An Open-Label, Multicenter, Extension Study of AG-348 in Adult Subjects with Pyruvate Kinase Deficiency Previously Enrolled in AG-348 Studies

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Objectives: Primary:• To evaluate the long-term safety and tolerability of AG-348Secondary:• To evaluate the long-term efficacy of AG-348• To evaluate the efficacy of AG-348 in increasing hemoglobin (Hb) concentrations in subjects who previously…

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

Summary

ID

NL-OMON52866

Source
ToetsingOnline

Brief title
AG348-C-011

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:

• To evaluate the long-term safety and tolerability of AG-348

Secondary outcome

Secondary:

• To evaluate the long-term efficacy of AG-348

• To evaluate the efficacy of AG-348 in increasing hemoglobin (Hb)

concentrations in subjects who previously received placebo in Study AG348-C-006

(Cohort 1 only)

• To determine the effect of AG-348 on health-related quality of life (HRQoL)

using patient reported outcomes (PROs)

• To evaluate the pharmacokinetics of AG-348 after oral administration (Cohort

1 only)

• To evaluate the relationship between AG-348 pharmacokinetics and safety

parameters (Cohort 1 only)

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

Objectives:
Primary:
• To evaluate the long-term safety and tolerability of AG-348
Secondary:
• To evaluate the long-term efficacy of AG-348
• To evaluate the efficacy of AG-348 in increasing hemoglobin (Hb) concentrations in subjects who previously received placebo in Study AG348-C-006 (Cohort 1 only)
• To determine the effect of AG-348 on health-related quality of life (HRQoL) using patient reported outcomes (PROs)
• To evaluate the pharmacokinetics of AG-348 after oral administration (Cohort 1 only)
• To evaluate the relationship between AG-348 pharmacokinetics and safety parameters (Cohort 1 only)
Exploratory:
• To evaluate the effect of AG-348 on pharmacodynamics (PD) markers related to pyruvate kinase deficiency (PK deficiency) (Cohort 1 only)
• To determine the effect of AG-348 on markers of iron metabolism and indicators of iron overload
• To evaluate the relationship between AG-348 pharmacokinetics and indicators of clinical activity (Cohort 1 only)

Study design

Overview:

This is a multicenter, open-label, extension study to evaluate the long-term safety, tolerability, and efficacy of treatment with AG-348 in subjects who were previously enrolled in Study AG348-C-006 or Study AG348C-007.

All subjects enrolled in this extension study, including those who received placebo in Study AG348 C-006, will receive AG-348 during participation in this extension study.
Subjects will be assigned to 1 of the following 3 cohorts, depending on the antecedent study and the previous treatment received in the antecedent study:
• Cohort 1: Subjects who received placebo in Study AG348 C 006
• Cohort 2: Subjects who received AG-348 in Study AG348 C 006
• Cohort 3: Subjects who received AG-348 in Study AG348-C-007

Cohort 1:
Cohort 1 will consist of subjects who received placebo in Study AG348-C-006 and meet the eligibility criteria of this extension study. The first visit of this extension study should coincide with the last visit of Study AG348-C-006. After completion of all scheduled assessments at the subject*s last visit of Study AG348-C-006 and before the start of study drug in this extension study, the subject, Investigator, and site personnel will be unblinded to the Study AG348-C-006 treatment allocation of the subject, and the Investigator will determine whether the subject meets all eligibility criteria of this extension study.
The first visit of this extension study should consist of subject consent, screening, confirmation of eligibility, and the start of study drug. If a subject in Cohort 1 cannot start study drug on the first visit of this extension study, discussion with and approval by the Medical Monitor, or designee, will be required for participation in this extension study, and to determine the timing and requirements for the start of study drug and assessments to be performed.
Subjects in Cohort 1 will participate in a 12-week Dose Optimization Period followed by a 12-week Fixed Dose Period. The goal of the Dose Optimization Period is to maximize a subject*s increase in Hb while maintaining an acceptable safety profile. Following the Dose Optimization Period, each subject will remain on his/her individually optimized dose and enter the Fixed Dose Period.
Following completion of the Fixed Dose Period, subjects who, in the opinion of the Investigator, have demonstrated clinical benefit from AG-348 treatment will continue AG-348 treatment in the Continued Treatment Period.

Cohort 2:
Cohort 2 will consist of subjects who received AG-348 in Study AG348-C-006 and meet the eligibility criteria of this extension study. The first visit of this extension study should coincide with the last visit of Study AG348-C-006. After completion of all scheduled assessments at the subject*s last visit of Study AG348-C-006 and before the start of study drug in this extension study, the subject, Investigator, and site personnel will be unblinded to the Study

AG348-C-006 treatment allocation of the subject, and the Investigator will determine whether the subject meets all eligibility criteria of this extension study.
In Cohort 2, the first visit of this extension study will consist of subject consent, screening, confirmation of eligibility, and the start of study drug on this extension study. Importantly, there will be no planned dosing interruption between the last dose of blinded AG-348 in Study AG348-C-006 and the first dose of open-label AG-348 in this extension study due to the potential for withdrawal hemolysis (an identified risk of AG-348). Specifically, the first dose of open-label AG-348 in this extension study will be administered approximately 12 hours (ie, 12 hours ± 2 hours) after the last dose in Study AG348-C-006. Subjects will continue the AG-348 dose regimen they were receiving at the last visit of Study AG348-C-006 (unless a dose modification is required for reasons related to safety, the subject*s dose optimization, or other reasons following discussion with and approval by the Medical Monitor or designee).

Cohort 3:
Cohort 3 will consist of subjects who received AG-348 in Study AG348-C-007 and meet the eligibility criteria of this extension study. The first visit of this extension study should coincide with the last visit of Study AG348-C-007. After completion of all scheduled assessments at the subject*s last visit of Study AG348-C-007 and before the start of study drug in this extension study, the Investigator will determine whether the subject meets all eligibility criteria of this extension study.
In Cohort 3, the first visit of this extension study will consist of subject consent, screening, confirmation of eligibility, and the start of study drug on this extension study. Importantly, there will be no planned dosing interruption between the last dose of AG-348 in Study AG348-C-007 and the first dose of AG-348 in this extension study due to the potential for withdrawal hemolysis (an identified risk of AG-348). Specifically, the first dose of AG-348 in this extension study will be administered approximately 12 hours (ie, 12 hours ± 2 hours) after the last dose in Study AG348 C 007. Subjects will continue the AG-348 dose regimen they were receiving at the last visit of Study AG348-C-007 (unless a dose modification is required for reasons related to safety, the subject*s dose optimization, or other reasons following discussion with and approval by the Medical Monitor or designee).

All Cohorts:
All subjects who interrupt or discontinue AG-348 at any time should undergo the recommended dose taper, unless an emergency situation justifies discontinuing or interrupting the study drug abruptly. Whether the dose taper is performed or not, subjects discontinuing or interrupting AG-348 should be monitored for signs of hemolysis and worsening of anemia. All subjects who permanently discontinue AG-348 at any time will attend a Safety Follow-up Visit 28 days (±4 days) after the last dose of AG 348 (including the time required to dose taper).

Subjects with AEs will continue to be followed until resolution of the AE to baseline (ie, baseline of the study during which AE onset occurred), the AE is considered stable within the context of the study, the subject is lost to follow up, or until 28 days after the last dose of AG-348. All SAEs will be followed until final outcome of the SAE is known or the subject is lost to follow-up.

Intervention

AG-348 will be administered orally as tablets of different sizes for the 5, 20, and 50 mg dose levels. Doses of AG-348 may be taken with or without food. Tablets should be swallowed whole with water and not crushed, chewed, or dissolved in water. The dose regimen will be 5, 20, or 50 mg twice daily (BID), with each dose administered approximately 12 hours (ie, 12 hours ± 2 hours) apart, unless a dose taper is required at any time during this extension study, in which case the frequency of administration will be once daily (QD) or once every other day (QOD) during different steps of the taper. At any time during this extension study, the Investigator can reduce the subject*s dose or interrupt dosing for reasons related to safety.
For subjects in Cohort 1, the initial dose will be 5 mg BID with the potential for 2 sequential dose level increases (from 5 mg BID to 20 mg BID and from 20 mg BID to 50 mg BID), which may occur at the Week 4 and/or Week 8 Visits. Subjects in Cohorts 2 and 3 will continue the dose regimen they were receiving at their last visit of Study AG348-C-006 or AG348-C-007, respectively (unless otherwise noted).

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)

Inclusion criteria

Subjects must meet all of the following criteria to be eligible for inclusion in this extension study:
1. Have provided signed written informed consent prior to participating in this extension study.
2. Have completed the antecedent AG-348 study through the Part 2 Week 24 Visit of Study AG348-C-006 or AG348-C-007.
3. Cohorts 2 and 3: Have demonstrated clinical benefit from AG-348 treatment in the antecedent study, in the opinion of the Investigator.
4. For women of reproductive potential*:
a. In Cohort 1, have a negative local serum (human chorionic gonadotropin [hCG]) pregnancy test during screening of this extension study.
b. In Cohort 2 or 3, have a negative local urine pregnancy test during screening of this extension study.
* 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 screening of this extension study and have an elevated follicle-stimulating hormone [FSH] level indicative of menopause during screening of this extension study or at screening of the antecedent study). If the result from FSH testing conducted during screening of this extension study is not available on the same day, the woman must have a negative local serum (hCG) or urine pregnancy test during screening and follow contraception requirements (Inclusion Criterion #5) until an elevated FSH result indicative of menopause is confirmed.
5. 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.
6. Be willing and able to comply with study visits and procedures.

Exclusion criteria

Subjects who meet any of the following criteria will not be enrolled in this extension study:
1. Have a significant medical condition (including clinically significant laboratory abnormality) that developed during his/her antecedent AG-348 study that confers an unacceptable risk to participating in this extension study, that could confound the interpretation of the study data, and/or that compromises the ability of the subject to complete study visits and procedures.
2. Are currently pregnant or breastfeeding.
3. Have a splenectomy scheduled during the study treatment period.
4. Meet the withdrawal criteria of his/her antecedent AG-348 study during screening of this extension study.
Withdrawal criteria of the antecedent AG-348 studies are as follows:
• Withdrawal of consent
• Development of an intercurrent medical condition that precludes further participation in the study

• Subject requires use of a prohibited concomitant medication
• Investigator decision
• Persistent nonadherence to protocol requirements
• Pregnancy
• Lost to follow-up
5. Are currently receiving medications that are strong inhibitors of CYP3A4 that have not been stopped for a duration of at least 5 days or a time frame equivalent to 5 half-lives (whichever is longer) before start of study drug; or strong inducers of CYP3A4 that have not been stopped for a duration of at least 28 days or a time frame equivalent to 5 half-lives (whichever is longer) before start of study drug on this extension study.
6. Have received anabolic steroids, including testosterone preparations, within 28 days prior to start of study drug on this extension study.
7. Have received hematopoietic stimulating agents (eg, erythropoietins, granulocyte colony stimulating factors, thrombopoietins) within 28 days prior to start of study drug on this extension study.
8. Have exposure to any investigational drug other than AG-348, device, or procedure within 3 months prior to start of study drug on this extension study.

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	12-09-2019
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	AG-348 sulfate hydrate
Generic name:	-

Ethics review

Approved WMO Date:	05-06-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	17-07-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	21-10-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-11-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-01-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-03-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-10-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-11-2020
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	13-10-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-12-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-02-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-03-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-03-2023
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
EudraCT	EUCTR2018-003459-39-NL
ClinicalTrials.gov	NCT03853798
CCMO	NL69361.041.19