A Phase 2 Open-Label Study to Evaluate Safety and Clinical Activity of FT-4202 in Patients with Thalassemia or Sickle Cell Disease

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Main Information

Primary registry identifying number
LBCTR2022074978

Protocol number
4202-HEM-201

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

Primary sponsor: Country of origin
forma Therapeutics

Date of registration in primary registry
08/09/2022

Date of registration in national regulatory agency

Public title
A Phase 2 Open-Label Study to Evaluate Safety and Clinical Activity of FT-4202 in Patients with Thalassemia or Sickle Cell Disease

Acronym

Scientific title
A Phase 2 Open-Label Study to Evaluate Safety and Clinical Activity of FT-4202 in Patients with Thalassemia or Sickle Cell Disease

Acronym

Brief summary of the study: English

This study is a multicenter, Phase 2, open-label, multiple-cohort study examining the safety and efficacy of FT-4202 for the treatment of patients, age 12 to 65 years, with SCD or thalassemia. Three treatment cohorts based on the patients hemoglobinopathy (SCD or thalassemia) and transfusion requirements will be evaluated.

Brief summary of the study: Arabic

دراسة مفتوحة التسمية من المرحلة الثانية لتقييم السلامة والنشاط الإكلينيكي لـ FT-4202 لدى المرضى المصابين بمرض الثلاسيميا أو الخلية المنجلية

Health conditions/problem studied: Specify

Patients, age 12 to 65 years, with Sickle Cell Disease or thalassemia.

Interventions: Specify

This study is a multicenter, Phase 2, open-label, multiple-cohort study examining the safety and efficacy of FT-4202 for the treatment of patients, age 12 to 65 years, with SCD or thalassemia. Three treatment cohorts based on the patients hemoglobinopathy (SCD or thalassemia) and transfusion requirements will be evaluated.
Patients will be enrolled into a 48-week treatment period; at the end of the 48-week treatment period, patients may enroll into a separate open-

label extension protocol . The dose of FT-4202 is 400 mg daily (QD) administered continuously; the selection of the starting dose is based on results from a Phase 1 study in patients with SCD who were not receiving chronic RBC transfusions.
Cohort A: Patients with SCD on Chronic RBC Transfusions: Patients enrolled will be receiving RBC transfusions every 3 to 5 weeks targeting a pre-transfusion % HbS of 30% (up to a maximum of 45% is allowed) with a post-transfusion Hb of ~ 10 to 12 g/dL (per individual patient's transfusion treatment plan). FT-4202 dosing will start within 24 hours of a patient receiving a scheduled RBC transfusion. While on FT-4202 treatment, if a patient has an increase in pre-transfusion Hb ≥ 1 g/dL over their baseline pre-transfusion Hb, the Investigator may choose to either delay the transfusion by one week, transfuse the patient with a reduced number of RBC units, or perform an RBC exchange.

Cohort B: Patients with Thalassemia on Chronic RBC Transfusions: Patients enrolled will be receiving RBC transfusions every 3 to 5 weeks targeting a pre-transfusion Hb of ~ 9 to
10 g/dL (per individual patient's transfusion treatment plan). FT-4202 dosing will start within
24 hours of a patient receiving a scheduled RBC transfusion. While on FT-4202 treatment, if a patient has an increase in pre-transfusion Hb ≥ 1 g/dL over their baseline pre-transfusion Hb, the investigator may delay the transfusion by one week or reduce the number of units infused.

Cohort C: Patients with Thalassemia not on Chronic RBC Transfusions: Baseline Hb will be based on an average of two or more measurements (one measure performed within one day prior to start of FT-4202 treatment and at least one other measure performed 7 to 28 days prior to study treatment). Hemoglobin measurements within 2 weeks following an RBC transfusion are excluded.

Key inclusion and exclusion criteria: Inclusion criteria

Inclusion Criteria - All Cohorts

Informed Consent

1.Patient has provided documented informed consent or assent (the informed consent form [ICF] must be reviewed and signed by each patient; in the case of adolescent patients, both the consent of the patient's legal representative or legal guardian, and the patient's assent must be obtained)

Age

2.Age 12 to 65 years, inclusive, at time of first dose

Sex and Contraceptive/Barrier Requirements

3.Patients, who if female and of childbearing 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.

Inclusion Criteria – Cohort Specific

Cohort A (SCD Transfusion Cohort)

1.Male or female study patient with a confirmed diagnosis of sickle cell disease

Documentation of SCD genotype (HbSS, HbSβ0-thalassemia or other sickle cell syndrome variants) may be based on history of laboratory testing or must be confirmed by laboratory testing during Screening

2.Chronically RBC transfused for primary stroke prevention or due to previous stroke.
Chronic RBC transfusion is defined as: ≥ 6 RBC units in the previous 24 weeks before the first dose of study treatment and no transfusion-free period for > 35 days during that period

3.Receiving chronic RBC transfusion by straight transfusions

4.At least 24 months of chronic monthly RBC transfusions for primary stroke prevention or treatment of primary stroke (initial completed overt clinical stroke with document infarction on brain computed tomography [CT] or magnetic resonance imaging [MRI])

5.On iron chelation therapy for > 3 months prior to enrollment

6.Documented adequate monthly transfusions with average HbS ≤ 45% (the upper limit of the established academic community standard) for the previous 12 weeks of RBC transfusions before the first dose of study treatment

Cohort B (Thalassemia Transfusion Cohort)

1. Male or female study patients with documented diagnosis of β-thalassemia, Hemoglobin E/ β-thalassemia or Hemoglobin H (α-thalassemia)

2. Chronically transfused, defined as: ≥ 6 RBC units in the previous 24 weeks before the first dose of study treatment and no transfusion-free period for > 35 days during that period

3. On iron chelation therapy for > 3 months prior to enrollment

Cohort C (Thalassemia Non-transfused Cohort)

1. Male or female study patients with documented diagnosis of β-thalassemia, Hemoglobin E/ β-thalassemia or Hemoglobin H (α-thalassemia)

2. Hemoglobin ≤ 10 g/dL

Key inclusion and exclusion criteria: Gender

Both

Key inclusion and exclusion criteria: Specify gender

Key inclusion and exclusion criteria: Age minimum

12

Key inclusion and exclusion criteria: Age maximum

65

Key inclusion and exclusion criteria: Exclusion criteria

Exclusion Criteria – All Cohorts

Medical Conditions

1.Female who is breast feeding or pregnant

2.Hepatic dysfunction characterized by:

Alanine aminotransferase (ALT) > 4.0 × upper limit of normal (ULN)

Direct bilirubin > 3.0 × ULN

History of cirrhosis

3.Patients with clinically significant and active bacterial, fungal, parasitic, or viral infection.

Patients with acute bacterial, fungal, parasitic, or viral infection requiring systemic therapy should delay Screening/ enrollment until active therapy has been completed.

Patients with acute viral infections without available therapies (eg, coronavirus disease 2019 [COVID-19]) should delay Screening/ enrollment until the acute infection has resolved.

Note: Infection prophylaxis is allowed (see concomitant medication restrictions).

4.Known human immunodeficiency virus (HIV) positivity

5.Active infection with hepatitis B virus (hepatitis B surface antigen [HepBsAg] and hepatitis B core antibody [HepBcAb] positive)

6.Active hepatitis C infection

7.Severe renal dysfunction (estimated glomerular filtration rate at the Screening visit; calculated by the local laboratory < 30 mL/min/1.73 m2) or on chronic dialysis.

8.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)

9.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

Heart disease, heart failure as classified by the New York Heart Association (NYHA) classification 3 or higher, or significant arrhythmia requiring treatment,

Pulmonary fibrosis or pulmonary hypertension which are clinically significant ie, ≥ Grade 3 National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (or higher)

10. Any condition affecting drug absorption, such as major surgery involving the stomach or small intestine (prior cholecystectomy is acceptable).

Prior/Concomitant Therapy

11. Chronic systemic glucocorticoids ≤ 3 months (90 Days) prior to the first dose of study treatment (physiologic replacement therapy for adrenal insufficiency is allowed). Single day glucocorticoid treatment (eg, for prevention or treatment of transfusion reactions, is allowed).

12. Receiving or use of concomitant medications that are strong inducers or moderate/strong inhibitors of cytochrome P450 (CYP)3A4/5 within

2 weeks of starting study treatment or anticipated need for such agents during the study.

13. Use of erythropoietin or other hematopoietic growth factor treatment within 30 days of starting study treatment or anticipated need for such agents during the study.

14. Receipt of prior cellular-based therapy (eg, hematopoietic cell transplant, gene modification therapy)

15. Initiation of a new chelation therapy within 3 months before the first dose of study treatment

Prior/Concurrent Clinical Study Experience

16. Participated in another clinical trial of an investigational agent (or medical device) within 30 days or 5 half-lives of date of informed consent, whichever is longer, or is currently participating in another trial of an investigational agent (or medical device).

Other Exclusions

17. Inadequate venous access as determined by the Investigator/ site staff.

18. 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.
Exclusion Criteria – Cohort Specific

Cohort A (SCD Transfusion Cohort)

19. History of severe brain vasculopathy by magnetic resonance angiography (MRA) showing moya-moya disease.

20. Undergone an exchange RBC transfusion (manual or erythrocytopheresis) within the previous 3 months

21. New auto- or alloantibody affecting the ability to phenotypically match donor RBCs at the start of study treatment (Day 1).

Note: a patient who previously screen failed for a new alloantibody may re-screen if the ability to phenotypically match donor RBC's has been confirmed.

22. Current use of other therapeutic agents for SCD (eg, HU, voxelotor, crizanlizumab) within 30 days of starting study treatment and until the end of the study treatment period

Cohort B (Thalassemia Transfusion Cohort)

23. Hemoglobin S/β-thalassemia

24. New auto- or alloantibody affecting the ability to phenotypically match donor RBCs at the start of study treatment (Day 1).

Note: a patient who previously screen failed for a new alloantibody may re-screen if the ability to phenotypically match donor RBC's has been confirmed.

25. Current use of HU within 30 days of starting study treatment and until the end of the study treatment period

26. Use of luspatercept within 9 months before starting study treatment

Cohort C (Thalassemia Non-transfused Cohort)

27. Hemoglobin S/β-thalassemia

28. Received ≥ 4 RBC units in the previous 6 months before enrollment or no transfusion-free period for > 35 days during that period or received an RBC transfusion within 8 weeks of enrollment.

29. Hydroxyurea treatment initiated within 3 months before starting study treatment.

30. Current use of luspatercept within 3 months before starting study treatment and until the end of the study treatment period

Type of study

Interventional

Type of intervention

Pharmaceutical

Type of intervention: Specify type

N/A

Trial scope

Trial scope: Specify scope

Safety

N/A

Study design: Allocation

Non-randomized controlled trial

Study design: Masking

Open (masking not used)

Study design: Control

Uncontrolled

Study phase

2

Study design: Purpose

Treatment

Study design: Specify purpose

N/A

Study design: Assignment

Other

Study design: Specify assignment

cohort

IMP has market authorization

No

IMP has market authorization: Specify

Name of IMP

Etavopivat-(FT-4202)

Year of authorization

Month of authorization

Type of IMP

Others

Pharmaceutical class

Etavopivat (FT-4202) is an orally bioavailable, small-molecule activator of pyruvate kinase red blood cell isozyme (PKR) being developed by Forma Therapeutics, Inc. and is intended for the treatment of sickle cell disease (SCD), a genetic disease resulting from mutations in the hemoglobin (Hb) molecule characterized by pathological conditions primarily resulting from damage to the red blood cell (RBC). Additional indications for treatment with etavopivat may include other inherited hemoglobinopathies, such as thalassemia, or other refractory anemias. The clinical hypothesis behind etavopivat is that PKR activation will initiate a cascade of molecular, cellular, and downstream changes that ultimately lessen the clinical manifestations of SCD. In short, it is proposed that PKR activation will reduce RBC sickling via a reduction in levels of 2,3-diphosphoglycerate (2,3-DPG), which will in turn reduce the polymerization of deoxygenated sickle Hb (HbS), shift the oxygen dissociation curve to the left and improve oxygenation delivery to tissue. Furthermore, PKR activation may contribute to an improved overall RBC membrane integrity via increasing levels of adenosine triphosphate (ATP). Through these 2 mechanisms, PKR activation is predicted to reduce vaso-occlusive and hemolytic events which cause acute pain crises and anemia in patients with SCD. Pharmacokinetic (PK) data and preliminary proof of mechanism data have been collected in a Phase 1 single ascending dose (SAD) and multiple ascending dose (MAD) study in healthy volunteers and patients with SCD; data on safety and tolerability in these subjects/patients have also been collected and evaluated. The safety and efficacy of etavopivat will continue to be investigated in additional clinical studies of patients with SCD, thalassemia, and other anemias.

Therapeutic indication

SCD, Thalassemia and other inherited hemoglobinopathies.

Therapeutic benefit

Etavopivat (FT-4202) is an orally bioavailable, small-molecule activator of pyruvate kinase red blood cell isozyme (PKR) being developed by Forma Therapeutics, Inc. and is intended for the treatment of sickle cell disease (SCD), a genetic disease resulting from mutations in the hemoglobin (Hb) molecule characterized by pathological conditions primarily resulting from damage to the red blood cell (RBC). Additional indications for treatment with etavopivat may include other inherited hemoglobinopathies, such as thalassemia, or other refractory anemias. The clinical hypothesis behind etavopivat is that PKR activation will initiate a cascade of molecular, cellular, and downstream changes that ultimately lessen the clinical manifestations of SCD. In short, it is proposed that PKR activation will reduce RBC sickling via a reduction in levels of 2,3-diphosphoglycerate (2,3-DPG), which will in turn reduce the polymerization of deoxygenated sickle Hb (HbS), shift the oxygen dissociation curve to the left and improve oxygenation delivery to tissue. Furthermore, PKR activation may contribute to an improved overall RBC membrane integrity via increasing levels of adenosine triphosphate (ATP). Through these 2 mechanisms, PKR activation is predicted to reduce vaso-occlusive and hemolytic events which cause acute pain crises and anemia in patients with SCD. Pharmacokinetic (PK) data and preliminary proof of mechanism data have been collected in a Phase 1 single ascending dose (SAD) and multiple ascending dose (MAD) study in healthy volunteers and patients with SCD; data on safety and tolerability in these subjects/patients have also been collected and evaluated. The safety and efficacy of etavopivat will continue to be investigated in additional clinical studies of patients with SCD, thalassemia, and other anemias

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

None retained

Biospecimen description

N/A

Target sample size

60

Actual enrollment target size

Date of first enrollment: Type

Anticipated

Date of first enrollment: Date

27/09/2022

Date of study closure: Type

Anticipated

Date of study closure: Date

Recruitment status

Pending

Recruitment status: Specify

Date of completion

IPD sharing statement plan

Yes

IPD sharing statement description

Patient's full identity will not be on any of the study documents or sample collected and kept by the sponsor for their studies .only the partial date of birth will be collected . only a unique participant number for the study will link the data or samples to the patient.

Additional data URL

Admin comments

Trial status

Approved

Secondary Identifying Numbers

Full name of issuing authority	Secondary identifying number
N.A	N.A

Sources of Monetary or Material Support

Name
Forma Therapeutics,Inc.

Secondary Sponsors

Name
N.A

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	009617100 8269	aziz.zoghbi@mct-cro.com	Director of Country Oversight and Management MENA, Gulf and Africa
Scientific	Ali Taher	American University of Beirut Medical Center	Lebanon	9613755 669	ataher@aub.edu.lb	PI
Scientific	Adlette Inati Inati	Nini Hospital, el Maarad Street, Triploli, Lebanon	Lebanon	009613228 033	adlette.inati@lau.edu.lb	PI
Scientific	Patrick Kelly	Forma Therapeutics	United States of America	617-880-9574	pfkelly@formatherapeutics.com	Forma Therapeutics

Centers/Hospitals Involved in the Study

Center/Hospital name	Name of principles investigator	Principles investigator speciality	Ethical approval
Nini Hospital	Adlette Inati	Professor of Pediatric Hematology and Oncology	Approved
Chronic Care Center	Ali Taher	Professor of Hematology and Oncology	Pending
American University of Beirut Medical Center	Ali Taher	Professor of Hematology and Oncology	Pending

Ethics Review

Ethics approval obtained	Approval date	Contact name	Contact email	Contact phone
Nini Hospital	06/04/2022	Nini Hospital	kamleh.ibrahim@hopitalnini.com	+ 961 6 431400
Chronic Care Center	10/06/2022	Chronic Care Center	sabinesaifi1@gmail.com	+961 71 599 207

Countries of Recruitment

No Countries

Health Conditions or Problems Studied

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

Interventions

Intervention	Description	Keyword
Etavopivat (FT-4202)	Patients will be enrolled into a 48-week treatment period; at the end of the 48-week treatment period, patients may enroll into a separate open-label extension protocol . The dose of FT-4202 is 400 mg daily (QD) administered continuously; the selection of the starting dose is based on results from a Phase 1 study in patients with SCD who were not receiving chronic RBC transfusions.	treatment

Primary Outcomes

Name	Time Points	Measure
To assess the erythroid response of FT-4202 in adolescents and adults with SCD or thalassemia	□ Cohorts A and B: Proportion of patients with ≥ 20% reduction in RBC transfusions over a continuous 12-week treatment period versus baseline RBC transfusion history □ Cohort C: Hemoglobin response rate at Week 12 (increase of ≥ 1.0 g/dL from baseline	reduction in RBC transfusion and Hemoglobin response rate at Week 12

Key Secondary Outcomes

Name	Time Points	Measure
To further assess the safety and clinical activity of FT-4202 in adolescents and adults with SCD or thalassemia	□ Number and percent of patients with SAEs, AEs leading to discontinuation, clinically significant laboratory measurements, and clinically significant abnormal ECGs	□ Number and percent of patients with SAEs, AEs leading to discontinuation, clinically significant laboratory measurements, and clinically significant abnormal ECGs □ Cohorts A and B: o Proportion of patients with ≥ 33% reduction in RBC transfusion over a continuous 12-week treatment period versus baseline RBC transfusion history o Reduction in RBC transfusions over 12, 24 and 48 weeks □ Cohort C: o Hemoglobin response rate at Week 24 and Week 48 (increase of ≥ 1.0 g/dL from baseline). o Change from baseline in Hb over 12, 24, and 48 weeks
To measure the effects of FT-4202 on measures of iron overload in all patients	Changes in serum ferritin levels at 12, 24, and 48 weeks versus baseline.Changes in liver iron concentration at 48 weeks versus baseline	Changes in serum ferritin levels at 12, 24, and 48 weeks versus baseline.Changes in liver iron concentration at 48 weeks versus baseline

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