An Open-Label Study to Evaluate the Efficacy and Safety of AG-348 in Regularly Transfused Adult Subjects With Pyruvate Kinase (PK) Deficiency

Published: 18-12-2017
Last updated: 12-04-2024

The primary objective of the study is to evaluate the efficacy of treatment with AG-348, as assessed by the reduction in transfusion burden.Secondary: The secondary objective of this study is to evaluate the safety of treatment with AG 348.

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

Summary

ID

NL-OMON48589

Source
ToetsingOnline

Brief title
AG348-C-007

Condition

- Other condition
- Red blood cell disorders

Synonym
Pyruvate kinase (PK) deficiency

Health condition

Lack of Pyruvate Kinase enzyme/ Pyruvate Kinase Deficiency

Research involving
Human

Sponsors and support

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

Intervention

Keyword: AG-348, Efficacy, Open-Label, Safety

Outcome measures

Primary outcome

Primary Endpoint:

The primary endpoint of this study is the proportion of subjects who achieve a reduction in transfusion burden, defined as a >=33% reduction in the number of RBC units transfused during the 24 weeks of Part 2 compared with the historical transfusion burden standardized to 24 weeks (Standardized Control Period).

Secondary outcome

Secondary Endpoints:

The secondary endpoints of the study are the following:

• Annualized total number of RBC units transfused during the study (both Part 1 and Part 2) compared with the historical transfusion burden

• Number of transfusion episodes during Part 2 compared with the Standardized Control Period

• Proportion of subjects who become transfusion-free, defined as 0 transfusions administered during Part 2

• Proportion of subjects who achieve Hb concentrations in the normal range at least once, 8 weeks or more after a transfusion in Part 2

• Safety endpoints, including the type, incidence, severity, and relationship to treatment of adverse events (AEs) and serious adverse events (SAEs), and AEs leading to treatment dose reduction, treatment interruption, and treatment discontinuation

• Laboratory tests over time (eg, serum chemistry, liver function tests [LFTs], hematology, coagulation, lipids, sex steroids, urinalysis), physical examination findings, dual energy X-ray absorptiometry (DXA) scans (hip and lumbar spine), vital signs, and 12-lead electrocardiogram (ECG) data

Exploratory Endpoints:

The exploratory endpoints of the study are the following:

• Change from baseline in the following markers of hemolysis: bilirubin, lactate dehydrogenase (LDH), and haptoglobin levels

• Change from baseline in markers of erythropoietic activity

• Change from baseline in markers of iron metabolism and indicators of iron overload

• Change from baseline over time in HRQoL scores (ie, Pyruvate Kinase Deficiency Impact Assessment [PKDIA], Pyruvate Kinase Deficiency Diary [PKDD], EuroQol-5D-5L [EQ 5D 5L])

• Characterization of pharmacokinetic profile (drug concentrations over time) and determination of pharmacokinetic parameters of AG-348 (eg, area under the plasma concentration × time curve [AUC], maximum [peak] concentration [Cmax], and others as applicable) in Part 2

• Exposure-response (or pharmacokinetic-pharmacodynamic) relationship between

relevant pharmacokinetic parameters and endpoints that are indicators of

clinical activity

• Changes in total PKR protein levels

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.
(See IB section 2.2)

Study objective

The primary objective of the study is to evaluate the efficacy of treatment with AG-348, as assessed by the reduction in transfusion burden.
Secondary: The secondary objective of this study is to evaluate the safety of treatment with AG 348.

Study design

Study AG348-C-007 is a 2-part, multicenter, open-label, Phase 3 study consisting of a Dose Optimization Period (Part 1) followed by a Fixed-Dose Period (Part 2). This study will evaluate the efficacy and safety of treatment with AG 348 in approximately 15 20 adult subjects with pyruvate kinase deficiency (PK deficiency) who are regularly receiving blood transfusions. Prior to Part 1 of the study, there will be an 8 week Screening Period in which a subject*s complete transfusion history from 52 weeks prior to signing the Informed Consent Form (ICF) will be collected and recorded on the source documentation and electronic case report form (eCRF).

All subjects will receive AG-348 in Parts 1 and 2 of the study. During Part 1

of the study, all subjects will start on a dose of 5 mg AG 348 administered twice daily (BID). Over the course of Part 1, each subject will undergo intrasubject dose optimization. Each subject*s dose level of AG 348 may be increased 2 times beyond the starting dose of 5 mg BID (ie, from 5 to 20 mg BID and from 20 to 50 mg BID). In the Fixed Dose Period of the study (Part 2), a subject will receive AG 348 at his/her optimized dose with no planned adjustments (ie, as a fixed dose) for a fixed period of 24 weeks.
All subjects who remain on study during Part 2 through the Week 24 Visit may be eligible for an open label extension study with AG-348. Subjects who continue on into an extension study will not be required to attend the Follow-up Visit. Subjects who continue the study through the Part 2 Week 24 Visit on study drug but do not continue on into an extension study will attend the Follow-up Visit 28±4 days after the last dose of study drug. Subjects who discontinue the study prior to the Part 2 Week 24 Visit should attend the End of Study Visit 28±4 days after the last study visit that the subject attended or 28±4 days after the last dose of study drug, whichever is later.
All subjects who discontinue study drug at any time during the study should undergo a dose taper as described in this protocol, unless an emergency situation justifies discontinuing the study drug abruptly. Whether the dose taper is performed or not, subjects discontinuing AG-348 should be monitored for signs of hemolysis and worsening of anemia.

Ref: Protocol synopsis - study design

Intervention

AG-348 will be supplied as 5, 20, and 50 mg strength tablets to be administered orally.
The maximum total duration that a subject could receive AG-348 in this study is 48 weeks (not including time required to taper study drug). The duration of AG-348 treatment at each dose level and the overall duration of the Dose Optimization Period (Part 1) of the study may vary among subjects from 16 to 24 weeks. The subject*s last visit in Part 1 (Week 16, 18, 20, 22, or 24 visit) will be the first visit in the Fixed-Dose Period (Part 2). In Part 2 of the study, subjects will receive their optimized dose of AG-348 for 24 weeks.

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 (AESI) 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 sulfate outweigh 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 study central genotyping laboratory.
4. Have a history of a minimum of 6 transfusion episodes in the 52-week period prior to date of informed consent as documented in the transfusion history of the subject, which reflects the subject*s typical transfusion burden.
5. Have complete records of transfusion history, defined as having the following available for the 52 weeks prior to the date of informed consent: (1) all the transfusion dates, (2) the number of blood units transfused for all the transfusions, and (3) Hb concentrations within 1 week prior to transfusion for at least 80% of the transfusions.
6. Have received at least 0.8 mg oral folic acid daily for at least 21 days prior to the first dose of study drug, to be continued daily during study participation.
7. Have adequate organ function, as defined by:
a. Serum aspartate aminotransferase (AST) <=2.5 × upper limit of normal (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 (ANC) >=1.0 × 109/L.
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.
f. Activated partial thromboplastin time (aPTT) and international normalized ratio (INR) <=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 drug for women and 90 days following

the last dose of study drug 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 drug.
10. Be willing to comply with all study procedures, in particular the Individual TT (calculated based on 52 weeks of transfusion history), 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 study 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 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. 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 RBC disorders).
i. Positive test for hepatitis B surface antigen (HBsAg) 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-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 [NCI CTCAE]) within 2 months prior to the first dose of study drug.
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 history of transfusions occurring on average more frequently than once every 3 weeks during the 52 weeks prior to signing informed consent.
4. Have a splenectomy scheduled during the study drug period or have undergone splenectomy within 12 months prior to signing informed consent.
5. 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.
6. Have exposure to any investigational drug, device, or procedure within 3 months prior to the first dose of study drug.
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 drug.
11. Are currently receiving hematopoietic stimulating agents (eg, erythropoietins [EPOs], 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 drug.
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 drug.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-10-2018
Enrollment:	3
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	18-12-2017
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	27-06-2018
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	24-09-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-11-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-02-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-03-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-07-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-07-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-10-2019

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-01-2020
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	EUCTR2017-003803-22-NL
ClinicalTrials.gov	NCT03559699
CCMO	NL63924.041.17

Study results

Results posted: 13-12-2021

First publication
01-01-1900

URL result
Type
ext
Naam
www.clinicaltrialsregister.eu
URL