PROTOCOL
IMR-BTL-201

Study Title:	A Phase 2 Study to Evaluate the Safety and Tolerability of IMR-687 in Subjects with Beta Thalassemia
Protocol Number:	IMR-BTL-201
Study Phase:	2
Study Drug:	IMR-687
US IND:	130549
EudraCT:	2019-002989-12
Indication:	Treatment of adults with either transfusion dependent or non-transfusion dependent β-thalassemia
Sponsor:	IMARA, Inc. 116 Huntington Avenue, 6th Floor Boston, MA 02116
Sponsor Representative:	Kenneth M. Attie, MD Senior Vice President and Chief Medical Officer, IMARA +1 617 710 0560 kattie@imaratx.com
Version Number:	5.0 **Release Date:** 15 Mar 2021
Replaces Version:	4.0 **Release Date:** 15 Jan 2020
GCP Statement:	This study is to be performed in compliance with International Council for Harmonisation (ICH), applicable Good Clinical Practice (GCP), and federal and local regulations.

SPONSOR'S APPROVAL

This protocol has been reviewed and approved by IMARA, Inc.

Kenneth M. Attie, MD
Senior Vice President and Chief Medical Officer
IMARA, Inc.

15 Mar 2021
Date

INVESTIGATOR'S AGREEMENT

I have read and reviewed this clinical study protocol (IMR-BTL-201), and I agree to conduct this study according to this protocol, to comply with its requirements subject to ethical and safety considerations, and to conduct this study in accordance with all Regulatory Authority requirements and International Council for Harmonisation (ICH) Guidelines on Good Clinical Practice (ICH E6[R2]). I further agree to comply with all other applicable national and local laws and regulations in connection with my conduct of this study, including, without limitation, all applicable medical information privacy rule requirements. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

I understand that the sponsor may decide to suspend or terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from the execution of the study I will communicate my intention immediately in writing to the sponsor.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

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2. SYNOPSIS

Name of Sponsor/Company: IMARA, Inc.
Name of Investigational Product: IMR-687
Name of Active Ingredient: 6-[(3S,4S)-4-methyl-1-(pyrimidin-2-ylmethyl)pyrrolidin-3-yl]-3-tetrahydropyran-4-yl-7H-imidazo[1,5-a]pyrazin-8-one
Title of Study: A Phase 2 Study to Evaluate the Safety and Tolerability of IMR-687 in Subjects with Beta Thalassemia
Indication: Treatment of adults with either transfusion-dependent (TDT) or non-transfusion-dependent (NTDT) β-thalassemia
Study Centers: This study will be conducted at approximately 50 study sites in North America, United Kingdom, European Union, Middle East, Asia-Pacific, and Africa.
Phase of Development: 2
Planned Number of Subjects: A total of approximately 120 adult subjects with β-thalassemia are expected to enroll: • Population 1 (TDT subjects): approximately 60 subjects • Population 2 (NTDT subjects): approximately 60 subjects
Objectives: *Primary Objective* The primary objective of this study in both Population 1 (TDT) and Population 2 (NTDT) is to assess the safety and tolerability of IMR-687 in adult subjects with β-thalassemia. *Secondary Objectives* The secondary objectives in Population 1 (TDT) subjects are: • To evaluate the effect of IMR-687 versus placebo on reduction in red blood cell (RBC) transfusion burden. • To evaluate the effect of IMR-687 versus placebo on the change in iron overload. • To characterize the pharmacokinetic (PK) profile of IMR-687 and collect data for population PK analysis The secondary objectives in Population 2 (NTDT) subjects are: • To evaluate the effect of IMR-687 versus placebo on anemia (as defined by total hemoglobin [Hb]). • To evaluate the effect of IMR-687 versus placebo on fetal hemoglobin (HbF). • To evaluate the effect of IMR-687 versus placebo on the change in iron overload. • To characterize the PK profile of IMR-687 and collect data for population PK analysis

Exploratory Objectives

The exploratory objectives in Population 1 (TDT) subjects are:

- To characterize the pharmacodynamic (PD) profile of IMR-687 versus placebo with respect to erythropoiesis, iron metabolism, and hemolysis.
- To evaluate the effect of IMR-687 versus placebo on the proportion of subjects who are transfusion independent.
- To evaluate the effect of IMR-687 versus placebo on time to and duration of reduction in RBC transfusion burden.
- To evaluate the effect of IMR-687 versus placebo on functional and health-related quality of life (QoL).
- To evaluate responses to IMR-687 per genotypes in subjects with TDT.

The exploratory objectives in Population 2 (NTDT) subjects are:

- To characterize the PD profile of IMR-687 versus placebo with respect to erythropoiesis, iron metabolism, and hemolysis.
- To evaluate the effect of IMR-687 versus placebo on functional and health-related QoL.
- To evaluate the effect of IMR-687 versus placebo on β-thalassemia-related symptoms and severity.
- To evaluate responses to IMR-687 per genotypes in subjects with NTDT.

The objectives will be assessed by the endpoints described in Table 1 of the protocol.

Study Design (Methodology):

This is a phase 2, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, PK, and PD of IMR-687 (phosphodiesterase (PDE) 9 inhibitor) administered once daily (qd) for 36 weeks in 2 populations of adult subjects with β-thalassemia: Population 1 (TDT subjects) and Population 2 (NTDT subjects). A schematic of the study is provided in Section 7 of the protocol.

This study will enroll approximately 120 subjects with β-thalassemia (60 subjects with TDT and 60 subjects with NTDT), aged 18 through 65 years. This study consists of a retrospective data collection period, a screening period, a double-blind treatment period, and a safety follow-up period. During the screening period of up to 28 days, subjects will provide informed consent and be evaluated on eligibility criteria as stated below.

Subjects will receive either IMR-687 (lower dose [≥3.0 to ≤5.0 mg/kg] or higher dose [>4.5 to ≤6.7 mg/kg]; the precise exposure ranges for different groups of subjects are dependent on the weight gate for tablet strength as summarized under Study Rationale below) 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 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). 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. During study conduct under Protocol Version 4.0, the DMC approved the opening of enrollment in the higher dose IMR-687 group, which went into effect on 01 February 2021.

Subjects will return to the investigational site at Week 1 for a safety assessment, and qualified site personnel will contact the subject by telephone at Week 2 to capture potential AEs and concomitant medications. Subjects will be seen at the investigational site approximately every 3 weeks (TDT subjects) or every 4 weeks (NTDT subjects) throughout the remainder of the study. Safety will be monitored throughout the study, and PK, PD, QoL, and clinical outcome measures will be performed at the visits shown in the schedule of assessments for the TDT and NTDT populations (Table 2 and Table 3, respectively, in the protocol).

The informed consent will specifically indicate that data will be retrospectively collected on transfusion burden, defined as the dates of transfusion events and the number of packed red blood cell (pRBC) units per event during the 12 weeks preceding the Baseline (Day 1) visit. If available, the following data should also be collected for each transfusion event: volume and hematocrit of each pRBC unit, pre-transfusion Hb, and pre-transfusion weight.

Study Rationale:

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 qd for 36 weeks in adult subjects with β-thalassemia.

Administration for 30 days of 30 mg/kg/day (human equivalent dose [HED] of 2.4 mg/kg/day) or 60 mg/kg/day (HED of 4.9 mg/kg/day) of IMR-687 in a β-thalassemia intermedia animal model ($Hbb^{th1/th1}$ mice) improves markers of β-thalassemia disease progression by increasing RBCs and Hb, and reducing reticulocytes. The degree of these changes was dose dependent, with significant improvement at the higher dose of 60 mg/kg. In addition, IMR-687 at 60 mg/kg improved erythroblast differentiation, suggesting a role for this compound in the improvement of ineffective erythropoiesis of β-thalassemia.

Clinical safety and tolerability data are available from Study IMR-SCD-101 in healthy volunteers for IMR-687 administered at doses up to 6 mg/kg/day in a fasted single ascending dose (SAD) portion (Part A) and at doses up to 4.5 mg/kg/day for 7 days in a fed multiple ascending dose (MAD) portion (Part C), as well as from the phase 2a study in fed subjects with sickle cell disease (IMR-SCD-102). Based on these data, exposure ranges from 3 mg/kg to approximately 6 mg/kg is expected to be tolerable, especially if taken with food because administration with food appears to reduce both the incidence and severity of nausea and/or gastrointestinal (GI) pain. The onset of nausea in the healthy volunteer study was rapid (between 30 to 120 minutes) and generally lasted 2 to 8 hours and was mild nature at doses ≤4.5 mg/kg (lower dose). These potential AEs of nausea, upper GI pain, and emesis are easily monitorable and are self-limited if dosing is stopped. Furthermore, following qd dosing for 7 days in fed healthy volunteers, steady state was achieved before Day 7. Exposure (area under the concentration-time curve [AUC]) in healthy volunteers increased in a near dose-proportional manner (a 4.1-fold increase for a 4.5-fold change in dose [see Section 4.1.3.1 of the protocol]), and the mean exposure (AUC from time 0 to 24 hours [AUC_{0-24}]) at 4.5 mg/kg on Day 7 was 26.3 µg•h/mL, which is approximately 3.3-fold below the Week 39 exposure (AUC_{0-24}) in the female dog (most conservative species/gender) at the respective no observed adverse effect level (NOAEL) in the repeat-dose toxicology study. Furthermore, the predicted Day 1 exposure in the higher dose arm of up to 6.7 mg/kg is 32.0 µg•h/mL, which remains approximately 2.7-fold below the Week 39 exposure (AUC_{0-24}) in the female dog (most conservative species/gender).

This study initially imposed a minimum weight threshold of 45 kg and a 67-kg weight gate for tablet strength to ensure that subjects in the lower dose IMR-687 group received a dose equating to no more than the 4.5 mg/kg evaluated in the MAD part of the healthy volunteer study. Subsequently, the DMC approved the opening of enrollment in the higher dose IMR-687 group (up to 6.7 mg/kg). Having established safety and tolerability of the lower dose, the DMC also approved a change in weight gate

to 60 kg and the resultant modified dose range of up to 5.0 mg/kg in the lower dose group (with the minimum weight threshold of 45 kg unchanged). Starting from Protocol Version 5.0, subjects in the IMR-687 lower dose group will receive ≥3.4 to ≤5.0 mg/kg and subjects in the higher dose group will receive >5.0 to ≤6.7 mg/kg; no subject will receive more than 6.7 mg/kg. Under Protocol Version 4.0, the exposure ranges were ≥3.0 to ≤4.5 mg/kg in the lower dose group and >4.5 to ≤6.7 mg/kg in the higher dose group. Therefore, the overall exposure ranges during the course of the study are ≥3.0 to ≤5.0 mg/kg and >4.5 to ≤6.7 mg/kg.

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 prior to Screening 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 in their medical history. Concomitant alpha gene deletion, duplication, or triplication is allowed.
4. ***For TDT subjects only:*** Subjects must be regularly transfused, defined as >3 to 10 pRBC units[1] in the 12 weeks prior to the Baseline (Day 1) visit 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 units[1] of pRBCs received during the 12-week period prior to the Baseline (Day 1) visit, 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 the dates of transfusion events and the number of pRBC units per event within the 12 weeks prior to the Baseline (Day 1) visit.
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 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

[1]One unit in this protocol refers to one bag of packed RBCs. The dates of transfusion events and the number of pRBC units per event during the 12 weeks preceding the Baseline (Day 1) visit will be collected. If available, the following data should also be collected for each transfusion event: volume and hematocrit of each pRBC unit, pre-transfusion Hb, and pre-transfusion weight. Transfusion burden as expressed in mL/kg transfused RBC may be calculated.

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 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 progesterone-only hormonal contraception that is associated with inhibition of ovulation, intrauterine device, and intrauterine hormone-releasing system.

9. Subjects receiving hydroxyurea 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.

10. ***For NTDT subjects only:*** Subjects must have Hb ≤10.0 g/dL at Screening; the screening Hb sample must be collected 7 to 28 days prior to randomization. Hb values within 21 days post-transfusion will be excluded.

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/m^2 or a total body weight <45 kg; or BMI >35 kg/m^2.

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 (<100 mg per day) is allowed before and during the study.
8. 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).
9. Platelet count >1000 × 10^9/L.
10. For subjects on iron chelation therapy (ICT) at the time of ICF signing, initiation of ICT less than 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, in the opinion of the investigator, for example 1) Hb A1c >9.0% within 12 weeks prior to randomization (in the medical history); 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 >3× ULN with proportion of direct/total bilirubin >0.3; or history/evidence of cirrhosis, liver transplant, or presence of clinically significant mass/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 overload.
    c. Severe lung disease, including pulmonary fibrosis or pulmonary hypertension, i.e., ≥Grade 3 NCI CTCAE version 5.0.
    d. Significant kidney disease as indicated by, for example, estimated glomerular filtration rate <45 mL/min/1.73 m^2 (per Modification of Diet in Renal Disease formula).
15. Subjects who have received chronic systemic glucocorticoids ≤12 weeks prior to randomization (≥5 mg/day prednisone or equivalent). Physiologic replacement therapy for adrenal insufficiency is allowed.
16. Major surgery ≤8 weeks 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 on 2 or more of the triplicate ECGs, 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 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.

23. Prior exposure to any of following:

    a. IMR-687 or gene therapy

    b. Sotatercept or luspatercept (Reblozyl®) within 6 months prior to randomization (Day 1)

24. In the opinion of the investigator, the subject is unable to meet the requirements of the study.

Investigational Product, Dose, and Mode of Administration:

IMR-687 will be supplied as 100, 150, or 200 mg white tablets to be taken orally. Subjects will be advised to take two IMR-687 tablets orally with food qd for 36 weeks. The different doses of IMR-687 are visually identical in tablet form.

Reference Therapy, Dosage and Mode of Administration:

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.

Duration of Treatment and Study Duration:

The planned maximum duration of study participation is approximately 44 weeks. This consists of a screening period of up to 4 weeks, a treatment period of 36 weeks, and a 4-week safety follow-up assessment after the last dose of study drug is administered. In addition, there is retrospective data review undertaken at the start of subject participation that aims to collect information on transfusion activity during the 12 weeks preceding the Baseline (Day 1) visit (historical transfusion burden).

Statistical Methods

General Considerations

Descriptive summary statistics will be provided for demographics, disposition, and IMR-687 exposure. The number and percentage of subjects who discontinue from the study, along with reasons for discontinuations will be tabulated.

Continuous data will be summarized using descriptive statistics (number of subjects, mean, SD, median, Q1, Q3, minimum, and maximum) and, where appropriate, coefficient of variation (%CV) and graphic representation. Categorical data will be summarized by sample size and proportions. Data will be summarized by population (TDT, NTDT) and dose cohort at each timepoint as appropriate. Graphs of actual values and changes over time may also be created as appropriate.

Interim analyses will be conducted at each of the following milestones:

- 30 subjects in the TDT population have completed 24 weeks of treatment
- 30 subjects in the NTDT population have completed 24 weeks of treatment
- 60 subjects in the TDT population have completed 24 weeks of treatment
- 60 subjects in the NTDT population have completed 24 weeks of treatment

Analysis Sets

Note that each of the following populations are defined for TDT and NTDT populations separately. Combined TDT and NTDT populations may also be used as appropriate.

The safety analysis set will include all subjects who have received any amount of study drug and from whom informed consent has been obtained and will be used to summarize all safety and tolerability data. In safety summaries, subjects will be analyzed according to the actual treatment they received.

The per protocol set will include all subjects in the safety population who have provided sufficient data without major protocol deviations or events that would be expected to affect the analysis. The per protocol set will be identified based on blinded data prior to unblinding the final analysis dataset. The per protocol set will be used to generate PD and clinical outcomes data.

The PK analysis set will be defined as a subset of the safety analysis set that includes all subjects who are enrolled in the study, have received at least 1 dose of IMR-687, and have sufficient IMR-687 concentration data; this set will be used in the PK analyses.

Safety Analyses

Descriptive statistics will be used to summarize all safety endpoints, by population and treatment

group as appropriate. Data summaries will be displayed for incidence of AEs, clinical laboratory variables, vital signs, and ECG parameters. Safety data summaries will use the safety analysis set. All AEs will be coded using MedDRA. Data will be summarized using preferred term and primary system organ class. AE summaries will include AEs leading to study discontinuation and severity and frequency of AEs and SAEs. All safety data will be summarized in by-subject listings.

Preliminary Efficacy Analyses

Population 1 (TDT)

Hematological improvement will be evaluated using a Cochran-Mantel-Haenzel (CMH) test to compare the proportion of subjects who achieved improvement between the placebo group to each of the 2 active treatment arms (IMR-687 lower dose and IMR-687 higher dose). Hematological improvement is defined as a ≥20% reduction in pRBC units transfused measured over 12 weeks (from Week 12 to Week 24 and from Week 24 to Week 36) as compared to the 12-week period prior to the Baseline (Day 1) visit. The safety and per protocol populations will be used, and no multiple comparisons adjustment will be made.

The mean number of transfusion events from baseline to Week 36 will be summarized by treatment group. Comparisons between placebo and each of the 2 active treatment arms (IMR-687 lower dose and IMR-687 higher dose) will be made using a t-test.

The mean change from baseline to Week 36 for ICT mean daily dose and serum ferritin will be analyzed using an analysis of covariance (ANCOVA) model with baseline value as a covariate and treatment as a factor.

Population 2 (NTDT)

The baseline value of Hb will be defined as the mean of non-missing Hb values from Screening (7 to 28 days prior to randomization) and randomization (Day 1) measurements. The baseline value of HbF will be defined in an analogous manner. The proportion of subjects with increase from baseline of ≥1.0 g/dL in mean Hb values (at Weeks 12 to 24 and Weeks 24 to 36) will be evaluated using a Cochran-Mantel-Haenzel (CMH) test to compare the proportion of subjects who achieved improvement between the placebo group and each of the 2 active treatment arms (IMR-687 lower dose and IMR-687 higher dose).

The average Hb concentrations in the absence of transfusions over a continuous 12-week interval (from Week 12 to Week 24 and from Week 24 to Week 36) as well as the change from baseline will be summarized by treatment group and timepoint. The change from baseline in average Hb at Weeks 12 to 24 and Weeks 24 to 36 will be compared between the placebo group and each of the 2 active treatment arms (IMR-687 lower dose and IMR-687 higher dose) using a mixed model for repeated measures (MMRM) with fixed effects for treatment group and timepoint and a random subject effect. The safety and per protocol populations will be used, and no multiple comparisons adjustment will be made. Mean change in HbF concentrations from baseline to Week 24 and to Week 36 will be analyzed in the same manner.

The number and proportion of subjects with HbF response of ≥3% using the mean values at Weeks 12 to 24 and Weeks 24 to 36 will be summarized by timeframe and treatment group. Comparisons of each of the 2 active treatment arms (IMR-687 lower dose and IMR-687 higher dose) to placebo will be made using a CMH test.

The mean change from baseline to Week 36 for ICT mean daily dose and serum ferritin will be analyzed using an ANCOVA model with baseline value as a covariate and treatment as a factor.

Pharmacokinetic Analyses

Summary statistics for trough plasma concentration (C_{trough}) data will be provided. Accumulation may be assessed.

PK data from this study will also be used to explore any relationship between IMR-687 exposure and

clinical response, PD endpoints, or AEs, as data permit. These data will be analyzed together with PK data from other clinical studies for a population PK analysis, as appropriate.

Analyses of Exploratory Endpoints

Exploratory PD and clinical outcomes data for each timepoint will be listed by subject and summarized by treatment group separately for Population 1 (TDT) and Population 2 (NTDT) as appropriate. Correlations between PK and the exploratory endpoints may be assessed. Descriptive statistics will be computed as appropriate.

Summary statistics for QoL scores from the prespecified domains will be calculated at each administration timepoint. Summary statistics will also be calculated for change from baseline in each score at each administration timepoint.

Exploratory PD outcomes will be based on the PD analysis set, and QoL outcomes will be based on the safety and per protocol sets.

Sample Size Calculations

Both populations will have primary objectives of safety, and the sample sizes are not based on statistical assumptions.

Population 1 (TDT)

For the secondary efficacy endpoint of percentage of subjects with hematologic improvement (reduction in transfusion burden), 16 subjects in each treatment arm provide 80% power to detect a difference of 10% of subjects improving in the placebo arm versus 50% of subjects improving in either of the active treatment arms, using an alpha level of 0.05. No multiple comparisons adjustments will be made as these are secondary analyses.

Population 2 (NTDT)

For the secondary efficacy endpoint of proportion of subjects with increase from baseline of ≥1.0 g/dL in mean Hb values at Weeks 12 to 24 and Weeks 24 to 36, 17 subjects in each treatment arm provide >90% power to detect a difference of 10% of subjects improving in the placebo arm versus 50% of subjects improving in either of the active treatment arms, using an alpha level of 0.05. No multiple comparisons adjustments will be made as these are secondary analyses.

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3. LIST OF ABBREVIATIONS

Abbreviation	Definition
%CV	coefficient of variation
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-24}	AUC from time 0 to 24 hours
BCRP	breast cancer resistance protein
CFR	Code of Federal Regulations
cGMP	cyclic guanosine monophosphate
C_{24}	concentration at 24 hours after study drug administration
C_{max}	maximum plasma concentration
CMH	Cochran-Mantel-Haenzel
CNS	central nervous system
COVID-19	coronavirus disease 2019
CRO	contract research organization
CSR	clinical study report
C_{trough}	trough plasma concentration
CYP	cytochrome P450
DMC	Data Monitoring Committee
DOAC	direct-acting oral anti-coagulant
ECG	electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
FE	food effect
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practice
Hb	hemoglobin
HbE	hemoglobin E (abnormal variant)
HbF	fetal hemoglobin
HbS	hemoglobin S (abnormal variant)

Abbreviation	Definition
HED	human equivalent dose
HIV	human immunodeficiency virus
hsCRP	highly sensitive C-reactive protein
IB	Investigator's Brochure
IC_{50}	half-maximal inhibitory concentration
IC_{90}	concentration at which inhibition is 90%
ICAM-1	intercellular adhesion molecule 1
ICF	informed consent form
ICH	International Council for Harmonisation
ICT	iron chelation therapy
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IWRS	interactive web response system
LDH	lactate dehydrogenase
MAD	multiple ascending dose
NCI CTCAE	National Cancer Institute Common Terminology for Adverse Events
NOAEL	No observed adverse effect level
NT-proBNP	N-terminal pro B-type natriuretic peptide
NTDT	non-transfusion-dependent (β)-thalassemia
NTDT-PRO	Non-transfusion Dependent β-thalassemia Patient Reported Outcome
OECD	Organization for Economic Cooperation and Development
PD	pharmacodynamic(s)
PDE	phosphodiesterase
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
pRBC	packed red blood cells
Q1	first quartile
Q3	third quartile
qd	once daily
QoL	quality of life
QTcF	corrected QT interval using Fridericia's formula

Abbreviation	Definition
RBC	red blood cell
SAD	single ascending dose
SAE	serious adverse event
SCD	sickle cell disease
SD	standard deviation
SF-36	Short Form (36) Health Survey
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	half-life
t_{max}	time to maximum plasma concentration
TDT	transfusion-dependent (β)-thalassemia
TEAE	treatment-emergent adverse event
TIBC	total iron binding capacity
TranQoL	Transfusion-dependent Quality of Life Questionnaire
ULN	upper limit of normal
VCAM-1	vascular cell adhesion molecule 1

4. INTRODUCTION

4.1. Overview of Disease Pathogenesis

The sponsor is developing IMR-687 for the treatment of adult subjects with β-thalassemia and sickle cell disease (SCD).

With an incidence of symptomatic individuals estimated at 1 in 100,000 worldwide (Galenello 2010), β-thalassemia is a rare inherited blood disorder characterized by the reduced or absent synthesis of the β chain of hemoglobin (Hb) and is caused by mutations in the hemoglobin beta (*HBB*) gene. The most common manifestations of β-thalassemia include reduced Hb in red blood cells (RBCs), decreased RBC production, and anemia (Galanello 2010). Clinically significant β-thalassemia is typically classified by the need for blood transfusions: non-transfusion-dependent β-thalassemia (NTDT) or transfusion-dependent β-thalassemia (TDT).

4.2. Overview of IMR-687 Development

4.2.1. IMR-687

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 (PDE) 9; PDE9 mediates cellular signaling pathways by degrading cyclic guanosine monophosphate (cGMP) to its inactive or monophosphate form.

By inhibiting PDE9, IMR-687 is intended to increase cGMP levels and in doing so, stimulate the production of fetal hemoglobin (HbF), which reduces the cellular concentration of abnormal Hb (HbS) within RBCs and its associated sequelae. The importance of increasing HbF in treating SCD is evidenced by results from large studies like the Cooperative Study of Sickle Cell Disease in the US and studies in a variety of patient cohorts outside of the US showing that HbF is among the most important modifiers of this disease (Platt 1991; Platt 1994; Alsultan 2013), as well as data showing that modifiers of HbF improve other hematological parameters of SCD (Akinsheye 2011; Alsultan 2013; Barbosa 2013; Sheehan 2013).

PDE9 is highly expressed in hematopoietic cells and is also widely distributed in the brain (Fisher 1998; Matsumoto 2003; Nagasaki 2012), with the highest expression measured in cerebellar Purkinje cells of rodents (van Staveren 2002). A potential advantage of IMR-687 for the β-thalassemia indication is that it does not readily distribute to the brain and, therefore, is less likely to result in the central nervous system (CNS) effects observed with other, brain-penetrating PDE9 inhibitors (Schwam 2014; Hutson 2011; Van der Staay 2008). Moreover, due to its specificity for PDE9, and the absence of evidence of genotoxicity and hepatotoxicity in Good Laboratory Practice (GLP) toxicology studies, IMR-687 could contribute to a meaningful improvement in the standard of care for patients.

4.2.2. Nonclinical Data

The IMR-687 nonclinical program for SCD supports its potential utility for the treatment of β-thalassemia.

In vitro studies have demonstrated IMR-687's ability to increase cGMP in K562 cells and increase HbF in both K562 and CD36+ RBCs cultured ex vivo from blood-derived CD34+ cells from SCD patients, supporting IMR-687's proposed mechanism of action. These findings were confirmed and extended by in vivo studies demonstrating IMR-687's ability to increase HbF and reduce RBC sickling in both Berkeley and Townes sickle cell transgenic mouse models and to reduce the degree of microvascular stasis observed following hypoxia and re-oxygenation in Townes mice. Administration of 10 or 30 mg/kg IMR-687 to C57Bl/6J mice for 5 days demonstrated low CNS exposure, with no effect on locomotor activity or memory.

In a series of GLP/OECD-compliant safety pharmacology studies evaluating behavioral, respiratory, and cardiovascular functions, no untoward adverse effects were noted. In addition, repeat-dose toxicology studies in rats (up to 6 months) and dogs (up to 9 months) were well tolerated and provided no observed adverse effect levels (NOAELs) that were comfortably in excess of those to be administered to humans.

IMR-687 had low-moderate plasma protein binding in the 5 species tested (<32%), and there was no notable partitioning into red blood cells (RBCs). IMR-687 has the potential for induction of CYP3A4 (half-maximal effective concentration [EC_{50}]= 32.4 to 133 µM). IMR-687 was not a competitive inhibitor of CYPs 1A2, 2B6, 3A4/5, 2C9, 2C19, 2C8, and 2D6. IMR-687 is a substrate of P-glycoprotein (P-gp) (K_m >500 µM) and breast cancer resistance protein (BCRP) (K_m = 45.5 µM). IMR-687 is an inhibitor of BCRP (half-maximal inhibitory concentration [IC_{50}] = 32.5 µM), OCT1 (IC_{50} = 834 µM), and MATE2-K (IC_{50} = 441 µM).

Fifteen metabolites have been detected to date. Metabolic pathways included dehydrogenation, hydration, and oxidation. Both renal and biliary excretion of ^{14}C-IMR-687-related radioactivity (as unchanged IMR-687 and metabolites) were observed in the rat. Metabolites found in rat hepatocytes were consistent with those observed in vivo. Metabolites in human hepatocytes were not unique relative to those observed in rat and dog hepatocytes. CYP phenotyping experiments have indicated that IMR-687 is primarily a substrate for CYP3A4 ($K_m \cong$ 127 µM). Metabolites M1 and M4 result from N-dealkylation of IMR-687 and may be major circulating metabolites.

4.2.2.1. Nonclinical Data in β-Thalassemia

Preliminary pharmacology studies of IMR-687 were conducted in a β-thalassemia intermedia animal model ($Hbb^{th1/th1}$ mice). This mouse model does not have functional Hbβ, leading to deficits in Hb and RBCs and defective RBC maturation. IMR-687 administration led to a dose-dependent increase in total Hb (increase of 1.3 g/dL compared to placebo at the highest dose tested of 60 mg/kg). Total RBCs increased in a similar fashion and differences from placebo administration were statistically significant for both measures. IMR-687 also showed enablement of RBC maturation, a key mechanistic component in reducing disease pathology. High-dose IMR-687 (60 mg/kg) produced a statistically significant difference in immature RBCs (polychromatic erythroblasts) and greater prevalence of mature RBCs (orthochromatic and reticulocytes) compared to placebo administration.

Administration for 30 days of 30 mg/kg/day or 60 mg/kg/day of IMR-687 improves markers of β-thalassemia disease progression by increasing RBCs and Hb and reducing reticulocytes. The degree of these changes was dose dependent. In addition, IMR-687 at 60 mg/kg/day improved

erythroblast differentiation, suggesting a role for this compound in the improvement of ineffective erythropoiesis of β-thalassemia.

Additional information on the nonclinical effects of IMR-687 is provided in the Investigator's Brochure.

4.2.3. Clinical Data

4.2.3.1. Phase 1a Study of IMR-687 in Healthy Adult Volunteers (IMR-SCD-101)

A first-in-human, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and pharmacokinetics (PK) of IMR-687 (capsule formulation) has been completed (IMR-SCD-101). The study enrolled 66 healthy male and female adults (aged 18 to 55 years, inclusive), of whom 16 subjects received placebo and 50 subjects received IMR-687. The study was divided into 3 parts: a single-ascending-dose (SAD) study (Part A), a food effect study (Part B), and a multiple-ascending-dose (MAD) study (Part C); all parts had oral dosing. In Part A, 20 subjects received single doses of IMR-687 in the fasted state. The initial planned doses were 0.3, 1, 3, 6, 9, and 12 mg/kg; a 4.5 mg/kg dose was added and the 9 and 12 mg/kg doses were removed after a dose-limiting toxicity of moderate emesis was observed at 6 mg/kg. In Part B, 12 subjects received 2 single doses of IMR-687 at 1 mg/kg under fed and fasting conditions. In Part C, 18 subjects received 7 doses of either 1, 3, or 4.5 mg/kg/day.

IMR-687 was safe and well-tolerated at doses up to 4.5 mg/kg when administered as single and multiple once daily (qd) doses (up to 7 days) of oral capsules to healthy volunteers in a weight-based dosing regimen. The most frequent drug-related adverse event (AE) was nausea. In Part A (SAD study in the fasted state), 35% of all IMR-687 subjects experienced nausea, compared to 0% of placebo subjects. Nausea was mild, transient, and self-limited at doses ≤4.5 mg/kg; the incidence of nausea was sporadic at single doses ≤3 mg/kg IMR-687. Headaches were also a notable, likely drug-related treatment-emergent adverse event (TEAE), particularly in the fasted state (30% of all IMR-687 subjects in the SAD Part A, compared to 0% in the placebo group).

Oral administration of IMR-687 with food significantly reduced both the incidence and severity of the nausea and headache TEAEs. Whereas single doses of 4.5 mg/kg IMR-687 in fasted subjects resulted in mild nausea in 75% of subjects, single doses of 4.5 mg/kg IMR-687 did not result in nausea when given after a high-fat meal. Only after at least 6 daily doses did mild nausea occur with 4.5 mg/kg IMR-687 given with a meal. The incidence of headaches when IMR-687 was given with food was similar between IMR-687-treated (11.1%) and placebo-treated (16.7%) groups.

Nausea onset was between 30 and 120 minutes after the oral administration of IMR-687, and generally lasted 2 to 8 hours. Timing of nausea onset preceded/overlapped with the IMR-687 time to maximum concentration (t_{max}). Together with the mitigating effects of food intake and the fact that IMR-687 is a P-gp substrate and unlikely to be CNS penetrant, these data are consistent with nausea/emesis resulting from a local effect of IMR-687 in the stomach or the gastrointestinal (GI) tract.

IMR-687 administration was not associated with any clinically significant changes in laboratory values, physical examinations, or standard 12-lead electrocardiograms (ECGs). Of note,

IMR-687 did not demonstrate any significant changes in white blood cell (WBC), platelet, or absolute neutrophil counts.

Exposure parameters following single or multiple qd doses of IMR-687 increased with dose in a near dose proportional manner (e.g., a 4.1-fold increase for a 4.5-fold change in dose). Administration with food slowed the rate of absorption of IMR-687 (median t_{max} delayed by approximately 3 hours), which resulted in an approximately 26% decrease in maximum plasma concentration (C_{max}), but no change in overall exposure (area under the concentration-time curve [AUC]). Multiple dose PK demonstrated that IMR-687 did not accumulate to a significant extent in healthy volunteers (<13%). In addition, steady state was achieved prior to dosing on Day 3.

4.2.3.2. Phase 2a Study of IMR-687 in Adult Subjects with Sickle Cell Anemia (IMR-SCD-102)

Study IMR-SCD-102 was a phase 2a, randomized, double-blind, placebo-controlled study in adult subjects with homozygous HbSS or sickle-β0-thalassemia that was completed in 2020.

The objectives of this study were to evaluate the safety, tolerability, PK, and pharmacodynamic (PD) effects of IMR-687 (tablet formulation) administered for 16 to 24 weeks in 2 subject populations: those not on HU (Population A) and those receiving a stable dose of HU according to standard of care (Population B). Eligible subjects in non-HU Population A were initially randomized 1:1:1 to receive 50 mg IMR-687, 100 mg IMR-687, or placebo for a total of 24 weeks. A planned interim analysis suggested that the 50 mg dose would not provide the exposure and efficacy needed to meet clinical outcomes, and the protocol was amended for subjects to receive 100 mg IMR-687 or placebo in a 2:1 randomization for 4 weeks and, if well tolerated, to escalate from 100 mg to 200 mg for the remaining 20 weeks of the study. Similarly, in stable HU Population B, subjects were randomized 2:1 to receive 50 mg IMR-687 or placebo; following the planned interim analysis, subjects received 50 mg IMR-687 or placebo for 4 weeks and, if well tolerated, escalated from 50 mg to 100 mg for the remaining 20 weeks of the study.

A total of 93 subjects with SCD were enrolled, randomized, and received study drug (IMR-687 or placebo) in Study IMR-SCD-102 (58 subjects in Populations A/A1 and 35 subjects in Populations B/B1; 63 subjects received IMR-687 and 30 subjects received placebo). In summary, qd dosing of IMR-687 was generally safe and well tolerated. Additional information on the study results is provided in the Investigator's Brochure.

5. RATIONALE

5.1. Study Rationale and IMR-687 Dose Rationale

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 qd for 36 weeks in adult subjects with β-thalassemia. The dose rationale is based on three important considerations as described below.

Nonclinical Safety and Efficacy

The NOAELs identified in repeat-dose toxicology studies were 100 mg/kg/day (600 mg/m^2/day) in male and female rats, 50 mg/kg/day (1000 mg/m^2) in male dogs, and 25 mg/kg/day (500 mg/m^2/day) in female dogs, which correspond to human equivalent doses (HEDs) of 16.2 and 13.5 mg/kg/day, respectively. These HEDs provide approximately 2-fold exposure margins based on body weight for the highest possible dose in the proposed clinical study (up to 6.7 mg/kg). Therefore, the dose exposure in this study is supported by the nonclinical program and considered safe for adult subjects. Additionally, administration for 30 days of 30 mg/kg/day (HED of 2.4 mg/kg/day) or 60 mg/kg/day (HED of 4.9 mg/kg/day) of IMR-687 in a β-thalassemia intermedia animal model (Hbb$^{th1/th1}$ mice) improves markers of β-thalassemia disease progression by increasing RBCs and Hb, and reducing reticulocytes. The degree of these changes was dose dependent, with significant improvement at the higher dose of 60 mg/kg. In addition, IMR-687 at 60 mg/kg improved erythroblast differentiation, suggesting a role for this compound in the improvement of ineffective erythropoiesis of β-thalassemia. Testing a broader dose range in this program is justified by the nonclinical efficacy data observed.

Actual and Predicted Human Safety Margins of IMR-687 Doses

Clinical safety and tolerability data are available from Study IMR-SCD-101 in healthy volunteers for IMR-687 administered at doses up to 6 mg/kg/day in a fasted single ascending dose (SAD) portion (Part A) and at doses up to 4.5 mg/kg/day for 7 days in a fed multiple ascending dose (MAD) portion (Part C), as well as from the phase 2a study in fed SCD subjects (IMR-SCD-102). Based on these data, an exposure range from 3 mg/kg to approximately 6 mg/kg is expected to be tolerable, especially if taken with food because administration with food appears to reduce both the incidence and severity of GI-related TEAEs, such as nausea and upper GI pain.

The onset of nausea in the healthy volunteer study was rapid (between 30 to 120 minutes), generally lasted 2 to 8 hours, and was mild nature at doses ≤4.5 mg/kg (lower dose). These potential AEs of nausea, upper GI pain, and emesis are easily monitorable and are self-limited if dosing is stopped. Furthermore, following qd dosing for 7 days in fed healthy volunteers, steady state was achieved before Day 7. Exposure (AUC) in healthy volunteers increased in a near dose-proportional manner (a 4.1-fold increase for a 4.5-fold change in dose [see Section 4.2.3.1]), and the mean exposure (AUC from time 0 to 24 hours [AUC$_{0\text{-}24}$]) at 4.5 mg/kg on Day 7 was 26.3 µg•h/mL, which is approximately 3.3-fold below the Week 39 exposure (AUC$_{0\text{-}24}$) in the female dog (most conservative species/gender) at the respective NOAEL in the repeat-dose toxicology study. Even for the higher dose arm of up to 6.7 mg/kg (assumed to be equivalent to approximately a 400 mg dose), the predicted Day 1 exposure is 32.0 µg•h/mL, which is

approximately 2.7-fold below the Week 39 exposure (AUC_{0-24}) in the female dog (most conservative species/gender). PK plotting (e.g., concentration at 24 hours after study drug administration [C_{24}]) predicted that higher exposure to IMR-687 should result in drug concentration levels above the estimated concentration at which inhibition is 90% (IC_{90}) for approximately 22 hours at a 300-mg dose and more than 24 hours at a 400-mg dose. This possible IC_{90} advantage with respect to inhibition of the target, PDE9, further supports evaluating both the lower and higher doses of IMR-687 and specifically doses of up to 6.7 mg/kg, which can provide adequate target coverage to potentially improve clinical benefit.

Independent Data Monitoring Committee Oversight

This study initially imposed a minimum weight threshold of 45 kg and a 67-kg weight gate for tablet strength to ensure that subjects in the lower dose IMR-687 group received a dose equating to no more than the 4.5 mg/kg evaluated in the MAD part of the healthy volunteer study. Subsequently, the Data Monitoring Committee (DMC) approved the opening of enrollment in the higher dose IMR-687 group (up to 6.7 mg/kg). Having established safety and tolerability of the lower dose, the DMC also approved a change in weight gate to 60 kg and the resultant modified dose range of up to 5.0 mg/kg in the lower dose group (with the minimum weight threshold of 45 kg unchanged). Starting from Protocol Version 5.0, subjects in the IMR-687 lower dose group will receive ≥3.4 to ≤5.0 mg/kg and subjects in the higher dose group will receive >5.0 to ≤6.7 mg/kg; no subject will receive more than 6.7 mg/kg. Under Protocol Version 4.0, the exposure ranges were ≥3.0 to ≤4.5 mg/kg in the lower dose group and >4.5 to ≤6.7 mg/kg in the higher dose group. Therefore, the overall exposure ranges during the course of the study are ≥3.0 to ≤5.0 mg/kg and >4.5 to ≤6.7 mg/kg and are presented as such hereafter.

For this first study evaluating IMR-687 in subjects with β-thalassemia, the DMC has noted some of the related pathology that is shared with patients who have SCD. The shared manifestations include chronic anemia, fatigue, delayed growth, cerebral ischemia, splenomegaly, gallstones, pulmonary hypertension, and leg ulcers. In the phase 2a study in adult subjects with SCD (IMR-SCD-102), IMR-687 has been shown to be well tolerated, with initial evidence of PD effects. The DMC has reviewed interim results from this study and is supportive of the dose exposure and duration of treatment in this first β-thalassemia study.

5.2. Benefit/Risk Assessment

IMR-687 is currently being investigated for the treatment of SCD as its primary indication. It is anticipated that it will differ from established therapy (i.e., HU) in maintaining a similar or improved efficacy profile, while having a much-improved safety profile, without myelosuppression or a mutagenicity/carcinogenicity risk.

Consequently, the frequent monitoring of blood counts required for patients who use HU would not be required for IMR-687. The proposed exposure in this study is between ≥3.0 to ≤5.0 mg/kg (lower dose) daily and, following DMC approval, >4.5 to ≤6.7 mg/kg (higher dose) daily; these exposures are anticipated to be in the pharmacologically active range based on available nonclinical and clinical data (see Section 5.1 for dose selection rationale). Based on the observed safety and tolerability of IMR-687 in the first-in-human study (Section 4.2.3.1) and subsequent study in SCD subjects, these dose levels should be tolerable and may have a clinically beneficial PD effect in subjects with β-thalassemia.

Based on the data from healthy volunteers and SCD subjects to date, IMR-687 is considered to be safe and well tolerated with the most common side effects being sickle cell anemia with crisis, abdominal pain, nausea, headache, indigestion, diarrhea/loose stools, and influenza-like illness which are mild and easily managed. Newly emerging safety data will be updated in the Investigator Brochure's (IB) and Informed Consent Form (ICF). The potential benefits and risks are summarized below.

5.2.1. Potential Benefits

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. As in SCD, 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. Like in SCD, infants with β-thalassemia major do not present clinical symptoms of their disorder until age 6 to 24 months, and sometimes later, when their HbF is replaced by mutated adult Hb. Natural history data show that patients with β-thalassemia who have high HbF levels, due to hereditary persistence of HbF, have less severe forms of the disorder. In addition, genetic variations associated with increased HbF production have been shown to correlate with reduced β-thalassemia severity (Borgna-Pignatti 2010).

5.2.2. Potential Risks

The potential risks of IMR-687 are inferred from the relevant nonclinical findings and the results of the first-in-human study in healthy volunteers (IMR-SCD-101) and the interim analysis from the phase 2a study (IMR-SCD-102). These potential risks are briefly summarized in the sections below. Further details are provided in the Investigator's Brochure.

5.2.2.1. Gastrointestinal

Based on the observed incidence of nausea in healthy volunteers in the first-in-human study, oral administration of IMR-687 may result in nausea within the first several hours of dosing. Nausea observed thus far was transient and self-limited. A dose-limiting toxicity of emesis occurred at 6 mg/kg when IMR-687 was administered in the fasted state. Oral administration of study drug with food significantly reduced the incidence and severity of the nausea TEAE. No correlated changes in liver function tests were observed in any healthy volunteers administered IMR-687, or specifically in those subjects with nausea, with or without emesis.

5.2.2.2. Central Nervous System

Mild headaches (self-limited or treatable with acetaminophen) were observed in the first-in-human study in healthy normal volunteers and appeared to occur with nausea. Headaches were also observed in the phase 2a study and as of the interim analysis, 21.4% of subjects had reported a TEAE of headache. Oral administration of study drug with food significantly reduced the incidence and severity of the headache TEAE.

5.2.2.3. Cardiovascular

In nonclinical safety pharmacology and 14-day GLP toxicology studies in beagle dogs, IMR-687 appeared to result in increases in heart rate that did not appear to be dose dependent. In the safety pharmacology study in dogs, at doses of 75 mg/kg, statistically significant changes in heart rates were observed. In the 14-day toxicology study in dogs, the highest heart rates were noted at the highest dose level of 75 mg/kg but did not reach statistical significance. In a subsequent 9-month study in dogs at doses up to and including 50 mg/kg/day, there was no evidence of any increases in heart rate and there were no histopathological abnormalities noted in cardiac tissue. In healthy volunteers in the first-in-human study, at doses between 0.3 to 6 mg/kg, sporadic observations of sinus tachycardia (i.e., heart rates >100 bpm) occurred in various subjects, including a subject in the MAD on placebo. The contribution of concomitant AEs such as headache to the rise in heart rate could not be excluded. No dose dependency or dose-duration dependency was noted for these heart rate observations. No signs of prolongation of corrected QT interval, Fridericia's formula (QTcF) were noted in any cohort of healthy volunteers at any dose of IMR-687. In the interim safety analysis of Study IMR-SCD-102, with respect to vital signs, there were no observable changes in systolic, diastolic blood pressure and pulse, and there were no changes in respiratory rate. In the IMR-SCD-102 clinical study, the mean interim steady state AUC_{0-24} was 16,300 ng•hr/mL for the 200 mg (~2.9 mg/kg) IMR-687 dose level. In the 39-week dog toxicology study mentioned above, mean AUC_{0-24} was ≥87,500 ng•hr/mL at the NOAEL in female dogs, resulting in safety margins of at least ~5.3-fold for the 200 mg clinical dose.

Monitoring of vital signs is recommended for subjects in IMR-687 studies. In the event of noted persistent and/or clinically significant tachycardia, other causes of tachycardia, particularly pain and dehydration, should also be considered.

5.2.3. Potential Interactions

In vitro studies indicate that IMR-687 is not expected to competitively inhibit the major human cytochrome P450 (CYP) enzymes, including CYPs 3A4, 2D6, 2C9, 2C19, 2C8, 1A2, and 2B6. IMR-687 does have the potential for induction of CYP3A4/5 (in vitro EC50 = 32.4 to 133 μM) and other drug metabolizing enzymes whose expression levels are also controlled by the pregnane X receptor (PXR). In addition, IMR-687 has been shown to primarily be a CYP3A4 substrate (K_m = 127 μM); IMR-687 may be at least partially cleared as unchanged drug.

After oral administration, concentrations of IMR-687 at the target exposure of ≥3.0 to ≤5.0 mg/kg for the lower dose or >4.5 to ≤6.7 mg/kg for the higher dose may reach sufficient exposure in the gastric mucosa and/or the liver (during absorption) to induce (upregulate) CYP3A4 and/or CYP3A5 protein expression in these organs.

Induced expression levels of CYP3A4 and CYP3A5 may not return to baseline levels until after discontinuation of IMR-687 dosing, which is likely to require approximately 1 week of washout due to the CYP3A protein half-life. Consequently, if a subject in this study is started on a medication that is primarily metabolized (and cleared) by CYP3A4/5, the subject should be followed appropriately to determine if the exposure to the concomitant medication is maintained at levels sufficient for efficacy. For example, if a subject is started on oxycodone for pain management or ondansetron for nausea, symptom resolution should be followed to determine if

higher doses of either medication are required to reach target outcomes, as co-administration of IMR-687 may result in a reduction in the overall exposure to oxycodone or ondansetron.

In addition, because IMR-687 is expected to be at least partially cleared by CYP3A4-mediated metabolism, a drug interaction could also result from co-administration of other concomitant medications, like oxycodone or ondansetron, that at least partially (or solely) rely on CYP3A4-mediated metabolism for their in vivo clearance. The underlying mechanism for this would be in vivo competition for CYP3A4 metabolism in the gastric mucosa and/or the liver. In this case, exposure increases in IMR-687 and/or the CYP3A-dependent concomitant drug(s) may occur. CYP3A competition could also result in exposure changes for active circulating metabolites that contribute to the overall efficacy. Finally, co-administration of CYP3A selective inhibitors, such as ketoconazole, should be avoided as this may increase the exposure of IMR-687.

It should be noted that there are examples of drugs that primarily rely on polymorphic CYPs (e.g., CYP2C19, CYP2D6) for their in vivo metabolism and/or clearance. In poor metabolizers, drug exposure may increase, and often other drug metabolizing enzymes then play an increased role in drug clearance. As a consequence, CYP3A4-mediated clearance may become more prominent in poor metabolizers. One example of this is cimetidine, which relies on CYP2C19 and/or CYP3A4/5 for its in vivo clearance. Caution should also be employed in administering such drugs with IMR-687.

CYP3A4/5-mediated drug-drug interactions (DDIs) are the largest group of clinically relevant metabolism-mediated interactions. In addition, CYP3A4/5-mediated drug interactions produce the largest magnitude changes in exposure for the victim drug. Moderate inhibitors can result in a 2- to 5-fold increase in exposure, while strong inhibitors may produce a 5-fold increase or greater. Sensitive CYP3A substrates can have at least a 5-fold change (or up to an approximately 240-fold change) in systemic exposure due to a CYP3A-mediated drug interaction. Moderate inducers can result in up to a 50% reduction in exposure, while strong inducers may cause exposure loss of up to 80% (or more). In the case of strong inducers, a 400% increase in clearance may occur. It should be noted that there are some drugs for which a formal clinical DDI assessment is not feasible because increased exposure may lead to SAEs such as death (e.g., fentanyl, paclitaxel). In instances such as these, it may be difficult to assess the potential for a CYP3A4-mediated DDI; however, these drugs generally have significant warnings on the front page of the corresponding package inserts. It is recommended that all warnings in the product package insert should be considered prior to concomitant use with IMR-687.

As IMR-687 is also a substrate of P-gp (K_m >500 µM) as well as a substrate of BCRP (K_m = 44.5 µM) and an inhibitor of BCRP (IC50 = 32.5 µM), co-administration of substrates or inhibitors of P-gp and BCRP should also proceed with caution. It should be noted that sometimes CYP3A4/5 substrates are also P-gp substrates just as IMR-687 is a substrate for both.

See the Appendix 3 references for a list of in vivo CYP3A-sensitive substrates, inhibitors of CYP3A probes, and inducers of CYP3A probes; a list of in vivo inhibitors of P-gp probes; and a list of in vivo inducers of CYP3A probes from published drug interactions. Currently there are no such listings for BCRP.

Finally, an earlier nonclinical (rat) study suggested the potential for co-administration of IMR-687 to decrease the exposure of HU when IMR-687 was administered at a supratherapeutic dose (HED ~40 mg/kg/day) and HU was administered at a therapeutic dose (HED

~10 mg/kg/day). In the absence of knowing the exact mechanism for HU clearance in rats or humans, it was unclear whether or not this observation would have clinical implications. However, an interim IMR-SCD-102 analysis found that 100 mg IMR-687 dosed qd had no notable impact on HU exposure for daily HU doses ranging from 500 to 1500 mg. In addition, PK was comparable for IMR-687 when administered as monotherapy or in combination with HU, implying no notable impact of HU on IMR-687 exposure.

The anti-platelet and anti-coagulant drugs with a **high** potential for a clinically relevant DDI include direct acting oral anti-coagulants (DOACs) apixaban, dabigatran, rivaroxaban, edoxaban, and ticagrelor, as well as the Vitamin K antagonist warfarin, based on published clinical drug interaction studies. This is due to their dependence on CYP3A4/5 and/or P-gp for in vivo clearance (e.g., the DOACs) or their limited therapeutic window (warfarin). Ticagrelor is a sensitive CYP3A substrate, i.e., there are published drug interactions with >7-fold changes in ticagrelor exposure when co-administered with strong CYP3A inhibitors or inducers.

The anti-platelet and anti-coagulant drugs with an **intermediate** potential (40% to 50% change in exposure) for a clinically relevant drug-drug interaction include rivaroxaban, dabigatran etexilate, and apixaban. Caution should be applied in the co-administration of IMR-687 and these drugs to ensure that anti-platelet and anti-coagulant activities are not compromised.

Caution may be required with co-administration of IMR-687 and clopidogrel. Co-administration of clopidogrel with danshen (herbal supplement; CYP3A induction possible) resulted in a 49% loss of clopidogrel exposure, and IMR-687 is a potential CYP3A inducer.

The anti-platelet and anti-coagulant drugs with a **low** potential for a clinically relevant DDI include heparin, enoxaparin, fondaparinux, prasugrel, dipyridamole, ticlopidine, and eptfibatide.

New DDIs are continually being discovered and published. Questions that are not fully addressed by the references in Appendix 3 should be directed to the medical monitor or may be addressed by review of the relevant package insert and prescribing information for the proposed concomitant medication. If there is any question as to whether a substance is permitted, please consult the medical monitor and/or sponsor.

See also Section 9.7.2 on prohibited concomitant medications/therapies.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Primary Objective

The primary objective of this study in both Population 1 (TDT) and Population 2 (NTDT) is to assess the safety and tolerability of IMR-687 in adult subjects with β-thalassemia.

6.2. Secondary Objectives

6.2.1. Population 1: Transfusion-dependent β-Thalassemia

The secondary objectives in TDT subjects are:

- To evaluate the effect of IMR-687 versus placebo on reduction in RBC transfusion burden.
- To evaluate the effect of IMR-687 versus placebo on the change in iron overload.
- To characterize the PK profile of IMR-687 and collect data for population PK analysis.

6.2.2. Population 2: Non-transfusion-dependent β-Thalassemia

The secondary objectives in NTDT subjects are:

- To evaluate the effect of IMR-687 versus placebo on anemia (as defined by total hemoglobin).
- To evaluate the effect of IMR-687 versus placebo on HbF.
- To evaluate the effect of IMR-687 versus placebo on the change in iron overload.
- To characterize the PK profile of IMR-687 and collect data for population PK analysis.

6.3. Exploratory Objectives

6.3.1. Population 1: Transfusion Dependent β-Thalassemia

The exploratory objectives in TDT subjects are:

- To characterize the PD profile of IMR-687 versus placebo with respect to erythropoiesis, iron metabolism, and hemolysis.
- To evaluate the effect of IMR-687 versus placebo on the proportion of subjects who are transfusion independent.
- To evaluate the effect of IMR-687 versus placebo on time to and duration of reduction in RBC transfusion burden.
- To evaluate the effect of IMR-687 versus placebo on functional and health-related QoL.
- To evaluate responses to IMR-687 per genotypes in subjects with TDT.

6.3.2. Population 2: Non-transfusion Dependent β-Thalassemia

The exploratory objectives in NTDT subjects are:

- To characterize the PD profile of IMR-687 versus placebo with respect to erythropoiesis, iron metabolism, and hemolysis.
- To evaluate the effect of IMR-687 versus placebo on functional and health-related QoL.
- To evaluate the effect of IMR-687 versus placebo on β-thalassemia-related symptoms and severity.
- To evaluate responses to IMR-687 per genotypes in subjects with of NTDT.

6.4. Endpoints

The objectives will be assessed by the endpoints described in Table 1 in the indicated populations.

Table 1: Study Endpoints

Primary Endpoint	**TDT**	**NTDT**
IMR-687 safety and tolerability as measured by: • Incidence and severity of adverse events and serious adverse events • Observed values and changes from baseline in 12-lead ECG parameters, clinical laboratory tests (chemistry, hematology, coagulation, urinalysis), and vital signs for any timepoint • Physical examination findings • Use of concomitant medications and therapies	X	X
Secondary Endpoints	**TDT**	**NTDT**
Proportion of subjects with a ≥20% hematological improvement (as measured by reduced transfusion burden)[a] from Week 12 to Week 24 and Week 24 to Week 36, compared to the 12 weeks prior to Baseline (Day 1).	X	
Proportion of subjects with a ≥20% hematological improvement (as measured by reduced transfusion burden)[a] from Week 12 to Week 36, compared to the 12 weeks prior to Baseline (Day 1).	X	
Proportion of subjects with a ≥33% hematological improvement (as measured by reduced transfusion burden)[a] from Week 12 to Week 24 and Week 24 to Week 36, compared to the 12 weeks prior to Baseline (Day 1).	X	
Proportion of subjects with a ≥33% hematological improvement (as measured by reduced transfusion burden)[a] from Week 12 to Week 36, compared to the 12 weeks prior to Baseline (Day 1).	X	
Mean number of transfusion events from baseline to Week 36.	X	

Secondary Endpoints (continued)	TDT	NTDT
The plasma PK profile of IMR-687 (and metabolites) after administration to subjects will be evaluated by determination of PK parameters (e.g., C_{max}, t_{max}, $t_{½}$, and AUC_{0-24}) and population PK, based on drug concentration levels in plasma obtained over time.	X	X
Mean change from baseline to Week 36 for iron chelation therapy daily dose and serum ferritin.	X	X
Proportion of subjects with an increase from baseline of ≥1.0 g/dL in mean Hb values at Weeks 12 to 24 and Weeks 24 to 36 in the absence of transfusions.		X
Mean change from baseline in mean Hb values at Weeks 12 to 24 and Weeks 24 to 36 in the absence of transfusions.		X
Mean change from baseline in mean HbF values at Weeks 12 to 24 and Weeks 24 to 36 in the absence of transfusions.		X
Proportion of subjects with an increase from baseline of ≥3% in mean HbF values at Weeks 12 to 24 and Weeks 24 to 36 in the absence of transfusions.		X
Exploratory Endpoints	**TDT**	**NTDT**
The PD effects of IMR-687 from baseline to Week 36, as measured by the mean change from baseline in serum PD markers of erythropoiesis, iron metabolism, and hemolysis.	X	X
Mean change in transfusion burden expressed as either units of RBCs or mL/kg as a continuous variable during Week 12 to Week 24, Week 24 to Week 36, and Week 12 to Week 36, compared to the 12 weeks prior to Baseline (Day 1).	X	
The proportion of subjects who are transfusion independent for ≥8 weeks during treatment.	X	
Mean change from baseline in TranQOL quality of life tool at Weeks 12, 24, and 36.	X	
Mean change from baseline in SF-36 quality of life tool at Weeks 12, 24, and 36.	X	X
Pharmacogenomic analyses of genes that may affect treatment response (including α-globin, gamma-globin *XmnI* polymorphism, and BLC11A).	X	X
Proportion of subjects who have an Hb increase of ≥1.0 g/dL from baseline for ≥14 days in the absence of RBC transfusions.		X
Proportion of subjects who are RBC transfusion-free over 36 weeks and other variables of transfusion burden.		X
Duration of the mean Hb increase from baseline of ≥1.0 g/dL over 36 weeks.		X

Exploratory Endpoints (continued)	TDT	NTDT
Proportion of subjects who have an increase from baseline ≥1.5 g/dL in mean of Hb values at Week 24 and Week 36 compared to baseline in the absence of transfusions.		X
Mean change from baseline in NTDT-PRO score over a continuous 12-week interval from Week 12 to Week 24 and Week 24 to Week 36.		X
Mean change from baseline in NTDT-PRO domain total score at Week 24.		X
Mean change in biomarkers from baseline to Week 36, stratified by genotype.	X	X

AUC = area under the concentration-time curve; AUC_{0-24} = AUC from time 0 to 24; C_{max} = maximum plasma concentration; ECG = electrocardiogram; Hb = hemoglobin; HbF = fetal hemoglobin; LDH = lactate dehydrogenase; NTDT = non-transfusion dependent β-thalassemia; NTDT-PRO = non-transfusion dependent β-thalassemia patient reported outcome; PD = pharmacodynamics; PK = pharmacokinetics; pRBC = packed red blood cells; PRO = patient-reported outcome; RBC = red blood cell; SF-36 = Short Form (36) Health Survey; $t_{½}$ = half-life; t_{max} = time to maximum plasma concentration; TDT = transfusion dependent β-thalassemia; TranQOL = transfusion-dependent quality of life.

[a] Hematological improvement is defined as a reduction in pRBC units (transfusion burden) with reduction of at least 2 units of RBCs, compared to the 12 weeks prior to Baseline (Day 1).

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a phase 2 randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, PK, and PD of IMR-687 (PDE9 inhibitor) administered qd for 36 weeks in 2 populations of adult subjects with β-thalassemia: Population 1 (TDT subjects) and Population 2 (NTDT subjects). A schematic of the study is provided in Figure 1.

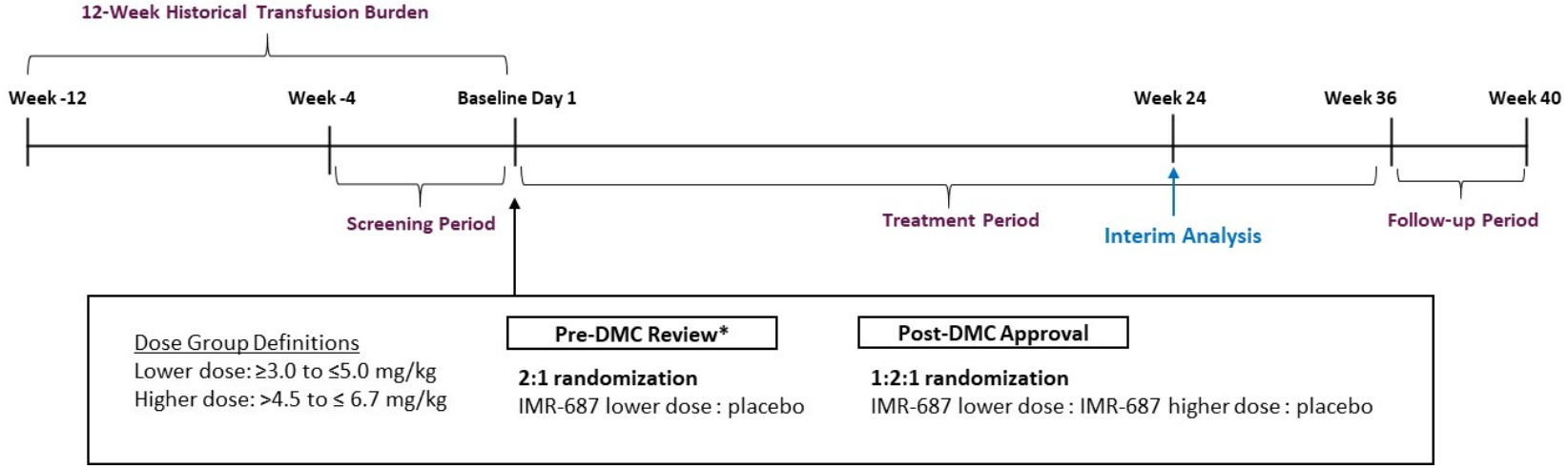
This study will enroll approximately 120 subjects with β-thalassemia (60 subjects with TDT and 60 subjects with NTDT), aged 18 through 65 years. This study consists of a retrospective data collection period, a screening period, a double-blind treatment period, and safety follow-up period. During the screening period of up to 28 days, subjects will provide informed consent and be evaluated on eligibility criteria as stated in Section 8.1 and Section 8.2.

Subjects will receive either IMR-687 (lower dose [≥3.0 to ≤5.0 mg/kg] or higher dose [>4.5 to ≤6.7 mg/kg]; the precise exposure ranges for different groups of subjects are dependent on the weight gate for tablet strength as summarized in Section 5.1) 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. During study conduct under Protocol Version 4.0, the DMC approved the opening of enrollment in the higher dose IMR-687 group, which went into effect on 01 February 2021.

Subjects will return to the investigational site at Week 1 for a safety assessment, and qualified site personnel will contact the subject by telephone at Week 2 to capture potential AEs and concomitant medications. Subjects will be seen at the investigational site approximately every 3 weeks (TDT subjects) or every 4 weeks (NTDT subjects) throughout the remainder of the study. Safety will be monitored throughout the study, and PK, PD, QoL, and clinical outcome measures will be performed at the visits shown in the schedule of assessments for the TDT and NTDT populations (Table 2 and Table 3, respectively).

The informed consent will specifically indicate that data will be retrospectively collected on transfusion burden, defined as the dates of transfusion events and the number of packed red blood cell (pRBC) units per event during the 12 weeks preceding the Baseline (Day 1) visit. If available, the following data should also be collected for each transfusion event: volume and hematocrit of each pRBC unit, pre-transfusion Hb, and pre-transfusion weight.

Figure 1: Overview of Study Design and Dose Groups



DMC = data monitoring committee

* Prior to the introduction of IMR-687 higher dose, the DMC will review safety data for at least 5 subjects who received IMR-687 lower dose. If the DMC recommends inclusion of the higher dose, randomization across 3 dose groups will then proceed as shown. The DMC may request additional data and/or meeting(s) in order to make its recommendations. During study conduct under Protocol Version 4.0, the DMC approved the opening of enrollment in the higher dose IMR-687 group, which went into effect on 01 February 2021. Refer to Section 5.1 for additional details on the dose groups.

Table 2: Schedule of Assessments: Population 1 (TDT β-Thalassemia)

	Screening	Baseline	Double-blind, Placebo-controlled Treatment													EOT[a] / ET	End of Study (Safety FU)
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
Study Week(s)	**-4 to 0**	**NA**	**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27**	**30**	**33**	**36**	**40**
Study Day(s)	**-28 to -1**	**1[b]**	**7 ±2**	**14 ±2**	**21 ±7**	**42 ±7**	**63 ±7**	**84 ±7**	**105 ±7**	**126 ±7**	**147 ±7**	**168 ±7**	**189 ±7**	**210 ±7**	**231±7**	**252±7**	**280±7**
On-site visits	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Telephone visits[c]				X													
Informed consent	X																
PGx ICF and blood draw (optional)[d]	X																
Demographic information	X																
Medical/disease history[e]	X																
Inclusion/exclusion criteria	X	X															
ECOG score	X																
Clinically indicated virology (Hep A, B, and C and HIV)	X																
Historical transfusion burden[f]	X	X															
Randomization		X															
Vital signs[g]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X

Table 2: Schedule of Assessments: Population 1 (TDT β-Thalassemia) (Continued)

	Screening	Baseline	Double-blind, Placebo-controlled Treatment													EOT[a] / ET	End of Study (Safety FU)
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
Study Week(s)	**-4 to 0**	**NA**	**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27**	**30**	**33**	**36**	**40**
Study Day(s)	**-28 to -1**	**1[b]**	**7 ±2**	**14 ±2**	**21 ±7**	**42 ±7**	**63 ±7**	**84 ±7**	**105 ±7**	**126 ±7**	**147 ±7**	**168 ±7**	**189 ±7**	**210 ±7**	**231±7**	**252±7**	**280±7**
Height	X																
Transfusion burden[h]					X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[i]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG[j]	X	X	X		X	X		X		X		X		X		X	X
Hematology and Chemistry	X	X	X		X	X		X		X		X		X		X	X
Coagulation studies	X							X				X				X	
Urinalysis	X	X			X			X				X				X	
Pregnancy testing[k]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Specialty hematology[l]	X	X			X			X		X		X		X		X	
PD markers[m]	X	X			X			X		X		X				X	
IMR-687 plasma PK[n]		X	X		X							X				X	
QOL assessments[o]		X						X				X				X	
Study drug dispensing		X			X	X	X	X	X	X	X	X	X	X	X		
Study drug admin at site[p]		X	X		X	X		X		X		X		X		X	
Study drug admin		Oral administration of IMR-687 or placebo qd															
AEs and concomitant medications	Continuous[q]																

AE = adverse event; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ET= early termination; EOT = end of treatment; FU = follow-up; Hb = hemoglobin; HbF = fetal hemoglobin; HIV = human immunodeficiency virus; hsCRP = highly sensitive C-reactive protein; ICAM-1 = intercellular adhesion molecule 1;

ICF = informed consent form; NT-proBNP = N-terminal pro B-type natriuretic peptide; PD = pharmacodynamics; PE = physical examination; PGx = pharmacogenomics; PK = pharmacokinetic; pRBC = packed red blood cells; QOL = quality of life; SD = standard deviation; SF-36 = Short Form (36) Health Survey; TEAE = treatment-emergent adverse event, TIBC = total iron binding capacity; TranQOL = Transfusion-dependent QoL Questionnaire; VCAM-1 = vascular cell adhesion molecule 1.

Note: Unless otherwise specified, all assessments should be completed prior to dosing at any given timepoint.

Note: Unscheduled visits may occur, limited to visits resulting from potential TEAEs, drug dispensation, or other urgent study-related procedures

a The last day of dosing will be at Week 36 visit; subject should consume their last dose of study drug on site, after pre-dose assessments have been completed. The Week 36 visit will also be the ET visit. During the study visit, assessments should be collected from any subject who discontinues study drug or study prematurely. Early termination visits will have the same procedures as the Week 36 visit, except that study drug will not be administered and trough PK will not be collected.

b The first day study drug is taken is considered Baseline (Day 1). Day 1 assessments should be performed prior to study drug administration. If a subject requires a transfusion on this day, the transfusion may occur only after all study assessments are completed.

c Qualified site personnel will contact the subject by telephone at Week 2 to capture potential TEAEs and concomitant medications. Subjects will also be reminded of compliance with drug and the next visit schedule. If any AEs of significant clinical concern are identified during the telephonic visit, the subject will be requested to come into the site to be assessed.

d Pharmacogenomic evaluation is optional and may be performed at screening if subject provides informed consent.

e Disease history should contain a confirmed diagnosis of β-thalassemia or hemoglobin E/β-thalassemia. Concomitant alpha gene deletion, duplication, or triplication is allowed.

f After obtaining signed informed consent, the subject's transfusion history for the 12 weeks prior to Baseline (Day 1) visit date should be recorded. In order to be eligible for the study, the dates of transfusion events and the number of pRBC units per event within the 12 weeks prior to the Baseline (Day 1) visit must be available. If available, the following data should also be collected for each transfusion event: volume and hematocrit of each pRBC unit, pre-transfusion Hb, and pre-transfusion weight.

g Vital signs include heart rate, respiratory rate, blood pressure, and body temperature. At Day 1 and Week 3, vital signs will be taken pre-dose and 2 hours (± 20 minutes) post-dose, during the PK assessments. At all other timepoints, vital signs can be taken irrespective of taking study drug. Vital signs should be consistently measured in either the sitting or semi-supine position.

h Transfusion burden will be assessed using the following variables: dates of transfusion events, number of pRBC units per event, volume and hematocrit of each pRBC unit, pre-transfusion Hb, and pre-transfusion weight.

i Complete PEs will be performed at Screening, Week 24, and Week 36 and will include 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.

j All ECGs to be performed in triplicate. At Baseline and Week 3, ECGs will be obtained at pre-dose and 2 hours (±30 minutes) post-dose. At all other timepoints, ECGs will be taken pre-dose.

k Females of childbearing potential only. A serum pregnancy test will be performed at screening via a central laboratory; all subsequent tests will be urine performed locally (with test kits provided by the central laboratory).

l Includes HbF and percent F cells. Blood samples should be obtained prior to administration of study drug.

m Includes serum ferritin, soluble transferrin receptor, hepcidin-25, haptoglobin, E-selectin, P-selectin, ICAM-1, VCAM-1, hsCRP, serum NT-proBNP, serum iron and TIBC for calculated transferrin saturation, and erythropoietin. Blood samples should be obtained prior to administration of study drug. PD markers will need to be collected prior to RBC transfusion (if applicable).

n At Baseline and Week 3, serial blood samples for IMR-687 and concentrations of metabolite(s) will be drawn pre-dose (within 30 minutes) and at 15 minutes (±5 minutes), 30 minutes (±5 minutes), and 3 hours (±20 minutes) after administration of study drug. A trough blood sample will be drawn pre-dose at Week 1, Week 24, and Week 36. The date/time of the previous dose will be recorded. If a subject requires a transfusion on the day of a PK draw, the transfusion can only be performed after the final PK sampling. For ET visits, a trough blood sample will not be collected.

o Quality of life assessments will be assessed by the TranQOL and SF-36 QoL tools. The QoL assessments will be administered at Baseline and at Weeks 12, 24, and 36. Baseline QoL assessments should be completed before administration of study drug.

p On days when study drug is taken in the clinic, food details will also be recorded.

q Adverse events and concomitant medications, including iron chelation therapy and hydroxyurea use, will be recorded at each visit throughout the study from Screening (after signing the ICF) through the end of study visit (Week 40).

Table 3: Schedule of Assessments: Population 2 (NTDT β-Thalassemia)

	Screening	Baseline	Double-blind, Placebo-controlled Treatment										EOT[a] / ET	End of Study (Safety FU)
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Study Week(s)	**-4 to 0**	**NA**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**
Study Day(s)	**-28 to -1**	**1[b]**	**7±2**	**14±2**	**28±5**	**56±7**	**84±7**	**112±7**	**140±7**	**168±7**	**196±7**	**224±7**	**252±7**	**280±7**
On-site visits	X	X	X		X	X	X	X	X	X	X	X	X	X
Telephone visits[c]				X										
Informed consent	X													
PGx ICF and blood draw (optional)[d]	X													
Demographic information	X													
Medical/disease history[e]	X													
Inclusion/exclusion criteria	X	X												
ECOG score	X													
Clinically indicated virology (Hep A, B, and C and HIV)	X													
Historical transfusion burden[f]	X	X												
Randomization		X												
Vital signs[g]	X	X	X		X	X	X	X	X	X	X	X	X	X
Weight	X	X	X		X	X	X	X	X	X	X	X	X	X
Height	X													
Transfusion burden[h]					X	X	X	X	X	X	X	X	X	X

Table 3: Schedule of Assessments: Population 2 (NTDT β-Thalassemia) (Continued)

	Screening	Baseline	Double-blind, Placebo-controlled Treatment										EOT[a] / ET	End of Study (Safety FU)
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Study Week(s)	**-4 to 0**	**NA**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**
Study Day(s)	**-28 to -1**	**1[b]**	**7±2**	**14±2**	**28±5**	**56±7**	**84±7**	**112±7**	**140±7**	**168±7**	**196±7**	**224±7**	**252±7**	**280±7**
Physical examination[i]	X	X	X		X	X	X	X	X	X	X	X	X	X
12-Lead ECG[j]	X	X	X		X	X	X	X	X	X	X	X	X	X
Hematology and chemistry	X	X	X		X	X	X	X	X	X	X	X	X	X
Coagulation studies	X						X			X			X	
Urinalysis	X	X			X		X			X			X	
Pregnancy testing[k]	X	X	X		X	X	X	X	X	X	X	X	X	X
Specialty hematology[l]	X	X			X		X			X			X	
PD markers[m]	X	X			X		X			X			X	
IMR-687 plasma PK[n]		X	X		X					X			X	
QOL assessments[o]		X					X			X			X	
Study drug admin at site[p]		X	X		X	X	X	X	X	X	X	X	X	
Study drug dispensing		X			X	X	X	X	X	X	X	X		
Study drug admin		Oral administration of IMR-687 or placebo qd												
AEs and concomitant medications	Continuous[q]													

AEs = adverse events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ET= early termination; EOT = end of treatment; FU = follow-up; Hb = hemoglobin; HIV = human immunodeficiency virus; hsCRP = highly sensitive C-reactive protein; ICAM-1 = intercellular adhesion molecule 1; ICF = informed consent form; NTDT-PRO = non-transfusion dependent β-thalassemia patient reported outcome; NT-proBNP = N-terminal pro B-type natriuretic peptide; PD = pharmacodynamics; PE = physical examination; PGx = pharmacogenomics; PK = pharmacokinetic; pRBC = packed red blood cells; QOL = quality of life; RBC = red blood cell; SD = standard

deviation; SF-36 = Short Form (36) Health Survey; TEAE = treatment-emergent adverse event; TIBC = total iron binding capacity; VCAM-1 = vascular cell adhesion molecule 1.

Note: Unless otherwise specified, all assessments should be completed prior to dosing at any given timepoint.

Note: In the case of a subject receiving a transfusion after signing the ICF, but prior to randomization, the investigator would inform the medical monitor. The intent is to avoid transfusions within the 2-week period leading to randomization. Approval could be obtained for the screening period to be extended by a maximum of 14 days.

Note: Unscheduled visits may occur, limited to visits resulting from potential TEAEs, drug dispensation, or other urgent study-related procedures.

a The last day of dosing will be at Week 36 visit; subject should consume their last dose of study drug on site, after pre-dose assessments have been completed. The Week 36 visit will also be the ET visit. During the study visit, assessments should be collected from any subject who discontinues study drug or study prematurely. Early termination visits will have the same procedures as the Week 36 visit, except that study drug will not be administered and trough PK will not be collected.

b The first day study drug is taken is considered Baseline (Day 1). Day 1 assessments should be performed prior to study drug administration. If a subject requires a transfusion on this day, the transfusion may occur only after all study assessments are completed.

c Qualified site personnel will contact the subject by telephone at Week 2 to capture potential TEAEs and concomitant medications. Subjects will also be reminded of compliance with drug and the next visit schedule. If any AEs of significant clinical concern are identified during the telephonic visit, the subject will be requested to come into the site to be assessed.

d Pharmacogenomic evaluation is optional and may be performed at screening if subject provides informed consent.

e Disease history should contain a confirmed diagnosis of β-thalassemia or hemoglobin E/β-thalassemia. Concomitant alpha gene deletion, duplication, or triplication is allowed.

f After obtaining signed informed consent, the subject's transfusion history for the 12 weeks prior to Baseline (Day 1) visit date should be recorded. In order to be eligible for the study, the dates of transfusion events and the number of pRBC units per event within the 12 weeks prior to the Baseline (Day 1) visit must be available. If available, the following data should also be collected for each transfusion event: volume and hematocrit of each pRBC unit, pre-transfusion Hb, and pre-transfusion weight.

g Vital signs include heart rate, respiratory rate, blood pressure, and body temperature. At Day 1 and Week 4, vital signs will be taken pre-dose and 2 hours (± 20 minutes) post-dose, during the PK assessments. At all other timepoints, vital signs can be taken irrespective of taking study drug. Vital signs should be consistently measured in either the sitting or semi-supine position.

h Transfusion burden will be assessed using the following variables: dates of transfusion events, number of pRBC units per event, volume and hematocrit of each pRBC unit, pre-transfusion Hb, and pre-transfusion weight.

i 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.

j All ECGs to be performed in triplicate. At Baseline and Week 4, ECGs will be obtained at pre-dose and 2 hours (±30 minutes) post-dose. At all other timepoints, ECGs will be taken pre-dose.

k Females of childbearing potential only. A serum pregnancy test will be performed at screening via central laboratory; all subsequent tests will be urine performed locally (with test kits provided by the central laboratory).

l Includes HbF and percent F cells. Blood samples should be obtained prior to administration of study drug.

mIncludes serum ferritin, soluble transferrin receptor, hepcidin-25, haptoglobin, E-selectin, P-selectin, ICAM-1, VCAM-1, hsCRP, serum NT-proBNP, serum iron and TIBC for calculated transferrin saturation, and erythropoietin. Blood samples should be obtained prior to administration of study drug. PD markers will need to be collected prior to RBC transfusion (if applicable).

n At Baseline and Week 4, serial blood samples for IMR-687 and concentrations of metabolite(s) will be drawn pre-dose (within 30 minutes) and at 15 minutes (±5 minutes), 30 minutes (±5 minutes), and 3 hours (±20 minutes) after administration of study drug. A trough blood sample will be drawn pre-dose at Week 1, Week 24, and Week 36. The date/time of the previous dose will be recorded. If a subject requires a transfusion on the day of a PK draw, the transfusion can only be performed after the final PK sampling. For ET visits, a trough blood sample will not be collected.

o Quality of life assessments will be performed by the NTDT-PRO and SF-36 QoL tools. The QoL assessments will be administered at Baseline and at Weeks 12, 24, and 36. Baseline QoL assessments should be completed before administration of study drug.

p On days when study drug is taken in the clinic, food details will also be recorded.

q Adverse events and concomitant medications, including iron chelation therapy and hydroxyurea use, will be recorded at each visit throughout the study from Screening (after signing the ICF) through the end of study visit (Week 40).

7.2. Data Monitoring Committee

The specific activities of the DMC will be governed by a charter which will define the DMC's membership, meeting frequency, procedures/conduct, and requirements for reporting its observations to the sponsor.

To ensure safety oversight throughout the trial, the DMC will review safety and preliminary efficacy data and provide recommendations to the sponsor as described below.

The DMC will convene at the following times and for the following activities during the trial:

- Review safety data for at least 5 subjects who received IMR-687 at the lower dose and make recommendation as to the inclusion of the higher dose.
- Review safety data to confirm acceptable safety and tolerability of the higher dose of IMR-687. Make recommendation as to whether the dose level(s) could be modified; the proposed modification would occur only after a substantial protocol amendment was submitted to and approved by any applicable regulatory authorities.
- At any time during the trial – upon request by the sponsor, medical monitor, or DMC– should a concern arise from emerging safety data for which DMC review and assessment is desired. This includes the emergence of a frequency or pattern of AEs or SAEs that suggest an unexpected or otherwise concerning safety signal.

The DMC may review the following subject data, depending on the scope of the meeting, and may recommend to continue the study as planned, modify the study, or terminate the study for safety or lack of efficacy concerns:

- Unblinded safety, preliminary efficacy, and PK data, which may include TEAEs, SAEs, PK data, clinical laboratory test results, vital signs, and other relevant data for all subjects randomized.
- Additionally, the DMC chairperson will receive copies of all SAE reports for ongoing review during the trial. The DMC chairperson may forward the SAE reports to the full DMC if he/she feels that their immediate input on, or awareness of the SAE would be helpful.

All assessments and decisions by the DMC will be documented in writing as noted in the DMC charter and prior to any resultant changes to the study unless their immediate implementation is considered necessary for subject safety. The composition of the DMC will be detailed in the DMC charter.

8. SELECTION OF STUDY POPULATION

Up to approximately 60 subjects in Population 1 (TDT) and 60 subjects in Population 2 (NTDT) are expected to enroll, for a total of approximately 120 enrolled subjects.

8.1. Inclusion Criteria

Subjects must meet **all** of the following criteria to be eligible for the study:

1. Subjects must understand and voluntarily provide informed consent and sign an ICF prior to any study-related assessments/procedures being conducted. Although RBC transfusions and associated Hb laboratory measurements prior to Screening 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 in their medical history. Concomitant alpha gene deletion, duplication, or triplication is allowed.
4. ***For TDT subjects only:*** Subjects must be regularly transfused, defined as >3 to 10 pRBC units[†] in the 12 weeks prior to the Baseline (Day 1) visit 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 units[†] of pRBCs received during the 12-week period prior to the Baseline (Day 1) visit, 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 the dates of transfusion events and the number of pRBC units per event within the 12 weeks prior to the Baseline (Day 1) visit.
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 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

[†] One unit in this protocol refers to one bag of packed RBCs. The dates of transfusion events and the number of pRBC units per event during the 12 weeks preceding the Baseline (Day 1) visit will be collected. If available, the following data should also be collected for each transfusion event: volume and hematocrit of each pRBC unit, pre-transfusion Hb, and pre-transfusion weight. Transfusion burden as expressed in mL/kg transfused RBC may be calculated.

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 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 progesterone-only hormonal contraception that is associated with inhibition of ovulation, intrauterine device, and intrauterine hormone-releasing system.

9. Subjects receiving hydroxyurea 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.
10. ***For NTDT subjects only:*** Subjects must have Hb ≤10.0 g/dL at Screening; the screening Hb sample must be collected 7 to 28 days prior to randomization. Hb values within 21 days post-transfusion will be excluded.

8.2. 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., HbH) or HbS/β-thalassemia.
4. Body mass index (BMI) <17.0 kg/m^2 or a total body weight <45 kg; or BMI >35 kg/m^2.
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 (<100 mg per day) is allowed before and during the study.
8. 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).
9. Platelet count >1000 × 10^9/L.
10. For subjects on iron chelation therapy (ICT) at the time of ICF signing, initiation of ICT less than 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, in the opinion of the investigator, for example
    1) Hb A1c >9.0% within 12 weeks prior to randomization (in the medical history);
    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 >3× ULN with proportion of direct/total bilirubin >0.3; or history/evidence of cirrhosis, liver transplant, or presence of clinically significant mass/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 overload.
   c. Severe lung disease, including pulmonary fibrosis or pulmonary hypertension, i.e., ≥Grade 3 NCI CTCAE version 5.0.
   d. Significant kidney disease as indicated by, for example, estimated glomerular filtration rate <45 mL/min/1.73 m^2 (per Modification of Diet in Renal Disease formula).

15. Subjects who have received chronic systemic glucocorticoids ≤12 weeks prior to randomization (≥5 mg/day prednisone or equivalent). Physiologic replacement therapy for adrenal insufficiency is allowed.
16. Major surgery ≤8 weeks 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) ECG demonstrating a QTcF >450 ms in men and >470 ms in women on 2 or more of the triplicate ECGs, 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-gp or 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 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.
23. Prior exposure to any of following:
    a. IMR-687 or gene therapy
    b. Sotatercept or luspatercept (Reblozyl®) within 6 months prior to randomization (Day 1)
24. In the opinion of the investigator, the subject is unable to meet the requirements of the study.

8.3. Screen Failures

Any subject who consents to participate in the study but is not randomized will be considered a screen failure. Demographics, eligibility criteria, primary reason for screen failure, and any SAEs (if applicable) will be recorded and reported in the subject's electronic case report form (eCRF) for subjects who are screen failures.

If a subject is considered a screen failure, then he/she may be rescreened once with sponsor approval.

8.4. Guidelines for Withdrawal of Subjects from Study Participation

Subjects will be informed that they can discontinue their participation in the study at any time and for any reason.

The investigator may also remove a subject from the study at their discretion if, in the investigator's opinion, it is not in the best interest of the subject to continue in the study.

If a subject must be discontinued from study participation, the medical monitor should be informed and consulted regarding possible appropriate assessments to be completed in advance of study discontinuation. In case of discontinuation from the study, every effort will be made to complete the early termination visit assessments, if possible. If a subject does not complete the early termination assessments, then every effort should be made to obtain end of study assessments. If a final visit is not feasible, every effort to collect follow-up medical records will be attempted.

In the case of subjects who are lost to follow-up, the study site must attempt to contact the subject by phone, making at least 3 documented attempts, each at least one week apart.

Additionally, one registered letter must have been sent with a copy on file. The study site should only deem the subject as lost to follow-up no less than 30 days following the first documented phone call attempt, unless circumstances preclude this (e.g., phone service has been discontinued or there is other evidence that contact is not feasible).

If the subject discontinues the study, the specific circumstances surrounding the discontinuation must be recorded in the subject's eCRF.

Refer to Section 7 for details about randomization and treatment assignments. All data collected prior to discontinuation must be recorded in the subject's eCRF.

Justifiable reasons to discontinue a subject from treatment (Section 8.5) and/or from the study may include, but are not limited to the following:

- The subject was erroneously included in the study (i.e., did not meet eligibility criteria)
- The subject experiences an SAE assessed as possibly or probably related to study drug
- The subject is unable to comply with the requirements of the protocol
- The subject participates in another investigational study
- The subject withdraws consent to participate in the study
- A subject for whom the blind is intentionally or accidentally broken

8.5. Guidelines for Study Drug Dose Withholding or Discontinuation

8.5.1. Safety Criteria for Study Dose Interruption or Discontinuation

In consultation with the medical monitor, the investigator may decide to withhold the study drug or withdraw the subject in cases where tolerability or safety concerns emerge. Table 4 provides recommended guidelines for these decisions.

If a study drug dosing is withheld due to an AE (Section 12), subjects who continue on the study will have all assessments (except study drug administration) performed as per protocol.

If study drug dosing is discontinued for any reason, the specific circumstances surrounding the discontinuation must be recorded in the subject's eCRF. Any subject who discontinues study drug dosing must also be withdrawn from the study; however, all appropriate safety assessments and follow-up should be completed prior to withdrawal (Section 8.4).

Table 4: Safety Guidelines for Study Dose Reduction, Interruption, or Discontinuation

Dose Reduction	
Event	**Recommended Action**
A Grade 2 or higher TEAE that, in the opinion of the investigator, is both study drug related **and** that makes continued dosing at the current dose level inadvisable due to safety concern or lack of tolerability.	Study drug may be reduced by one tablet for up to 14 continuous days. If, in the opinion of the investigator, a longer dose reduction is clinically needed, the medical monitor should be contacted. If, in the opinion of the investigator, the severity of the Grade ≥2 TEAE has reduced to Grade ≤1, the subject may resume study drug at the original dose. If the TEAE recurs after re-introduction of the original dose, the subject should be withdrawn from the study.
Dose Interruption (Hold)	
Event	**Recommended Action**
A Grade 3 or higher TEAE that, in the opinion of the investigator, is both study drug related **and** that makes continued dosing at the current dose level inadvisable due to safety concern or lack of tolerability.	Study drug should be held for up to 7 continuous days until reduction in severity of the TEAE to Grade ≤2, then resumed at the original dose. If, in the opinion of the investigator, dosing should be resumed at a lower dose, the medical monitor should be contacted. If, in the opinion of the investigator, a longer dose hold is clinically needed, the medical monitor should be contacted or the subject should be withdrawn from the study.
Positive test results for COVID-19 and/or similar illness (asymptomatic and symptomatic).	Study drug should be held until 7 days after subject tests negative. Please consult with the medical monitor if there are any questions.

COVID-19 = coronavirus disease 2019; TEAE = treatment-emergent adverse event.

8.6. Replacement of Subjects

If a subject discontinues or is discontinued at the discretion of the investigator or DMC up to and including the Week 12 visit, the subject may be replaced with another subject meeting the eligibility criteria; up to 10 subjects for Population 1 and up to 10 subjects for Population 2 may be replaced. Refer to Section 7 for details about randomization and treatment assignments. Refer to Section 8.5 for guidelines on study drug dose withholding and discontinuation and to Section 8.4 for guidelines on withdrawal of subjects from study participation. All data collected prior to withdrawal must be recorded in the replaced subject's eCRF.

8.7. Stopping Rules and Study Termination

It is anticipated that AEs will occur frequently in this population based on the underlying disease, and that these can also be SAEs. There is no predefined type or frequency of AEs or SAEs for a stopping rule in this study. Review of SAEs and deaths on study will be performed routinely by the DMC, as defined in this protocol and in the DMC charter.

If a safety concern arises that warrants review for possible study termination, the DMC (or party identifying such concern) will notify the sponsor immediately. Enrollment in the study may be temporarily halted for further review of safety data. This further assessment of safety and/or preliminary efficacy data will include review by the DMC, which may include the recommendation to terminate the study early or stop a treatment arm for safety or lack of efficacy, as outlined in the DMC charter.

Termination of the clinical study may also occur due to a regulatory authority decision or if the sponsor or regulatory authority decides that subject safety may be compromised by continuing the study.

If the study is halted temporarily or prematurely terminated, a written statement fully documenting the reasons for study halt or termination will be provided to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and appropriate regulatory authorities.

9. STUDY TREATMENTS

9.1. Storage Conditions

Upon receipt of the study drug, an inventory must be performed, and a drug receipt log completed and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory.

Only subjects enrolled in the study may receive study drug, and only authorized site staff may supply or administer study drug to subjects. All study drug must be stored in a secure, environmentally controlled, and monitored (manual or automatic) location in accordance with the labelled storage conditions and with access limited to the investigator and authorized site staff.

The study site must maintain accurate records demonstrating dates and quantity of study drug received, to whom dispensed (subject-by-subject accounting), any amount returned, and accounts of any study drug that was accidentally destroyed.

9.2. Study Drug

IMR-687 will be supplied as 100, 150, or 200 mg white tablets. Subjects will be advised to take two IMR-687 tablets orally with food qd for 36 weeks. To maintain appropriate exposures, 60 kg will be used as the weight gate for tablet strength. Subjects in the lower dose group weighing <60 kg will be dispensed 100 mg tablets and those weighing ≥60 kg will be dispensed 150 mg tablets. Subjects in the higher dose group weighing <60 kg will be dispensed 150 mg tablets and those weighing ≥60 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.

Subjects will be directed to take study drug (either IMR-687 or placebo) with food, but if a subject does not do so, it will not be considered a protocol deviation.

9.3. Packaging and Labeling

Finished tablets will be packaged in round, 60 cc high-density polyethylene bottles with a polypropylene cap. Each bottle contains 84 tablets. The bottles are induction sealed and capped. Each bottle will be labelled with a suitable Annex 13 country compliant product label.

9.4. Study Drug Preparation

9.5. Administration

Subjects will be advised to take two IMR-687 or matched placebo tablets orally with food qd for 36 weeks. On days when study drug is taken in the clinic, food details will also be recorded.

9.6. Treatment Compliance

The investigator or designee must ensure that all subjects are adequately informed of study drug administration requirements for compliance/adherence with the study protocol.

Treatment compliance/adherence with scheduled oral administration of study drug will be assessed at the study site starting at Week 3 for TDT subjects or Week 4 for NTDT subjects; all study drug administration will be documented on the appropriate pages of the eCRF. Subjects falling below an 80% treatment compliance rate between consecutive visits will be reported as a protocol deviation.

9.7. Concomitant Medications

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject receives from the time of signing the ICF through the end of the study must be recorded along with:

- Reason for use
- Dates of administration, including start date/time and stop date/time
- Dose and frequency of administration

Subjects receiving hydroxyurea must have received it continuously for at least 6 months prior to signing the ICF, and 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.

Over-the-counter medications such as analgesics and nonsteroidal anti-inflammatory drugs that are taken on an as needed basis can be continued as long as they are not medications that interfere with metabolism, transport, or assessments (refer to Appendix 3 for additional information). All concomitant medications and/or therapies must be recorded on the appropriate pages of the eCRF. Use of any prohibited medication and/or therapy must also be recorded on the eCRF and must be documented as a protocol deviation.

9.7.1. Non-investigational Medicinal Products

Not applicable.

9.7.2. Prohibited Concomitant Medications/Therapies

The investigator, in consultation with the medical monitor, will determine if any of the following concomitant medications/therapies are necessary for the well-being of the subject. The subject will be withdrawn from the study if the following are determined to be necessary:

- PDE5 inhibitors; any drugs or substances, including grapefruit juice or herbal supplements with CYP altering properties, that are known to strongly or moderately inhibit or induce CYP/CYP3A enzymes; and any drugs or substances that are substrates or significant inhibitors of P-gp or BCRP. Sensitive substrates of CYP3A4/5 are also prohibited. 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.

- Concomitant use of erythropoietin.
- Any concomitant use of sotatercept or luspatercept (Reblozyl®), or previous use within 6 months prior to randomization (Day 1).
- Any other investigational drug or device.

Because IMR-687 is a CYP3A4 substrate as well as a possible CYP3A4 inducer, caution should be employed in the co-administration of IMR-687 with other medications that are known CYP3A4 substrates. This potentially helps manage the competition for in vivo CYP3A4-mediated clearance, which could result in a DDI. This approach includes applying caution with dosing other oral medications to minimize the chance of a drug interaction at the site of absorption (e.g., the GI tract). Additional information on potential drug interactions and how to proceed can be found in Section 5.2.3.

Medications prohibited prior to study entry are described in the exclusion criteria in Section 8.2.

9.7.3. Prohibited Concomitant Procedures

Procedures prohibited prior to study entry are described in the exclusion criteria in Section 8.2.

Subjects should not receive a blood transfusion at the Day 1 or Week 4 visit. If a subject does require a blood transfusion at the Day 1 or Week 4 visit, the medical monitor should be notified for further guidance.

9.8. Handling and Disposal

At the end of the study, a final reconciliation must be made between the quantity of study drug supplied, dispensed, and subsequently returned to the sponsor. A written explanation must be provided for any discrepancies. After accountability has been performed by the sponsor or sponsor's designee, any unused study drug remaining at the end of the study will be returned to the sponsor for destruction. Onsite destruction of unused study drug will be permitted with prior notice and approval from the sponsor.

10. RANDOMIZATION AND BLINDING

10.1. Randomization

All subjects who are screened (including screen failures) will be assigned a unique subject identification number.

On Day 1, eligible subjects in Population 1 (TDT) and Population 2 (NTDT) will be assigned another unique number (randomization number) in sequential order. The randomization number codes the subject's initial treatment assignment according to the randomization schedule generated prior to the study. Initially, subjects will be randomly assigned in a 2:1 ratio to receive either IMR-687 lower dose or placebo. 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).

Subject randomization will be stratified by TDT/NTDT status.

Randomization numbers will not be re-used once assigned. If a subject discontinues or is discontinued at the discretion of the investigator or DMC up to and including the Week 12 visit, the subject may be replaced with another subject meeting the eligibility criteria. In the event that a subject is replaced, the replacement subject will receive the same treatment as the replaced subject, and a different leading number will be used for the replacement randomization number.

10.2. Blinding

To ensure that the subject and site are blinded with respect to each subject's treatment assignment, placebo tablets and tablets for each dose level of IMR-687 are identical in appearance and are supplied in identical packaging. Each bottle will contain a code that identifies the contents as either 100 mg IMR-687, 150 mg IMR-687, 200 mg IMR-687, or placebo.

Every attempt should be made to preserve the integrity of study drug blinding. Except for cases of emergency unblinding, as described in Section 10.4, the randomization code will remain unbroken for subjects and study personnel at the site until the database has been locked for each study population. The blinded sponsor and CRO study team members will only be unblinded to the analysis results at the conclusion of the study (e.g., database lock).

10.3. Unblinding for Interim Analysis

To facilitate the analyses, certain sponsor representatives and designees will be unblinded to treatment assignments prior to and during the interim analysis (including the unblinded contract research organization [CRO] biostatistician and external groups for bioanalytical, PK, and PK/PD analyses and QoL analyses). Details will be provided in the study unblinding plan.

10.4. Emergency Unblinding

Unblinding is not always necessary to provide effective medical intervention and subject management in the event a subject experience an SAE, or an event that results in cessation of treatment (see Section 8.7). However, in the exceptional circumstance where the investigator believes that knowledge of the study drug assignment is essential to provide appropriate medical management, the treatment assignment for that subject will be provided to the investigator

according to standard operating procedures at the CRO. The medical monitor and sponsor are available to the investigator as needed for any considerations of unblinding a specific subject; however, the decision to unblind a specific subject relies solely on the clinical judgement of the investigator. That is, there is no requirement to discuss with the medical monitor and/or sponsor prior to unblinding a specific subject by the investigator; however, consultation is preferred. In the event that the investigator must unblind a subject and has not consulted with the medical monitor and/or sponsor, the investigator should notify the medical monitor and sponsor of the unblinding within 24 hours of breaking the blind.

After breaking the blind, the site staff should record the reason(s) for breaking the blind and any AEs leading to the breaking of the blind in the source documents and the appropriate eCRF pages. After breaking the blind, the subject will be discontinued from the study and should proceed with early termination and end of study visits as described in Section 8.4 and per the schedule of assessments (Table 2 and Table 3).

11. ASSESSMENTS

Table 2 and Table 3 list all of the study assessments and procedures for Population 1 (TDT) and Population 2 (NTDT), respectively. All data obtained from these assessments must be documented in the subject's source documentation.

Subjects should be seen for all visits on the designated day or within the defined allowable visit window (Table 2 and Table 3). The visits are as follows:

- Screening (up to 28 days prior to Baseline)
- Baseline (Day 1)
- Treatment Period (Week 1 to Week 36)
  - Telephone visit will be performed at Week 2
- End of Treatment/Early Termination (Week 36)
- End of Study (Week 40)

Unless otherwise specified, all assessments should be completed prior to dosing at any given timepoint.

11.1. Screening and Baseline Activities

The descriptions below are for screening-specific activities. For descriptions of activities that occur during both the screening and treatment periods, refer to Section 11.2 for preliminary efficacy and PD assessments, Section 11.3 for safety assessments, and Section 11.4 for PK assessments.

11.1.1. Informed Consent

The subject must read, understand, and sign the IRB/IEC-approved ICF confirming his or her willingness to participate in this study before initiating any screening activity that is not standard of care. The investigator will ensure that the subject has received adequate language translation if needed and understands the ICF before signing as per the local IRB/IEC's requirement. Subjects must also grant permission or be informed of national laws for the processing and dissemination of their personal data, including data concerning health (sensitive/protected health information) and the use and retention of their specimens for study-related purposes.

Informed consent for an optional pharmacogenomics evaluation will be offered at screening.

11.1.2. Demographic Information and Medical/Disease History

Subject demographics (age, sex, race, and ethnicity) and medical disease history (by thorough review of medical records and by interview) will be recorded at screening, in accordance with country requirements and institutional policies, and captured in the eCRF. Concurrent medical signs and symptoms must be documented to establish baseline severities.

Disease history should contain a confirmed diagnosis of β-thalassemia or HbE/β-thalassemia. Concomitant alpha gene deletion, duplication, or triplication is allowed.

11.1.3. Inclusion/Exclusion Criteria Evaluation

Eligibility will be assessed at screening and baseline based on the inclusion and exclusion criteria provided in Section 8. All inclusion and exclusion criteria will be assessed at the Screening visit; continued eligibility based on these criteria will be confirmed on Day 1.

11.1.4. Eastern Cooperative Oncology Group Performance Score

Subjects' performance status will be measured by ECOG at Screening (Appendix 1).

11.1.5. Historical Transfusion Burden

After obtaining signed informed consent, the subject's transfusion history for the 12 weeks prior to Baseline (Day 1) visit date should be recorded, relying on the documentation examples detailed below. Note that any transfusion on Day 1 (i.e., after randomization) should not be included in the transfusion history.

In order to be eligible for the study, the dates of transfusion events and the number of pRBC units per event within the 12 weeks preceding the Baseline (Day 1) visit must be available. If available, the following data should also be collected for each transfusion event: volume and hematocrit of each pRBC unit, pre-transfusion Hb, and pre-transfusion weight.

For TDT subjects: In the case of a subject receiving a transfusion after signing the ICF, a transfusion on the day of the Baseline (Day 1) visit may occur only after all study assessments are completed, including all PK sampling.

For NTDT subjects: In the case of a subject receiving a transfusion after signing the ICF, but prior to randomization, the investigator would inform the medical monitor. The intent is to avoid transfusions within the 2-week period leading to randomization. Approval could be obtained for the screening period to be extended by a maximum of 14 days.

11.1.6. Height

Height in centimeters (cm) will be measured at screening.

11.1.7. Serum Virology

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.

11.1.8. Pharmacogenomic Evaluation (Optional)

Blood samples may be collected at screening if the subject provides informed consent. The pharmacogenomic evaluation will include alpha-globin, gamma-globin *XmnI* polymorphism, and BAF chromatin remodeling complex subunit 11A (BCL11A), among other potential markers. The results of pharmacogenomic analyses may be reported separately from the clinical study report. Pharmacogenomic samples will be stored for up to 5 years post-study completion.

11.2. Preliminary Efficacy and Pharmacodynamic Assessments

11.2.1. Transfusion Burden

Transfusion burden will be assessed according the schedule of assessments (Table 2 and Table 3) using the following variables: dates of transfusion events, number of pRBC units per event, volume and hematocrit of each pRBC unit, pre-transfusion Hb, and pre-transfusion weight. These variables may also follow the same documentation requirements outlined in Section 11.1.5.

If a subject requires a transfusion on days when PK samples will be drawn (i.e., the Baseline [Day 1] or the Week 1, Week 3 [TDT]/Week 4 [NTDT], Week 24, or Week 36 visits), the transfusion can only be performed after the final PK sampling.

11.2.2. Quality of Life

Quality of life will be assessed using the TranQOL and SF-36 QoL tools in the TDT population (Table 2) and the NTDT-PRO and SF-36 QoL tools in the NTDT population (Table 3).

The TranQoL (Klaassen 2013; Klaassen 2014) is a disease-specific QoL measure for children and adults with thalassemia major. It has four versions: (i) a child self-report, (ii) an adult self-report, (iii) a parent self- report (measuring the impact of the disease on the parent), and (iv) a parent proxy report (measuring the child's QoL). The questionnaire length ranges from 29 items (child) to 39 items (parent). The questions are grouped into 4 domains: physical health, emotional health, family functioning, and school and career functioning. The adult and parent self-report questionnaires include a fifth category on sexual activity which is only one item. For this study only, the adult self-report will be used.

The SF-36 (Hays 2004) is a 36-item, patient-reported survey of patient health. The SF-36 consists of 8 scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0 to 100 scale based on each scale having equal weight. The lower the score the more disability and the higher the score the less disability (i.e., a score of 0 is equivalent to maximum disability and a score of 100 is equivalent to no disability). The 8 sections are: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health.

The NTDT-PRO (Taher 2019) is a new disease-specific health-related QoL tool for patients with NTDT. The NTDT-PRO was designed as a daily diary with recall of thalassemia-related symptoms over the previous 24 hours. The relatively short recall period is used due to the high level of day-to-day variation in symptoms experienced by patients with NTDT.

The 6 NTDT-PRO items assess the presence or severity of specific symptoms using a numerical rating scale ranging from 0 ("absent/minimal") to 10 ("extreme/high"): tiredness with or without physical activity, weakness with or without physical activity, and shortness of breath with or without physical activity. NTDT-PRO items are grouped into 2 domains: tiredness/weakness (tiredness with physical activity, tiredness without physical activity, weakness with physical activity, and weakness without physical activity) and shortness of breath (shortness of breath with physical activity, shortness of breath without physical activity). For this study, the

NTDT-PRO will not be used as a daily diary; data will be collected as per the schedule of assessments (Table 3).

11.2.3. Specialty Hematology

Blood samples will be collected prior to study drug administration for HbF and percent F-cells at selected study visits as shown in the schedule of assessments (Table 2 and Table 3). Refer to the specialty laboratory manual for details on the collection, handling, and processing of blood samples.

11.2.4. Pharmacodynamic Markers

Blood samples will be collected prior to study drug administration for the following PD laboratory assessments at selected study visits as shown in the schedule of assessments (Table 2 and Table 3).

Pharmacodynamic assessments will include the following:

- Haptoglobin
- Hepcidin-25
- Serum ferritin
- Soluble transferrin receptor
- Soluble E-selectin
- Soluble P-selectin
- Soluble intercellular adhesion molecule 1 (ICAM-1)
- Vascular cell adhesion molecule 1 (VCAM-1)
- High-sensitivity C-reactive protein (hsCRP)
- Serum N-terminal pro-B-type natriuretic peptide (serum NT-proBNP)
- Serum iron and total iron binding capacity (TIBC) for calculated transferrin saturation
- Erythropoietin

Refer to the central laboratory manual for details on the collection, handling, and processing of blood samples.

11.3. Safety Assessments

11.3.1. Telephone Visits

Qualified site personnel will contact the subject by telephone at Week 2 to capture potential TEAEs and concomitant medications. Subjects will also be reminded of compliance with study drug and the next visit schedule. If any AEs of significant clinical concern are identified during the telephonic visit, the subject will be requested to come into the site to be assessed.

11.3.2. Vital Signs

Vital signs include heart rate, respiratory rate, blood pressure, and body temperature. Vital signs should be consistently measured in either the sitting or semi-supine position. Vital signs will be collected at every visit except for the telephone visits. Vital signs will be taken pre-dose and 2 hours (±20 minutes) post-dose 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. Vital signs that are clinically significant and not explained by the underlying disease or concomitant medications should be recorded as AEs in the eCRF.

11.3.3. Weight

Weight in kilograms (kg) will be measured at every visit except for the telephone visits.

11.3.4. Physical Examinations

A complete PE will be conducted at selected study visits (including screening) as shown in the schedule of assessments (Table 2 and Table 3); at other visits, a symptom-driven PE may be conducted. The complete physical examination will include a general examination of the body, including the abdomen, heart, lungs, lymph nodes, back/neck, neurological system, skin, extremities, head, eyes, nose, and throat.

A symptom-directed physical examination will be conducted throughout the course of the study (except on visits where a complete physical examination will be conducted) following identification of AEs of significant clinical relevance as determined by the investigator.

Clinically significant findings that were present prior to the signing of informed consent must be included in the medical history eCRF. Clinically significant new findings that begin (or pretreatment findings that worsen) after signing the ICF and that meet the definition of adverse events must be recorded on the AE eCRF.

11.3.5. Electrocardiogram

Triplicate 12-lead ECGs will be performed to evaluate the change from baseline in ECG parameters (heart rate, PR interval, RR interval, QRS duration, QT interval, and QTcF interval). For TDT subjects, ECGs will be obtained at pre-dose and 2 hours (±30 minutes) post-dose at Baseline and at Week 3. For NTDT subjects, ECGs will be obtained at pre-dose and 2 hours (±30 minutes) post-dose at Baseline and at Week 4. At all other timepoints, ECGs will be taken pre-dose.

Interpretation of ECG tracings must be made by a qualified physician and documented on the ECG eCRF(s). The instrument used in the study to assess the ECG should be calibrated per the institution's standard policy.

Clinically significant abnormalities present prior to the subject's signed informed consent should be reported on the medical history eCRF. New or worsened clinically significant findings occurring after informed consent must be recorded on the AE eCRF as described in Section 12.1.2.3.

11.3.6. Central Laboratory Assessments

Blood and urine samples will be collected for routine clinical safety laboratory assessments according to the schedule of assessments (Table 2 and Table 3). Clinical safety tests will be assessed to evaluate IMR-687 safety and tolerability.

All abnormal clinical laboratory pages should be initialed and dated by an investigator, along with a comment regarding clinical significance. Each clinically significant laboratory result is to be recorded as medical history at screening and as an AE subsequently. If known, the diagnosis associated with an abnormality in clinical laboratory results considered clinically significant by the investigator should be recorded on the AE eCRF.

11.3.6.1. Hematology

Hematology assessments will be performed through a central laboratory and will include the following: RBC count (mean corpuscular volume [MCV], mean corpuscular Hb, and mean corpuscular Hb concentration), hematocrit (Hct), Hb, platelets, WBC count (with differential: basophils, eosinophils, neutrophils, monocytes, and lymphocytes), erythrocyte count, reticulocyte count, and reticulocyte percentage. Some of these assessments are also considered PD endpoints (refer to Section 11.2).

11.3.6.2. Coagulation

Coagulation assessments will include PT, aPTT, and INR. Some of these assessments are also considered PD endpoints (refer to Section 11.2).

11.3.6.3. Serum Chemistry

Serum chemistries will be performed through a central laboratory and will include but not be limited to the following: ALT, albumin, alkaline phosphatase (ALP), AST, bicarbonate, blood urea nitrogen (BUN), chloride, calcium, creatinine, glucose, LDH, sodium, potassium, magnesium, phosphate, bilirubin (total, direct, and indirect), creatine kinase, total protein, glomerular filtration rate (GFR), and gamma-glutamyl transferase. FSH is added for post-menopausal women at screening. Some of these assessments are also considered PD endpoints (refer to Section 11.2).

11.3.6.4. Urinalysis

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).

11.3.6.5. Pregnancy Test

Serum pregnancy tests will be performed during screening via a central laboratory for all female subjects of childbearing potential who are not post-menopausal or surgically sterile. All subsequent pregnancy tests will be urine pregnancy tests performed locally (with test kits provided by the central laboratory). If a urine pregnancy test is positive, the result must be confirmed with a serum pregnancy test.

11.3.7. Adverse Event Collection

Details of AE data collection are described in Section 12. Adverse events will be collected at every visit.

11.3.8. Concomitant Medications

Concomitant medications will be recorded at every visit in the medical record and on the appropriate eCRF. Any additions, discontinuations, or changes of these medications will be documented.

11.4. Pharmacokinetic Assessments

11.4.1. Plasma Pharmacokinetics

Serial blood samples will be collected at the timepoints indicated in the schedule of assessments (Table 2 and Table 3) for determination of IMR-687 concentration (including metabolites). At Baseline (all subjects) and Week 3 (TDT subjects) or Week 4 (NTDT subjects), serial blood samples will be drawn pre-dose (within 30 minutes) and at 15 minutes (±5 minutes), 30 minutes (±5 minutes), and 3 hours (±20 minutes) after administration of study drug. A trough blood sample will be drawn pre-dose at Week 1, Week 24, and Week 36. The date/time of the previous dose will be recorded.

Refer to the laboratory manual for details on the collection, handling, and processing of blood samples.

12. SAFETY MONITORING AND REPORTING

12.1.1. Adverse Event and Serious Adverse Event Collection

12.1.1.1. Time Period Adverse Event Collection

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). Events that occur following administration of study drug will be considered TEAEs.

All SAEs will be recorded and reported to the sponsor or sponsor's designee within 24 hours, as indicated in Section 12.1.2.3. The investigator will also submit any updated SAE data to the sponsor within 24 hours of the data being available.

12.1.1.2. Follow-up

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits and phone contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up.

12.1.2. Adverse Event Recording and Reporting

12.1.2.1. Definitions

12.1.2.1.1. Definition of an Adverse Event

An AE is defined as any untoward medical occurrence in a clinical study subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable or unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

Examples of AEs include but are not limited to:

- Abnormal test findings
- Clinically significant symptoms and signs
- Changes in physical examination findings
- Hypersensitivity
- Drug abuse
- Drug dependency

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose
- Drug withdrawal
- Drug misuse

- Drug interactions
- Extravasation
- Exposure during pregnancy
- Exposure via breastfeeding
- Medication error

12.1.2.1.2. Definition of a Serious Adverse Events

An SAE is any AE that results in one or more of the following outcomes:

- **Death**
- **Requires or prolongs hospitalization** (In general, hospitalization signifies that the subject has been detained, usually involving at least an overnight stay, at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.)
- **Is life-threatening** (In general, an AE is considered to be life-threatening if the subject is at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.)
- **Persistent or significant disability/incapacity** (In general, this means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, or accidental trauma [e.g., sprained ankle] that may interfere with or prevent everyday life functions, but do not constitute a substantial disruption.)
- **Congenital anomaly or birth defect** (that occurs in the offspring of a subject exposed to the investigational product)
- **Other medically important event** (In general, this means an AE that based upon appropriate medical judgment is considered to jeopardize the subject's safety and may require medical or surgical intervention to prevent one of the outcomes listed above.)

Reporting requirements for SAEs are described in Section 12.1.2.3.

12.1.2.1.3. Definition of a Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is an SAE that, in the opinion of the investigator, is believed with reasonable probability (i.e., suspected) to be due to the investigational product, but the nature or severity of which is not consistent with the reference safety information (i.e., is unexpected).

Reporting requirements for SUSARs are described in Section 12.1.2.4.

12.1.2.2. Evaluation of Adverse Events/Serious Adverse Events

12.1.2.2.1. Assessment of Severity

Adverse event severity (intensity) will be graded using NCI CTCAE, version 5.0 (Appendix 2). The CTCAE is a descriptive terminology utilized for AE reporting. A grading scale is provided for each AE term.

Grade refers to the severity (intensity) of the AE. The CTCAE provides unique clinical descriptions of severity for each AE based on the following general guideline:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL. *
Grade 3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
Grade 4	Life-threatening consequences: urgent intervention indicated.
Grade 5	Death related to AE.

ADL = activities of daily living; AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events
*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
Note: The CTCAE terminology provides grading for specific laboratory test abnormalities (Appendix 2). Grade 4 laboratory abnormalities do not automatically signify life-threatening AEs. Abnormal laboratory test results will be considered AEs only if the investigator, based on his or her medical judgement, deems the abnormality to be clinically significant.

Change in severity of an AE should be documented based on specific guidelines in the eCRF Completion Guidelines.

Severity and seriousness must be differentiated: Severity describes the intensity of an AE, while the term seriousness refers to an AE that has met the criteria for an SAE (defined in Section 12.1.2.1.2).

12.1.2.2.2. Assessment of Causality

The investigator will assess the potential relatedness of each AE to the investigational product. An investigator causality assessment (unlikely/not related, possible, probable/likely, or certain/related) must be provided for all AEs (both serious and non-serious). This assessment must be recorded on the eCRF and any additional forms as appropriate.

Unlikely/Not Related:	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Possible:	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Probable/Likely:	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Certain/Related:	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary

12.1.2.2.3. Outcome of Adverse Events

Outcome describes the status of the AE. Once the outcome is clear or at the end of the study, the investigator assigns one of the following outcomes for each AE: fatal, not recovered/not resolved, recovering/resolving, recovered/resolved, recovered/resolved with sequelae, or unknown.

12.1.2.3. Recording and Reporting Adverse Events and Serious Adverse Events

All AEs, both serious and non-serious, must be recorded in the eCRF.

Study site personnel must notify the sponsor or its designee of any SAE within 24 hours of becoming aware of the event. The notification must occur via a sponsor-approved (official) method. If the sponsor or its designee is initially notified by telephone, the phone call is to be immediately followed by notification via sponsor-approved method. The investigator must

complete, sign, and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy via email. Facsimile transmission may be used in the event of electronic submission or email failure.

Safety Reporting: North America

Telephone: +1 800 772 2215 or +1 434 951 3489

Fax: +1 888 772 6919 or +1 434 951 3482

Safety Reporting: Europe, Middle East, Asia-Pacific, and Africa

Telephone: +49 621 878 2154

Fax: +44 1792 525 720

Initial SAE reports must be followed by detailed descriptions. These should include copies of de-identified hospital case records and other documents when requested. If further information becomes available, the SAE Form should be updated with the new information and reported. The 24-hour notification requirement refers to reporting both initial SAE information and all follow-up SAE information once the site is made aware.

Serious adverse events occurring up to and including the subject's last study visit will be collected, regardless of the investigator's opinion of causation. A death occurring during the study and within 30 days after the last study visit must be reported to the sponsor or its designee with 24 hours of knowledge of the death regardless of causality. In addition, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the investigator must promptly notify the sponsor.

For all SAEs the investigator must provide the following:

- Appropriate and requested follow-up information in the timeframe detailed above
- Causality of the SAE(s)
- Outcome of the SAE(s)
- Medical records and laboratory/diagnostic information

12.1.2.4. Regulatory Reporting Requirements

Sponsor's Reporting Requirements

The sponsor or its legal representative is responsible for notifying the relevant regulatory authorities of SAEs and SUSARs meeting the reporting criteria. This protocol will use the current Investigator's Brochure as the Reference Safety Document. The expectedness and reporting criteria of an SAE will be determined by the sponsor from the Reference Safety Document.

Investigator's Reporting Requirements

The investigator must fulfil all local regulatory obligations required of investigators for the study. It is the investigator's responsibility to notify the IRB/IEC of all SAEs that occur at his or her site. Investigators will also be notified of all SUSARs that occur during the clinical study.

Investigators will receive blinded information unless unblinded information is judged necessary for safety reasons.

12.1.2.5. Exposure During Pregnancy

Pregnancy data will be collected for all subjects. Exposure during pregnancy (also referred to as exposure in utero) can be the result of either maternal exposure or transmission of the investigational product via semen following paternal exposure.

Exposure during pregnancy must be recorded and the subject must be followed until the outcome of the pregnancy is known (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) even though the subject will be withdrawn from the study per Section 8.7.

If a subject or a subject's partner becomes pregnant while treated or exposed to investigational product, the investigator must submit a pregnancy form to the sponsor via the same method as SAE reporting. When the outcome of the pregnancy becomes known, the form should be completed and returned to the sponsor or the sponsor's designee. If additional follow-up is required, the investigator will be requested to provide the information.

12.1.3. Medication Error and Reporting

In the event of a medication error, including overdose (accidental or intentional), it will be captured as an AE. A medication error associated with an SAE (including overdose, inadvertent exposure, and/or accidental exposure) will also be reported (see Section 12.1.2.3).

Medication errors that result, for example, from the administration or consumption of the wrong drug, by the wrong subject, at the wrong time, or at the wrong dosage strength will also be captured as a protocol deviation. In the event of medication dosing error or an overdose, the medical monitor and sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the product.
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

The sponsor does not recommend specific treatment for an overdose with IMR-687. Decisions regarding dose withholding will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the subject.

Whether or not the medication error is accompanied by an AE, the medication error and, if applicable, any associated adverse event(s) is captured as an AE.

13. STATISTICAL METHODS

13.1. General Considerations

Descriptive summary statistics will be provided for demographics, disposition, and IMR-687 exposure. The number and percentage of subjects who discontinue from the study, along with reasons for discontinuations will be tabulated.

Continuous data will be summarized using descriptive statistics (number of subjects, mean, SD, median, Q1, Q3, minimum, and maximum) and, where appropriate, coefficient of variation (%CV) and graphic representation. Categorical data will be summarized by sample size and proportions. Data will be summarized by population (TDT, NTDT) and dose cohort at each timepoint as appropriate. Graphs of actual values and changes over time may also be created as appropriate.

Interim analyses will be conducted at each of the following milestones:

- 30 subjects in the TDT population have completed 24 weeks of treatment
- 30 subjects in the NTDT population have completed 24 weeks of treatment
- 60 subjects in the TDT population have completed 24 weeks of treatment
- 60 subjects in the NTDT population have completed 24 weeks of treatment

13.2. Analysis Sets

Note that each of the following populations are defined for TDT and NTDT populations separately. Combined TDT and NTDT populations may also be used as appropriate.

The safety analysis set will include all subjects who have received any amount of study drug and from whom informed consent has been obtained and will be used to summarize all safety and tolerability data. In safety summaries, subjects will be analyzed according to the actual treatment they received.

The per protocol set will include all subjects in the safety population who have provided sufficient data without major protocol deviations or events that would be expected to affect the analysis. The per protocol set will be identified based on blinded data prior to unblinding the final analysis dataset. The per protocol set will be used to generate PD and clinical outcomes data.

The PK analysis set will be defined as a subset of the safety analysis set that includes all subjects who are enrolled in the study, have received at least 1 dose of IMR-687, and have sufficient IMR-687 concentration data; this set will be used in the PK analyses.

13.3. Safety Analyses

Descriptive statistics will be used to summarize all safety endpoints, by population and treatment group as appropriate. Data summaries will be displayed for incidence of AEs, clinical laboratory variables, vital signs, and ECG parameters.

Safety data summaries will use the safety analysis set.

All AEs will be coded using MedDRA. Data will be summarized using preferred term and primary system organ class. AE summaries will include AEs leading to study discontinuation and severity and frequency of AEs and SAEs.

All safety data will be summarized in by-subject listings.

13.4. Preliminary Efficacy Analyses

13.4.1. Population 1: Transfusion Dependent β-Thalassemia

Hematological improvement will be evaluated using a Cochran-Mantel-Haenzel (CMH) test to compare the proportion of subjects who achieved improvement between the placebo group and each of the 2 active treatment arms (IMR-687 lower dose and IMR-687 higher dose). Hematological improvement is defined as a ≥20% reduction in pRBC units transfused measured over 12 weeks (from Week 12 to Week 24 and from Week 24 to Week 36) as compared to the 12-week period prior to the Baseline (Day 1) visit. The safety and per protocol populations will be used, and no multiple comparisons adjustment will be made.

The mean number of transfusion events from baseline to Week 36 will be summarized by treatment group. Comparisons between placebo and each of the 2 active treatment arms (IMR-687 lower dose and IMR-687 higher dose) will be made using a t-test.

The mean change from baseline to Week 36 for ICT mean daily dose and serum ferritin will be analyzed using an analysis of covariance (ANCOVA) model with baseline value as a covariate and treatment as a factor.

13.4.2. Population 2: Non-Transfusion Dependent β-Thalassemia

The baseline value of Hb will be defined as the mean of non-missing Hb values from Screening (7 to 28 days prior to randomization) and randomization (Day 1) measurements. The baseline value of HbF will be defined in an analogous manner.

The proportion of subjects with increase from baseline of ≥1.0 g/dL in mean Hb values (at Weeks 12 to 24 and Weeks 24 to 36) will be evaluated using a Cochran-Mantel-Haenzel (CMH) test to compare the proportion of subjects who achieved improvement between the placebo group and each of the 2 active treatment arms (IMR-687 lower dose and IMR-687 higher dose).

The average Hb concentrations in the absence of transfusions over a continuous 12-week interval (from Week 12 to Week 24 and from Week 24 to Week 36) as well as the change from baseline will be summarized by treatment group and timepoint. The change from baseline in average Hb at Weeks 12 to 24 and Weeks 24 to 36 will be compared between the placebo group and each of the 2 active treatment arms (IMR-687 lower dose and IMR-687 higher dose) using a mixed model for repeated measures (MMRM) with fixed effects for treatment group and timepoint and a random subject effect. The safety and per protocol populations will be used, and no multiple comparisons adjustment will be made. Mean change in HbF concentrations from baseline to Week 24 and to Week 36 will be analyzed in the same manner.

The number and proportion of subjects with HbF response of ≥3% using the mean values at Weeks 12 to 24 and Weeks 24 to 36 will be summarized by timeframe and treatment group.

Comparisons of each of the 2 active treatment arms (IMR-687 lower dose and IMR-687 higher dose) to placebo will be made using a CMH test.

The mean change from baseline to Week 36 for ICT mean daily dose and serum ferritin will be analyzed using an ANCOVA model with baseline value as a covariate and treatment as a factor.

13.5. Pharmacokinetic Analyses

Summary statistics for trough plasma concentration (C_{trough}) data will be provided. Accumulation may be assessed.

PK data from this study will also be used to explore any relationship between IMR-687 exposure and clinical response, PD endpoints, or AEs, as data permit. These data will be analyzed together with PK data from other clinical studies for a population PK analysis, as appropriate.

13.6. Analyses of Exploratory Endpoints

Exploratory PD and clinical outcomes data for each timepoint will be listed by subject and summarized by treatment group separately for Population 1 (TDT) and Population 2 (NTDT) as appropriate. Correlations between PK and the exploratory endpoints may be assessed. Descriptive statistics will be computed as appropriate.

Summary statistics for QoL scores from the prespecified domains will be calculated at each administration timepoint. Summary statistics will also be calculated for change from baseline in each score at each administration timepoint.

Exploratory PD outcomes will be based on the PD analysis set, and QoL outcomes will be based on the safety and per protocol sets.

13.7. Sample Size Calculations

Both populations will have primary objectives of safety, and the sample sizes are not based on statistical assumptions.

13.7.1. Population 1: Transfusion Dependent β-Thalassemia

For the secondary efficacy endpoint of percentage of subjects with hematologic improvement (reduction in transfusion burden), 16 subjects in each treatment arm provide 82% power to detect a difference of 10% of subjects improving in the placebo arm versus 50% of subjects improving in either of the active treatment arms, using an alpha level of 0.1. No multiple comparisons adjustments will be made as these are secondary analyses.

13.7.2. Population 2: Non-transfusion Dependent β-Thalassemia

For the secondary efficacy endpoints of proportion of subjects with increase from baseline of ≥1.0 g/dL in mean Hb values at Weeks 12 to 24 or Weeks 24 to 36, 17 subjects in each treatment arm provide 84% power to detect a difference of 10% of subjects improving in the placebo arm versus 50% of subjects improving in either of the active treatment arms, using an alpha level of 0.1. No multiple comparisons adjustments will be made as these are secondary analyses.

14. DATA COLLECTION AND QUALITY CONTROL

Data collection is the responsibility of the staff at the study site under the supervision of the investigator. The designated study site staff will enter the data required by the protocol into the eCRFs. The eCRF is the primary data collection instrument for the study. The eCRFs have been built using fully validated secure web-enabled software that conforms to US Code of Federal Regulations (CFR) Title 21 Part 11 requirements. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the eCRFs and all other required reports. Data reported on the eCRF that are derived from source documents should be consistent with the source documents, or the discrepancies should be explained. All data requested on the eCRF must be recorded. Any missing data must be explained. For eCRFs, an audit trail will be maintained by the system to capture data changes. Study site staff will not be given access to the electronic data capture system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and allow modification or verification of the entered data by the study site staff.

The investigator is responsible for assuring that the data recorded on eCRFs are complete and accurate, and that entry and updates are performed in a timely manner.

14.1. Database Management and Data Quality Control

The sponsor or designee will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values by generating appropriate error messages. In addition, the outsourced vendor Data Management staff will review the data using validation programs and database listings and enter electronic queries for discrepancies allowing modification or verification of the entered data by the designated study staff.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (version 21.0) terminology.

14.2. Study Site Monitoring

Before study initiation at a study site, sponsor personnel or designee will review the protocol and eCRFs with the investigators and their study staff during an initiation visit or at an investigator's meeting. During the study, the blinded clinical monitors will visit the study site regularly to check the completeness of subject records, the accuracy of entries on the eCRFs, the adherence to the protocol and Good Clinical Practice (GCP), the progress of enrollment, and to ensure that IMR-687/placebo is being stored, dispensed, and accounted for according to sponsor specifications. Key study personnel must be available to assist the clinical monitors during these visits.

The investigator must maintain source documents for each subject in the study, consisting of hospital or clinic medical records including but not limited to demographic and medical information, laboratory data, ECGs, and the results of any other tests or assessments. All information recorded on eCRFs must be traceable to source documents in the subject's file.

The investigator must also keep the original signed ICF (a signed and dated copy is given to the subject/legally authorized representative).

The investigator must give the clinical monitors access to all relevant source documents to confirm their consistency with the eCRF entries. Monitoring standards require verification for the presence of signed/dated informed consent, adherence to the inclusion/exclusion criteria, and documentation of SAEs. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan.

14.3. Subject Data Protection and Confidentiality

Information about study subjects will be obtained, processed, kept confidential, and protected according to the applicable laws and regulations, such as the US Health Insurance Portability and Accountability Act of 1996 (HIPAA) or General Data Protection Regulation (GDPR) on the protection of natural persons with regard to the processing of personal data and on the free movement of such data.

Those regulations require a signed and dated subject consent informing the subject of the following:

- The sponsor's (e.g., Data Controller's) identity.
- The EU Data Protection Representative's identity.
- Contact information for the Data Protection Officer of the site and the Data Controller.
- The right to complain with a Data Protection Authority and the address of it.
- What personal data, including sensitive/personal health information will be collected from subjects in the study and for what purpose.
- Who will have access to that information and why.
- Who will process or disseminate that information.
- The right of a research subject to discontinue study participation and revoke consent at any time for any reason.
- In the event that a subject revokes consent, the investigator retains the ability to use all information collected prior to the revocation. For subjects who have revoked consent, attempts should be made to obtain permission to collect follow-up safety information (e.g., has the subject experienced any new or worsened AEs) at the end of their scheduled study period.
- Possible risks to the subject associated with the transfer of his/her data to third countries or international organizations.
- The suitable safeguards implemented to protect subject confidentiality and ensure subject data protection.
- An explanation that study subjects who do not consent to the forwarding of such data will not be included in the clinical study.

The data collection system for this study uses built-in security features to encrypt all transmitted data, preventing unauthorized access to confidential subject information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel.

In order to maintain subject confidentiality and to ensure subject data protection, the system will not solicit subject's initials or exact date of birth. Instead, each subject will be identified by a subject identification number and age will be solicited to establish that the subject satisfies protocol age requirements.

Any subject-related study documents sent to the sponsor (or designee) must be pseudonymized, i.e., must not contain direct identifiers such as subject's name, initials, date of birth, etc.

15. ADMINISTRATIVE, ETHICAL, AND REGULATORY CONSIDERATIONS

15.1. Protocol

15.1.1. Protocol Amendments

Any change to the protocol will be in the form of a written protocol amendment or administrative change document that will be issued by the sponsor or designee.

Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require additional approval by the applicable IRB(s)/IEC(s) of all study sites. Sites will not implement the protocol changes as described in an amendment until both regulatory authority and IRB/IEC approvals have been received.

The protocol requirements should in no way prevent any immediate action from being taken by the investigator/medically qualified designee (must be MD), or by the sponsor (or designee), in the interest of preserving the safety of subjects included in the study. Changes affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC approval, but the IRB/IEC must be kept informed of such changes. Therefore, the study site will send the administrative change document to the IRB/IEC according to the IRB's/IEC's documented process.

15.1.2. Protocol Adherence

It is the responsibility of the investigators to apply due diligence to avoid protocol deviations. If protocol deviations are identified, the sponsor or designee may be consulted to determine the best course of action to protect subject safety and maintain the integrity of the study data. The sponsor does not anticipate approving protocol deviations (i.e., waiving of inclusion/exclusion criteria or planned protocol deviations). If the investigator feels a protocol deviation would improve the conduct of the study, this must be considered a protocol amendment, and unless such an amendment is agreed upon by the sponsor and approved by the regulatory authority and IRB/IEC, it cannot be implemented. All significant protocol deviations will be recorded and reported in the clinical study report.

15.1.3. Discontinuation of Site Participation

If, in the opinion of the investigator or sponsor, the clinical observations in the study suggest that it may be unwise to continue, the investigator may discontinue their participation in the study or part of the study. A written statement fully documenting the reasons for discontinuation will be provided to the sponsor (or designee) and IRB/IEC.

15.1.4. Protocol Disclosure and Confidentiality

This protocol will be registered and maintained on ClinicalTrials.gov and other regulatory registries in accordance with applicable regulations.

The contents of this protocol and any amendments and results obtained during the course of this study will be kept confidential by the investigator, the study site staff, and IRB/IEC and will not

be disclosed in whole or in part to others or used for any purpose other than reviewing or performing the study without the written consent of the sponsor. Accordingly, the investigator is prohibited from publishing any data collected or results obtained during the course of this study without the prior written approval of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in the confidentiality agreement between the sponsor and the investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in the confidentiality agreement between the investigator and sponsor or designee.

15.2. Institutional Review Board (IRB) or Independent Ethics Committee (IEC)

The protocol, any protocol amendments, and the ICF will be reviewed and approved by each site's IRB/IEC before subjects are screened for entry into the study. Verification of the IRB's/IEC's unconditional approval of the protocol will be transmitted to the sponsor (or designee) prior to the study site(s) being initiated. The investigator(s) will submit, depending on local regulations, periodic reports and inform the IRB/IEC of any reportable AEs per ICH guidelines and local IRB/IEC standards of practice.

A list of IRBs/IECs that approved this study will be included in the clinical study report.

15.3. Ethical Conduct of the Study

The study will be conducted in accordance with this protocol and applicable country-specific laws and regulations, including but not limited to:

- US Code of Federal Regulations
- ICH E6(R2) Good Clinical Practice: Consolidated Guidance (GCP)
- Declaration of Helsinki ("Recommendations Guiding Physicians in Biomedical Research Involving Human Patients") and all its accepted amendments to date concerning medical research in humans

15.4. Subject Informed Consent

In accordance with ICH E6 (Section 4.8) and US CFR Title 21 Part 50, informed consent will be documented by the use of a written ICF approved by the IRB/IEC prior to protocol-specific procedures being performed.

The investigator (or designee) will explain the nature of the study and the action(s) of IMR-687. The subjects will be informed that participation is voluntary and that they can withdraw from the study at any time. They will be provided ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study.

The subjects must read, understand, sign, and date the IRB/IEC-approved ICF confirming their willingness to participate in this study before any screening activity that is not standard of care is initiated. Subjects must also agree and grant permission for the collection, use and retention of their biological samples, as applicable, until the end of the study when select samples will be

analyzed, and to the processing and dissemination of their personal data, including data concerning health (sensitive/protected health information). Specifically, in relation to biological samples, once study-related testing has been completed, any remaining samples will be destroyed in compliance with the subject informed consent and applicable law. Samples will not be processed for future use. The subjects or their guardians/legally authorized representatives will be given a signed and dated copy of the ICF and any other written subject information, and the original ICF will be maintained at the study site with the subjects' records.

The investigator must ensure that the subject has received adequate language translation if needed and understands the ICF before signing as per the local IRB's/IEC's requirement. Subjects who refuse to have their biological specimens collected and retained until the end of the study when select samples will be analyzed, and/or do not agree and grant permission for the processing and dissemination of their personal data, including data concerning health (sensitive/protected health information), may not participate in the study.

15.5. Publication of Study Protocol and Results

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.

15.6. Correlative Studies

Correlative studies may be proposed in the context of this clinical study and must include appropriate documentation including ethics approval and subject informed consent prior to proceeding. In addition, investigators interested in conducting correlative studies must obtain the sponsor's prior approval. Correlative studies will consider the impact on study data, if any, and priority will be given to samples defined in this protocol. Requests for correlative studies must be made in writing to the sponsor.

15.7. Investigators and Study Personnel

This study will be conducted by qualified investigators under the sponsorship of IMARA, Inc. at multiple study sites internationally. In relevant countries, all study staff members will receive and acknowledge a data processing notice.

A CRO will be retained by the sponsor to implement and manage the study and is referred to in this protocol as the sponsor's designee.

The names of the CRO and the medical monitor, along with contact information (email addresses, telephone and fax numbers, etc.) of other contact persons at the CRO, will be listed in study-related documents retained at each study site.

The names of study site staff trained for this study and their responsibilities must appear on the site delegation of authority log.

A DMC will be established early in the study to monitor subject safety. The DMC will meet periodically as the study is ongoing to review the accumulating safety data and make recommendations as necessary to the sponsor regarding early termination of the study, continuation of the study, or modification of the study protocol as needed based on safety assessments. Additional details are provided in the DMC charter.

15.8. Study Documentation, Record Keeping, and Retention of Documents

The investigator has the responsibility to retain all study documents, including but not limited to the protocol, study site source documents, copies of eCRFs, Investigator's Brochure, and regulatory documents (e.g., Form FDA 1572/Statement of Investigator, ICFs, and IRB/IEC correspondence) in accordance with Section 4.9 of the ICH E6(R2) GCP, US CFR 21 Part 312.62(c), and other regulatory and institutional requirements.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical study.

The investigator/institution should maintain the study documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6[R2] Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Sponsor-specific essential documents (hard copy and electronic) should be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational medicinal product. However, these documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor.

The study site should plan on retaining study documents per the study site contract.

15.9. Audits and Inspections

Upon request by representatives of national regulatory authorities, IRBs/IECs, or the sponsor or the sponsor's designee, investigators and institutions involved in the clinical study will permit study-related monitoring, audits, and regulatory inspections, including direct access to source data and documents generated by this study. Audits and inspections may be conducted during the study or after its completion. If an audit or inspection is requested by parties other than sponsor, the investigator or designee must immediately inform the sponsor that a request has been made.

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17. APPENDICES

Appendix 1: Eastern Cooperative Oncology Group (ECOG) Performance Status

The ECOG performance status scoring criteria were developed by the Eastern Cooperative Oncology Group (Oken, Creech, and Torney et al. 1982).

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Appendix 2: National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, v5.0)

Adverse events will be graded according to CTCAE v5.0.

The NCI CTCAE criteria are available at the following web location:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

Appendix 3: Lists of Potential In Vivo CYP3A Drug-Drug Interactions

The list of in vivo CYP3A-sensitive substrates, inhibitors of CYP3A probes, inducers of CYP3A probes; list of in vivo inhibitors of P-gp probes; and list of in vivo inducers of CYP3A probes can be found online at, for instance, the following websites:

- https://www.druginteractionsolutions.org
- https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

If there is any question as to whether a substance is permitted, the medical monitor and/or sponsor should be consulted.