An Adaptive, Randomized, Placebo-controlled, Double-blind, Multi-center Study of Oral FT-4202, a Pyruvate Kinase Activator in Patients with Sickle Cell Disease

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Main Information

Primary registry identifying number
LBCTR2021124934

Protocol number
4202-HEM-301

MOH registration number

Study registered at the country of origin
Yes

Study registered at the country of origin: Specify

Type of registration
Prospective

Type of registration: Justify
N/A

Date of registration in national regulatory agency

Primary sponsor
Forma Therapeutics, Inc.

Primary sponsor: Country of origin
United Stated of America

Date of registration in primary registry
27/01/2022

Date of registration in national regulatory agency

Public title
An Adaptive, Randomized, Placebo-controlled, Double-blind, Multi-center Study of Oral FT-4202, a Pyruvate Kinase Activator in Patients with Sickle Cell Disease

Acronym

Scientific title
An Adaptive, Randomized, Placebo-controlled, Double-blind, Multi-center Study of Oral FT-4202, a Pyruvate Kinase Activator in Patients with Sickle Cell Disease

Acronym

Brief summary of the study: English

FT-4202 is an experimental medication that may help treat sickle cell disease by acting to lower the rate of red blood cell (RBC) sickling. RBC sickling can cause hemolysis (breaking apart of RBCs) that leads to anemia and vasoocclusion (painful blockage of blood vessels).
This research is being performed to determine the effects of FT-4202, good and bad, in individuals with sickle cell disease.
This study is made up of 2 parts:
•Double-blind treatment period: Research patients will take the study drug (FT 4202 or placebo, depending on which treatment group they are in) for 52 weeks. This part of the study is “double-blind,” meaning neither the patient nor study doctor will know which specific treatment (FT-4202 or placebo) the patient is receiving.
•Open-label extension: Patients who complete the double-blind treatment period may be eligible to receive FT-4202 in the 52-week open-label extension. In this part of the study, the patient will receive FT-4202 even if they were assigned to receive placebo in the double-blind treatment period.

Brief summary of the study: Arabic

عبارة عن دواء تجريبي قد يساعد في علاج مرض الخلايا المنجلية من خلال العمل على خفض معدل خلايا الدم الحمراء المنجلية FT-4202.
يمكن أن تتسبب خلايا الدم الحمراء المنجلية في انحلال الدم والذي يؤدي إلى فقر الدم وانسداد الأوعية الدموية (انسداد مؤلم للأوعية الدموية).يُجرى هذا البحث لتحديد آثار عقار FT-4202، على الأشخاص المصابين بمرض الخلايا المنجلية، الجيدة والسيئة.
تتكون هذه الدراسة من جزأين:
•فترة العلاج مزدوجة التعمية: سيتناول المرضى المشاركين في البحث عقار الدراسة (FT-4202 أو الدواء الإرضائي، بناءً على مجموعة "مزدوج التعمية"، مما يعني أنه لن يعرف المريض ولا طبيب الدراسة أي علاج52العلاج المشاركين بها) لمدة أسبوعًا. هذا الجزء من الدراسة يتلقاه المريض (أو الدواء الإرضائي FT-4202) بعينه.
•فترة التوسع مفتوحة التسمية: قد يكون المرضى الذين يكملون فترة العلاج مزدوجة التعمية مؤهلين لتلقي عقار FT-4202 في فترة التوسع حتى لو كان تلقي الدواء الإرضائي في فترة أسبوعًا. في هذا الجزء من الدراسة، سيتلقى المريض عقار52مفتوحة التسمية البالغة العلاج مزدوجة التعمية.

Health conditions/problem studied: Specify

Sickle Cell Disease

Interventions: Specify

Dose Determination Group: In the dose determination portion of the study, up to 90 patients will be randomized in a 1:1:1 ratio to receive FT-4202 low dose (200 mg once daily [QD]), high dose (400 mg QD), or placebo. Patients will be stratified by age (12 to 17, or 18 to 65 years old, inclusive, where applicable), number of VOCs in the preceding 12 months (2 to 3 or 4 to 10), and prior/concomitant hydroxyurea (HU) use in the preceding 12 months (Yes or No). Following randomization, all patients enrolled in the Dose Determination Group will continue blinded treatment for up to a total of 52 weeks.
Twelve weeks after the 60th patient has received their first dose of study drug, both safety and Hb response at Week 12 will be unblinded to the Data and Safety Monitoring Board (DSMB) to select the appropriate dose level for further study. Between the time when the 60th patient has received their first dose and the dose determination has been made by the DSMB, enrollment may continue for a maximum of 30 additional patients. After 30 patients are enrolled, enrollment will pause until the dose is selected. Thus, a maximum of 10 patients may be randomized to the unselected dose but not contribute to the dose determination decision. These patients will contribute to the safety analyses.
Efficacy Continuation Group: This portion of the study will further establish the efficacy and safety of FT-4202 at the selected dose with planned enrollment up to 274 patients. Patients will be randomized in a 1:1 ratio to receive the selected FT-4202 dose or placebo. Patients will be enrolled using the same inclusion/exclusion criteria and stratified using the same stratification factors in the Dose Determination Group.
Open Label Extension Period: All patients, after completion of 52 weeks of double-blind treatment, may enter a 52-week FT-4202 open-label extension period. If some patients in the Dose Determination Group complete 52 weeks of double-blind treatment prior to the DSMB determination of dose selection for the Efficacy Continuation Group, the dose of FT-4202 administered in this open-label extension period will be the high dose of FT-4202. After dose selection by the DSMB at IA1, the dose of FT-4202 administered for all patients in the open-label extension period will be the dose selected for Efficacy Continuation. Patients who do not complete 52 weeks of the double-blinded treatment period may not enter the open-label extension period.

Key inclusion and exclusion criteria: Inclusion criteria

Participants are eligible to be included in the study only if all the following criteria apply:
Informed Consent
1. Patient has provided documented informed consent or assent (the informed consent form [ICF] must be reviewed and signed by each patient)
Age
2. Age 18 to 65 years, inclusive, at time of randomization
Type of Participant and Disease Characteristics
3. Patient has a confirmed diagnosis of sickle cell disease
• Documentation of SCD genotype (HbSS, HbSβ0-thalassemia or other sickle cell syndrome variants) based on prior history of laboratory testing; if unavailable, must be confirmed by laboratory testing during screening
4. Patient has had at least 2 episodes of VOC in the past 12 months
• For study eligibility, VOC is defined as a previously documented episode of ACS or acute painful crisis (for which there was no explanation other than VOC) which required prescription or healthcare professional-instructed use of analgesics for moderate to severe pain (documentation must exist in the patient medical record prior to Screening)
5. Hemoglobin ≥ 5.5 and ≤ 10 g/dL (≥ 55 and ≤ 100 g/L) during screening
6. For participants taking HU, the dose of HU (mg/kg) must be stable (no more than a 20% change in dosing) for at least 90 days prior to start of study treatment with no anticipated need for dose adjustments during the study, in the opinion of the Investigator
Sex and Contraceptive/Barrier Requirements
7. Patients, who if female and of child bearing potential, are using highly effective methods of contraception and agree not to donate ova from study start to 90 days after the last dose of study drug, and who if male are willing to use barrier methods of contraception and agree not to donate sperm, from study start to 90 days after the last dose of study drug

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

65

Key inclusion and exclusion criteria: Exclusion criteria

Patients are excluded from the study if they meet any of the following criteria:
Medical Conditions
1. More than 10 VOCs (as defined in Inclusion Criterion 4) within the past 12 months
2. Hospitalized for sickle cell crisis or other vaso-occlusive event within 14 days of signing the ICF
3. Female who is breast feeding or pregnant

4. Hepatic dysfunction characterized by:
• Alanine aminotransferase (ALT) > 4.0 × upper limit of normal (ULN)
• Direct bilirubin > 3.0 × ULN
5. Patients with clinically significant bacterial, fungal, parasitic, or viral infection requiring systemic therapy
• Patients with acute bacterial, fungal, parasitic, or viral infection requiring systemic therapy should delay screening/enrollment until active therapy has been completed
Note: Infection prophylaxis is allowed (see concomitant medication restrictions)
6. Known human immunodeficiency virus (HIV) positivity
7. Active infection with hepatitis B virus (hepatitis B surface antigen [HepBsAg] and hepatitis B core antibody [HepBcAb] positive)
8. Active hepatitis C infection
9. Severe renal dysfunction (estimated glomerular filtration rate at the Screening visit; calculated by the central laboratory < 30 mL/min/1.73 m2) or on chronic dialysis
10. History of malignancy within the past 2 years prior to treatment Day 1 requiring systemic chemotherapy and/or radiation
• Patients with malignancy considered surgically cured are eligible (eg, non-melanoma skin cancer, cancer of the cervix in-situ, ductal carcinoma in situ [stage 1], grade 1 endometrial cancer)
11. History of unstable or deteriorating cardiac or pulmonary disease within 6 months prior to consent including but not limited to the following:
• Unstable angina pectoris or myocardial infarction or elective coronary intervention
• Congestive heart failure requiring hospitalization
• Uncontrolled clinically significant arrhythmias
• Symptomatic pulmonary hypertension
12. History of overt clinical stroke within previous 2 years or any history of an intracranial hemorrhage
13. Any condition affecting drug absorption, such as major surgery involving the stomach or small intestine (prior cholecystectomy is acceptable)
14. Patients with iron deficiency (eg, serum iron less than the lower limit of normal [LLN] or ferritin < 10 µg/L) who are not taking or are unable to take iron supplements at the time of consent and during the study
15. Patients with folate (or folic acid or Vitamin B9) or Vitamin B12 deficiency (eg, folate or Vitamin B12 levels less than the LLN) who are not taking or are unable to take supplements before the first dose of study drug and during the study
16. Patients who are not taking or are unable to take antimalarial prophylaxis at the time of consent and during the study if they live in areas of endemic malaria where prophylaxis is recommended
Prior/Concomitant Therapy
17. Patients receiving regularly scheduled blood (RBC) transfusion therapy (also termed chronic, prophylactic, or preventive transfusion)
• Patients who have received an RBC transfusion for any reason within 60 days of the Screening period are eligible if HbA (adult Hb) < 10% by Hb electrophoresis before start of study treatment
18. Receiving or use of concomitant medications that are strong inducers or moderate/strong inhibitors of CYP3A4/5 within 2 weeks of starting study treatment or anticipated need for such agents during the study
19. Use of voxelotor within 28 days prior to starting study treatment or anticipated need for this agent during the study
20. Use of a selectin antagonist (eg, crizanlizumab or other monoclonal antibody or small molecule) within 28 days of starting study treatment or anticipated need for such agents during the study
21. Use of erythropoietin or other hematopoietic growth factor treatment within 28 days of starting study treatment or anticipated need for such agents during the study
22. Receipt of prior cellular-based therapy (eg, hematopoietic cell transplant, gene modification therapy)
Prior/Concurrent Clinical Study Experience
23. Participated in another clinical trial of an investigational agent (or medical device) within 28 days or 5 half-lives of first dose of study drug, whichever is longer, or is currently participating in another trial of an investigational agent (or medical device)
Other Exclusions
24. Inadequate venous access as determined by the Investigator/ site staff
25. Medical, psychological, or behavioral conditions, which, in the opinion of the Investigator, may preclude safe participation, confound study interpretation, interfere with compliance, or preclude informed consent

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

Study design: Specify assignment

Parallel

N/A

IMP has market authorization

No

IMP has market authorization: Specify

Name of IMP

FT-4202

Year of authorization

Month of authorization

Type of IMP

Others

Pharmaceutical class

Small-molecule activator of pyruvate kinase-red blood cell (PKR)

Therapeutic indication

Sickle Cell Disease

Therapeutic benefit

The clinical hypothesis is that PKR activation will reduce the rate of sickle cell polymerization and improve red blood cell (RBC) membrane function, thereby reducing RBC sickling and RBC hemolysis that lead to vascular obstruction and anemia, two hallmarks of SCD pathology.

Study model

N/A

Study model: Explain model

N/A

Study model: Specify model

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 and Urine

Target sample size

344

Actual enrollment target size

Date of first enrollment: Type

Anticipated

Date of first enrollment: Date

07/03/2022

Date of study closure: Type
Anticipated

Date of study closure: Date
31/07/2025

Recruitment status
Recruiting

Recruitment status: Specify

Date of completion

IPD sharing statement plan
No

IPD sharing statement description
NAP

Additional data URL

Admin comments

Trial status
Approved

Secondary Identifying Numbers

Full name of issuing authority	Secondary identifying number
No secondary identifiers	NAP

Sources of Monetary or Material Support

Name
Forma Therapeutics, Inc.

Secondary Sponsors

Name
None

Contact for Public/Scientific Queries

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Public	Reem Bejjani	Syneos Health, Berytech Technological Pole Mar Roukoz, 1107 2240 Mkalles | Lebanon	Lebanon	+961 4 531 375	reem.bejjani@syneoshealth.com	Syneos Health
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Centers/Hospitals Involved in the Study

Center/Hospital name	Name of principles investigator	Principles investigator speciality	Ethical approval
Nini Hospital	Dr. Adlette Inati	Pediatric Hematology and Oncology Specialist	Approved
American University of Beirut Medical Center	Dr. Miguel Abboud	Pediatric Hematology and Oncology Specialist	Pending

Ethics Review

Ethics approval obtained	Approval date	Contact name	Contact email	Contact phone
Nini Hospital	11/10/2021	Kamleh Ibrahim	kamleh.ibrahim@hopitalnini.com	+961 70 500 375

Countries of Recruitment

Name
Lebanon
France
Germany
Italy
Spain
United Kingdom
Canada

Health Conditions or Problems Studied

Condition	Code	Keyword
Sickle Cell Disease	Sickle-cell disorders (D57)	SCD

Interventions

Intervention	Description	Keyword
Dose Determination Group	90 patients will be randomized in a 1:1:1 ratio to receive FT-4202 low dose (200 mg once daily [QD]), high dose (400 mg QD), or placebo	Dose Determination
Efficacy Continuation Group	Patients will be randomized in a 1:1 ratio to receive the selected FT-4202 dose or placebo.	Efficacy
Open Label Extension Period	The dose of FT-4202 administered in this open-label extension period will be the high dose of FT-4202	OLE

Primary Outcomes

Name	Time Points	Measure
To assess the efficacy of FT-4202 in patients with SCD as compared to placebo as measured by improvement in hemoglobin (Hb)	During the blinded treatment period	Hb response rate at Week 24 (increase of > 1 g/dL [> 10 g/L] from baseline)
To assess the efficacy of FT-4202 as compared to placebo on the annualized vaso-occlusive crisis (VOC) rate	During the 52-week blinded treatment period based on adjudicated VOC review	Annualized VOC rate

Key Secondary Outcomes

Name	Time Points	Measure
To measure the effects of FT-4202 on clinical measures and sequelae of hemolysis	t Week 24 during the blinded treatment period	Change from baseline in Hb
To measure the effects of FT-4202 on clinical measures and sequelae of hemolysis	At Week 24 during the blinded treatment period	% reticulocytes, Unconjugated bilirubin, and Lactate dehydrogenase (LDH)
To evaluate the effects of FT-4202 on the sequelae of VOC	During the blinded treatment period	Time to first VOC
To assess changes in fatigue of sickle cell patients taking FT-4202	at Week 24 during the blinded treatment period	Change from baseline in Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue Scale

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