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Phase IIa/IIb study of AG-946 in patients with anaemia due to lower-risk myelodysplastic syndromes

Submission date
16/09/2022

Recruitment status
Recruiting

Registration date
11/10/2022

Overall study status
Ongoing

Last Edited
29/11/2024

Condition category
Haematological Disorders

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Myelodysplastic Syndromes (MDS) are a group of rare haematological malignancies characterised by ineffective haematopoiesis (the process by which the body produces blood cells and blood plasma), progressive cytopenia (a condition in which there is a lower-than-normal number of blood cells) and abnormal cellular maturation. Anaemia is the most common cytopenia in MDS which leads to symptoms such as fatigue that can impact normal daily lives. Approximately 50% of all MDS patients require regular red blood cell (RBC) transfusions. However, RBC transfusions do not completely alleviate health-related quality of life aspects, they contribute to iron overload and lead to a substantial human and financial burden.

The investigational drug, AG-946, is a novel small molecule that activates the enzyme pyruvate kinase which contributes to the production of energy in the RBC. By helping to increase energy, RBC functionality and survival may be improved. Preclinical studies have demonstrated that AG-946 has high potency, a pharmacokinetic half-life that supports once-daily administration, a long duration of the pharmacodynamic activity, and no observed off-target effects, suggesting that AG-946 has the potential to improve ineffective erythropoiesis and thus anaemia due to MDS.

Who can participate?
Adults with MDS

What does the study involve?
As such, Sponsor Agios Pharmaceuticals, Inc. designed this phase IIa/IIb study with the purpose to determine the safety, tolerability and efficacy of AG-946 when administered with standard treatment for anaemia due to MDS. There are 2 parts to this study - phase IIa and phase IIb. In phase IIa, about 20 participants will take part, which will test 1 dose level (5mg once daily) of AG-946. This part is open-label and the study duration will be up to 180 weeks. In Phase IIb, about 96 participants will take part, which will test 3 dose levels (2mg, 3mg, or 5mg once daily) of AG-946. This part is double-blinded and the study duration will be up to 188 weeks.

The study doctor will discuss all information regarding possible side effects of the study drug and procedures with patients during the consent process. These are detailed at length in the PIS /ICF.

What are the possible benefits and risks of participating?
No benefits were provided at the registration of the trial.
In prior clinical studies, AG-946 use may be associated with the risks below:
1. Headache

Reproductive Risks: A study of AG-946 performed on pregnant animals showed that it has the potential to cause birth defects. Birth defects were seen at doses close to the doses expected to be given to humans. Therefore, AG-946 should not be administered to pregnant women or to women of childbearing potential unless 2 forms of contraception control, one of which must be considered highly effective, are used.

Participants will be under constant supervision by the Principal Investigator and site staff and every effort will be made to ensure that any side effects are treated promptly and to maintain the patient's comfort and wellbeing throughout the study

Where is the study run from?
Agios Pharmaceuticals (United States of America)

When is the study starting and how long is it expected to run for?
April 2022 to November 2028

Who is funding the study?
Agios Pharmaceuticals (United States of America)

Who is the main contact?
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Additional identifiers

Clinical Trials Information System (CTIS)
2022-500609-42-00

Integrated Research Application System (IRAS)
1006035

ClinicalTrials.gov (NCT)
NCT05490446

Protocol serial number
AG946-C-002, IRAS 1006035, CPMS 53223

Study information

Scientific Title
A phase IIa/IIb, open-label, proof of concept (phase 2a) and open-label (phase 2b), multicenter, efficacy, and safety study of AG-946 in participants with anemia due to lower-risk myelodysplastic syndromes

Study objectives

Current study hypothesis as of 29/11/2024:
Phase IIa:
1. To establish proof-of-concept (POC) for AG-946 in participants with lower-risk myelodysplastic syndromes (LR-MDS)

Phase IIb:
2. To evaluate the effect of AG-946 on transfusion independence (TI) in participants with LR-MDS

Phase IIa:
3. To evaluate the safety of AG-946
4. To evaluate the effect of AG-946 on additional measures of anaemia
5. To evaluate the effect of AG-946 on transfusion burden (participants with LTB only)
6. To evaluate the pharmacokinetics of AG 946
7. To evaluate the effect of AG-946 on pharmacodynamic biomarkers

Phase IIb:
8. To evaluate the safety of AG-946
9. To evaluate the effect of AG-946 on anaemia
10. To evaluate the effect of AG-946 on transfusion burden
11. To evaluate the pharmacokinetics of AG-946
12. To evaluate the effect of AG-946 on pharmacodynamic biomarkers

Previous study hypothesis:
Phase IIa:
1. To establish proof-of-concept (POC) for AG-946 in participants with lower-risk myelodysplastic syndromes (LR-MDS)

Phase IIb:
2. To compare the effect of AG-946 versus placebo and to detect a dose-response for erythroid response in participants with LR-MDS

Phase IIa:
3. To evaluate the safety of AG-946
4. To evaluate the effect of AG-946 on additional measures of anaemia
5. To evaluate the effect of AG-946 on transfusion burden (participants with LTB only)
6. To evaluate the pharmacokinetics of AG 946
7. To evaluate the effect of AG-946 on pharmacodynamic biomarkers

Phase IIb:
8. To evaluate the safety of AG-946 versus placebo
9. To evaluate the effect of AG-946 versus placebo on anaemia (participants who are NTD and participants with LTB only)
10. To evaluate the effect of AG-946 versus placebo on transfusion burden (participants with LTB and HTB only)
11. To evaluate the effect of AG-946 versus placebo on additional measures of erythroid response
12. To evaluate the pharmacokinetics of AG-946
13. To evaluate the effect of AG-946 on pharmacodynamic biomarkers
14. To evaluate the relationship between pharmacokinetic and pharmacodynamic effects of AG 946

Ethics approval required

Old ethics approval format

Ethics approval(s)
Approved 11/10/2022, ref: 22/NW/0277

Study design
Open-label multicentre study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Anaemia due to lower-risk myelodysplastic syndromes

Interventions
Current interventions as of 29/11/2024:
The study consists of 2 parts - Phase IIa and Phase IIb. UK trial sites will participate in both phases. In Phase IIa part, about 20 participants will take part, which will test 1 dose level (5mg once daily) of AG-946. This part is open-label to establish proof of concept of AG-946 in LR-MDS. Participants who complete the 16-week Core Period will be eligible to continue receiving the same dose of AG-946 for up to 156 weeks in the Extension Period.

In Phase IIb part, about 60 participants will take part. Eligible participants will receive 10 mg QD AG-946 (Dose Level 1), 15 mg QD AG-946 (Dose Level 2), or 20 mg QD AG-946 (Dose Level 3) for QD oral administration. Enrollment will be sequential, starting with Dose Level 1; enrollment in subsequent dose levels will begin once the last participant has enrolled in the prior dose level. The Sponsor will review all available data, including safety data, on an ongoing basis and after completion of enrollment in a dose level; no formal enrollment hold is planned before enrollment in the next dose level. This part is to evaluate the efficacy and safety of AG-946 at 3 dose levels. At the discretion of the Investigator, participants who complete the 24-week Core Period will be eligible to continue receiving the same dose of AG-946 for up to 156 weeks in the Extension Period. Intrapatient dose escalation up to 20 mg QD may be considered.

Previous interventions:
The study consists of 2 parts - Phase IIa and Phase IIb. UK trial sites will participate in both phases. In Phase IIa part, about 20 participants will take part, which will test 1 dose level (5mg once daily) of AG-946. This part is open-label to establish proof of concept of AG-946 in LR-MDS. Participants who complete the 16-week Core Period will be eligible to continue receiving the same dose of AG-946 for up to 156 weeks in the Extension Period.

In Phase IIb part, about 96 participants will take part, patients will be randomly assigned in a 1:1: 1:1 ratio to receive the study drug for QD (daily) administration (AG-946 2mg, 3mg, 5mg or placebo). This part is double-blinded to evaluate the efficacy and safety of AG-946. Participants who complete the 24-week Double-blind Period will be eligible to receive AG-946 for up to 156 weeks in the Extension Period. During the Extension Period, all participants will receive AG-946. Participants who received a placebo during the Double-blind Period will be randomized 1:1:1 to receive 2 mg QD AG-946 (Dose Level 1), 3 mg QD AG-946 (Dose Level 2), or 5 mg QD AG-946 (Dose Level 3) to enable the assessment of the long-term safety and efficacy of these multiple

doses of AG-946. Participants who received AG-946 during the Double-blind Period will be eligible to continue receiving the same dose of AG-946.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
AG-946

Primary outcome(s)
Current primary outcome measures as of 29/11/2024:
Phase IIa:
1. Haemoglobin (Hb) response, defined as a ≥1.5-g/dL increase from baseline in the average Hb concentration, measured using Hb concentration assessments according to the Clopper-Pearson method and recorded in medical notes from week 8 to 16
2. Transfusion independence (TI), defined as transfusion-free for ≥8 consecutive weeks, measured using assessments with the Clopper-Pearson method and recorded in medical notes during the Core Period (participants with low transfusion burden [LTB] only) at weeks 1 to 16

Phase IIb:
1. Transfusion independence, defined as transfusion-free for ≥8 consecutive weeks (TI8) during the Core Period

Previous primary outcome measures:
Phase IIa:
1. Haemoglobin (Hb) response, defined as a ≥1.5-g/dL increase from baseline in the average Hb concentration, measured using Hb concentration assessments according to the Clopper-Pearson method and recorded in medical notes from week 8 to 16
2. Transfusion independence (TI), defined as transfusion-free for ≥8 consecutive weeks, measured using assessments with the Clopper-Pearson method and recorded in medical notes during the Core Period (participants with low transfusion burden [LTB] only) at weeks 1 to 16

Phase IIb - all measured using medical records for ≥8 consecutive weeks during the Double-blind Period:
Modified hematologic improvement-erythroid (mHI-E) response, defined as:
1. ≥1.5-g/dL increase from baseline in Hb concentration (participants who are NTD)
2. Transfusion independence, defined as transfusion-free (participants with LTB only)
3. ≥50% reduction from baseline in total transfused RBC units (participants with HTB only)

Key secondary outcome(s))
Current secondary outcome measures as of 29/11/2024:
Phase IIa:
1. AEs, SAEs, discontinuations due to AEs, and laboratory abnormalities measured using SAE/AE reporting forms during the core period (week 1 to 16)
2. Hb 1.0+ response, defined as a ≥1.0-g/dL increase from baseline in the average Hb concentration measured using medical notes from week 8 to 16
3. Change from baseline in Hb concentration during the Core Period measured using medical notes during the core period (week 1 to 16)

4. ≥1.5-g/dL increase from baseline in the Hb concentration at ≥2 consecutive time points measured using medical notes from week 8 to 16
5. Change from baseline in total transfused red blood cell (RBC) units measured using medical notes during the core period (week 1 to 16)
6. ≥50% reduction in total transfused RBC units for ≥8 consecutive weeks measured using medical notes throughout ≥8 consecutive weeks in core period (week 1 to 16)
7. Plasma concentration and pharmacokinetic parameters of AG-946 measured using laboratory assessment of blood samples collected. Results will be noted down in medical notes/CRF during the core period (week 1 to 16)
8. Whole blood concentrations of pharmacodynamic parameters, including 2,3-diphosphoglycerate (2,3-DPG) and adenosine triphosphate (ATP) measured using laboratory assessment of blood samples collected. Results will be noted down in medical notes/CRF during the core period (week 1 to 16)

Phase IIb:
1. AEs, SAEs, discontinuations due to AEs, and laboratory abnormalities measured using SAE/AE reporting forms during the core period
2. Change from baseline in Hb concentration measured using medical notes during the core period
3. Change from baseline in total transfused RBC units measured using medical notes from week 8 to 24
4. ≥50% reduction in total transfused RBC units for ≥8 consecutive weeks during the Core Period compared with baseline (participants with high transfusion burden [HTB] only)
5. Time to first TI8 during the Core Period
6. Transfusion-free for ≥12 consecutive weeks (TI12) during the Core Period
7. ≥50% reduction in total transfused RBC units for ≥12 consecutive weeks during the Core Period compared with baseline (participants with HTB only)
8. Time to first TI12 during the Core Period
9. Duration of TI, defined as the longest transfusion-free period during the Core Period
10. Plasma concentration and pharmacokinetic parameters of AG-946 during the Core Period
11. Whole blood concentrations of pharmacodynamic parameters, including 2,3-DPG and ATP during the Core Period

Previous secondary outcome measures:
Phase IIa:
1. AEs, SAEs, discontinuations due to AEs, and laboratory abnormalities measured using SAE/AE reporting forms during the core period (week 1 to 16)
2. Hb 1.0+ response, defined as a ≥1.0-g/dL increase from baseline in the average Hb concentration measured using medical notes from week 8 to 16
3. Change from baseline in Hb concentration during the Core Period measured using medical notes during the core period (week 1 to 16)
4. ≥1.5-g/dL increase from baseline in the Hb concentration at ≥2 consecutive time points measured using medical notes from week 8 to 16
5. Change from baseline in total transfused red blood cell (RBC) units measured using medical notes during the core period (week 1 to 16)
6. ≥50% reduction in total transfused RBC units for ≥8 consecutive weeks measured using medical notes throughout ≥8 consecutive weeks in core period (week 1 to 16)
7. Plasma concentration and pharmacokinetic parameters of AG-946 measured using laboratory assessment of blood samples collected. Results will be noted down in medical notes/CRF during the core period (week 1 to 16)
8. Whole blood concentrations of pharmacodynamic parameters, including 2,3-diphosphoglycerate (2,3-DPG) and adenosine triphosphate (ATP) measured using laboratory

assessment of blood samples collected. Results will be noted down in medical notes/CRF during the core period (week 1 to 16)

Phase IIb:
1. AEs, SAEs, discontinuations due to AEs, and laboratory abnormalities measured using SAE/AE reporting forms during the double-blind period
2. Change from baseline in Hb concentration measured using medical notes during the double-blind period
3. Change from baseline in total transfused RBC units measured using medical notes from week 8 to 24
4. Transfusion independence, defined as transfusion-free for ≥8 consecutive weeks measured using medical notes for ≥8 consecutive weeks during the Double-blind Period
5. Time to first mHI-E response measured using medical notes during the double-blind period
6. Maximum duration of mHI-E response for participants who achieved an mHI-E response measured using medical notes during the double-blind period
7. Plasma concentration and pharmacokinetic parameters of AG-946 measured using laboratory assessment of blood samples collected. Results will be noted down in medical notes/CRF during the double-blind period
8. Whole blood concentrations of pharmacodynamic parameters, including 2,3-DPG and ATP measured using laboratory assessment of blood samples collected. Results will be noted down in medical notes/CRF during the double-blind period
9. Exposure-response (or pharmacokinetic/pharmacodynamic) relationship between relevant pharmacokinetic parameters and endpoints that are indicators of clinical activity and safety measured using laboratory assessment of blood samples collected. Results will be noted down in medical notes/CRF during the double-blind period

Completion date
30/11/2028

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 29/11/2024:
Phase IIa:
1. At least 18 years of age at the time of providing informed consent
2. Documented diagnosis of MDS according to World Health Organization (WHO) classification, that meets IPSS-R classification of lower-risk disease (risk score: ≤3.5) and <5% blasts as determined by the participant’s bone marrow biopsy/aspirate during the Screening Period
3. Nontransfused or with LTB, based on transfusion history from the participant’s medical record, according to revised IWG 2018 criteria:
3.1. NTD: <3 RBC units in the 16-week period before administration of the first dose of the study drug and no transfusions in the 8-week period before administration of the first dose of the study drug, or
3.2. LTB: 3 to 7 RBC units in the 16-week period before administration of the first dose of the study drug and <4 RBC units in the 8-week period before administration of the first dose of the study drug
4. An Hb concentration <11.0 g/dL during the 4-week Screening Period
5. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0, 1, or 2
6. If taking iron chelation therapy, the iron chelation therapy dose must have been stable and started ≥56 days before administration of the first dose of the study drug
7. For women of childbearing potential (WOCBP) and men with partners who are WOCBP, must

be abstinent from sexual activities that may result in a pregnancy as part of their usual lifestyle or agree to use 2 forms of contraception, 1 of which must be considered highly effective, from the time of providing informed consent, throughout the study, and for 28 days after the last dose of study drug for women and 90 days after the last dose of study drug for men. The second form of contraception can be an acceptable barrier method
8. Written informed consent from the participant before any study-related procedures are conducted and willing to comply with all study procedures for the duration of the study

Phase IIb:
1. At least 18 years of age at the time of providing informed consent
2. Documented diagnosis of MDS according to WHO classification that meets IPSS-R classification of lower-risk disease (risk score: ≤3.5) and <5% blasts as determined by the participant's bone marrow biopsy/aspirate during the Screening Period
3. With LTB or HTB, based on transfusion history from the participant's medical record according to revised IWG 2018 criteria (Appendix 4):
3.1. LTB: 3 to 7 RBC units from at least 2 transfusion episodes in the 16-week period before administration of the first dose of study drug AND <4 RBC units in the 8-week period before administration of the first dose of study drug, or
3.2. HTB: ≥8 RBC units in the 16-week period before administration of the first dose of the study drug AND ≥4 RBC units in the 8-week period before administration of the first dose of the study drug
If a participant's transfusion burden does not fall into either the LTB or HTB category, as defined per IWG 2018 criteria, then the transfusion burden will be categorized based on their transfusion history in the 16-week period before administration of the first dose of study drug.
4. Pretransfusion Hb concentration available for a minimum of 2 and at least half (50%) of the transfusions received in the 16-week period before administration of the first dose of the study drug
5. An Hb concentration <10.0 g/dL during the 4-week Screening Period
6. Up to 2 prior therapies including erythropoiesis-stimulating agents (ESAs) (eg, erythropoietin [EPO], EPO + granulocyte colony-stimulating factor [G-CSF]) and/or luspatercept
7. ECOG Performance Status score of 0, 1, or 2
8. If taking iron chelation therapy, the iron chelation therapy dose must have been stable and started ≥56 days before administration of the first dose of the study drug
9. WOCBP must be abstinent of sexual activities that may result in pregnancy as part of their usual lifestyle or agree to use a highly effective method of contraception from the time of providing informed consent throughout the study and for 28 days after the last dose of study drug; if the highly effective method of contraception is hormonal contraception, then an acceptable barrier method must also be used (see Appendix 1 for the definition of WOCBP and acceptable contraception methods). Men with partners who are WOCBP must be abstinent of sexual activities that may result in pregnancy as part of their usual lifestyle or agree to use a condom from the time of providing informed consent throughout the study and for 28 days after the last dose of the study drug.
10. Written informed consent from the participant before any study-related procedures are conducted and willing to comply with all study procedures for the duration of the study

Previous participant inclusion criteria:
Phase IIa:
1. At least 18 years of age at the time of providing informed consent
2. Documented diagnosis of MDS according to World Health Organization (WHO) classification, that meets IPSS-R classification of lower-risk disease (risk score: ≤3.5) and <5% blasts as determined by the participant's bone marrow biopsy/aspirate during the Screening Period
3. Nontransfused or with LTB, based on transfusion history from the participant's medical

record, according to revised IWG 2018 criteria:
a. NTD: <3 RBC units in the 16-week period before administration of the first dose of study drug and no transfusions in the 8-week period before administration of the first dose of study drug, or
b. LTB: 3 to 7 RBC units in the 16-week period before administration of the first dose of the study drug and <4 RBC units in the 8-week period before administration of the first dose of the study drug
4. An Hb concentration <11.0 g/dL during the 4-week Screening Period
5. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0, 1, or 2
6. If taking iron chelation therapy, the iron chelation therapy dose must have been stable and started ≥56 days before administration of the first dose of the study drug
7. For women of childbearing potential (WOCBP) and men with partners who are WOCBP, must be abstinent from sexual activities that may result in a pregnancy as part of their usual lifestyle or agree to use 2 forms of contraception, 1 of which must be considered highly effective, from the time of providing informed consent, throughout the study, and for 28 days after the last dose of study drug for women and 90 days after the last dose of study drug for men. The second form of contraception can be an acceptable barrier method
8. Written informed consent from the participant before any study-related procedures are conducted and willing to comply with all study procedures for the duration of the study

Phase IIb:
1. At least 18 years of age at the time of providing informed consent
2. Documented diagnosis of MDS according to WHO classification that meets IPSS-R classification of lower-risk disease (risk score: ≤3.5) and <5% blasts as determined by the participant's bone marrow biopsy/aspirate during the Screening Period
3. Nontransfused, with LTB, or with HTB, based on transfusion history from the participant's medical record, according to revised IWG 2018 criteria:
a. NTD: <3 RBC units in the 16-week period before randomization and no transfusions in the 8-week period before randomization, or
b. LTB: 3 to 7 RBC units in the 16-week period before randomization and <4 RBC units in the 8-week period before randomization, or
c. HTB: ≥8 RBC units in the 16-week period before randomization and ≥4 RBC units in the 8-week period before randomization
4. An Hb concentration <11.0 g/dL during the 4-week Screening Period
5. Up to 2 prior therapies including erythropoiesis-stimulating agents (ESAs) (eg, erythropoietin [EPO], EPO + granulocyte colony-stimulating factor [G-CSF]) and/or luspatercept
6. ECOG Performance Status score of 0, 1, or 2
7. If taking iron chelation therapy, the iron chelation therapy dose must have been stable and started ≥56 days before randomization
8. For WOCBP and men with partners who are WOCBP, must be abstinent from sexual activities that may result in a pregnancy as part of their usual lifestyle or agree to use 2 forms of contraception, 1 of which must be considered highly effective, from the time of providing informed consent, throughout the study, and for 28 days after the last dose of study drug for women and 90 days after the last dose of study drug for men. The second form of contraception can be an acceptable barrier method
9. Written informed consent from the participant before any study-related procedures are conducted and willing to comply with all study procedures for the duration of the study

Participant type(s)
Patient

Healthy volunteers allowed

No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
Phase IIa and Phase IIb:
1. Known history of acute myeloid leukaemia (AML)
2. Secondary MDS, defined as MDS that is known to have arisen as a result of chemical injury or treatment with chemotherapy and/or radiation for other diseases
3. Prior exposure to a pyruvate kinase activator, treatment administered for high-risk MDS (hypomethylating agents [HMAs], isocitrate dehydrogenase [IDH] inhibitors, or allogeneic or autologous stem cell transplant), and/or disease-modifying agents (eg, immunomodulatory drugs such as lenalidomide). If a participant received ≤1 week of treatment with a disease-modifying agent ≥8 weeks before administration of the first dose of the study drug, then they may not be excluded, at the Investigator's discretion.
4. Currently receiving treatment with luspatercept, EPO, or G-CSF. Treatment with EPO or G-CSF must have been stopped for ≥28 days before administration of the first dose of the study drug; treatment with luspatercept must have been stopped for ≥65 days before administration of the first dose of the study drug.
5. History of active and/or uncontrolled cardiac or pulmonary disease within 6 months before providing informed consent, including but not limited to: a. New York Heart Association Class III or IV heart failure or clinically significant dysrhythmia; b. Myocardial infarction, unstable angina pectoris, or unstable hypertension; high-risk thrombosis; hemorrhagic, embolic, or thrombotic stroke; deep venous thrombosis; or pulmonary or arterial embolism; c. Heart rate–corrected QT interval using Fridericia's method of ≥470 milliseconds for female participants and ≥450 milliseconds for male participants, except for right or left bundle branch block; d. Severe pulmonary fibrosis as defined by severe hypoxia, evidence of right-sided heart failure, and radiographic pulmonary fibrosis >50%; e. Severe pulmonary hypertension as defined by severe symptoms associated with hypoxia, right-sided heart failure, and oxygen indicated
6. History of hepatobiliary disorders, as defined by: a. Serum AST >2.5 × upper limit of normal (ULN) (unless due to haemolysis and/or hepatic iron deposition) and ALT >2.5 × ULN (unless due to hepatic iron deposition); b. Serum bilirubin >ULN, if the elevation is associated with clinically symptomatic choledocholithiasis, cholecystitis, biliary obstruction, or hepatocellular disease
7. Renal dysfunction, as defined by an estimated glomerular filtration rate (eGFR) <45 mL/min
8. Active infection requiring systemic antimicrobial therapy at the time of providing informed consent. If antimicrobial therapy is required during the Screening Period, screening procedures should not be performed while antimicrobial therapy is being administered, and the last dose of antimicrobial therapy must be administered ≥7 days before administration of the first dose of the study drug.
9. Major surgery within 12 weeks before administration of the first dose of the study drug. Participants must have completely recovered from any previous surgery before administration of the first dose of the study drug.
10. History of any malignancy, except for non-melanomatous skin cancer in situ, cervical carcinoma in situ, or breast carcinoma in situ. Participants must not have active disease or have

received anticancer treatment ≤5 years before providing informed consent.
11. Positive test for hepatitis C virus (HCV) antibody (Ab) with evidence of active HCV infection, or positive test for hepatitis B surface antigen (HBsAg)
12. Positive test for HIV-1 Ab or HIV-2 Ab
13. Absolute neutrophil count (ANC) <500/μL (0.5 × 10^9/L)
14. Platelet count ≤75,000/μL (75 × 10^9/L) assessed in the absence of platelet transfusions within 28 days before Screening
15. Nonfasting triglyceride concentration >500 mg/dL
16. Receiving inhibitors of P-glycoprotein (P-gp) that have not been stopped for ≥5 days or a time frame equivalent to 5 half-lives (whichever is longer) before administration of the first dose of the study drug
17. Current enrolment or past participation (within 4 weeks or a time frame equivalent to 5 half-lives of the investigational study drug before administration of the first dose of the study drug or, whichever is longer) in any other clinical study involving an investigational treatment or device
18. Known allergy to AG-946 or its excipients (silicified microcrystalline cellulose, croscarmellose sodium, sodium stearyl fumarate, and the Opadry® II Blue film coat [polyvinyl alcohol, titanium dioxide, macrogol/polyethylene glycol, talc, FD&C blue #2/indigo carmine aluminium lake/E132])
19. Pregnant or breastfeeding
20. Any medical, hematologic, psychological, or behavioural condition(s) or prior or current therapy that, in the opinion of the Investigator, may confer an unacceptable risk to participating in the study and/or could confound the interpretation of the study data

Date of first enrolment
07/11/2023

Date of final enrolment
30/11/2025

Locations

Countries of recruitment
United Kingdom

Australia

Austria

France

Germany

Greece

Israel

Italy

Poland

Spain

Türkiye

Study participating centre
-
United Kingdom
-

Sponsor information

Organisation
Agios Pharmaceuticals (United States)

ROR
https://ror.org/002x06r10

Funder(s)

Funder type
Industry

Funder Name
Agios Pharmaceuticals

Alternative Name(s)
Agios, Agios, Inc., Agios Pharmaceuticals Inc.

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan
A description of this clinical research study will be available at http://www.ClinicalTrials.gov. This website will not include information that can identify patients. At most, the website will include

a summary of the results. This can be searched and accessed at any time. The data collected from the study may be further submitted to other National or local Health Authorities outside of the United Kingdom as mandated and governed by data protection laws in those countries. In ALL circumstances, any identifiable information about patients will be protected and not shared.

IPD sharing plan summary

Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes