A Phase 2, Open Label, Randomized, Dose Ranging, Safety, Efficacy, Pharmacokinetic and Pharmacodynamic Study of AG-348 in Adult Patients with Pyruvate Kinase Deficiency

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CORE PERIODPrimary:* Evaluate the safety and tolerability of up to 24 weeks of AG-348 administration in patients with pyruvate kinase deficiency (PK deficiency).Secondary:* Evaluate the pharmacokinetics (PK) of AG-348 and the metabolite AGI-8702.*...

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

Summary

ID

NL-OMON47068

Source
ToetsingOnline

Brief title
AG348-C-003

Condition

- Red blood cell disorders

Synonym
anemia; enzym deficiencies

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, Open label, Phase II, Pyruvate Kinase Deficiency, Red Blood Cell Disorder

Outcome measures

Primary outcome

The primary outcome measure for the study is the description of safety and tolerability: AEs, including determination of SAEs, AESIs and AEs leading to discontinuation; safety laboratory parameters (hematology, chemistry, urinalysis, coagulation); physical examination findings; vital signs (VS); 12 lead electrocardiograms (ECGs); and DXA scans. Adverse events will be graded using Common Toxicity Criteria for Adverse Events (CTCAE), Version 4.03. Serum sex hormone levels (testosterone [total and free], , estrone, and estradiol), bone turnover markers (serum osteocalcin-N-mid and serum C terminal telopeptide [CTX]), 25-hydroxy vitamin D2 and D3, total cholesterol, high-density lipoprotein-cholesterol (HDL-C), and triglycerides will be monitored for evidence of potential inhibition of aromatase by AG-348. Menstruating female patients will also keep a paper-based menstrual cycle diary throughout the study.

Indicators of Clinical Activity:

Monitoring of potential indicators of clinical activity will include evaluating changes in Hb, HCT, reticulocyte count, COHb, ETCO, LDH, total and indirect bilirubin, EPO, hepcidin, ferritin, and transferrin saturation.

Pharmacokinetics:

Approximately the first 10 patients treated, contingent on clinical site feasibility, will undergo extensive PK sampling as detailed in Appendix 15.1, Table 5. The remainder of treated patients will undergo limited PK sampling as detailed in Appendix 15.1, Table 6. Serial blood sampling for determination of concentration-time profiles of AG-348 and its metabolite AGI-8702 will be conducted following the first dose and the morning Day 15 dose, and additional trough levels of AG-348 and AGI-8702 will be obtained. AG-348 and AGI-8702 will be analyzed using qualified assays to determine concentrations in plasma. Pharmacokinetic parameters on Day 1 and Day 15 will be computed using standard non-compartmental methods based on observed plasma AG-348 and AGI-8702 concentrations.

Pharmacodynamics:

Pharmacodynamic assessments will include 2,3-DPG, ATP (secondary objectives), and PKR activity assay, PKR protein, and glycolytic flux assay (exploratory objectives). The PKR Flux assay and PKR activity assay will only be conducted in clinical sites able to perform these assessments. Approximately the first 10 patients treated will undergo extensive PD sampling as detailed in Appendix 15.1, Table 5. The remainder of treated patients will undergo limited PD sampling as detailed in Appendix 15.1, Table 6. Serial blood sampling for determination of levels of ATP and, 2,3-DPG will be conducted following the first dose and the morning Day 15 dose, and additional trough levels of ATP and 2,3-DPG will be obtained. Adenosine triphosphate and 2,3 DPG will be analyzed using qualified assays to determine concentrations in whole blood.

Pharmacodynamic parameters on Day 1 and Day 15 will be computed based on observed whole blood ATP and 2,3-DPG concentrations.

Secondary outcome

Exploratory

Blood samples will be taken for evaluation of PKR activity in RBCs as well as assessment of glycolytic flux in whole blood through ex-vivo labeling with 13C-glucose. Blood will also be taken to evaluate total PKR protein levels. Levels of additional metabolites may also be assessed in blood samples to further elucidate the mechanism and effects of PKR activation by AG-348.
If sufficient data are obtained, exposure-response analysis to evaluate the relationship of AG-348 exposure and PD effects with changes in indicators of clinical activity (e.g., changes in Hb levels) may be performed.

Study description

Background summary

Pyruvate Kinase (PK) deficiency with its attendant chronic hemolytic anemia, transfusion therapy, frequent treatment in early childhood by splenectomy, and iron overload is reasonably regarded as a serious medical condition. Any therapy that could reduce the need for blood transfusion support, reduce the frequency of splenectomy, and minimize iron overload would be a meaningful benefit to affected patients.

The objectives of this study are to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD), and indicators of clinical activity of AG-348 in patients with PK deficiency. The choice of dose and schedule of administration of AG -348 for Arms 1 and 2 was based on the highest safely tolerated dose (Arm 1: 300 mg BID) and the lowest dose with potentially relevant PD activity (Arm 2: 50 mg BID) from the forerunner AG348-C-002 multiple ascending dose (MAD) study in healthy volunteers exposed to 14 day dosing. Decisions regarding continuing enrollment and treatment in will be based on Data Review Team (DRT; composed of treating investigators known for

their prominence and expertise in hematology and medicine) review of safety, PK and PD data, and indicators of clinical activity collected from all patients. The DRT will execute their duties every 6 weeks, and ad hoc as needed, throughout the study. This design was chosen to minimize risk to patients while allowing evaluation of safe and pharmacologically active dose levels of AG-348, and to allow the necessary flexibility to adjust dose and schedule should the safety, tolerability, PK, and/or PD be different in patients with PK deficiency compared with healthy volunteers. Pre-testing of AG-348 in healthy adult volunteers provided important safety and dosing information to minimize risk to patients in the proposed study.

The present safety profile of AG-348 derived from two studies in healthy adult volunteers; the significant salutary pharmacodynamic effects on the glycolytic pathway observed in healthy volunteers at well tolerated doses of AG-348; and the rigorous safety monitoring (DRT) in place for the proposed study are deemed appropriate to mitigate and justify the potential risk of study participation for patients with a disease as serious as PK deficiency

Study objective

CORE PERIOD

Primary:
* Evaluate the safety and tolerability of up to 24 weeks of AG-348 administration in patients with pyruvate kinase deficiency (PK deficiency).

Secondary:
* Evaluate the pharmacokinetics (PK) of AG-348 and the metabolite AGI-8702.
* Evaluate the pharmacodynamic (PD) response of adenosine triphosphate (ATP) and 2,3 diphosphoglycerate (2,3-DPG) after administration of AG-348.
* Evaluate indicators of clinical activity of AG-348 in patients with PK deficiency, including changes in hemoglobin (Hb), hematocrit (HCT), reticulocyte count, haptoglobin (Hp), carboxyhemoglobin (COHb), end tidal carbon monoxide (ETCO), lactate dehydrogenase (LDH), total and indirect bilirubin, erythropoietin (EPO), hepcidin, ferritin, and transferrin saturation (serum iron/iron binding capacity).

Exploratory:
* Evaluate the relationship of additional PD biomarkers including pyruvate kinase R (PKR) activity assay, glycolytic flux assays, and total PKR protein levels in whole blood, after administration of AG 348.
* Evaluate the relationship of AG-348 exposure and PD effects with changes in indicators of clinical activity.

EXTENSION PERIOD

Primary:

* Evaluate the long-term safety and tolerability of up to 4,5 years of AG-348 administration in patients with PK deficiency.

Secondary:
* Evaluate the PK of AG-348 and the metabolite AGI-8702.
* Evaluate the PD response of ATP and 2,3-DPG after administration of AG-348.
* Evaluate indicators of clinical activity of AG-348 in patients with PK deficiency, including changes in Hb, HCT, reticulocyte count, Hp, COHb, LDH, total and indirect bilirubin, EPO, ferritin, and transferrin saturation (serum iron/iron binding capacity)
* Evaluate optimal maintenance dose of AG-348 for each individual subject during the extension period.

Exploratory:
* Evaluate the relationship of total PKR protein levels in whole blood after administration of AG-348.
* Evaluate the relationship of AG-348 exposure and PD effects with changes in indicators of clinical activity.

Study design

Study AG348-C-003 is a Phase 2, open label, two arm, multicenter, randomized, dose-ranging study in adult patients with PK deficiency;the study will be divided in to a Core Period and an Extension Period. During the Core Period, patients will receive multiple doses of AG 348 for up to 24 weeks; patients who are eligible can enter the Extension Period to receive AG-348 for up to 4 years following the end of the Core Period. Patients with PK deficiency confirmed by red blood cell (RBC) PK enzymatic assay performed at Screening will be eligible to participate in this study. At Week 25, patients who safely tolerate AG 348 and demonstrate clinical activity of AG 348 may be eligible to immediately roll over to the Extension Period for continued treatment. Patients who complete treatment at the end of the Core Period (24 weeks) will undergo follow-up assessment 4 weeks after the last dose of study drug. If a patient discontinues at any other time (including early discontinuation or discontinuation during the Core or Extension Period), the follow-up assessments will be conducted 4 weeks after discontinuation.
Patients with toxicity suspected to be related to study drug will continue follow-up until the adverse event (AE) resolves, is declared chronic by the Investigator, or the patient is lost to follow-up.
For the Core Period, up to 25 patients will be initially randomized on an open-label 1:1 basis to each of two twice-daily (BID) doses of AG-348 (up to 50 patients total; see Figure 1, Study Schema). The dose of Arm 1 is 300 mg of AG-348 administered orally (PO) every 12 hours (q12h, BID). The dose of Arm 2 is 50 mg of AG 348 administered PO q12h (BID). Randomization will be stratified by PKR mutation in order to maintain balance as much as possible across the dose arms for the specific mutations expected to be most frequently enrolled. The PKR mutation stratification factor will consist of 4 levels (R510Q, R486W,

and R479H) and all other mutations (*other*). Mutation status is defined by the presence of at least one of the indicated mutations; patients with more than one stratified mutation will be assigned based on Sponsor*s discretion.
The doses for each arm of the Core Period have been selected from the AG348-C-001 single ascending dose (SAD) and AG348-C-002 multiple ascending dose (MAD) studies in healthy adult volunteers to represent the range of doses/exposures that were safely tolerated and resulted in maximal or near-maximal PD effects on 2,3-DPG and ATP.
Because PK deficiency is a rare disease with a limited eligible patient population and because the underlying pathophysiology and clinical phenotype of affected patients is heterogeneous due to the wide variety of mutations in PKR that cause the disease, it is important to focus closely on dose findings in this first-in-patient study. Therefore, in addition to initiating this study with 2 different doses of AG-348 administered q12h, a Data Review Team (DRT) will be established to review study data on a regular basis and adapt the study design, dose and schedule of AG-348.
The DRT will monitor safety on an on-going basis and meet at regular intervals of approximately every 6 weeks, or ad hoc, as necessary, for as long as any patients are still in the Core Period to review AEs, vital signs (VS), clinical laboratory assessments (hematology, clinical chemistry, coagulation, and urinalysis), and electrocardiograms (ECGs). The DRT will also review available PK/PD data and indicators of clinical activity (e.g., changes from baseline in Hb). These DRT meetings will also include data review for all patients that may be under treatment in the Extension Period. If there are no patients still being treated in the Core Period, and the only patients being treated are those in the Extension Period, then the frequency of the DRT meetings will reduce to approximately every 3 months in order to match the frequency of patient visits (and new data collection) in the Extension Period.
The DRT will be comprised of the study Coordinating Investigator, treating Investigators, Medical Monitor, Clinical Pharmacologist, Statistician, and Sponsor*s Responsible Medical Officer.
Beginning 6 weeks after the first patient is dosed in the Core Period or ad hoc as necessary, and proceeding according to the schedule indicated above (approximately every 6 weeks during the Core Period, and approximately every 3 months during the Extension Period once all patients have completed the Core Period), the DRT will review cumulative safety data, available PK/PD data, and clinical activity data. Based on the DRT*s recurring reviews, the DRT may exercise one or more of the following options during the Core Period:
* Continue treatment and enrollment in existing arms without change.
* Add 1 new dose arm (Arm 3) to enroll up to 25 patients at a dose to be determined; the dose for Arm 3 may be lower or higher than Arm 1 and Arm 2 doses, but will not exceed 360 mg q12h; and the dose regimen may be less frequent than q12h.
* Terminate or suspend enrollment to allow further review of clinical data in Arm 1 and/or Arm 2 (and/or potential Arm 3). Enrollment in an arm could be terminated or suspended to allow further review, for example, for unacceptable safety/tolerability, poor PD response, or lack of signs of clinical activity.

* Re-assign patients* doses and schedule in a terminated arm to match the dose and schedule of another arm of the study. In this case, the patients in the terminated arm will remain in their original arm, i.e., they will not count towards the enrollment quota of the arm whose dose and schedule is being adopted.
* Implement specific genotype restrictions to enrollment in one or more arms to ensure representation of patients with genotypes of greatest clinical relevance.

The DRT may exercise one or more of the following options during the Extension Period:
* Continue treatment without change;
* Re-assign patients* doses and schedule to an existing dose and schedule that has been determined to be safer, and/or have a better PD response, or produce signs of clinical activity;
* Terminate or suspend treatment to allow further review of clinical data (eg, for unacceptable safety/tolerability, poor PD response, or lack of signs of clinical activity).

The data that the DRT will review to make these decisions is expected to include, but are not necessarily limited to, the following:
* Safety Observations: all AEs; VS, clinical laboratory (hematology, clinical chemistry, coagulation, and urinalysis), and ECG;
* PK and PD Observations: including changes in 2,3-DPG and ATP;
* Indicators of Clinical Activity: including changes in Hb, HCT, reticulocyte count, Hp, COHb, ETCO (Core Period only), LDH, EPO, total and indirect bilirubin, hepcidin, ferritin, and transferrin saturation.
If a third dose arm is implemented, the dose of AG-348 selected will not exceed 360 mg BID, as this was the highest dose that demonstrated acceptable safety and tolerance in the 14-day multiple BID dosing study in healthy volunteers. The PK/PD sampling schedule in a potential third dosing arm will be determined by Sponsor*s discretion and may follow either the extensive or limited PK/PD sampling schedules as specified.
The DRT will monitor the data in an ongoing manner as described and may make a decision to terminate enrollment in an arm if unacceptable AEs are observed, PD activity is limited, and/or markers of clinical activity indicate no effect. Unacceptable AEs are defined as * Grade 3 AEs (using National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAEv4.03]) that are assessed as at least possibly related to AG 348, with the exception of Grade 3 headache, hot flash/flushing, nausea, vomiting, and/or diarrhea that is transient in duration (< 24 hours) or able to be medically managed to * Grade 2 within 24 hours. The DRT may also exercise discretion to terminate enrollment in an arm if it observes a frequency of Grade 2 AEs that would make it difficult to support long-term dosing.

Patients in the Extension Period will continue on the dose they were randomized to in the Core Period, unless the DRT had reason to establish a different dose/schedule during the course of the Core Period (the DRT will not propose a

dose higher than 360 mg q12h), or unless the treating Investigator exercises the option for intra-patient dose escalation (see Section 9.7.2).

Due to the potential for AG-348-mediated aromatase inhibition, dual-energy x-ray absorptiometry (DXA) scan (hip and spine) will be performed at Screening (if patient has not had prior DXA scan within 3 months of Day 1) to obtain T and Z scores. These data are intended to serve as a baseline measure of bone mineral density for all enrolling patients, and are deemed of particular importance for those who enter the longer term Extension Period after completing 24 weeks of treatment (Core Period). All patients will have a second DXA scan in the interval between Weeks 24 and 28 for theCore Period. Patients in the Extension Period will have additional DXA scans at Months 12,18, 24, 30, 42, 54 and 55.
As the number of enrolling arms changes in the study (for example, from 2 to 3), the randomization scheme will adjust to enable balanced randomization into each actively accruing arm. Randomization and stratification will cease in the event that only a single arm is left enrolling.
Depending on possible early termination of 1 or both of the initial 2 arms, or the addition of a third arm, the study could enroll up to a maximum of 75 patients.

Gradual dose taper period
At the 1st scheduled visit of the patient, the study doctor will explain the gradual dose taper process and start the 1st step.
One week and 2 weeks after the patient have started on a lower dose, blood collection for blood count and haptoglobin will be done at the study site, or, if the patient wishes and the study doctor agrees, at patient's home by a visiting nurse, or at the local doctor*s office, or at a local laboratory.
Three weeks after thet patient have started on a lower dose, the patient will come back to the study to allow the doctor to assess how the patient is doing and decide whether the dose can be decreased further or should be increased back to its previous level.

Intervention

AG-348 sulfate hydrate capsules will be provided as 5 mg, 25 mg or 100 mg (free-base equivalent) of AG-348 sulfate hydrate without excipients in dark green opaque (5 mg), Swedish orange (25 mg) or white opaque (100 mg) gelatin capsules (size 2 capsules for all dose strengths). AG-348 will be administered PO BID. The number of capsules per dose will vary by assigned dose group. AG-348 will be administered with water and may be administered with or without food.

There are now 2 different formulations of AG-348, capsules and tablets. While this study (AG348-C-003) was started with the capsule formulation, the tablet formulation will be introduced to gradually replace the capsule formulation.

No dose adjustment is required following a switch to the tablet formulation. When the patient will switched from receiving AG-348 capsules to AG-348 tablets, the same dose of tablet as the capsule dose should be administered (f.e. if the patient is taking 25 mg capsules, for each 25 mg capsule the patient was taking before, he/she will take one 20 mg tablet and one 5 mg tablet). The patient will be switched from receiving the capsule to the tablet formulation of AG 348 when the supply of the capsule formulation is exhausted or sooner as deemed appropriate by the Investigator and Medical Monitor.

Patients who are eligible can enter the Extension Period to receive AG-348 for up to 4 years following the end of the Core Period.

Study burden and risks

Patients are asked to undergo procedures described in the flowchart of the study protocol. These procedures
include physical examination, vital signs, urine pregnancy tests (female;chidbearing patients, ECG, DXA scan, extended lab tests,completing questionnaire, diaries and adminsitration of study drug (oral). Additionally, fertile patients who are sexually active must agree to use an effective form of contraception with their sexual partners throughout participation in the study. Patients are also asked to inform their study doctor on their medication use and change in health status.
For side effects see section E9.

Contacts

Public
Agios Pharmaceuticals, Inc.

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Scientific
Agios Pharmaceuticals, Inc.

Sidney Street 88
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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

For entry into the Core Period, patients must meet all of the following criteria during the Screening or other specified period:
1.Signed written informed consent obtained prior to performing any study procedure, including screening procedures.
2.Male or female, aged 18 years and older.
3.Known medical history of PK deficiency.
4.All patients must have documented clinical laboratory confirmation of PK deficiency by RBC pyruvate kinase enzymatic assay performed at Screening either by a designated central laboratory or by any participating investigative site*s local hematology laboratory. Patients with prior documentation of PK deficiency by RBC enzymatic assay will have a reconfirmation of this result during Screening as a condition of enrollment.
a.In the event that a patient*s screening pyruvate kinase enzymatic assay is negative (i.e., shows normal pyruvate kinase activity), the patient will be eligible for enrollment if the genotyping shows a mutant genotype that has been previously documented in the literature to be associated with PK deficiency. If the genotyping shows a previously undescribed mutation in the PKR gene, then the eligibility for enrollment will be determined on a case-by-case basis by the Coordinating Investigator and Medical Monitor in discussion with the Investigator. If no mutation is defined, then the patient will not be eligible.
5.ALL patients must have a blood sample for genotypic characterization of the mutant PKR gene performed by a designated central laboratory at Screening. The designated central laboratory-determined genotype will generally serve as the basis for genotyping for enrollment. However, patients whose genotype has already been determined by another laboratory may be enrolled on the basis of that report, with the approval of the Medical Monitor, in case of unexpected delay in return of the designated central laboratory result during the Screening Period. Enrollment on the basis of a result from a laboratory other than the designated central genotyping laboratory does not relieve the inclusion requirement that ALL patients must have a sample sent to the designated central genotyping laboratory.
6.All patients must have genotypic characterization of the UGT1A1 gene performed by a designated central laboratory to document whether they may have underlying Gilbert's Disease. Patients with Gilbert*s Disease are eligible to enroll.
7.Males must have Hb * 12.0 g/dL; females must have Hb * 11.0 g/dL.
8.All patients must be considered transfusion independent as defined by: no greater than 3

units of RBCs transfused in the 12-month period up to the first day of study dosing and no transfusions within 4 months of first day of study dosing. Patients who have received more transfusion support than described above will be evaluated for eligibility on a case-by-case basis by the Medical Monitor.
9. Eligible patients may still have their spleens in place, or may have undergone prior splenectomy. For splenectomized patients:
a.Must have undergone their procedure at least 6 months prior to Screening.
b.Must be current in their vaccinations for Pneumococcal Conjugate (PCV13), Pneumococcal Polysaccharide (PPSV23), Quadrivalent Meningococcal vaccine, and Haemophilus influenzae type b as recommended by Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) or immunization advisory groups in Canada and the European Union (for patients enrolled in Canada and the EU).
[http://www.cdc.gov/vaccines/schedules/downloads/adult/adult-schedule.pdf] [Any missing vaccinations may be administered starting with the Screening Period and during the trial following the initiation of AG-348 dosing as necessary according to recommended vaccination guidance.]
10.Eastern Cooperative Oncology Group (ECOG) Performance Status * 2.
11.Patients must be taking at least 1 mg of folic acid daily for at least 21 days prior to first dose and continue daily during study participation.
12.Adequate organ function, defined as:
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 patients with serum bilirubin > ULN, the elevation must be attributed to hemolysis with or without Gilbert's syndrome and must not be choledocholithiasis, cholecystitis, biliary obstruction, or hepatocellular disease.
c.Serum creatinine * 1.25 × ULN. If serum creatinine > 1.25 × ULN, then 24-hour measured or calculated (Cockcroft-Gault) glomerular filtration rate (GFR) * 60 mL/min.
d.Absolute neutrophil count (ANC) * 1.0 × 109/L.
e.Platelet count * 100 × 109/L.
f.Activated partial thromboplastin time (aPTT) and international normalized ratio (INR) * 1.25 × ULN, unless the patient is receiving therapeutic anticoagulants.
13.Women of childbearing potential (WOCBP) must agree to abstain from sexual intercourse or to use an acceptable/effective method of contraception (i.e., condom plus spermicide, condom plus oral contraceptive, condom plus intrauterine device [IUD], condom plus diaphragm with spermicide) from as soon as feasible during the Screening period until 30 days following the last dose of AG-348.
i.WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, and/or bilateral oophorectomy) or is not post-menopausal. Post-menopausal is defined as:
ii.Amenorrhea * 12 consecutive months without another cause, and a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL;
iii.Amenorrhea * 12 consecutive months in women * 62 years old (FSH testing is not required).
14.WOCBP must have a negative serum or urine pregnancy test within 72 hours before start of AG 348 dosing.

15.Women must not be breastfeeding.
16.Male patients, with the exception of those who have undergone vasectomy at least 6 months prior to Screening, must agree to abstain from sexual intercourse or, if sexually active, to use a condom with spermicide as contraception (regardless of their female partner's childbearing potential or their partner's use of their own contraception) from Day 1 of dosing until 30 days following the last dose of AG-348.;For entry into the Extension Period, patients must meet the following criteria:
17. Signed written informed consent obtained prior to performing any study procedure during the Extension Period.
18. Patient must have completed 24 weeks of treatment during the Core Period and tolerated AG-348 (defined as having completed 24 weeks with or without permitted dose modifications)
19. The patient*s treating Investigator agrees that there is a potential for clinical benefit to continued treatment and recommends participation in the Extension Period
20. The Sponsor's designated Medical Monitor or Responsible Medical Officer approves the patient*s participation in the Extension Period
21. As applicable, the patient must agree to continue to follow the same sexual abstinence/contraception rules as stated in Inclusion Criteria 13 and 16.

Exclusion criteria

Patients who meet any of the following criteria at Screening or prior to dosing on Day 1 will not be enrolled in the Core Period:
1.Hemoglobin level > 12.0 g/dL if male; Hb > 11.0 g/dL if female.
2.Additional diagnosis of any other congenital or acquired blood disorder, including glucose 6 phosphate-dehydrogenase (G6PD) deficiency, or any other hemolytic anemia process except for mild allo-immunization as a consequence of transfusion therapy.
3.Iron overload (hemosiderosis or concurrent hemochromatosis) sufficiently severe to result in a clinical diagnosis by the Investigator of cardiac, hepatic, or pancreatic insufficiency.
4.Prior bone marrow or stem cell transplant.
5.Clinically symptomatic cholelithiasis or cholecystitis. (Prior cholecystectomy is not exclusionary. Patients with symptomatic cholelithiasis or cholecystitis may be rescreened once the disorder has been treated and clinical symptoms have resolved.)
6.Currently enrolled in another therapeutic clinical trial involving on-going therapy with any investigational or marketed product or placebo. Concurrent participation in the Pyruvate Kinase Deficiency Natural History Study (NCT02053480) is permitted.
7.Exposure to any investigational drug, device, or procedure within 28 days prior to Screening or during trial participation.
8.Concurrent medical condition that could compromise participation in the study such as:
a.Poorly controlled hypertension (defined as systolic blood pressure (BP) > 150 mm Hg or diastolic BP > 90 mm Hg) refractory to medical management.
b.History of recent (within < 6 months from Screening date) congestive heart failure; myocardial infarction or unstable angina pectoris; or hemorrhagic, embolic, or thrombotic stroke; deep venous thrombosis; or pulmonary or arterial embolism.
c.Currently active infection requiring the use of parenteral anti-microbial agents or that is

greater than Grade 3 (CTCAEv4.03) within 6 months of first dose.
d.A pattern or frequency of post-splenectomy sepsis that in the assessment of the Investigator could reasonably be expected to interfere with the ability of the patient to complete the 24 week Core Period study participation.
e.Positive test for hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV) antibody with signs of active Hepatitis B or C virus infection.
f.Positive test for human immunodeficiency virus (HIV) 1 or 2 antibody.
g.Diabetes mellitus judged to be in poor control by the Investigator or requiring > 3 anti-diabetic agents counting insulin (all insulins are considered one agent); use of insulin per se is not exclusionary.
h.History of any primary malignancy with the exception of: curatively treated non-melanomatous skin cancer; curatively treated cervical or breast carcinoma in situ; or other primary tumor treated with curative intent and no known active disease present and no treatment administered during the last 3 years.
9.Undergone major surgery within 6 months of first dose.
10.Current or recent history of psychiatric disorder that in the opinion of the Investigator or Medical Monitor could compromise the ability of the patient to cooperate with study visits and procedures.
11.Use of any of the restricted list of products known to strongly inhibit cytochrome P450 (CYP) 3A4 drug metabolism (Appendix 15.4, Table 9) within 5 days prior to Day 1 dosing; or to strongly induce CYP3A4 metabolism (Appendix 15.4, Table 10) within 28 days prior to Day 1 dosing; or to strongly inhibit P-glycoprotein (P-gp) transporter (Appendix 15.4, Table 11) within 5 days prior to Day 1 dosing; or digoxin within 5 days prior to Day 1 dosing.
12.Serum bilirubin > ULN attributable to factors other than hemolysis and/or Gilbert's syndrome.
13.Male patients with heart-rate corrected QT interval Fridericia's method (QTcF) interval > 450 msec, or female patients with QTcF interval > 470 msec with the exception of patients with a left bundle branch block (LBBB). Medical Monitor approval needed in patients with a LBBB.
14.Cardiac dysrhythmias judged as clinically significant by the Investigator or requiring therapy with drugs that are primarily substrates of CYP3A4.
15.History of allergy to sulfonamides if characterized by acute hemolytic anemia, anaphylaxis, or rash of erythema multiforme type or Stevens-Johnson syndrome.
16.Any other medical or psychological condition deemed by the Investigator to be likely to interfere with a patient's ability to understand and sign informed consent; cooperate with study visits, tests, and procedures; or otherwise safely and reliably participate in the study.;Patients will not be permitted to enter the Extension Period if:
17. The patient experienced AEs during the Core Period that are considered by the treating Investigator or the Sponsor*s designated Medical Monitor or Responsible Medical Officer to pose a significant safety risk to the patient if treatment were to be extended.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-01-2016
Enrollment:	15
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	01-10-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	09-12-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	01-03-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	17-08-2016

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	10-10-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
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Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	12-09-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	13-12-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	26-02-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	11-04-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2015-000484-13-NL
ClinicalTrials.gov	NCT02476916
CCMO	NL53542.041.15