes (PROs)
• To evaluate the pharmacokinetics of AG-348 after oral administration
• To evaluate the relationship between AG-348 pharmacokinetics and safety parameters

Study design

This is a Phase 3, randomized, multicenter, double-blind, placebo-controlled study consisting of a Dose Optimization Period (Part 1) followed by a Fixed Dose Period (Part 2).
After a Screening Period of up to 42 days, eligible subjects will be randomized 1:1 to receive either AG-348 or matching placebo (ie, study treatment). The randomization will be stratified by the average of screening Hb concentrations (<8.5 vs >=8.5 g/dL) and the PKLR gene mutation category (missense/missense vs missense/non-missense). In rare instances in which PKLR gene mutation category cannot be made definitively (eg, if a subject harbors 3 mutant PKLR alleles), the subject will be assigned to the missense/non-missense category.

Following randomization, all subjects will enter the Dose Optimization Period (Part 1), during which the study treatment (ie, AG-348/matching placebo) will be titrated up to their individually optimized dose. The initial dose of study treatment for all subjects will be 5 mg twice daily (BID) with 2 potential sequential steps for dose level increases (ie, from 5 to 20 mg BID and from 20 to 50 mg BID), depending on safety and Hb change.

Intervention

AG-348 will be administered orally BID as tablets of different sizes for the 5, 20, and 50 mg dose levels. Subjects will be receiving 1 of 3 potential doses, each of which is supplied in a different sized tablet. Thus, to maintain blinding, each dose of study treatment will be supplied as 3 different sized tablets: 1 tablet will be the active drug and the other 2 tablets will be placebo for subjects who are randomized to active, and all 3 tablets will be placebo for subjects who are randomized to placebo.
Doses of AG-348 may be taken with or without food.
For subjects randomized to AG-348, the initial dose of AG-348 will be 5 mg BID with 2 potential sequential steps for dose level increases (ie, from 5 to 20 mg BID and from 20 to 50 mg BID).

Study burden and risks

Mitapivat sulfate has been generally well tolerated in both healthy adult subjects and adult subjects with PK deficiency, although aromatase inhibition and transaminase increases have been observed in both subject populations. The doses of Mitapivat sulfate planned for future clinical studies will not exceed a 200 mg total daily dose, which is expected to reduce the risks associated with aromatase inhibition and potential liver toxicity. Liver function tests will be monitored in clinical studies of Mitapivat sulfate, and transaminase elevations of more than 2.5× patient individual baseline or to Grade 2 will be reported as an AE of special interest. Moreover, data available at this time also indicate that Mitapivat sulfate does not have a significant QT/QTc prolongation effect. Based on currently available data, reported benefits of treatment with Mitapivat sulfateoutweigh the observed risks of treatment. (see IB section 7)

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. Have provided signed written informed consent prior to performing any study procedure, including screening procedures.
2. Be aged 18 years or older.
3. Have documented 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 central genotyping laboratory.
4. Have an Hb concentration less than or equal to 10.0 g/dL (6.21 mmol/L) regardless of gender (average of at least 2 Hb measurements [separated by a minimum of 7 days] during the Screening Period).
5. Be considered not regularly transfused, defined as having had no more than 4 transfusion episodes in the 12-month period up to the first day of study treatment and no transfusions in the 3 months prior to the first day of study treatment.
6. Have received at least 0.8 mg oral folic acid daily for at least 21 days prior to the first dose of study treatment, to be continued daily during study participation.
7. Have adequate organ function, as defined by:
a. Serum aspartate aminotransferase (AST) <=2.5 × ULN (unless the increased AST is assessed by the Investigator as due to hemolysis and/or hepatic iron

deposition) and alanine aminotransferase (ALT) <=2.5 × ULN (unless the increased ALT is assessed by the Investigator as due to hepatic iron deposition).
b. Normal or elevated levels of serum bilirubin. In subjects with serum bilirubin >ULN, the elevation 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. Estimated glomerular filtration rate (GFR) >=60 mL/min/1.73 m2, measured GFR >=60 mL/min, or calculated creatinine clearance (CrCL; Cockcroft-Gault) >=60 mL/min.
d. Absolute neutrophil count >=1.0 × 109/L (based on an average of at least 2 measurements [separated by a minimum of 7 days] during the Screening Period).
e. Platelet count >=100 × 109/L in the absence of a spleen, or platelet count >=50 × 109/L in the presence of a spleen and in the absence of any other cause of thrombocytopenia (based on an average of at least 2 measurements [separated by a minimum of 7 days] during the Screening Period).
f. Activated partial thromboplastin time and international normalized ratio <=1.25 × ULN, unless the subject is receiving therapeutic anticoagulants.
8. For women of reproductive potential, have a negative serum pregnancy test during the Screening Period. 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 (ie, who have not menstruated at all for at least the preceding 12 months prior to signing informed consent and have an elevated follicle stimulating hormone level indicative of menopause during the Screening Period).
9. For women of reproductive potential as well as men with partners who are women of reproductive potential, be abstinent 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 giving informed consent, during the study, and for 28 days following the last dose of study treatment for women and 90 days following the last dose of study treatment for men. A highly effective form of contraception is defined as combined (estrogen and progestin containing) hormonal contraceptives (oral, intravaginal, or transdermal) known to be associated with inhibition of ovulation; progestin-only hormonal contraceptives (oral, injectable, or implantable) known to be associated with inhibition of ovulation; intrauterine device; intrauterine hormone releasing system; bilateral tube occlusion; or vasectomized partner. The second form of contraception can include an acceptable barrier method, which includes male or female condoms with or without spermicide, and cervical cap, diaphragm, or sponge with spermicide. Women of reproductive potential using hormonal contraception as a highly effective form of contraception must also utilize an acceptable barrier method while enrolled in the study and for at least 28 days after their last dose of study treatment.
10. Be willing to comply with all study procedures for the duration of the study.

Exclusion criteria

1. Are homozygous for the R479H mutation or have 2 non-missense mutations, without the presence of another missense mutation, in the PKLR gene as determined per the genotyping performed by the central genotyping laboratory.
2. Have a significant medical condition that confers an unacceptable risk to participating in the study, and/or that could confound the interpretation of the study data. Such significant medical conditions include, but are not limited to the following:
a. Poorly controlled hypertension (defined as systolic blood pressure [BP] >150 mmHg or diastolic BP >90 mmHg) refractory to medical management.
b. History of recent (within 6 months prior to signing informed consent) congestive heart failure; myocardial infarction or unstable angina pectoris; hemorrhagic, embolic, or thrombotic stroke; deep venous thrombosis; or pulmonary or arterial embolism.
c. Cardiac dysrhythmias judged as clinically significant by the Investigator.
d. Heart-rate corrected QT interval-Fridericia's method (QTcF) >450 msec (average of triplicate electrocardiograms [ECGs]) 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. Genetic findings that in isolation are predicted to be insufficient to explain the observed clinical phenotype may be allowed (eg, heterozygous status for certain recessive red blood cell disorders).
i. Positive test for hepatitis B surface antigen or hepatitis C virus (HCV) antibody (Ab) with signs of active hepatitis B or C virus infection. If the subject is positive for HCVAb, a reverse transcriptase-polymerase chain reaction test will be conducted. Subjects with hepatitis C may be rescreened after receiving appropriate hepatitis C treatment.
j. Positive test for human immunodeficiency virus (HIV) 1 or 2 Ab.
k. Active infection requiring the use of parenteral antimicrobial agents or Grade >=3 in severity (per National Cancer Institute Common Terminology Criteria for Adverse Events) 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

nonmelanomatous 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. Current or recent history of psychiatric disorder that, in the opinion of the Investigator or Medical Monitor or designee,, could compromise the ability of the subject to cooperate with study visits and procedures.
3. Have a splenectomy scheduled during the study treatment period or have undergone splenectomy within 12 months prior to signing informed consent.
4. Are currently enrolled in another therapeutic clinical trial involving ongoing therapy with any investigational or marketed product or placebo. Prior and subsequent participation in the PK Deficiency Natural History Study (NHS) (NCT02053480) or PK Deficiency Registry is permitted, however, concurrent participation is not. Therefore, subjects enrolling in this current study will be expected to temporarily suspend participation in the NHS or Registry.
5. Have exposure to any investigational drug, device, or procedure within 3 months prior to the first dose of study treatment.
6. Have had any prior treatment with a pyruvate kinase activator.
7. Have a prior bone marrow or stem cell transplant.
8. Are currently pregnant or breastfeeding.
9. 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.
10. Are currently receiving medications that are strong inhibitors of cytochrome P450 (CYP)3A4, strong inducers of CYP3A4, strong inhibitors of P-glycoprotein (P-gp), or digoxin (a P-gp sensitive substrate medication) 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.
11. 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.
12. Have a history of allergy to sulfonamides if 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.
13. Have a history of allergy to AG-348 or its excipients (microcrystalline cellulose, croscarmellose sodium, sodium stearyl fumarate, and mannitol).
14. Are currently receiving anabolic steroids, including testosterone preparations, within 28 days prior to the first dose of study treatment.

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:	Recruitment stopped
Start date (anticipated):	15-02-2019
Enrollment:	3
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	03-10-2018
Application type:	First submission
Review commission:	METC NedMec

Approved WMO Date:	19-12-2018
Application type:	First submission
Review commission:	METC NedMec

Approved WMO

Date:	25-03-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-04-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-05-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	31-05-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-10-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-11-2019
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
EudraCT	EUCTR2017-003823-31-NL
ClinicalTrials.gov	NCT03548220
CCMO	NL63923.041.18

Study results

Results posted: 30-11-2021

First publication
01-01-1900

URL result
Type
ext
Naam
www.clinicaltrialsregister.eu
URL