A Phase 2b Study to Evaluate the Safety and Efficacy of IMR-687 in Subjects with Sickle Cell Disease

31/07/2025 05:15:26

Main Information

Primary registry identifying number
LBCTR2020083421

Protocol number
IMR-SCD-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
IMARA, Inc.

Primary sponsor: Country of origin
116 Huntington Avenue, 6th Floor Boston, MA 02116

Date of registration in primary registry
18/09/2020

Date of registration in national regulatory agency

Public title
A Phase 2b Study to Evaluate the Safety and Efficacy of IMR-687 in Subjects with Sickle Cell Disease

Acronym

Scientific title
A Phase 2b Study to Evaluate the Safety and Efficacy of IMR-687 in Subjects with Sickle Cell Disease

Acronym

Brief summary of the study: English

This is a phase 2b, randomized, double-blind, placebo-controlled, multicenter study of subjects aged 18 to 65 years with sickle cell disease (SCD; homozygous sickle hemoglobin [HbSS], sickle-β^0 [HbSB^0] thalassemia, or sickle-β□ [HbSB□] thalassemia) to evaluate the safety and efficacy of the phosphodiesterase type 9 (PDE9) inhibitor, IMR-687, administered once daily (qd) for 52 weeks. This study will enroll approximately 99 subjects with SCD. This study consists of a screening period (up to 4 weeks), a double-blind treatment period (52 weeks), and a safety follow-up period (4 weeks).

Brief summary of the study: Arabic

هذه هي المرحلة 2ب ، والعشوائية ، مزدوجة التعمية ، وهمي تسيطر عليها ، دراسة متعددة المراكز من الأشخاص الذين تتراوح أعمارهم من 18 إلى 65 عامًا مع مرض الخلايا المنجلية (SCD الهيموغلوبين المنجلي المتماثل اللزوجة [HbSS] ؛ المنجلية [HbSB^0] أو الثلاسيمية ، المنجلية [□HbSB] الثلاسيميا) لتقييم سلامة وفعالية مثبط نوع الفسفوديستراز 9 (PDE9) ، IMR-687 يعطى مرة واحدة يوميًا (qd) لمدة 52 أسبوعًا. هذه سوف الدراسة تسجيل ما يقرب من 99 مواضيع مع SCD. حتى تتكون هذه الدراسة من فترة الفحص (حتى 4 أسابيع) ، فترة علاج 52 (مزدوجة التعمية) ، وفترة متابعة السلامة (4 أسبوعًا) .

Health conditions/problem studied: Specify

The population for this study includes subjects with the following forms of SCD: homozygous sickle hemoglobin (HbSS), sickle-β^0 (HbSB^0) thalassemia, and sickle-β□ (HbSB□) thalassemia.

Interventions: Specify

This study will enroll approximately 99 adult (18-65 years) subjects with Sickle Cell Disease. Initially, subjects will be randomly assigned in a

2:1 ratio
to receive either IMR-687 lower dose or placebo.Prior to the introduction of IMR-687 higher dose, the Data Monitoring Committee (DMC) will review safety data for at least 5 subjects who received IMR-687. If the DMC recommends inclusion of the higher dose, randomization will then proceed in a 1:2:1 ratio (IMR-687 lower dose, IMR-687 higher dose, or placebo).

Key inclusion and exclusion criteria: Inclusion criteria

1. Male or female aged ≥18 to ≤65 years at the time of informed consent form (ICF) signing.
2. Confirmed diagnosis of SCD (HbSS, HbSBº thalassemia, or HbSB□ thalassemia) in the medical record; if not available, the diagnosis must be confirmed at the site's local laboratory instead.
3. Subjects must have had at least 1 and no more than 12 documented episodes of VOC in the past 12 months at the time of ICF signing and at randomization (Day 1). For study eligibility, VOC is defined as a documented episode of an acute painful crisis (for which there was not an explanation other than VOC) that involved moderate to severe pain lasting for at least 2 hours and at least one of the following:
• Use of escalated analgesia (including healthcare professional-instructed use of an analgesic prescription)
• A hospital, emergency department, or clinic visit and/or healthcare telephone consultation at the time of occurrence
• Diagnosis of acute chest syndrome (ACS) (defined as an acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on a chest X-ray), hepatic sequestration, or splenic sequestration
4. Hemoglobin (Hb) of >5.5 and <10.5 g/dL.
5. Absolute reticulocyte count ≥80 × 10^9/L.
6. Subjects receiving HU must have received it continuously for at least 6 months prior to signing the ICF, and must have been on a stable dose for at least 3 months prior to signing the ICF, with no anticipated need for dose adjustments during the study including the screening period, in the opinion of the investigator.
7. Female subjects must not be pregnant or breastfeeding and be highly unlikely to become pregnant. Male subjects must be unlikely to impregnate a partner. Male or female subjects must meet at least one of the following criteria:
• A female subject who is not of reproductive potential is eligible without requiring the use of contraception. A female subject who is not of reproductive potential is defined as one who: (1) has reached natural menopause (defined as 12 months of spontaneous amenorrhea without an alternative medical cause, and can be confirmed with serum follicle-stimulating hormone levels in the postmenopausal range as determined by the central laboratory); (2) is 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy; or(3) has undergone bilateral tubal ligation. Spontaneous amenorrhea does not include cases for which there is an underlying disease that causes amenorrhea (e.g., anorexia nervosa).
• A female of reproductive potential must have 2 negative pregnancy tests as verified by the investigator prior to starting study therapy. She must agree to ongoing pregnancy testing during the course of the study, at the end of treatment visit, and at the end of study visit. This applies even if the subject practices true abstinence from heterosexual contact.
• A male subject who is not of reproductive potential is eligible without requiring the use of contraception. A male subject who is not of reproductive potential is defined as one who has undergone a successful vasectomy. A successful vasectomy is defined as (1) microscopic documentation of azoospermia or (2) a vasectomy more than 2 years ago with no resultant pregnancy despite sexual activity post-vasectomy.
• A male or female subject who is of reproductive potential agrees to remain truly abstinent or use (or have their partner use) acceptable methods of highly effective contraception starting from the time of consent through 3 months after the completion of study drug. True abstinence is defined as abstinence that is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of the study, and withdrawal are not acceptable methods of contraception. Acceptable methods of highly effective birth control are combined or progesterone-only hormonal contraception that is associated with inhibition of ovulation, intrauterine device, and intrauterine hormone-releasing system.
8. Be capable of giving informed consent and reading and signing the ICF after the nature of the study has been fully explained by the investigator or investigator designee.
9. Be willing and able to complete all study assessments and procedures and to communicate effectively with the investigator and site staff.

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

Subjects who meet any of the following criteria will be excluded from the study:
1. Hospital discharge for sickle cell crisis or other vaso-occlusive event within the 4 days prior to randomization (Day 1).
2. Red blood cell transfusion within 60 days of signing the ICF or on chronic transfusion therapy regimen. Transfusion status must be reassessed at randomization (Day 1).
Note: If a subject requires a transfusion during the screening period, they may be rescreened up to one time.
3. Subjects with hereditary persistence of HbF (i.e., HbF >25% at screening).
4. Subjects with known active hepatitis A, hepatitis B, or hepatitis C, with active or acute event of malaria, or who are known to be positive for human immunodeficiency virus (HIV).
5. For female subjects of childbearing potential, a positive serum human chorionic gonadotropin (hCG) test (screening) or a positive urine hCG test at randomization (Day 1).
6. Estimated glomerular filtration rate (eGFR) <45 mL/min as calculated by the equation from the Modification of Diet in Renal Disease Study using creatinine, age, sex, and ethnicity.
7. Alanine aminotransferase or aspartate aminotransferase >3 × the upper limit of normal.
8. Body mass index (BMI) <17.0 kg/m² and a total body weight <45 kg; or a BMI >35 kg/m2.
9. Current or history of malignancies (solid tumors and hematological malignancies), unless the subject has been free of the disease (including completion of any active or adjuvant treatment for prior malignancy) for ≥5 years. However, subjects with the following history/concurrent conditions are allowed if, in the opinion of the investigator, the condition has been adequately diagnosed and is determined to be clinically in remission, and the subject's participation in the study would not represent a safety concern:
a. Basal or squamous cell carcinoma of the skin

b. Carcinoma in situ of the cervix
c. Carcinoma in situ of the breast
d. Incidental histologic finding of prostate cancer (T1a or T1b using the tumor, nodes, metastasis clinical staging system)
10. A history of a clinically significant allergic reaction or hypersensitivity, as judged by the investigator, to any drug or any component of the study drug formulations used in the study (see Investigator's Brochure).
11. History of unstable or deteriorating cardiac or pulmonary disease within 6 months before signing the ICF, including but not limited to the following:
a. Unstable angina pectoris or myocardial infarction or elective coronary intervention
b. Congestive heart failure requiring hospitalization
c. Uncontrolled clinically significant arrhythmias
12. Any condition affecting drug absorption, such as major surgery involving the stomach or small intestine (prior cholecystectomy is acceptable).
13. On ECG testing at ICF signing and/or randomization (Day 1), a corrected QT interval, Fridericia's formula (QTcF) >450 ms in men and >470 ms in women or the presence of clinically significant ECG abnormalities as determined by the investigator.
14. A history of major surgery within 4 weeks or minor surgery within 2 weeks of randomization (Day 1).
15. Stroke requiring medical intervention within 24 weeks prior to randomization (Day 1).
16. Subjects taking direct acting oral anti-coagulants (DOACs) apixaban, dabigatran, rivaroxaban, edoxaban, or ticagrelor, or taking warfarin, are excluded due to the possibility of a cytochrome P450 (CYP)3A-mediated drug interaction, unless they stopped the treatment at least 28 days
prior to randomization (Day 1); other oral anti-coagulants and anti-platelet drugs are permitted. Anti-coagulant therapies for prophylaxis of venous thromboembolism, including pulmonary emboli including when undergoing surgery or high-risk procedures, are allowed if low molecular weight heparins are used in the peri-operative period. Aspirin use is allowed before and during the study.
17. Poorly controlled diabetes mellitus as defined by 1) fructosamine levels of >340 µmol/L within 12 weeks prior to randomization (Day 1); 2) short-term hyperglycemia leading to hyperosmolar or ketoacidotic crisis; and/or 3) history of diabetic cardiovascular complications.
18. Subject has received chronic systemic glucocorticoids within 12 weeks prior to randomization (≥5 mg/day). Physiologic replacement therapy for adrenal insufficiency is allowed.
19. Any clinically significant bacterial, fungal, parasitic, or viral infection requiring antibiotic therapy should delay screening/randomization (Day 1) until the course of antibiotic therapy has been completed. This includes, but is not limited to, long-term tuberculosis treatment.
20. Participated in another clinical study 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 study of an investigational agent (or medical device).
21. Prior exposure to IMR-687.
22. A history of use of crizanlizumab or voxelotor within 6 months prior to signing the ICF.
23. Consumption/use of the following drugs or other substances within the specified time periods before randomization or plans to consume/use at any time during the study. If there is any question as to whether a substance is permitted, please review the product labeling (if applicable) and consult the medical monitor and/or sponsor.
a. PDE5 inhibitors (including but not limited to sildenafil, tadalafil, and vardenafil) within 7 days prior to randomization (Day 1) or plans to use during the study.
b. Grapefruit, grapefruit juice, grapefruit products, or herbal supplements with CYP-alteringabilities within 1 week prior to randomization (Day 1) or plans to consume during the study.
c. CYP3A-sensitive substrates, including the opioids fentanyl and alfentanil, or moderate to strong CYP3A inhibitors or inducers within 28 days prior to randomization (Day 1) or plans to use during the study
d. Any drugs or substances known to be substrates or inhibitors of P-glycoprotein (P-gp) orbreast cancer resistance protein (BCRP) within 28 days prior to randomization (Day 1) or plans to use during the study.
24. Receipt of erythropoietin or other hematopoietic growth factor treatment within 3 months of signing the ICF or anticipated need for such agents during the study.
25. Prior gene therapy.
26. Any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study, including the presence of laboratory abnormalities that may place the subject at unacceptable risk if he/she were to participate in the study.
27. Other prior or ongoing medical condition, physical findings, or laboratory abnormality that, in the investigator's opinion, could adversely affect the safety of the subject, make it unlikely that the course of treatment or follow-up would be completed, or impair the assessment of study results (e.g., a history of drug or alcohol abuse within the past 1 year, as judged by the investigator).

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

Study design: Purpose

Study design: Specify purpose

Other

Safety and efficacy

Study design: Assignment

Parallel

Study design: Specify assignment

N/A

IMP has market authorization

No

IMP has market authorization: Specify

Name of IMP

IMR-687

Year of authorization

Month of authorization

Type of IMP

Cell therapy

Pharmaceutical class

IMR-687 (6-[(3S,4S)-4-methyl-1-(pyrimidin-2-ylmethyl)pyrrolidin-3-yl]-3-tetrahydropyran-4-yl-7H-imidazo[1,5-a]pyrazin-8-one) is a potent, specific, and highly selective small molecule inhibitor of phosphodiesterase type 9 (PDE9); PDE9 mediates cellular signaling pathways by degrading cGMP to its inactive or monophosphate form.

Therapeutic indication

Treatment of patients with sickle cell disease (SCD); homozygous sickle hemoglobin (HbSS), sickle-β^0 (HbSB^0) thalassemia, and sickle-β□ (HbSB□) thalassemia.

Therapeutic benefit

By inhibiting PDE9, IMR-687 is intended to increase cGMP levels and thus stimulate the production of HbF, which reduces the cellular concentration of abnormal Hb (HbS) within RBCs and its associated sequelae.

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 samples will be collected for routine clinical safety laboratory assessments according to the schedule of assessments.

Target sample size

Actual enrollment target size

99

Date of first enrollment: Type
Anticipated

Date of first enrollment: Date
02/11/2020

Date of study closure: Type
Anticipated

Date of study closure: Date
02/11/2022

Recruitment status
Pending

Recruitment status: Specify

Date of completion

IPD sharing statement plan
Yes

IPD sharing statement description
The sponsor assures that the key design elements of this protocol will be posted in a publicly accessible database such as ClinicalTrials.gov. The clinical study report will be submitted to the IRBs/IECs and regulatory authorities within 1 year of the end of the study (worldwide). The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor.

Additional data URL

Admin comments

Trial status
Approved

Secondary Identifying Numbers

Full name of issuing authority	Secondary identifying number
EMA	2019-004471-39
FDA US IND	130549

Sources of Monetary or Material Support

Name
IMARA 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	009611612500	zog_az@mct-cro.com	Regional Manager
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Centers/Hospitals Involved in the Study

Center/Hospital name	Name of principles investigator	Principles investigator speciality	Ethical approval
Chronic Care Center	Dr Suzanne Koussa	MD Hematology	Approved
Nini Hospital	Dr Adlette Inati	MD hematology/oncology	Approved
American University of Beirut Medical Center	Dr Miguel Abboud	MD Pediatric hematology/oncology	Not approved

Ethics Review

Ethics approval obtained	Approval date	Contact name	Contact email	Contact phone
Chronic Care Center	24/06/2020	Michelle Abi Saad	cccmas@chroniccare.org.lb	9615455101
Nini Hospital	15/06/2020	Sara Kharsa	sarah.kharsa@hopitalnini.com	9616431400 ext 1062

Countries of Recruitment

Name
Egypt
Ghana
Greece
Italy
Kenya
Lebanon
Morocco
Netherlands
Oman
Senegal
Tunisia
Uganda
United Kingdom
United States of America

Health Conditions or Problems Studied

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

Interventions

Intervention	Description	Keyword
100, 150, or 200 mg white tablets.	IMR-687 will be supplied as 100, 150, or 200 mg white tablets. Subjects will be advised to take 2 tablets orally, qd. The different doses of IMR-687 are visually identical. Subjects will be directed to take their study drug with food.In order to maintain an exposure of ≥3.0 to ≤4.5 mg/kg, subjects in the lower dose group weighing <67 kg will be dispensed 100 mg tablets and those weighing ≥67 kg will be dispensed 150 mg tablets. In order to maintain an exposure of >4.5 to ≤6.7 mg/kg, subjects in the higher dose group weighing <67 kg will be dispensed 150 mg tablets and those weighing ≥67 kg will be dispensed 200 mg tablets. The different doses of IMR-687 are visually identical in tablet form. Placebo will be supplied as white tablets containing matrix absent IMR-687. The placebo tablets are visually identical to the IMR-687 tablets.	IMR-687

Primary Outcomes

Name	Time Points	Measure
Changes in vital signs	Vital signs will be collected at every on-site visit .At the Day 1 and Week 4 visits, vital signs will be taken predose and 2 hours (±20 minutes) postdose, during the PK assessments. At all other timepoints, vital signs can be taken irrespective of taking study drug.	heart rate, respiratory rate, blood pressure, and body temperature
Changes in 12-Lead ECG	All ECGs to be performed in triplicate. From Baseline (Day 1 visit) through EOT (Week 52 visit), ECGs will be obtained at both pre-dose and 2 hours (±30 minutes) post-dose. During the screening, ET, and EOS (Week 56) visits, ECG will be obtained irrespective of taking study drug.	heart rate, PR interval, QRS duration, QT interval, and QTcF interval
Incidence of Adverse Event AEs and Serious Adverse Event.	All AEs and SAEs, related and unrelated, will be recorded from the signing of informed consent through the end-of-study safety follow-up visit.	All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA)
Physical Examination	Complete PEs will be performed at Screening and at Weeks 12, 24, 36, 52, and 56; these consist of a general examination of the body, including the abdomen, heart, lungs, lymph nodes, back/neck, neurological system, skin, extremities, head, eyes, nose, and throat. At all other visits, symptom-directed PEs will be obtained after identification of AEs deemed by the investigator to be of significant clinical concern.	abdomen, heart, lungs, lymph nodes, back/neck, neurological system, skin, extremities, head, eyes, nose, and throat.
Clinical Laboratory Variables	over 52 weeks of treatment	hematology,coagulation,serum chemistry,urinalysis and pregnancy test

Key Secondary Outcomes

Name	Time Points	Measure
Quality of life	at Baseline and weeks 4,12,24,36 and 52	ASCQ-Me®, PROPr, SCSES
Pharmacokinetic Assessment	At the Day 1 and Week 4 visits, serial blood samples for IMR-687 (including metabolites and HU, if applicable) plasma concentrations will be drawn pre-dose (within 30 minutes) and at 30 minutes (±5 minutes), 1.5 hours (±15 minutes), 6 hours (±1 hour), and 24 hours (±2 hours) after administration of study drug. On these full profile PK days, food details will also be recorded at the study sites. A trough blood sample will be drawn pre-dose at Week 24 and on the last day of dosing (Week 52).	Cmax, tmax, and AUC(0-24), 0 to the last measurable timepoint (AUC(last)), and extrapolated to infinity (AUC(0-infinity)
Pharmacodynamic Assessment	Screening,baseline and throughout treatment period	E-selectin, P-selectin, ICAM-1, VCAM-1, MPO, and transferrin receptor.

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