



A Study Evaluating the Efficacy and Safety of Mitapivat in Subjects With Sickle Cell Disease (SCD)

11/04/2025 19:32:36

Main Information

Primary registry identifying number

LBCTR2022034916

Protocol number

AG348-C-020

MOH registration number

Study registered at the country of origin

Yes

Study registered at the country of origin: Specify

USA

Type of registration

Prospective

Type of registration: Justify

N/A

Date of registration in national regulatory agency

Primary sponsor

Agios Pharmaceuticals, Inc.

Primary sponsor: Country of origin

USA

Date of registration in primary registry

20/04/2022

Date of registration in national regulatory agency

Public title

A Study Evaluating the Efficacy and Safety of Mitapivat in Subjects With Sickle Cell Disease (SCD)

Acronym

Scientific title

A Phase 2/3, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Mitapivat in Subjects With Sickle Cell Disease

Acronym

Brief summary of the study: English

This clinical trial is a Phase 2/3 study that will determine the recommended dose of mitapivat and evaluate the efficacy and safety of mitapivat in sickle cell disease by testing how well mitapivat works compared to placebo to increase the amount of hemoglobin in the blood and to reduce or prevent the occurrence of sickle cell pain crises. In addition, the long-term effect of mitapivat on efficacy and safety will be explored in an open-label extension portion.

Brief summary of the study: Arabic

في مرض mitapivat وتقييم فعالية وسلامة mitapivat التي ستحدد الجرعة الموصى بها من 2/3 هذه التجربة السريرية هي دراسة المرحلة مقارنة مع الدواء الوهمي لزيادة كمية الهيموغلوبين في الدم والحد من أو منع حدوث mitapivat الخلايا المنجلية عن طريق اختبار مدى عمل أزمتات ألم الخلايا المنجلية. وبالإضافة إلى ذلك، سيتم استكشاف تأثير الميتايبفات على المدى الطويل على الفعالية والسلامة في جزء تمديد التسمية المفتوحة.

Health conditions/problem studied: Specify

Sickle Cell Disease (SCD) / Patients with SCD endure chronic hemolytic anemia and acute and recurrent clinical events that vary in frequency and severity, the most common being VOCs (vaso-occlusions). The use of curative options for SCD is currently limited to a small subgroup of patients who are deemed fit for bone marrow transplantation and have available donors. The current treatment options are not universally effective or globally available, tend to address only a single component of the disease, or are limited by their safety profile. Therefore, a significant unmet medical need exists for safe and effective therapies for the treatment of SCD that result in both an improvement in anemia and reduction in sickle cell-related crises.





Interventions: Specify

Study AG348-C-020 is a Phase 2/3, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Mitapivat in Subjects With Sickle Cell Disease. In the phase 2 portion of the study, eligible subjects will be randomized in a 1:1:1 ratio to receive 50 mg mitapivat, 100 mg mitapivat, or matched placebo for BID oral administration. Subjects who did not participate in the Phase 2 portion of the study and who meet the eligibility criteria will be randomized in a 2:1 ratio to receive the selected Phase 3 dose of mitapivat or matched placebo for BID oral administration. Subjects who have completed the 12-week (Phase 2) or 52-week (Phase 3) Double-blind Period and do not have ongoing Grade ≥ 3 treatment-related AEs, unless approved by the Medical Monitor, will be eligible to receive mitapivat for up to 216 weeks (not including time to taper dose) in the Open-label Extension Period.

Key inclusion and exclusion criteria: Inclusion criteria

1. Age ≥ 16 years; subjects age 16 or 17 years must be documented Tanner Stage 5.
2. Documented diagnosis of SCD (HbSS, HbSC, HbS/ $\beta 0$ -thalassemia, HbS/ $\beta +$ -thalassemia, or other sickle cell syndrome variants).
3. At least 2 SCPCs and no more than 10 SCPCs in the 12 months prior to providing informed assent/consent.
4. Hemoglobin ≥ 5.5 and ≤ 10.5 g/dL.
5. If taking hydroxyurea, the hydroxyurea dose must be stable for at least 90 days prior to randomization.
6. Women of childbearing potential (WOCBP) and men with partners who are WOCBP must be abstinent of sexual activities that may induce pregnancy as part of their usual lifestyle or agree to use 2 forms of contraception, one of which must be considered highly effective, from the time of providing informed assent/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 include an acceptable barrier method.
7. Written informed assent/consent (for subjects under 18 years of age, parental permission and child assent will be obtained) must be obtained before any study-related procedures are conducted and subjects must be willing to comply with all study procedures for the duration of the study.

Key inclusion and exclusion criteria: Gender

Both

Key inclusion and exclusion criteria: Specify gender

Key inclusion and exclusion criteria: Age minimum

16

Key inclusion and exclusion criteria: Age maximum

99

Key inclusion and exclusion criteria: Exclusion criteria

1. Pregnant or breastfeeding.
2. Receiving regularly scheduled RBC transfusion therapy (also termed chronic, prophylactic, or preventative transfusion); episodic transfusion in response to worsened anemia or VOC is permitted. Additionally, subjects may not have received a transfusion within 60 days before providing informed assent/consent or during the Screening Period.
3. Hospitalized for an SCPC or other vaso-occlusive event within 14 days prior to providing informed assent/consent or during the Screening Period.
4. Currently receiving treatment with a disease-modifying therapy for SCD (eg, voxelotor, crizanlizumab, L-glutamine), with the exception of hydroxyurea. The last dose of such therapies must have been administered at least 90 days before randomization.
5. History of any malignancy except for nonmelanomatous skin cancer in situ, cervical carcinoma in situ, or breast carcinoma in situ. Subjects must not have active disease or received anticancer treatment ≤ 5 years before providing informed assent/consent.
6. History of active and/or uncontrolled cardiac or pulmonary disease within 6 months before providing informed assent/consent, including but not limited to:
 - a. New York Heart Association Class III or IV heart failure or clinically significant dysrhythmia.
 - b. Myocardial infarction or unstable angina pectoris; 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 subjects and ≥ 450 milliseconds for male subjects, 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 heart failure, and oxygen indicated.
7. Hepatobiliary disorders including but not limited to:
 - a. Liver disease with histopathological evidence of cirrhosis or severe fibrosis.
 - b. Clinically symptomatic cholelithiasis or cholecystitis (subjects with prior cholecystectomy are eligible).
 - c. History of drug-induced cholestatic hepatitis.
 - d. Aspartate aminotransferase $> 2.5 \times$ the upper limit of normal (ULN) (unless due to hemolysis and/or hepatic iron deposition) and alanine aminotransferase $> 2.5 \times$ the ULN (unless due to hepatic iron deposition).
8. Renal dysfunction as defined by an estimated glomerular filtration rate < 30 mL/min/1.73 m² by the Chronic Kidney Disease Epidemiology Collaboration creatinine equation.
9. Nonfasting triglycerides > 440 mg/dL (5 mmol/L).
10. Active uncontrolled infection requiring systemic antimicrobial therapy.
11. Positive test for hepatitis C virus antibody with evidence of active hepatitis C virus infection, or positive test for hepatitis B surface antigen.
12. Positive test for HIV-1 antibody or HIV-2 antibody.
13. History of major surgery (including splenectomy) ≤ 16 weeks before providing informed assent/consent and/or planning on undergoing a major surgical procedure during the study.
14. Current enrollment or past participation (within 90 days before randomization or a time frame equivalent to 5 half-lives of the investigational study drug, whichever is longer) in any other clinical study involving an investigational study drug or device.
15. Prior exposure to gene therapy or prior bone marrow or stem cell transplantation.
16. Currently receiving treatment with hematopoietic stimulating agents; the last dose must have been administered at least 90 days before randomization.
17. Receiving products that are strong inhibitors of CYP3A4/5 that have not been stopped for ≥ 5 days or a time frame equivalent to 5 half-lives (whichever is longer), or strong inducers of CYP3A4 that have not been stopped for ≥ 28 days or a time frame equivalent to 5 half-lives (whichever is longer), prior to randomization.



18. Receiving anabolic steroids, including testosterone preparations, that have not been stopped for at least 28 days before randomization.
19. Known allergy to mitapivat or tablet excipients (microcrystalline cellulose, croscarmellose sodium, sodium stearyl fumarate, mannitol, and magnesium stearate).
20. Any medical, hematological, psychological, or behavioral 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.
21. Phase 3 only: Participated in the Phase 2 portion of Study AG348-C-020.

Type of study

Interventional

Type of intervention

Pharmaceutical

Type of intervention: Specify type

N/A

Trial scope

Therapy

Trial scope: Specify scope

N/A

Study design: Allocation

Randomized controlled trial

Study design: Masking

Blinded (masking used)

Study design: Control

Placebo

Study phase

2 to 3

Study design: Purpose

Treatment

Study design: Specify purpose

N/A

Study design: Assignment

Parallel

Study design: Specify assignment

N/A

IMP has market authorization

No

IMP has market authorization: Specify

Name of IMP

Mitapivat

Year of authorization

Month of authorization

Type of IMP

Others

Pharmaceutical class

The investigational drug mitapivat (also known as mitapivat sulfate and AG-348) is a first-in-class, orally bioavailable, potent, allosteric activator of wild-type RBC-specific form of pyruvate kinase (PKR) and a range of PKR-mutant enzymes (Kung et al, 2017). The RBC-specific form of pyruvate kinase is 1 of 4 pyruvate kinase isoenzymes expressed in human tissues from 2 separate genes, liver-specific form of pyruvate kinase (PKL) and pyruvate kinase muscle isozyme (PKM). Both PKR and PKL are splice isoforms of the PKLR gene, while PKM1 and PKM2 are both expressed from the PKM gene. Mitapivat is an allosteric activator of the PKR, PKL, and PKM2 isoenzymes, with similar potency against each.

Therapeutic indication

Sickle Cell Disease (SCD).

Therapeutic benefit

Mitapivat is a therapeutic candidate for the treatment of adult patients with SCD with the potential to provide clinical benefit by both improvement of anemia and reduction in sickle cell pain crises (SCPCs).

In addition, based on the cumulative nonclinical and clinical data generated with mitapivat in SCD and other hemolytic anemias, the potential benefits outweigh the potential risks in patients with SCD, the intended population for this study.

Study model

N/A

Study model: Explain model

Study model: Specify model



N/A

N/A

Time perspective

N/A

Time perspective: Explain time perspective

N/A

Time perspective: Specify perspective

N/A

Target follow-up duration

Target follow-up duration: Unit

Number of groups/cohorts

Biospecimen retention

Samples without DNA

Biospecimen description

Blood samples may also be collected for exploratory analyses of the following biomarkers: blood smears, C-reactive protein, free Hb, haptoglobin, hepcidin, N-terminal-prohormone brain natriuretic peptide, selectin, soluble erythroferrone, soluble transferrin receptor, and vascular cell adhesion molecule. Blood samples will be analyzed by a central laboratory. Samples may be retained for a maximum of 5 years (or according to local regulations) after the end of the study at a facility selected by the Sponsor for further exploratory analysis of biomarker responses to mitapivat for those subjects who consent to this optional research in the ICF.

Target sample size

267

Actual enrollment target size

Date of first enrollment: Type

Anticipated

Date of first enrollment: Date

11/02/2022

Date of study closure: Type

Anticipated

Date of study closure: Date

30/11/2030

Recruitment status

Pending

Recruitment status: Specify

Date of completion

IPD sharing statement plan

No

IPD sharing statement description

NA

Additional data URL



Admin comments

Trial status

Approved

Secondary Identifying Numbers

Full name of issuing authority	Secondary identifying number
NA	NA

Sources of Monetary or Material Support

Name
Agios Pharmaceuticals, Inc.

Secondary Sponsors

Name
NA

Contact for Public/Scientific Queries

Contact type	Contact full name	Address	Country	Telephone	Email	Affiliation
Public	Aziz Zoghbi	MCT-CRO, Berytech Technology and Health, 5th Floor Damascus Road, Beirut, Lebanon	Lebanon	+961 71 008 269	aziz.zoghbi@mct-cro.com	Director of Country Oversight and Management MENA, Gulf and Africa
Scientific	Ali Taher	American University Of Beirut Medical Center, Cairo Street, Beirut, Lebanon	Lebanon	+9613 755 669	ataher@aub.edu.lb	PI
Scientific	Adlette Inati	Nini hospital, Al Maarad Street, Tripoli, Lebanon	Lebanon	+9613 228 033	adlette.inati@lau.edu.lb	PI
Scientific	Wissam Houhou	Hammoud Hospital University Medical Center, Dr. Ghassan Hammoud Street, Saida , Lebanon	Lebanon	+9617 723 111	dr.wissam.h@hotmail.com	PI



Centers/Hospitals Involved in the Study

Center/Hospital name	Name of principles investigator	Principles investigator speciality	Ethical approval
American University Of Beirut Medical Center	Dr. Ali Taher	Professor of Medicine, Hematology & Oncology	Approved
Nini hospital	Dr. Adlette Inati	Pediatric Hematology/Oncology	Approved
Hammoud Hospital University Medical Center	Dr. Wissam Houhou	Hematologist/Oncologist	Approved

Ethics Review

Ethics approval obtained	Approval date	Contact name	Contact email	Contact phone
Nini Hospital	08/02/2022	Dr Nabil Kabbara	nabil.kabbara@hopitalnini.com	06 431 400, Ext 3165
Hammoud Hospital University Medical Center	11/02/2022	Ghada Aoun	medical@hammoudhospital.org	00961 3 408 947

Countries of Recruitment

Name
United States of America

Health Conditions or Problems Studied

Condition	Code	Keyword
Sickle Cell Disease	Sickle-cell disorders (D57)	Anemia, Sickle Cell Anemia, Hemolytic, Congenital Anemia, Hemolytic Anemia, Hematologic Diseases Hemoglobinopathies Genetic Diseases, Inborn



Interventions

Intervention	Description	Keyword
Mitapivat	<p>In the Phase 2 portion of the study, eligible subjects will be randomized 1:1:1 to receive 50 mg BID mitapivat, 100 mg BID mitapivat, or matched placebo. In the Phase 3 portion of the study, eligible subjects will be randomized 2:1 to receive mitapivat or matched placebo. Subjects who have completed the Phase 2 portion of the study and had been receiving active treatment will be eligible to continue receiving the same dose in the Open-label Extension Period. Subjects who had been receiving placebo will be randomized 1:1 to receive either 50 mg BID mitapivat or 100 mg BID mitapivat in the Open-label Extension Period. Subjects who have completed the Phase 3 portion of the study will be eligible to continue to receive, if previously receiving active treatment, or begin to receive, if previously receiving placebo, the selected dose of mitapivat for the Phase 3 portion of the study.</p>	Treatment

Primary Outcomes

Name	Time Points	Measure
Phase 2: To determine the recommended Phase 3 dose of mitapivat by evaluating the effect of 2 dose levels of mitapivat versus placebo on Anemia in subjects with sickle cell disease (SCD)	Week 12	Hemoglobin (Hb) response, defined as a ≥ 1.0 g/dL increase in average Hb concentration from Week 10 through Week 12 compared with baseline
Phase 2: To determine the recommended Phase 3 dose of mitapivat by evaluating the effect of 2 dose levels of mitapivat versus placebo on Safety	Up to Week 12	Type, severity, and relationship to study drug of adverse events (AEs) and serious (SAEs)
Phase 3: To determine the effect of mitapivat versus placebo on Anemia in subjects with sickle cell disease (SCD)	Week 52	Hemoglobin (Hb) response, defined as a ≥ 1.0 g/dL increase in average Hb concentration from Week 24 through Week 52 compared with baseline
Phase 3: To determine the effect of mitapivat versus placebo on Sickle cell pain crises (SCPCs) in subjects with SCD	Up to Week 52	Annualized rate of SCPCs



Key Secondary Outcomes

Name	Time Points	Measure
Phase 2: To evaluate the effect of 2 doses of mitapivat versus placebo on Anemia	Baseline, Week 10 up to Week 12	Average change from baseline in Hb concentration from Week 10 through Week 12
Phase 2: To evaluate the effect of 2 doses of mitapivat versus placebo on Markers of hemolysis and erythropoiesis	Baseline, Week 10 up to Week 12	Average change from baseline in markers of hemolysis, including indirect bilirubin and lactate dehydrogenase (LDH), from Week 10 through Week 12. Average change from baseline in markers of erythropoiesis, including absolute reticulocyte count, percent reticulocyte, and erythropoietin, from Week 10 through Week 12
Phase 2: To evaluate the effect of 2 doses of mitapivat versus placebo on Patient-reported fatigue	Baseline, Week 10 up to Week 12	Average change from baseline in Patient-Reported Outcomes Measurement Information System® (PROMIS) Fatigue 13a Short Form (SF) score from Week 10 through Week 12
Phase 2: To evaluate the effect of 2 doses of mitapivat versus placebo on Sickle cell pain crises (SCPCs)	Up to Week 12	Annualized rate of SCPCs
Phase 2: To evaluate the pharmacokinetic and pharmacodynamic effects of mitapivat	Day 1 up to Week 8	Pharmacokinetic/Pharmacodynamic Relationship: Evaluate the Exposure of Mitapivat to the Change in Adenosine Triphosphate (ATP) and 2,3-Diphosphoglycerate (2,3-DPG)
Phase 2: To evaluate the pharmacokinetic and pharmacodynamic effects of mitapivat	Day 1 up to Week 8	Mitapivat Concentration Over Time/Mitapivat Area Under the Concentration/Mitapivat Maximum (Peak) Concentration
Phase 3: To evaluate the effect of mitapivat versus placebo on Anemia in subjects with SCD	Baseline, Week 24 up to Week 52	Change from baseline in average Hb concentration from Week 24 through Week 52
Phase 3: To evaluate the effect of mitapivat versus placebo on Markers of hemolysis	Baseline, Week 24 up to Week 52	Change from baseline in average indirect bilirubin from Week 24 through Week 52
Phase 3: To evaluate the effect of mitapivat versus placebo on Markers of erythropoiesis	Baseline, Week 24 up to Week 52	Change from baseline in average percent reticulocyte from Week 24 through Week 52
Phase 3: To evaluate the effect of mitapivat versus placebo on Patient-reported fatigue	Baseline, Week 24 up to Week 52	Change from baseline in average Patient-Reported Outcomes Measurement Information System® (PROMIS) Fatigue 13a Short Form (SF) scores from Week 24 through Week 52
Phase 3: To evaluate the effect of mitapivat versus placebo on Additional clinical efficacy measures related to SCPC	Up to Week 52	Annualized frequency of hospitalizations for SCPC



Trial Results

Summary results

Study results globally

Date of posting of results summaries

Date of first journal publication of results

Results URL link

Baseline characteristics

Participant flow

Adverse events

Outcome measures

URL to protocol files