





## Health conditions/problem studied: Specify

$\alpha$ - or  $\beta$ -Transfusion Dependent Thalassemia. Transfusion dependent is defined as 6 to 20 RBC units transfused and a  $\leq 6$ -week transfusion-free period during the 24-week period before randomization.

## Interventions: Specify

Study AG348-C-018 is a Phase 3, double-blind, randomized, placebo-controlled, multicenter study evaluating the efficacy and safety of mitapivat versus placebo in adult subjects with  $\alpha$ - or  $\beta$ -TDT followed by an Open-label Extension Period. Subject eligibility will be determined during the (up to 8 weeks) Screening Period.

## Key inclusion and exclusion criteria: Inclusion criteria

1.  $\geq 18$  years of age at the time of providing informed consent.
2. Documented diagnosis of thalassemia ( $\beta$ -thalassemia with or without  $\alpha$ -globin gene mutations, HbE/ $\beta$ -thalassemia, or  $\alpha$ -thalassemia/HbH disease) based on DNA analysis from the subject's medical record. If this information is not available from the subject's medical record, DNA analysis can be performed by a local laboratory during the Screening Period. If a local laboratory is unable to perform the test, results from the comprehensive  $\alpha$ - and  $\beta$ -globin genotyping performed by the study central laboratory can be used.
3. Transfusion dependent, defined as 6 to 20 RBC units transfused and a  $\leq 6$ -week transfusion-free period during the 24-week period before randomization.
4. If taking hydroxyurea, the hydroxyurea dose must be stable for  $\geq 16$  weeks before randomization.
5. 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, 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.
6. Written informed consent before any study-related procedures are conducted and 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

18

## Key inclusion and exclusion criteria: Age maximum

99

## Key inclusion and exclusion criteria: Exclusion criteria

1. Pregnant or breastfeeding.
2. Documented history of homozygous or heterozygous HbS or HbC.
3. Prior exposure to gene therapy or prior bone marrow or stem cell transplantation.
4. Currently receiving treatment with luspatercept; the last dose must have been administered  $\geq 36$  weeks before administration of the first dose of study drug.
5. Currently receiving treatment with hematopoietic stimulating agents; the last dose must have been administered  $\geq 36$  weeks before administration of the first dose of study drug.
6. 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  $\leq 5$  years before providing informed consent.
7. History of active and/or uncontrolled cardiac or pulmonary disease  $\leq 6$  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 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  $\geq 450$  milliseconds, 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
8. Hepatobiliary disorders, including but not limited to:
  - a. Liver disease with histopathological evidence of cirrhosis or severe fibrosis
  - b. Clinically symptomatic cholelithiasis or cholecystitis (prior cholecystectomy is not exclusionary)
  - c. History of drug-induced cholestatic hepatitis
  - d. Aspartate aminotransferase  $> 2.5 \times$  upper limit of normal (ULN); unless due to hemolysis and hepatic iron deposition) and alanine aminotransferase  $> 2.5 \times$  ULN (unless due to hepatic iron deposition)
9. Estimated glomerular filtration rate  $< 45$  mL/min/1.73 m<sup>2</sup> by Chronic Kidney Disease Epidemiology Collaboration creatinine equation.
10. Nonfasting triglycerides  $> 440$  mg/dL (5 mmol/L).
11. 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  $\geq 7$  days before randomization.
12. Positive test for hepatitis C virus (HCV) antibody (Ab) with evidence of active HCV infection, or positive test for hepatitis B surface antigen.
13. Positive test for HIV-1 Ab or HIV-2 Ab.
14. History of major surgery (including splenectomy)  $\leq 6$  months before providing informed consent and/or a major surgical procedure planned during the study.
15. Current enrollment or past participation ( $\leq 12$  weeks before administration of the first dose of study drug or a time frame equivalent to 5 half-



- lives of the investigational treatment, whichever is longer) in any other clinical study involving an investigational treatment or device.
16. Receiving strong cytochrome P450 (CYP)3A4/5 inhibitors that have not been stopped for  $\geq 5$  days or a time frame equivalent to 5 half-lives (whichever is longer), or strong CYP3A4 inducers that have not been stopped for  $\geq 4$  weeks or a time frame equivalent to 5 half-lives (whichever is longer), before administration of the first dose of study drug.
17. Receiving anabolic steroids, including testosterone preparations, that have not been stopped for  $\leq 4$  weeks before administration of the first dose of study drug.
18. Known allergy to mitapivat or its excipients (microcrystalline cellulose, croscarmellose sodium, sodium stearyl fumarate, mannitol, and magnesium stearate).
19. 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.

## Type of study

Interventional

## Type of intervention

Pharmaceutical

## Type of intervention: Specify type

N/A

## Trial scope

Other

## Trial scope: Specify scope

## Study design: Allocation

Randomized controlled trial

## Study design: Masking

Blinded (masking used)

## Study design: Control

Placebo

## Study phase

3

## Study design: Purpose

Treatment

## Study design: Specify purpose

efficacy and safety

## 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

$\alpha$ - or  $\beta$ -Transfusion Dependent Thalassemia (TDT)

## Therapeutic benefit

Mitapivat, has the potential to improve the transfusion burden in patients with TDT with the added benefit of oral administration.

## 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 with DNA\*\*

**Biospecimen description**

Blood samples collected for comprehensive  $\alpha$ - and  $\beta$ -globin genotyping and for UGT1A1 and PKLR genotyping will be analyzed by Centogene. Samples will be maintained in a secure storage facility with adequate measures to protect subject confidentiality. Samples will be retained for a maximum of 10 years.

**Target sample size**

240

**Actual enrollment target size**

**Date of first enrollment: Type**

Anticipated

**Date of first enrollment: Date**

01/02/2022

**Date of study closure: Type**

Anticipated

**Date of study closure: Date**

**Recruitment status**

Pending

**Recruitment status: Specify**

**Date of completion**

**IPD sharing statement plan**

No

**IPD sharing statement description**

No IPD sharing statement plan

**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	0096171008269	aziz.zoghbi@mct-cro.com	Director of Country Oversight and Management MENA, Gulf and Africa
Scientific	Ali Taher	Chronic Care Center (CCC), Hazmieh, Lebanon	Lebanon	+9613 755 669	ataher@aub.edu.lb	PI

## Centers/Hospitals Involved in the Study

Center/Hospital name	Name of principles investigator	Principles investigator speciality	Ethical approval
Chronic Care Center	Dr.Ali Taher	Professor of Medicine, Hematology & Oncology	Pending



## Ethics Review

Ethics approval obtained	Approval date	Contact name	Contact email	Contact phone
Chronic Care Center	18/11/2021	Michelle Abi Saad	cccmass@chroniccare.org.lb	05-455101

## Countries of Recruitment

No Countries

## Health Conditions or Problems Studied

Condition	Code	Keyword
Transfusion dependent thalassemia	Thalassaemia (D56)	Thalassemia beta-Thalassemia alpha-Thalassemia Anemia, Hemolytic, Congenital Anemia, Hemolytic Anemia Hematologic Diseases

## Interventions

Intervention	Description	Keyword
Mitapivat	Subjects will receive 100 mg twice-daily mitapivat for oral administration. Subjects will be randomly assigned in a 2;1 ratio to receive study drug (mitapivat or placebo, respectively)	Treatment

## Primary Outcomes

Name	Time Points	Measure
Effect of mitapivat versus placebo on transfusion burden	any consecutive 12-week period through Week 48 compared with baseline	Transfusion reduction response (TRR), defined as a $\geq 50\%$ reduction in transfused red blood cell (RBC) units with a reduction of $\geq 2$ units of transfused RBCs

## Key Secondary Outcomes

Name	Time Points	Measure
To compare the durability of the effect of mitapivat versus placebo on transfusion burden	Week 13 through Week 48 compared with baseline	<ul style="list-style-type: none"><li><math>\geq 33\%</math> reduction in transfused RBC units from Week 13 through Week 48 compared with baseline (TRR3)</li><li><math>\geq 50\%</math> reduction in transfused RBC units in any consecutive 24-week period through Week 48 compared with baseline (TRR2)</li><li><math>\geq 50\%</math> reduction in transfused RBC units from Week 13 through Week 48 compared with baseline (TRR4)</li></ul>





## 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**