# A Phase 2 Study to Evaluate the Safety and Tolerability of IMR-687 in Subjects with Beta Thalassemia

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## Main Information

**Primary registry identifying number**
LBCTR2020093402

**Protocol number**
IMR-BTL-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**
IMARA, Inc.

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

**Date of registration in primary registry**
02/10/2020

**Date of registration in national regulatory agency**

**Public title**
A Phase 2 Study to Evaluate the Safety and Tolerability of IMR-687 in Subjects with Beta Thalassemia

**Acronym**

**Scientific title**
A Phase 2 Study to Evaluate the Safety and Tolerability of IMR-687 in Subjects with Beta Thalassemia

**Acronym**

**Brief summary of the study: English**
This is a phase 2 study intended to explore the potential use of IMR -687 to treat subjects with β-thalassemia. This is the first study of IMR-687 in a β-thalassemia population, and, as such, is designed to examine the safety, tolerability, and PK, as well as the potential PD effects, of IMR-687 administered once daily for 36 weeks in adult subjects with β-thalassemia.

**Brief summary of the study: Arabic**
هذه دراسة مرحلة 2 تهدف إلى استكشاف الاستخدام المحتمل لـ IMR-687 لعلاج الأشخاص المصابين به β-الثلاسيميا. هذه هي الدراسة الأولى في عدد سكان IMR-687 المصابين بالثلاسيمية ، وعلى هذا النحو ، هي مصممة لدراسة السلامة والتسامح والحرائك الدوائية ، فضلاً عن الآثار الدوائية المحتملة لـ IMR-687 ، الخاصة بـ الديناميكا الدوائية ، تُدار مرة واحدة يوميًا لمدة 36 أسبوعًا في الأشخاص البالغين المصابين بالثلاسيمية بيتا .

**Health conditions/problem studied: Specify**
Reduced Hb in red blood cells (RBCs), decreased RBC production, and anemia due to reduced or absent synthesis of the β chain of hemoglobin (Hb) and mutations in the hemoglobin beta (HBB) gene in subjects with β-thalassemia.

**Interventions: Specify**
This study will enroll approximately 120 subjects with β-thalassemia (60 subjects with TDT and 60 subjects with NTDT), aged 18 through 65 years.Subjects will receive either IMR-687 (lower dose [≥3.0 to ≤4.5 mg/kg] or higher dose [>4.5 to ≤6.7 mg/kg]) or placebo in a blinded fashion. 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 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). The DMC may request additional data and/or

meeting(s) in order to make the recommendation on whether to move forward with inclusion of the higher dose.

**Key inclusion and exclusion criteria: Inclusion criteria**

Subjects must meet all of the following inclusion criteria to be eligible for the study:
1. Subjects must understand and voluntarily provide informed consent and sign an informed consent form (ICF) prior to any study-related assessments/procedures being conducted. Although RBC transfusions and associated Hb laboratory measurements 12 weeks prior to the Screening visit are not study related, the ICF will specifically request subject consent to collect these data.
2. Subjects must be ≥18 to ≤65 years of age at the time of signing the ICF.
3. Subjects must have documented diagnosis of β-thalassemia or HbE/β-thalassemia. Concomitant single alpha gene deletion, duplication, or triplication is allowed.
4. For TDT subjects only: Subjects must be regularly transfused, defined as >3 to 10 RBC units1 in the 12 weeks prior to screening and no transfusion-free period for ≥35 days during that period.
For NTDT subjects only: Subjects must be transfusion independent, defined as 0 to ≤3 units1 of RBCs received during the 12-week period prior to randomization, must not be on a regular transfusion program, must be RBC transfusion-free for at least ≥ 4 weeks prior to randomization, and must not be scheduled to start a regular hematopoietic stem cell transplantation within 9 months.
5. Subjects must have documentation of dates of transfusions and the number of all RBC units within the 12 weeks prior to Screening.
6. Subjects must be willing and able to complete all study assessments and procedures, and to communicate effectively with the investigator and site staff.
7. Subjects must have Eastern Cooperative Oncology Group (ECOG) performance score of 0 to 1 (Appendix 1).
8. Female subjects must not be pregnant, not be breast feeding, 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 spontaneousamenorrhea 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 therapy. 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 progestogen-only hormonal contraception that is associated with inhibition of ovulation, intrauterine device, and intrauterin hormone-releasing system.
9. Subjects receiving hydroxyurea musthave 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.
10. For NTDT subjects only: Subjects must have mean baseline Hb ≤10.0 g/dL, based on a minimum of 2 measurements ≥1 week apart within 4 weeks prior to randomization; Hb values within 21 days post-transfusion will be excluded.

**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 meeting any of the following criteria must be excluded from the study:
1. 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.
2. Any situation or condition that confounds the ability to interpret data from the study (e.g., subjects also receiving RBC transfusions at centers not able to obtain laboratory samples for central processing).
3. Diagnosis of α-thalassemia (e.g., hemoglobin H [HbH]) or hemoglobin S (HbS)/ β-thalassemia.
4. Body mass index (BMI) <17.0 kg/m² or a total body weight <45 kg; or BMI >35 kg/m².
5. 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).
6. Stroke requiring medical intervention ≤24 weeks prior to randomization.
7. 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.
8. Treatment with an investigational drug or device or participation in an investigational drug or device study ≤28 days prior to randomization.
9. Platelet count >1000 × $10^9$/L.

10. Subjects on iron chelation therapy (ICT) at the time of ICF signing must have initiated the treatment with ICT at least 24 weeks before the predicted randomization date. ICT can be initiated at any time during treatment and should be used according to the label.
11. Subjects who have had treatment with erythropoietin-stimulating agents ≤24 weeks prior to randomization.
12. Uncontrolled hypertension as defined by systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg, medical intervention indicated, and more than one drug or more intensive therapy than previously used indicated.
13. Poorly controlled diabetes mellitus as defined by 1) fructosamine levels of >340 µmol/L within 12 weeks prior to randomization; 2) short term hyperglycemia leading to hyperosmolar or ketoacidotic crisis; and/or 3) history of diabetic cardiovascular complications.
14. Subjects who have major organ damage, including:
a. Liver disease with ALT or AST >3× ULN, direct bilirubin >2× ULN, or history/evidence of cirrhosis, as well as presence of masses/tumor.
b. Heart disease, heart failure as classified by the New York Heart Association
classification 3 or higher, or significant arrhythmia requiring treatment, or recent myocardial infarction within 6 months of randomization, or significant cardiac iron T2* <15 ms, or left ventricular ejection fraction <56%.
c. Severe lung disease, including pulmonary fibrosis or pulmonary hypertension, i.e., ≥Grade 3 NCI CTCAE version 5.0.
d. Estimated glomerular filtration rate <45 mL/min/1.73 m2 (per Modification of Diet in Renal Disease formula).
e. Nephrotic range proteinuria (>3 g/L).
15. Subjects who have received chronic systemic glucocorticoids ≤12 weeks prior to randomization (≥5 mg/day). Physiologic replacement therapy for adrenal insufficiency is allowed.
16. Major surgery ≤12 weeks prior to randomization (subjects must have completely recovered from any previous surgery prior to randomization).
17. 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).
18. History or current 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)
19. Screening or Baseline (Day 1) electrocardiogram (ECG), demonstrating a QTcF >450 ms in men and >470 ms in women, or the presence of clinically significant ECG abnormalities as determined by the investigator.
20. 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 labelling (if applicable) and consult the medical monitor and/or sponsor.
a. PDE type 5 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-altering abilities within 1 week prior to randomization (Day 1) or plans to consume during the study.
c. CYP3A-sensitive substrates, including the synthetic opioid 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) or breast cancer resistance protein (BCRP) within 28 days prior to randomization (Day 1) or plans to use during the study.
21. 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 as judged by the investigator within the past 1 year).
22. Any clinically significant bacterial, fungal, parasitic, or viral infection requiring antibiotictherapy 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.
23. Prior exposure to sotatercept, luspatercept, IMR-687, or gene therapy.
24. In the opinion of the investigator, the subject is unable to meet the requirements of the study.

**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**

Other

**Study design: Specify purpose**

safety and tolerability

**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 is a potent, specific, and highly selective small molecule inhibitor of phosphodiesterase (PDE) 9; PDE9 mediates cellular signaling pathways by degrading cyclic guanosine monophosphate (cGMP) to its inactive or monophosphate form.

**Therapeutic indication**

Treatment of adults with either transfusion dependent or non-transfusion dependent β-thalassemia

**Therapeutic benefit**

This is the first study of IMR-687 in β-thalassemia subjects; therefore, the primary objective of this study is to determine the safety and tolerability of qd oral doses of IMR-687 across several doses anticipated to be pharmacologically active.Potential benefits of IMR-687 include addressing the missing or decreased presence of the beta globin subunit by pharmacologic induction of HbF production. In addition to resolving persistent anemia, HbF induction rectifies the missing or mutated beta globin subunit and thereby reduces the overabundance of free-floating alpha globin subunits. These benefits have the potential to result in increased functional RBC production, higher Hb levels, reduced hemolysis and the reduction of adhesion and inflammation.

**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 samples will be collected for serum virology (screening assessment) only if clinically indicated. Testing will be performed through a central laboratory and may include hepatitis B surface antigen (HBsAg), hepatitis A immunoglobulin M (IgM), and hepatitis C virus (HCV) antibody, as well as HIV testing also for hematology,PD, PK, clinical chemistry and coagulation.
Urine will be assessed for appearance, color, pH, specific gravity, ketone, protein, glucose,bilirubin, and urobilinogen, including occult blood and microscopic examination of sediment(only if occult blood is detected).

**Target sample size**

120

**Actual enrollment target size**

**Date of first enrollment: Type**

Anticipated

**Date of first enrollment: Date**

01/10/2020

**Date of study closure: Type**

Anticipated

**Date of study closure: Date**

01/10/2021

**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 one 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 |
|---|---|
| FDA US IND | 130549 |
| EMA | 2019-002989-12 |

## Sources of Monetary or Material Support

| Name |
|---|
| IMARA Inc. |

## Secondary Sponsors

No Sponsors

## 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@mctcro.com | Regional Manager |
| Scientific | Ali Taher | Chronic Care Center, Hazmieh, Lebanon | Lebanon | 009613755669 | ataher@aub.edu.lb | Principal Investigator |

## 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 | 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 |
| American University of Beirut Medical Center | 28/07/2020 | Dr Deborah Mukherji | irb@aub.edu.lb | 961350000 ext 5445 |

## Countries of Recruitment

| Name |
|---|
| Italy |
| France |
| Greece |
| Denmark |
| Turkey |
| Tunisia |
| Egypt |
| Morocco |
| Lebanon |
| Georgia |
| Malaysia |
| United Kingdom |
| Netherlands |
| United States of America |

## Health Conditions or Problems Studied

| Condition | Code | Keyword |
|---|---|---|
| TDT and NTDT Thalassemia | Thalassaemia (D56) | Thalassemia |

## Interventions

| Intervention | Description | Keyword |
|---|---|---|
| 100, 150, or 200 mg white tablets of IMR-687 | Subjects will be advised to take two IMR-687 tablets orally with food qd for 36 weeks. 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 consist of tablets containing matrix absent IMR-687 and will be identical in appearance to the IMR-687 tablets. Subjects will be advised to take two placebo tablets orally with food qd for 36 weeks. | IMR-687 |

## Primary Outcomes

| Name | Time Points | Measure |
|---|---|---|
| Changes in Vital Signs | Vital signs will be taken predose and 12 hours (±20 minutes) postdose on Day 1 and Week 3 for TDT subjects and on Day 1 and Week 4 for NTDT subjects (during 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 from baseline in 12-Lead-ECG | ECGs to be performed in triplicate. At Baseline and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, and 36, ECGs will be obtained at predose and 2 hours (±30 minutes) postdose. At all other timepoints, ECGs can be taken irrespective of taking study drug. | heart rate, PR interval, QRS duration, QT interval, and QTcF interval |
| Incidence and severity of Adverse Event 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 (Week 40). | AEs will be coded using MedDRA: Abnormal test findings ,Clinically significant symptoms and signs, Changes in physical examination findings, Hypersensitivity ,Drug abuse ,Drug dependency, Drug overdose , Drug withdrawal , Drug misuse, Drug interactions, Extravasation , Exposure during pregnancy , Exposure via breastfeeding , Medication error |
| Physical Examinations findings | Complete PEs will be performed at Screening, Week 24, and Week 36 and will include a general examination 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. | general examination of the body, including the abdomen, heart, lungs, lymph nodes, back/neck, neurological system, skin, extremities, head, eyes, nose, and throat. |
| Changes in Clinical laboratory variables | over 36 week treatment | hematology,coagulation,serum chemistry, urinalysis and pregnancy test. |

## Key Secondary Outcomes

| Name | Time Points | Measure |
|---|---|---|
| Quality of life | at Baseline and at Weeks 12, 24, and 36. | TranQOL and SF-36 QoL tools in the TDT population and the NTDT-PRO and SF-36 QoL tools in the NTDT population |
| Pharmacokinetic Analyses | At Baseline (all subjects) and either Week 3 (TDT) or Week 4 (NTDT), serial blood samples will be drawn pre-dose (within 30 minutes) and at 30 minutes (±5 minutes), 1.5 hours (±15 minutes), 4 hours (±15 minutes), 6 hours (±1 hour) and 24 hours (±2 hours) after administration of study drug. A trough blood sample will be drawn pre-dose at Week 1, Week 24, and Week 36. | Maximum concentration (Cmax); Time to maximum concentration (tmax); Apparent terminal half-life (t½); and • AUC from time 0 to 24 hours (AUC(0-24)), 0 to the last measurable timepoint (AUClast), and extrapolated to infinity (AUC(0-∞)). |
| Pharmacodynamic markers | Blood samples should be obtained prior to administration of study drug. PD markers will need to be collected prior to each RBC transfusion (if applicable) | 1) serum ferritin, soluble transferrin receptor, hepcidin-25, and haptoglobin levels; 2) WBC adhesion markers: sE-sel, sP-sel, sICAM-1; VCAM-1, hsCRP; 3) cardiovascular marker: serum NT-proBNP. |

## 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**