PROTOCOL
IMR-SCD-301

Study Title:	A Phase 2b Study to Evaluate the Safety and Efficacy of IMR-687 in Subjects with Sickle Cell Disease
Protocol Number:	IMR-SCD-301
Study Phase:	2b
Study Drug:	IMR-687
US IND:	130549
EudraCT:	2019-004471-39
Indication:	Treatment of sickle cell disease
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:** 17 Feb 2022
Replaces Version:	4.0 **Release Date:** 08 Apr 2021
GCP Statement:	This study is to be performed in compliance with International Council for Harmonization (ICH) and applicable Good Clinical Practices (GCPs) and federal and local regulations.

SPONSOR'S APPROVAL

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

Docusigned by:
Ken Attie
Signer Name: Ken Attie
Signing Reason: I approve this document
Signing Time: 18-Feb-2022 | 3:56 PM EST
CC2D298D7B1348AFBBC7BEAAFB5CEA06

18-Feb-2022 | 4:00 PM EST

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

Date

INVESTIGATOR'S AGREEMENT

I have read and reviewed this clinical study protocol (IMR-SCD-301), 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

<table>
<tr><td colspan="3">Name of Sponsor/Company:
IMARA Inc.</td></tr>
<tr><td colspan="3">Name of Investigational Product:
IMR-687</td></tr>
<tr><td colspan="3">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</td></tr>
<tr><td>Protocol Number: IMR-SCD-301</td><td>Phase: 2b</td><td>Locations: North America, Europe, Africa, Middle East, and Asia</td></tr>
<tr><td colspan="3">Title of Study:
A Phase 2b Study to Evaluate the Safety and Efficacy of IMR-687 in Subjects with Sickle Cell Disease</td></tr>
<tr><td colspan="3">Study Centers:
This study will be conducted at approximately 70 sites.</td></tr>
<tr><td colspan="3">Objectives:
Primary Efficacy Objective:
• To evaluate the effect of IMR-687 versus placebo on the annualized rate of vaso-occlusive crises (VOCs)
Primary Safety Objective:
• To evaluate the safety and tolerability of IMR-687 versus placebo
Key Secondary Efficacy Objectives
• To evaluate the effect of IMR-687 versus placebo on the time to the first occurrence of a VOC
• To evaluate the fetal hemoglobin (HbF) response to IMR-687 versus placebo
Other Secondary Efficacy Objectives
• To evaluate the effect of IMR-687 versus placebo on other measures of VOCs
• To evaluate the effect of IMR-687 versus placebo on percentage of cells positive for fetal hemoglobin (HbF) (% F-cells) and total hemoglobin (Hb)
• To evaluate the effect of IMR-687 versus placebo on biomarkers of red blood cell (RBC) hemolysis
• To evaluate the effect of IMR-687 versus placebo on quality of life (QoL) measures
• To evaluate the effect of IMR-687 versus placebo on biomarkers of adhesion, inflammation, and cardiac stress and on RBC indices
Secondary Pharmacokinetic Objective
• To evaluate the pharmacokinetic (PK) exposure of IMR-687
Exploratory Objective
• To evaluate the effect of IMR-687 versus placebo on renal function
The objectives will be assessed by the endpoints described in Section 6.2 of the protocol.</td></tr>
</table>

Methodology:

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

The study schematic is provided in Figure 1, and the schedule of assessments is provided in Table 1.

Screening

After providing documented informed consent, subjects will enter an up to 28-day screening period. The following information will be obtained, and procedures will be performed for all potential subjects at the screening visit: medical/disease history, vital signs, electrocardiogram (ECG), complete physical examination (PE), laboratory tests (including safety, specialty hematology, and pharmacodynamic [PD] assessments). For a complete list of screening procedures, refer to the schedule of assessments.

Treatment Period

Subjects will receive either IMR-687 (lower dose [≥3.4 to ≤5.0 mg/kg; administered as either 200 or 300 mg] or higher dose [>5.0 to ≤6.7 mg/kg; administered as either 300 or 400 mg]) or placebo in a blinded fashion. Initially, subjects will be randomly assigned in a 2:1 ratio to receive either IMR-687 lower dose or placebo. Prior to the introduction of IMR-687 higher dose, the Data Monitoring Committee (DMC) will review safety data for at least 5 subjects who received IMR-687. If the DMC recommends inclusion of the higher dose, randomization will then proceed in a 1:2:1 ratio (IMR-687 lower dose, IMR-687 higher dose, or placebo). During study conduct under Protocol Version 3.0, the DMC approved the opening of enrollment in the higher dose IMR-687 group, which went into effect on 12 March 2021.

Subjects may or may not be concomitantly receiving a stable dose of hydroxyurea (HU) according to the subject's established treatment plan. Randomization will be stratified by use of HU and by region.

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 and Week 6 to capture potential adverse events (AEs) and concomitant medications.

Subjects will be seen at the investigational site approximately every 4 weeks through Week 24, then every 6 weeks through Week 36, and then every 8 weeks through Week 52 (end of treatment [EOT]), with a safety follow-up visit at Week 56 (end of study [EOS]). 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 (Table 1, in the protocol). QoL assessments include the Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me®), Patient-Reported Outcomes Measurements Information System - Preference (PROMIS® 29 + 2 Profile v2.1 [PROPr]), and Sickle Cell Self-Efficacy Scale (SCSES).

Open-label Extension

Subjects who complete treatment (Week 52) in this study may be eligible to enroll in a planned open-label extension (OLE) study. The EOS safety follow-up visit (Week 56) will not be expected for subjects who directly roll over to the OLE study.

Sample Size Calculation:

The sample size of this study was previously determined based on HbF responder rate, comparing the highest tolerated dose of IMR-687 to placebo, as the primary endpoint:

The sample size was determined assuming that the percentage of subjects who are HbF responders (i.e., have an HbF increase of ≥3% from baseline) at Week 24 is 5% in the placebo arm and 35% in either of the IMR-687 arms, with a 20% dropout rate prior to Week 24. Based on these assumptions, 26 subjects/arm at Week 24 is sufficient to achieve 80% power to detect a difference between the highest tolerated IMR-687 dose and placebo in HbF responders at Week 24 at a 2-sided significance level of 0.05.

Based on regulatory feedback, annualized rate of VOCs was elevated from a key secondary endpoint to the primary endpoint, with a corresponding change in statistical methodology:

Assuming that the actual data distribution is normal when the significance level (alpha) of the test is 0.05, the standard deviation is 2.7 in both groups, and there are no dropouts, there will be 88% power to detect a difference between the medians of 5.0 and 3.0 for the placebo and the IMR-687 highest tolerated dose groups, respectively (i.e., a 40% difference), using a 2-sided Wilcoxon rank-sum test.

Number of Subjects (Planned):

A total of approximately 99 adult subjects are expected to enroll in this study.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

Each subject must meet all the following criteria to be enrolled in the study:

1. Male or female aged ≥18 to ≤65 years at the time of informed consent form (ICF) signing.
2. Confirmed diagnosis of SCD (HbSS, HbSβ^0 thalassemia, or HbSβ^+ thalassemia) in the medical record; if not available, the diagnosis must be confirmed at the site's local laboratory instead.
3. Subjects must have had at least 2 and no more than 12 documented episodes of VOC in the past 12 months at the time of ICF signing and at randomization (Day 1).

   For study eligibility, VOC is defined as a documented episode of an acute painful crisis (for which there was not an explanation other than VOC) that involved moderate to severe pain lasting for at least 2 hours and at least one of the following:

   - Use of escalated analgesia (including healthcare professional-instructed use of an analgesic prescription)
   - A hospital, emergency department, or clinic visit and/or healthcare telephone consultation at the time of occurrence
   - Diagnosis of acute chest syndrome (ACS) (defined as an acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on a chest X-ray), hepatic sequestration, splenic sequestration, or priapism (in males)
4. Hb of >5.5 and <10.5 g/dL; Hb values within 21 days post-transfusion will be excluded.
5. *This inclusion criterion has been removed.*
6. Subjects receiving HU must have received it continuously for at least 6 months prior to signing the ICF, and must have been on a stable dose for at least 3 months prior to signing the ICF, with no anticipated need for dose adjustments during the study including the screening period, in the opinion of the investigator.

7. Female subjects must not be pregnant or breastfeeding and be highly unlikely to become pregnant. Male subjects must be unlikely to impregnate a partner. Male or female subjects must meet at least one of the following criteria:
    - A female subject who is not of reproductive potential is eligible without requiring the use of contraception. A female subject who is not of reproductive potential is defined as one who: (1) has reached natural menopause (defined as 12 months of spontaneous amenorrhea without an alternative medical cause, and can be confirmed with serum follicle-stimulating hormone levels in the postmenopausal range as determined by the central laboratory); (2) is 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy; or (3) has undergone bilateral tubal ligation. Spontaneous amenorrhea does not include cases for which there is an underlying disease that causes amenorrhea (e.g., anorexia nervosa).
    - A female of reproductive potential must have 2 negative pregnancy tests as verified by the investigator prior to starting study therapy. She must agree to ongoing pregnancy testing during the course of the study, at the EOT visit, and at the EOS visit. This applies even if the subject practices true abstinence from heterosexual contact.
    - A male subject who is not of reproductive potential is eligible without requiring the use of contraception. A male subject who is not of reproductive potential is defined as one who has undergone a successful vasectomy. A successful vasectomy is defined as (1) microscopic documentation of azoospermia or (2) a vasectomy more than 2 years ago with no resultant pregnancy despite sexual activity post-vasectomy.
    - A male or female subject who is of reproductive potential agrees to remain truly abstinent or use (or have their partner use) acceptable methods of highly effective contraception starting from the time of consent through 3 months after the completion of study drug. True abstinence is defined as abstinence that is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of the study, and withdrawal are not acceptable methods of contraception. Acceptable methods of highly effective birth control are combined or progesterone-only hormonal contraception that is associated with inhibition of ovulation, intrauterine device, and intrauterine hormone-releasing system.
8. Be capable of giving informed consent and reading and signing the ICF after the nature of the study has been fully explained by the investigator or investigator designee.
9. Be willing and able to complete all study assessments and procedures and to communicate effectively with the investigator and site staff.

<u>Exclusion Criteria</u>

Subjects who meet any of the following criteria will be excluded from the study:

1. Hospital discharge for sickle cell crisis or other vaso-occlusive event within the 4 days prior to randomization (Day 1).
2. Subjects participating in a chronic/prophylactic RBC transfusion program (i.e., regularly scheduled RBC transfusions); any transfusions within 21 days of screening or baseline Hb measurements.

3. Subjects with HbF >25% at screening.
4. Subjects with known active hepatitis A, hepatitis B, or hepatitis C, with active or acute event of malaria, or who are known to be positive for human immunodeficiency virus (HIV).
5. For female subjects of childbearing potential, a positive serum human chorionic gonadotropin (hCG) test (screening) or a positive urine hCG test at randomization (Day 1).
6. Significant kidney disease as indicated by, for example, estimated glomerular filtration rate (eGFR) <45 mL/min as calculated by the equation from the Modification of Diet in Renal Disease (MDRD) Study using creatinine, age, sex, and ethnicity (modified MDRD formula).
7. Alanine aminotransferase or aspartate aminotransferase >3× the upper limit of normal.
8. Body mass index (BMI) <17.0 kg/m^2 or >35 kg/m^2; or total body weight <45 kg.
9. Current or history of malignancies (solid tumors and hematological malignancies), unless the subject has been free of the disease (including completion of any active or adjuvant treatment for prior malignancy) for ≥5 years. However, subjects with the following history of/concurrent conditions are allowed if, in the opinion of the investigator, the condition has been adequately diagnosed and is determined to be clinically in remission, and the subject's participation in the study would not represent a safety concern:
    a. Basal or squamous cell carcinoma of the skin
    b. Carcinoma in situ of the cervix
    c. Carcinoma in situ of the breast
    d. Incidental histologic finding of prostate cancer (T1a or T1b using the tumor, nodes, metastasis clinical staging system)
10. 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 the Investigator's Brochure).
11. History of unstable or deteriorating cardiac or pulmonary disease within 6 months before signing the ICF, including but not limited to the following:
    a. Unstable angina pectoris or myocardial infarction or elective coronary intervention
    b. Congestive heart failure requiring hospitalization
    c. Uncontrolled clinically significant arrhythmias
12. Any condition affecting drug absorption, such as major surgery involving the stomach or small intestine (prior cholecystectomy is acceptable).
13. On ECG testing at ICF signing and/or randomization (Day 1), a corrected QT interval, Fridericia's formula (QTcF) >450 ms in men and >470 ms in women on 2 or more of the triplicate ECGs, or the presence of clinically significant ECG abnormalities as determined by the investigator.
14. Major surgery within 8 weeks or minor surgery within 2 weeks of randomization (Day 1).
15. Stroke requiring medical intervention within 24 weeks prior to randomization (Day 1).
16. Subjects taking direct acting oral anti-coagulants (apixaban, dabigatran, rivaroxaban, edoxaban, or ticagrelor) or taking warfarin, unless they stopped the treatment at least 28 days

prior to randomization (Day 1); low molecular weight heparins are allowed in the peri-operative period; aspirin use (<100 mg per day) is allowed before and during the study.

17. 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.
18. Subject has received chronic systemic glucocorticoids within 12 weeks prior to randomization (≥5 mg/day prednisone or equivalent). Physiologic replacement therapy for adrenal insufficiency is allowed.
19. Any clinically significant bacterial, fungal, parasitic, or viral infection requiring antibiotic therapy should delay screening/randomization (Day 1) until the course of antibiotic therapy has been completed. This includes, but is not limited to, long-term tuberculosis treatment.
20. Participated in another clinical study of an investigational agent (or medical device) within 30 days or 5 half-lives of date of informed consent, whichever is longer, or is currently participating in another study of an investigational agent (or medical device).
21. Prior exposure to IMR-687.
22. History of crizanlizumab (Adakveo®) or voxelotor (Oxbryta®) use within 6 months prior to signing the ICF or anticipated need for such agents during the study.
23. Consumption/use of the following drugs or other substances within the specified time periods before randomization or plans to consume/use at any time during the study. If there is any question as to whether a substance is permitted, please review the product labeling (if applicable) and consult the medical monitor and/or sponsor.
    a. Phosphodiesterase 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 opioids fentanyl and alfentanil, or moderate to strong CYP3A inhibitors or inducers within 28 days prior to randomization (Day 1) or plans to use during the study
    d. Any drugs or substances known to be substrates or inhibitors of P-glycoprotein or breast cancer resistance protein within 28 days prior to randomization (Day 1) or plans to use during the study.
24. Receipt of erythropoietin, luspatercept (Reblozyl®), or other erythropoiesis-stimulating or erythroid maturation agent within 6 months prior to signing the ICF or anticipated need for such agents during the study.
25. Prior gene therapy.
26. Any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study, including the presence of laboratory abnormalities that may place the subject at unacceptable risk if he/she were to participate in the study.

27. Other prior or ongoing medical condition, physical findings, or laboratory abnormality that, in the investigator's opinion, could adversely affect the safety of the subject, make it unlikely that the course of treatment or follow-up would be completed, or impair the assessment of study results (e.g., a history of drug or alcohol abuse within the past 1 year, as judged by the investigator).

Investigational Product, Dosage, and Mode of Administration:

IMR-687 will be supplied as 100, 150, or 200 mg white tablets. Subjects will be advised to take 2 tablets orally, qd. The different doses of IMR-687 are visually identical. Subjects will be directed to take their study drug with food.

Reference Therapy, Dosage, and Mode of Administration:

Placebo will be supplied as white tablets containing matrix absent IMR-687. The placebo tablets are visually identical to the IMR-687 tablets. Subjects will be advised to take 2 tablets orally, qd. Subjects will be directed to take their study drug with food.

Duration of Treatment:

The maximum treatment duration for a given subject is 52 weeks.

Assessments:

For both safety and efficacy evaluations, laboratory tests specified in the protocol will be performed by a central laboratory. Because knowledge of certain laboratory assessments (HbF, % F-cells, mean corpuscular volume [MCV], total and unconjugated [indirect] bilirubin, and absolute and % reticulocyte count) may unblind the treatment assignment, these measurements will be blinded at the central laboratory. Based on predefined safety laboratory alerts, these blinded laboratory assessments may be communicated to the investigator.

Safety

Safety assessments include vital signs, weight, ECGs, evaluation of clinical laboratory parameters, AEs, concomitant medications, and PEs.

Efficacy and Pharmacodynamics

Efficacy and PD assessments include laboratory measurements based on blood samples (HbF-associated biomarkers and Hb; biomarkers of RBC hemolysis, adhesion, inflammation, and cardiac stress; RBC indices); clinical outcome measures (VOCs and related parameters); and QoL measures (ASCQ-Me®, PROPr, and SCSES).

Pharmacokinetics

PK assessments include IMR-687 plasma concentration measurements from blood samples that will be collected pre-dose and serially up to 3 hours post-dose on Day 1 and at Week 4 visits; additional trough samples will be collected pre-dose at Week 24 and on the last day of dosing (Week 52).

Statistical Methods:

Primary Efficacy Analysis

The primary efficacy endpoint, annualized rate of VOCs, will be analyzed using a stratified Wilcoxon rank-sum test based on stratification factors of region (North America/Europe versus Africa/Middle East) and HU use (Yes versus No) to compare the treatment effect of the highest tolerated dose of IMR-687 to placebo. VOCs are defined for this study in Inclusion Criterion 3 (Section 8.1).

An interim analysis (IA) will be performed after all randomized subjects have reached Week 24 or terminated early. A Lan-DeMets alpha spending function will be used to determine the significance levels for the IA to maintain an overall type I error rate of 5% for 2-sided tests.

Secondary Efficacy Analyses

The first key secondary efficacy endpoint, time to first VOC, will be analyzed using a stratified log rank test (stratification factors of HU use and region) and stratified Cox regression model to compare the treatment effect of the highest tolerated dose of IMR-687 to placebo.

The second key secondary efficacy endpoint, proportion of HbF responders (defined as the proportion of subjects with an absolute increase of ≥3% in HbF from baseline) at Week 24, will be analyzed using a stratified Cochran-Mantel-Haenszel (CMH) test based on stratification factors of HU use and region to compare the highest tolerated dose of IMR-687 to placebo.

Other secondary endpoints that will be tested at the highest tolerated dose include the following:

- Proportion of VOC-free subjects
- Annualized rate of hospitalizations for VOCs
- Time to second VOC
- Proportion of HbF responders (defined as the proportion of subjects with an absolute increase of ≥3% in HbF from baseline) at Week 52
- Change from baseline in HbF (%) and F-cells (%) at Week 24 and Week 52
- Proportion of Hb responders (defined as the proportion of subjects with an increase of ≥1.0 g/dL in total Hb from baseline) at Week 24 and Week 52
- Change from baseline in total Hb (g/dL) at Week 24 and Week 52
- Change from baseline in biomarkers of RBC hemolysis (% and absolute reticulocytes, unconjugated [indirect] bilirubin, and lactate dehydrogenase [LDH]) at Week 24 and Week 52
- Change from baseline in each measured subdomain of the ASCQ-Me® questionnaire at Week 24 and Week 52
- Change from baseline in total preference score and individual domain scores of the PROPr questionnaire at Week 24 and Week 52
- Change from baseline in overall score of the SCSES at Week 24 and Week 52
- Change from baseline in biomarkers of adhesion such as soluble E-selectin (E-sel), P-selectin (P-sel), intercellular adhesion molecule 1 (ICAM-1), and vascular cell adhesion molecule 1 (VCAM-1) at Week 24 and Week 52
- Change from baseline in biomarkers of inflammation such as high-sensitivity C-reactive protein (hsCRP) and myeloperoxidase (MPO) at Week 24 and Week 52
- Change from baseline in biomarkers of cardiac stress such as N-terminal prohormone of brain natriuretic peptide (NT-proBNP) at Week 24 and Week 52
- Change from baseline in RBC indices, such as MCV, at Week 24 and Week 52

The secondary endpoints of proportion of HbF responders at Week 52 and proportion of Hb responders at Week 24 and Week 52 will each be analyzed in a similar manner as the second key secondary efficacy endpoint using a stratified CMH test based on stratification factors of HU use and region.

The annualized rate of hospitalizations for VOCs will be analyzed using a stratified Wilcoxon rank-sum test based on stratification factors of HU use and region.

Change from baseline endpoints for continuous variables will be analyzed using mixed models for repeated measures (MMRM) with treatment, visit, and treatment-by-visit interaction as fixed effects, and baseline value, HU use, and region as covariates. Unstructured covariance matrices will be used.

Time-to-event endpoints will be analyzed using log-rank tests, and Kaplan-Meier plots will be provided.

A final analysis (FA) will be conducted at study completion (i.e., when all subjects have reached Week 56 or terminated early). A Lan-DeMets alpha spending function will be used to determine the significance level for the IA and FA to maintain an overall type I error rate of 5% for 2-sided tests. At the FA, endpoints will be tested in a sequential hierarchical order at the highest tolerated dose.

Safety Analyses

Safety will be evaluated by the frequency of AEs and by changes from baseline in subjects' vital signs, clinical laboratory results, and ECG parameters.

Pharmacokinetic Analyses

Summary statistics for trough (C_{trough}) and other plasma concentration 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.

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3. LIST OF ABBREVIATIONS

Abbreviation	Definition
%CV	coefficient of variation
ACS	acute chest syndrome
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ASCQ-Me	Adult Sickle Cell Quality of Life Measurement Information System
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
BMI	body mass index
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
cGMP	cyclic guanosine monophosphate
C_{max}	maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
COVID-19	coronavirus disease 2019
CRO	contract research organization
C_{trough}	trough plasma concentration
CYP	cytochrome P450
DDI	drug-drug interaction
DMC	Data Monitoring Committee
DOAC	direct acting oral anti-coagulant
EC_{50}	half-maximal effective concentration
ECG	Electrocardiogram
eGFR	estimated glomerular filtration rate
eCRF	electronic case report form
EOS	end of study
EOT	end of treatment

Abbreviation	Definition
E-sel	E-selectin
ET	early termination
F-cells	cells positive for HbF
FA	final analysis
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GLP	Good Laboratory Practice
Hb	hemoglobin
HbF	fetal hemoglobin
HBsAg	hepatitis B surface antigen
HbSβ^0	sickle-β^0 hemoglobin
HbSβ^+	sickle-β^+ hemoglobin
HbSS	homozygous sickle hemoglobin
hCG	human chorionic gonadotropin
Hct	hematocrit
HCV	hepatitis C virus
HED	human equivalent dose
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
hsCRP	high-sensitivity C-reactive protein
HU	hydroxyurea
IA	interim analysis
IB	Investigator's Brochure
IC_{50}	half-maximal inhibitory concentration
ICAM-1	intercellular adhesion molecule 1
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee

Abbreviation	Definition
IgM	immunoglobulin M
INR	international normalized ratio
IRB	Institutional Review Board
IXRS	interactive voice/web response system
LDH	lactate dehydrogenase
MAD	multiple-ascending dose
MCV	mean corpuscular volume
MDRD	Modification of Diet in Renal Disease Study
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed models for repeated measures
MPO	myeloperoxidase
NCI CTCAE	National Cancer Institute Common Terminology for Adverse Events
NO	nitric oxide
NOAEL	no observed adverse effect level
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
OECD	Organization for Economic Cooperation and Development
OLE	open-label extension
P-gp	P-glycoprotein
PA	primary analysis
PD	pharmacodynamic(s)
PDE5	phosphodiesterase type 5
PDE9	phosphodiesterase type 9
PE	physical examination
PK	pharmacokinetic(s)
PP	per protocol
Pr:Cr	protein-to-creatinine (ratio)
PROMIS	Patient-Reported Outcomes Measurements Information System
PROPr	PROMIS – Preference
P-sel	P-selectin
PT	prothrombin time
PXR	pregnane X receptor

Abbreviation	Definition
Q1	first quartile
Q3	third quartile
qd	once daily
QoL	quality of life
QTcF	corrected QT interval, Fridericia's formula
RBC	red blood cell
SAD	single-ascending dose
SAE	serious adverse event
SCD	sickle cell disease
SCSES	Sickle Cell Self-Efficacy Scale
SD	standard deviation
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
t_{max}	time to maximum concentration
US	United States
VCAM-1	vascular cell adhesion molecule 1
VOC	vaso-occlusive crisis
WBC	white blood cell

4. INTRODUCTION

4.1. Overview of Disease Pathogenesis

The sponsor is developing IMR-687 for the treatment of patients with sickle cell disease (SCD) and β-thalassemia. The population for this study includes subjects with the following forms of SCD: homozygous sickle hemoglobin (HbSS), sickle-β^0 (HbSβ^0) thalassemia, and sickle-β^+ (HbSβ^+) thalassemia.

With a neonatal incidence of 294,000 to 330,000 patients worldwide (Piel 2013), SCD is a rare inherited disorder of red blood cells (RBCs) that is both serious and life-threatening. The most common manifestations of SCD include vaso-occlusive crisis (VOC), chronic and acute severe pain, acute chest syndrome (ACS), stroke, priapism, acute anemia (particularly from aplastic crisis and splenic sequestration), increased susceptibility to infection, and progressive damage to major organs, including the spleen, brain, kidney, heart, lung, skin, retina, vestibular cochlear systems, and bone. In developed countries where there is prenatal screening and widespread access to prophylactic and acute interventions, the median age of death remains in the 40s to 50s, although many patients succumb to the disease much earlier (Platt 1994; Lanzkron 2013; Paulukonis 2016).

SCD is caused by a specific point mutation (E6V) in the gene encoding hemoglobin (Hb) subunit beta that leads to the production of abnormal Hb ("sickle hemoglobin" or HbS). Under conditions of hypoxia, acidity, and/or dehydration, the intracellular concentration of deoxygenated HbS increases, which favors its polymerization and causes RBCs to deform (i.e., sickle) or become rigid, leading to a complex cascade of hemolysis, inflammation, elevated cell adhesion, leukocytosis, oxidative stress, and endothelial dysfunction that culminates in the vascular obstruction and ischemia responsible for much of the observed morbidity in SCD.

Prior to July 2017, the only drug specifically approved for the treatment of SCD was hydroxyurea (HU), a small molecule inhibitor of ribonucleotide reductase that was originally developed for the treatment of myeloproliferative disorders. HU (also known as hydroxycarbamide) has been approved to treat SCD since 1998 in the United States (US) and since 2001 in Europe. In SCD, HU reduces painful crises and the need for blood transfusions (Charache 1995), at least in part by increasing levels of fetal hemoglobin (HbF), which reduces RBC sickling and improves blood flow. These effects are mediated, at least in part, by increased nitric oxide (NO) and cyclic guanosine monophosphate (cGMP) production (Erard 1981; Platt 1984; Cokic 2003). Unfortunately, HU is often poorly tolerated, and its widespread use is limited by concerns about its potential impact on fertility and reproduction, challenges achieving and maintaining an efficacious dose due to its hematologic toxicities, and requirements for monthly monitoring (Heeney and Ware 2008).

In July 2017, L-glutamine oral powder (Endari™) was approved in the US to reduce complications of SCD. In November 2019, crizanlizumab (Adakveo®) and voxelotor (Oxbryta®) were approved by the Food and Drug Administration (FDA). Crizanlizumab (Adakveo®) is a humanized, anti-P-selectin monoclonal antibody that reduces the frequency of VOCs in adults and adolescents over the age of 16 years. Voxelotor (Oxbryta®) is an oral, once daily (qd) drug that binds to the α-chain of HbS, stabilizing the molecule in the R-state conformation, which is known to interrupt HbS polymerization. Both drugs are among the new therapies targeting

multiple pathways in the complex pathophysiology of SCD (Ballas 2020); however, due to the current cost of voxelotor (Oxbryta®) and crizanlizumab (Adakveo®), these therapies may not be accessible globally, especially for patients in resource-poor countries. Thus, additional accessible, novel, safe, and effective treatments to prevent the morbid complications of SCD in patients of all ages are still urgently needed.

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

By inhibiting PDE9, IMR-687 is intended to increase cGMP levels and thus stimulate the production of HbF, which reduces the cellular concentration of abnormal Hb (HbS) within RBCs and its associated sequelae. 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 SCD and β-thalassemia indications 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 supports its potential safety and efficacy for the treatment of SCD.

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/Organization for Economic Cooperation and Development (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 RBCs. IMR-687 has the potential for induction of cytochrome P450 (CYP)3A4 (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 (half-maximal inhibitory concentration [IC_{50}] >100 µM). 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 (IC_{50} = 32.5 µM), OCT1 (IC_{50} = 834 µM), and MATE2-K (IC_{50} = 441 µM).

Fifteen metabolites have been detected (in nonclinical testing) 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.

4.2.3. 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 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. 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 (PEs), or standard 12-lead electrocardiograms (ECGs). Of note, IMR-687 did not result in 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 time to maximum concentration [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%).

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 HbSS or HbSβ^0 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 (IA) 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 IA, 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 (IB).

5. RATIONALE

5.1. Study Rationale and IMR-687 Dose Rationale

This is a phase 2b, randomized, double-blind, placebo-controlled, multicenter study of subjects aged 18 to 65 years with SCD (HbSS, HbSβ^0 thalassemia, or HbSβ^+ thalassemia) to evaluate the safety and efficacy of the PDE9 inhibitor, IMR-687, administered qd for 52 weeks. Overall, this study will provide data on IMR-687 doses of ≥3.0 to ≤6.7 mg/kg (200 to 400 mg).

In a relevant model of anemia ($Hbb^{th1/th1}$ mice), oral administration of IMR-687 for 30 days at 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) increased RBCs and Hb, and reduced reticulocytes. The degree of these changes was dose dependent, with statistically 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, a problem in a number of Hb disorders.

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 the fasted SAD portion (Part A) and at doses up to 4.5 mg/kg/day for 7 days in the fed MAD portion (Part C), as well as from the completed phase 2a study in fed SCD subjects (IMR-SCD-102). Based on these data, a dose 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/or 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 in 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, 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]). 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 from time 0 to 24 hours [AUC_{0-24}]) in the female dog (most conservative species/gender). PK plotting (e.g., mean trough concentrations at 24 hours after study drug administration [C_{24}]) predicted that higher exposure to IMR-687 should result in drug levels above the estimated concentration at which inhibition is 90% (IC_{90}) for approximately 22 hours at a 300-mg dose and approximately 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.

This study initially imposed a minimum allowable body weight for enrollment of 45 kg and a 67-kg body weight gate for the administered 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(s), the DMC also approved a change in body

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 4.0, 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 3.0, the dose 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 dose range during the course of the study is ≥3.0 to ≤6.7 mg/kg.

5.2. Benefit/Risk Assessment

IMR-687 is currently being investigated for the treatment of SCD as its primary indication. It is anticipated that IMR-687, when compared to established therapy (i.e., HU), will maintain a similar or improved efficacy profile while potentially having a better safety profile, without the side effects that limit the use of HU (e.g., myelosuppression and mutagenicity/carcinogenicity risk) or the need for close monitoring and dose adjustments to balance benefit and risk.

Consequently, the frequent monitoring of blood counts required for patients who use HU would not be required for IMR-687. The proposed dosing in this study is between ≥3.4 to ≤6.7 mg/kg daily; the resultant 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 phase 2a study in SCD subjects, these dose levels should be tolerable and may have a clinically beneficial PD effect in subjects with SCD.

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 IB and informed consent form (ICF). The potential benefits and risks are summarized below.

5.2.1. Potential Benefits

Potential benefits include the production of increased levels of HbF, which is associated with decreased RBC sickling and improved blood flow, and decreases in biomarkers of adhesion and inflammation; individually and together, these PD changes may lead to fewer painful SCD-associated crises.

5.2.2. Potential Risks

The potential risks of IMR-687 are inferred from the relevant nonclinical findings as well as the results of the first-in-human study in healthy volunteers (IMR-SCD-101) and the results of the phase 2a study in subjects with SCD (IMR-SCD-102). These potential risks are briefly summarized in the sections below. Further details are provided in the IB.

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. 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 and 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 safety analysis of Study IMR-SCD-102, with respect to vital signs, there were no changes in systolic or 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. With dosing in the current study being up to 400 mg (≤6.7 mg/kg), safety margins of at least 2.7-fold are maintained.

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 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 EC_{50} = 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 ($K_m \cong 127$ µM); IMR-687 may be at least partially cleared as unchanged drug.

After oral administration, concentrations of IMR-687 in this study 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 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 moderate to strong CYP3A selective inhibitors, such as ketoconazole, should be avoided as this may increase the exposure of 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 (IC_{50} = 32.5 µM), co-administration of substrates or inhibitors of P-gp and BCRP should also proceed with caution.

See the Appendix 1 references for a list of in vivo CYP3A-sensitive substrates, inhibitors of CYP3A probe substrates, and inducers of CYP3A probe substrates; a list of in vivo inhibitors of P-gp probe substrates; and a list of in vivo inducers of CYP3A probe substrates from published drug interactions. Currently there are no such listings for BCRP.

Analysis of IMR-SCD-102 data found that 100 mg IMR-687 dosed qd had no notable impact on HU exposure for daily HU doses ranging from 500 to 2000 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 drug-drug interaction (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.

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

See also Section 9.6.2 on prohibited concomitant medications/therapies.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Objectives

6.1.1. Primary Efficacy Objective

- To evaluate the effect of IMR-687 versus placebo on the annualized rate of vaso-occlusive crises (VOCs)

6.1.2. Primary Safety Objective

- To evaluate the safety and tolerability of IMR-687 versus placebo

6.1.3. Key Secondary Efficacy Objectives

- To evaluate the effect of IMR-687 versus placebo on the time to the first occurrence of a VOC
- To evaluate the fetal hemoglobin (HbF) response to IMR-687 versus placebo

6.1.4. Other Secondary Efficacy Objectives

- To evaluate the effect of IMR-687 versus placebo on other measures of VOCs
- To evaluate the effect of IMR-687 versus placebo on percentage of cells positive for HbF (% F-cells) and total Hb
- To evaluate the effect of IMR-687 versus placebo on biomarkers of RBC hemolysis
- To evaluate the effect of IMR-687 versus placebo on quality of life (QoL) measures
- To evaluate the effect of IMR-687 versus placebo on biomarkers of adhesion, inflammation, and cardiac stress and on RBC indices

6.1.5. Secondary Pharmacokinetic Objective

- To evaluate the PK exposure of IMR-687

6.1.6. Exploratory Objective

- To evaluate the effect of IMR-687 versus placebo on renal function

6.2. Endpoints

6.2.1. Primary Efficacy Endpoint

- Annualized rate of VOCs

  VOC is defined as a documented episode of an acute painful crisis (for which there was not an explanation other than VOC) that involves moderate to severe pain lasting for at least 2 hours and at least one of the following:

  – Use of escalated analgesia (including healthcare professional-instructed use of an analgesic prescription)

– A hospital, emergency department, or clinic visit and/or healthcare telephone consultation at the time of occurrence

– Diagnosis of ACS (defined as an acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on a chest X-ray), hepatic sequestration, splenic sequestration, or priapism (in males)

6.2.2. Safety Endpoints

- AEs, serious adverse events (SAEs), clinically significant changes in laboratory tests, clinically significant changes in vital signs, and clinically significant changes in ECGs

6.2.3. Key Secondary Efficacy Endpoints

- Time to first VOC
- Proportion of HbF responders (defined as the proportion of subjects with an absolute increase of ≥3% in HbF from baseline) at Week 24

6.2.4. Other Secondary Efficacy Endpoints

Other secondary endpoints that will be tested include the following:

- Proportion of VOC-free subjects
- Annualized rate of hospitalizations for VOCs
- Time to second VOC
- Proportion of HbF responders (defined as the proportion of subjects with an absolute increase of ≥3% in HbF from baseline) at Week 52
- Change from baseline in HbF (%) and F-cells (%) at Week 24 and Week 52
- Proportion of Hb responders (defined as the proportion of subjects with an increase of ≥1.0 g/dL in total Hb from baseline) at Week 24 and Week 52
- Change from baseline in total Hb (g/dL) at Week 24 and Week 52
- Change from baseline in biomarkers of RBC hemolysis (% and absolute reticulocytes, unconjugated [indirect] bilirubin, and lactate dehydrogenase [LDH]) at Week 24 and Week 52
- Change from baseline in each measured subdomain of the Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me®) questionnaire at Week 24 and Week 52
- Change from baseline in total preference score and individual domain scores of the Patient-Reported Outcomes Measurements Information System – Preference (PROMIS® 29 + 2 Profile v2.1 [PROPr]) questionnaire at Week 24 and Week 52
- Change from baseline in overall score of the Sickle Cell Self-Efficacy Scale (SCSES) at Week 24 and Week 52

- Change from baseline in biomarkers of adhesion such as soluble E-selectin (E-sel), P-selectin (P-sel), intercellular adhesion molecule 1 (ICAM-1), and vascular cell adhesion molecule 1 (VCAM-1) at Week 24 and Week 52
- Change from baseline in biomarkers of inflammation such as high-sensitivity C-reactive protein (hsCRP) and myeloperoxidase (MPO) at Week 24 and Week 52
- Change from baseline in biomarkers of cardiac stress such as N-terminal prohormone of brain natriuretic peptide (NT-proBNP) at Week 24 and Week 52
- Change from baseline in RBC indices, such as mean corpuscular volume (MCV), at Week 24 and Week 52

6.2.5. Secondary Pharmacokinetic Endpoint

- PK profile (concentration-time measurements) and population PK of IMR-687

6.2.6. Exploratory Endpoint

- Change from baseline in renal function as measured by the urine protein-to-creatinine (Pr:Cr) ratio and microalbumin at Week 24 and Week 52

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a phase 2b, randomized, double-blind, placebo-controlled, multicenter study of subjects aged 18 to 65 years with SCD (HbSS, HbSβ^0 thalassemia, or HbSβ^+ thalassemia) to evaluate the safety and efficacy of the PDE9 inhibitor, IMR-687, administered qd for 52 weeks. This study will enroll approximately 99 subjects with SCD. This study consists of a screening period (up to 4 weeks), a double-blind treatment period (52 weeks), and a safety follow-up period (4 weeks).

The study schematic is provided in Figure 1, and the schedule of assessments is provided in Table 1.

7.1.1. Screening

After providing informed consent and signing the ICF, subjects will enter an up to 28-day screening period. The following information will be obtained, and procedures will be performed for all potential subjects at the screening visit: medical/disease history, vital signs, ECG, complete PE, laboratory tests (including safety, specialty hematology, and PD assessments). For a complete list of screening procedures, refer to the schedule of assessments (Table 1) and Section 11.

All screening procedures will be completed within 28 days before randomization. In some cases, there may be subjects who are eligible for the study but fall outside of the 28-day screening window. In these specific cases, the medical monitor may use his/her clinical judgment and allow a patient to be randomized without full re-screening in order to prevent having the subject undergo additional screening assessments unduly, provided that the patient's safety is not at risk and the integrity of the study will not be compromised. The medical monitor will be explicit as to which screening assessments must be repeated, if any, and will clearly document all decisions.

If a subject is considered a screen failure, he/she may be rescreened once with sponsor approval. If the investigator would like to repeat a screening assessment, such as chemistry laboratory testing, more than once, prior approval by the medical monitor is required.

7.1.2. Treatment Period

Subjects will receive either IMR-687 (lower dose [≥3.4 to ≤5.0 mg/kg; administered as either 200 or 300 mg] or higher dose [>5.0 to ≤6.7 mg/kg; administered as either 300 or 400 mg]) or placebo in a blinded fashion. Initially, subjects will be randomly assigned in a 2:1 ratio to receive either IMR-687 lower dose or placebo. Prior to the introduction of IMR-687 higher dose, the 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). During study conduct under Protocol Version 3.0, the DMC approved the opening of enrollment in the higher dose IMR-687 group, which went into effect on 12 March 2021.

Subjects may or may not be concomitantly receiving a stable dose of HU according to the subject's established treatment plan. Randomization will be stratified by use of HU and by region.

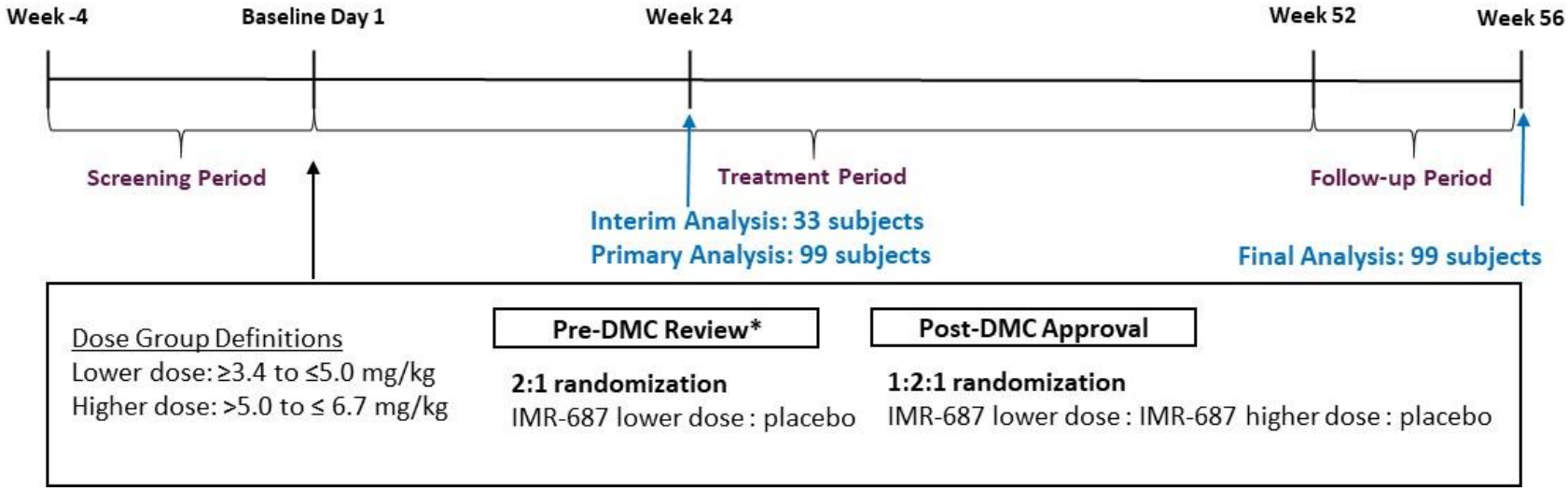
Subjects will return to the investigational site at Week 1 for a safety assessment, and qualified site personnel will contact the subject by telephone at Week 2 and Week 6 to capture potential AEs and concomitant medications.

Subjects will be seen at the investigational site approximately every 4 weeks through Week 24, then every 6 weeks through Week 36, and then every 8 weeks through Week 52 (end of treatment [EOT]), with a safety follow-up visit at Week 56 (end of study [EOS]). 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 (Table 1). QoL assessments include ASCQ-Me®, PROPr, and SCSES.

7.1.3. Open-Label Extension

Subjects who complete treatment (Week 52) in this study may be eligible to enroll in a planned open-label extension (OLE) study The EOS safety follow-up visit (Week 56) will not be expected for subjects who directly roll over to the OLE study.

Figure 1: Study Design



Abbreviation: 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. If the DMC recommends inclusion of the higher dose, randomization across 3 dose groups will then proceed as shown.
During study conduct under Protocol Version 3.0, the DMC approved the opening of enrollment in the higher dose IMR-687 group, which went into effect on 12 March 2021.

Table 1: Schedule of Assessments

	Screening Period	Baseline	Treatment Period													Follow-up Period
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Study Week	**-4 to 0**	**NA**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**30**	**36**	**44**	**ET/EOT 52[p]**	**EOS 56**
Study Day	**-28 to -1**	**1[a]**	**7 ± 2**	**14 ± 3**	**28 ± 5**	**42 ± 5**	**56 ± 5**	**84 ± 5**	**112 ±7**	**140 ± 7**	**168 ± 7**	**210 ± 7**	**252 ± 7**	**308 ± 7**	**364 ± 7**	**392 ± 7**
Administrative Procedures																
Informed consent	X															
Demographic information	X															
Medical/disease history	X															
Inclusion/exclusion criteria[b]	X	X														
Randomization		X														
Telephone visits[c]				X		X										
Safety Assessments																
Vital signs[d]	X	X	X		X		X	X	X	X	X	X	X	X	X	X
Weight	X	X			X			X			X		X		X	X
Height	X														X	
Physical examination[e]	X	X	X		X		X	X	X	X	X	X	X	X	X	X
12-lead ECG[f]	X	X	X		X		X	X	X	X	X	X	X	X	X	X
Hematology and serum chemistry	X	X	X		X		X	X	X	X	X	X	X	X	X	X
Coagulation studies	X							X			X				X	
Urinalysis with urine creatinine, Pr:Cr ratio, and microalbumin	X	X	X		X		X	X	X	X	X	X	X	X	X	

Table 1: Schedule of Assessments (Continued)

	Screening Period	Baseline	Treatment Period													Follow-up Period
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Study Week	**-4 to 0**	**NA**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**30**	**36**	**44**	**ET/EOT 52[p]**	**EOS 56**
Study Day	**-28 to -1**	**1[a]**	**7 ± 2**	**14 ± 3**	**28 ± 5**	**42 ± 5**	**56 ± 5**	**84 ± 5**	**112 ±7**	**140 ± 7**	**168 ± 7**	**210 ± 7**	**252 ± 7**	**308 ± 7**	**364 ± 7**	**392 ± 7**
Serum pregnancy test[g]	X															
Urine pregnancy test[g]		X	X		X		X	X	X	X	X	X	X	X	X	X
Clinically indicated virology[h]	X															
Adverse events[i]	Continuous															
Concomitant medications[i]	Continuous															
Efficacy and Pharmacodynamic Assessments																
Specialty hematology[j]	X	X			X		X	X	X		X		X		X	
PD biomarkers[k]	X	X			X		X	X	X		X		X		X	
QoL tools[l]		X			X			X			X		X		X	
CV marker	X	X						X			X		X		X	
Pharmacokinetic Assessments																
IMR-687 plasma PK sampling[m]		X			X						X				X	
Study Drug Procedures																
Study drug dispensing		X			X		X	X	X	X	X[n]	X[n]	X[n]	X[n]		
Study drug administration[o]		Oral administration IMR-687 or matching placebo qd														

Table 1 Schedule of Assessments (Continued)

Abbreviations: AE = adverse event; ASCQ-Me = Adult Sickle Cell Quality of Life Measurement Information System; BP = blood pressure; CV = cardiovascular; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; ET = early termination; F-cells = cells positive for HbF; HbF = fetal hemoglobin; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HR = heart rate; HU = hydroxyurea; ICAM-1 = intercellular adhesion molecule 1; IgM = immunoglobulin M; MPO = myeloperoxidase; NA = not applicable; PD = pharmacodynamic; PE = physical examination; PK = pharmacokinetics; Pr:Cr = protein-to-creatinine (ratio); PROPr = Patient-Reported Outcomes Measurements Information System – Preference; qd = once daily; QoL = quality of life; SCSES = Sickle Cell Self-Efficacy Scale; TEAE = treatment-emergent adverse event; VCAM-1 = vascular cell adhesion molecule 1.

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

[a] Day 1 assessments should be performed prior to study drug administration.

[b] All inclusion and exclusion criteria will be assessed at the Screening Visit; continued eligibility based on these criteria will be confirmed on Day 1.

[c] Qualified site personnel will contact the subject at Week 2 and Week 6 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] Vital signs include HR, respiratory rate, BP, and body temperature and should be consistently measured in either the sitting or semi-supine position. At the Day 1 and Week 4 visits, 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.

[e] Complete PEs will be performed at Screening and at Weeks 12, 24, 36, 52, and 56; these consist of a general examination of the body, including the abdomen, heart, lungs, lymph nodes, back/neck, neurological system, skin, extremities, head, eyes, nose, and throat. At all other visits, symptom-directed PEs will be obtained after identification of AEs deemed by the investigator to be of significant clinical concern.

[f] All ECGs to be performed in triplicate. At the Baseline, Week 1, and Week 4 visits, ECGs will be obtained pre-dose and 2 hours (±30 minutes) post-dose. At all other timepoints, ECG will be taken pre-dose.

[g] Females of childbearing potential only. A serum pregnancy test will be performed during screening via a central laboratory. 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.

[h] Serum virology (screening assessment) will be conducted only if clinically indicated. Testing will be performed through a central laboratory and may include HBsAg, hepatitis A IgM, and HCV antibody.

[i] AEs and concomitant medications, including opioids and HU use, will be recorded at each visit throughout the study from screening through the EOS (Week 56) follow-up.

[j] Includes HbF and % F-cells. Blood samples should be obtained prior to administration of study drug.

[k] PD biomarkers that are not already assessed as part of standard hematology or serum chemistry testing may include, but are not limited to, the following: soluble E-selectin, P-selectin, ICAM-1, VCAM-1, and MPO.

[l] QoL assessments include the specified components of the ASCQ-Me®, PROPr, SCSES. Refer to Section 11.2.4. The translated QoL assessments from PROPr will be used when available.

[m] At the Day 1 and Week 4 visits, serial blood samples for IMR-687 (including metabolites and HU, if applicable) plasma concentrations will be drawn pre-dose (within 30 minutes) and at 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 24 and on the last day of dosing (Week 52). The date/time of the last administered dose will be recorded.

[n] Each study drug bottle will contain 84 tablets. The indicated visits will require 2 bottles to be dispensed.

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

[P] The EOS (Week 56 follow-up) visit will not be expected for subjects who directly roll over to the OLE study. Refer to Section 7.1.3.

7.2. Data Monitoring Committee

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

To ensure safety oversight throughout the study, a 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 study:

- 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 and make recommendation as to whether the dose levels could be modified.
- Review safety data on a periodic basis as defined in the DMC charter. For example, results of blinded laboratory tests will be communicated to the investigator if a subject's absolute reticulocyte count declines to $<80 \times 10^8$/L, Hb declines to <5.0 g/dL, or Hb declines to ≥3 g/dL from baseline (Day 1) (but this does not require breaking of the treatment assignment blind). This is to ensure subject safety by allowing the investigator to monitor relevant safety data.
- At any time during the study – 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. At any time, the DMC may recommend to stop a dose arm or the study.

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 concerns:

- Unblinded safety, PK, and preliminary efficacy/PD 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 study. 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, decisions, and recommendations 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.

7.3. Number of Subjects

A total of up to approximately 99 adult subjects are expected to enroll in this study.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

Each subject must meet all the following criteria to be enrolled in the study:

1. Male or female aged ≥18 to ≤65 years at the time of ICF signing.
2. Confirmed diagnosis of SCD (HbSS, HbSβ^0 thalassemia, or HbSβ^+ thalassemia) in the medical record; if not available, the diagnosis must be confirmed at the site's local laboratory instead.
3. Subjects must have had at least 2 and no more than 12 documented episodes of VOC in the past 12 months at the time of ICF signing and at randomization (Day 1).

   For study eligibility, VOC is defined as a documented episode of an acute painful crisis (for which there was not an explanation other than VOC) that involved moderate to severe pain lasting for at least 2 hours and at least one of the following:

   - Use of escalated analgesia (including healthcare professional-instructed use of an analgesic prescription)
   - A hospital, emergency department, or clinic visit and/or healthcare telephone consultation at the time of occurrence
   - Diagnosis of ACS (defined as an acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on a chest X-ray), hepatic sequestration, splenic sequestration, or priapism (in males)
4. Hb of >5.5 and <10.5 g/dL; Hb values within 21 days post-transfusion will be excluded.
5. *This inclusion criterion has been removed.*
6. Subjects receiving HU must have received it continuously for at least 6 months prior to signing the ICF, and must have been on a stable dose for at least 3 months prior to signing the ICF, with no anticipated need for dose adjustments during the study including the screening period, in the opinion of the investigator.
7. Female subjects must not be pregnant or breastfeeding and be highly unlikely to become pregnant. Male subjects must be unlikely to impregnate a partner. Male or female subjects must meet at least one of the following criteria:

   - A female subject who is not of reproductive potential is eligible without requiring the use of contraception. A female subject who is not of reproductive potential is defined as one who: (1) has reached natural menopause (defined as 12 months of spontaneous amenorrhea without an alternative medical cause, and can be confirmed with serum follicle-stimulating hormone [FSH] levels in the postmenopausal range as determined by the central laboratory); (2) is 6 weeks postsurgical 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 EOT visit, and at the EOS visit. This applies even if the subject practices true abstinence from heterosexual contact.
- A male subject who is not of reproductive potential is eligible without requiring the use of contraception. A male subject who is not of reproductive potential is defined as one who has undergone a successful vasectomy. A successful vasectomy is defined as (1) microscopic documentation of azoospermia or (2) a vasectomy more than 2 years ago with no resultant pregnancy despite sexual activity post-vasectomy.
- A male or female subject who is of reproductive potential agrees to remain truly abstinent or use (or have their partner use) acceptable methods of highly effective contraception starting from the time of consent through 3 months after the completion of study drug. True abstinence is defined as abstinence that is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of the study, and withdrawal are not acceptable methods of contraception. Acceptable methods of highly effective birth control are combined or progesterone-only hormonal contraception that is associated with inhibition of ovulation, intrauterine device, and intrauterine hormone-releasing system.

8. Be capable of giving informed consent and reading and signing the ICF after the nature of the study has been fully explained by the investigator or investigator designee.
9. Be willing and able to complete all study assessments and procedures and to communicate effectively with the investigator and site staff.

8.2. Subject Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

1. Hospital discharge for sickle cell crisis or other vaso-occlusive event within the 4 days prior to randomization (Day 1).
2. Subjects participating in a chronic/prophylactic RBC transfusion program (i.e., regularly scheduled RBC transfusions); any transfusions within 21 days of screening or baseline Hb measurements.
3. Subjects with HbF >25% at screening.
4. Subjects with known active hepatitis A, hepatitis B, or hepatitis C, with active or acute event of malaria, or who are known to be positive for human immunodeficiency virus (HIV).

5. For female subjects of childbearing potential, a positive serum human chorionic gonadotropin (hCG) test (screening) or a positive urine hCG test at randomization (Day 1).
6. Significant kidney disease as indicated by, for example, estimated glomerular filtration rate (eGFR) <45 mL/min as calculated by the equation from the Modification of Diet in Renal Disease (MDRD) Study using creatinine, age, sex, and ethnicity (modified MDRD formula).
7. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3× the upper limit of normal.
8. Body mass index (BMI) <17.0 kg/m^2 or >35 kg/m^2; or total body weight <45 kg.
9. Current or history of malignancies (solid tumors and hematological malignancies), unless the subject has been free of the disease (including completion of any active or adjuvant treatment for prior malignancy) for ≥5 years. However, subjects with the following history of/concurrent conditions are allowed if, in the opinion of the investigator, the condition has been adequately diagnosed and is determined to be clinically in remission, and the subject's participation in the study would not represent a safety concern:
    a. Basal or squamous cell carcinoma of the skin
    b. Carcinoma in situ of the cervix
    c. Carcinoma in situ of the breast
    d. Incidental histologic finding of prostate cancer (T1a or T1b using the tumor, nodes, metastasis clinical staging system)
10. 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 the IB).
11. History of unstable or deteriorating cardiac or pulmonary disease within 6 months before signing the ICF, including but not limited to the following:
    a. Unstable angina pectoris or myocardial infarction or elective coronary intervention
    b. Congestive heart failure requiring hospitalization
    c. Uncontrolled clinically significant arrhythmias
12. Any condition affecting drug absorption, such as major surgery involving the stomach or small intestine (prior cholecystectomy is acceptable).
13. On ECG testing at ICF signing and/or randomization (Day 1), a 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.
14. Major surgery within 8 weeks or minor surgery within 2 weeks of randomization (Day 1).

15. Stroke requiring medical intervention within 24 weeks prior to randomization (Day 1).
16. Subjects taking DOACs (apixaban, dabigatran, rivaroxaban, edoxaban, or ticagrelor) or taking warfarin, unless they stopped the treatment at least 28 days prior to randomization (Day 1); low molecular weight heparins are allowed in the peri-operative period; aspirin use (<100 mg per day) is allowed before and during the study.
17. 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.
18. Subject has received chronic systemic glucocorticoids within 12 weeks prior to randomization (≥5 mg/day prednisone or equivalent). Physiologic replacement therapy for adrenal insufficiency is allowed.
19. Any clinically significant bacterial, fungal, parasitic, or viral infection requiring antibiotic therapy should delay screening/randomization (Day 1) until the course of antibiotic therapy has been completed. This includes, but is not limited to, long-term tuberculosis treatment.
20. Participated in another clinical study of an investigational agent (or medical device) within 30 days or 5 half-lives of date of informed consent, whichever is longer, or is currently participating in another study of an investigational agent (or medical device).
21. Prior exposure to IMR-687.
22. History of crizanlizumab (Adakveo®) or voxelotor (Oxbryta®) use within 6 months prior to signing the ICF or anticipated need for such agents during the study.
23. Consumption/use of the following drugs or other substances within the specified time periods before randomization or plans to consume/use at any time during the study. If there is any question as to whether a substance is permitted, please review the product labeling (if applicable) and consult the medical monitor and/or sponsor.
    a. Phosphodiesterase type 5 (PDE5) inhibitors (including but not limited to sildenafil, tadalafil, and vardenafil) within 7 days prior to randomization (Day 1) or plans to use during the study.
    b. Grapefruit, grapefruit juice, grapefruit products, or herbal supplements with CYP altering abilities within 1 week prior to randomization (Day 1) or plans to consume during the study.
    c. CYP3A-sensitive substrates, including the opioids fentanyl and alfentanil, or moderate to strong CYP3A inhibitors or inducers within 28 days prior to randomization (Day 1) or plans to use during the study.
    d. Any drugs or substances known to be substrates or inhibitors of P-gp or BCRP within 28 days prior to randomization (Day 1) or plans to use during the study.

24. Receipt of erythropoietin, luspatercept (Reblozyl®), or other erythropoiesis-stimulating or erythroid maturation agent within 6 months prior to signing the ICF or anticipated need for such agents during the study.
25. Prior gene therapy.
26. Any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study, including the presence of laboratory abnormalities that may place the subject at unacceptable risk if he/she were to participate in the study.
27. Other prior or ongoing medical condition, physical findings, or laboratory abnormality that, in the investigator's opinion, could adversely affect the safety of the subject, make it unlikely that the course of treatment or follow-up would be completed, or impair the assessment of study results (e.g., a history of drug or alcohol abuse within the past 1 year, as judged by the investigator).

8.3. Screen Failures

Any subject who consents to participate in the study but is not randomized will be considered a screen failure. Demographic data, 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 considered 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 withdraw from participation in the study at any time and for any reason, without prejudice to further medical care.

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 withdrawn from study participation, the medical monitor should be informed and consulted regarding possible appropriate assessments to be completed in advance of study withdrawal. In case of withdrawal from the study, every effort will be made to complete both the early termination (ET) visit assessments and the EOS visit assessments, if possible. If a subject does not complete the ET assessments, every effort should be made to obtain the EOS assessments; in this case, the ET and EOS visits will coincide. 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 1 week apart. Additionally, a 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 withdraws from the study, the specific circumstances surrounding the withdrawal must be recorded in the subject's eCRF.

Refer to Section 8.6 for details on subject replacement.

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

In consultation with the medical monitor, the investigator may decide to withhold or discontinue study drug dosing in cases where tolerability or safety concerns emerge. Table 2 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 2: Safety Guidelines for Study Drug Dose Reduction, Withholding, 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 1 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 regarding when to resume study drug.

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

8.6. Replacement of Subjects

If a subject withdraws or is withdrawn from the study 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. The replacement subject will receive the same treatment assignment as the replaced subject. Up to 10 subjects total may be replaced. Refer to Section 7 and Section 10.1 for details about treatment assignments and randomization. Refer to Section 8.5 for guidelines on study drug dose reduction, 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 data will include review by the DMC, which may include the recommendation to terminate the study early, 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. Study Drug

Study drug (IMR-687 or placebo) is to be taken as 2 tablets orally qd.

IMR-687 will be supplied as 100, 150, or 200 mg white tablets. To optimize dosing, 60 kg will be used as the body weight gate for the administered 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 be supplied as white tablets containing matrix absent IMR-687. The placebo tablets are visually identical to the IMR-687 tablets.

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.

9.2. 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 labeled with a suitable Annex 13 country compliant product label.

9.3. 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 labeled 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.

9.4. Administration

Subjects will be advised to take 2 tablets (IMR-687 or matched placebo) orally qd during the treatment period. Subjects will be directed to take their study drug with food. On days when study drug is taken in the clinic, food details will also be recorded.

9.5. 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 4; 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.

9.6. 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 ICF signing through the end of the study must be recorded along with the following:

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

Subjects receiving HU must have received it continuously for at least 6 months prior to signing the ICF, and must have been on a stable dose for at least 3 months prior to signing the ICF, with no anticipated need for dose adjustments during the study including the screening period, in the opinion of the investigator.

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 1 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.

9.6.1. Non-investigational Medicinal Products

Not applicable.

9.6.2. 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 CYP3A enzymes; and any drugs or substances that are substrates or 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.

- Previous use (within 6 months prior to signing the ICF) or concomitant use of erythropoietin, luspatercept (Reblozyl®), or other erythropoiesis-stimulating or erythroid maturation agent.
- Previous use (within 6 months prior to signing the ICF) or concomitant use of crizanlizumab (Adakveo®) or voxelotor (Oxbryta®).
- 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.

9.6.3. Prohibited Concomitant Procedures

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

If a subject requires a blood transfusion at the Day 1 or Week 4 visit, the medical monitor should be notified, and the visit will be rescheduled while the subject proceeds with the transfusion. If a subject requires a blood transfusion during the study, the subject may continue to receive study drug and participate in the study.

9.7. 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. On-site 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 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. Randomization will be stratified by use of HU and by region (regions will be defined in the statistical analysis plan). 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).

Randomization numbers will not be re-used once assigned. In the event that a subject is replaced (refer to Section 8.6), the replacement subject will receive the same treatment assignment as the replaced subject, and a different leading number will be used for the replacement randomization number. Additional details on randomization will be specified in the randomization plan provided by the interactive voice/web response system (IXRS) vendor.

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. The blinded sponsor and contract research organization (CRO) study team members will be unblinded to the analysis results at the conclusion of the study (e.g., database lock).

10.3. Unblinding for Interim Analyses

To facilitate the IAs, certain sponsor representatives and designees will be unblinded to treatment assignments prior to and during the IAs (including the unblinded CRO biostatistician and external groups for bioanalytical, PK, and PK/PD 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 that a subject experiences a VOC, an SAE, or an event that results in cessation of treatment (see Section 8.7). However, in the exceptional circumstance in which 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 the ET and EOS visits according to the schedule of assessments (Table 1).

11. ASSESSMENTS

Refer to the schedule of assessments (Table 1) for the timing of the assessments described below. 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 1). The visits are as follows:

- Screening (up to 28 days prior to Baseline)
- Baseline (Day 1)
- Treatment Period (Week 1 to Week 52)
  - Telephone visits will be performed at Week 2 and Week 6
- EOT/ET (Week 52)
- EOS (Week 56)

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 PD/efficacy 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.

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.

The diagnosis of SCD (HbSS, HbSβ^0 thalassemia, or HbSβ^+ thalassemia) should be confirmed in the medical record; if not available, the diagnosis must be confirmed at the site's local laboratory instead.

11.1.3. Inclusion/Exclusion Criteria Evaluation

Eligibility will be assessed 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. Height

Height in centimeters (cm) will be measured at the screening and EOT/ET visits (Table 1).

11.1.5. 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.

11.2. Efficacy and Pharmacodynamic Assessments

11.2.1. Specialty Hematology

Blood samples will be collected for HbF and % F-cells at selected study visits as shown in the schedule of assessments (Table 1). Refer to the specialty laboratory manual for details on the collection, handling, and processing of blood samples.

11.2.2. Pharmacodynamic Assessments

Blood samples will be collected for the following efficacy/PD laboratory assessments, many of which are routine clinical safety laboratory assessments, at selected study visits as shown in the schedule of assessments (Table 1).

- Biomarkers of RBC hemolysis (% and absolute reticulocytes, unconjugated [indirect] bilirubin, and LDH)
- Biomarkers of adhesion: soluble E-sel, P-sel, ICAM-1, and VCAM-1
- Biomarkers of inflammation: hsCRP and MPO
- Biomarker of cardiac stress: NT-proBNP
- RBC indices (e.g., MCV) and total Hb

Refer to Section 11.3.6 for additional details on clinical laboratory assessments.

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

11.2.3. Clinical Assessment: VOCs

VOC is defined as a documented episode of an acute painful crisis (for which there was not an explanation other than VOC) that involves moderate to severe pain lasting for at least 2 hours and at least one of the following:

- Use of escalated analgesia (including healthcare professional-instructed use of an analgesic prescription)
- A hospital, emergency department, or clinic visit and/or healthcare telephone consultation at the time of occurrence
- Diagnosis of ACS (defined as an acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on a chest X-ray), hepatic sequestration, splenic sequestration, or priapism (in males)

11.2.4. Quality of Life Assessments

Data on QoL will be collected as per the schedule of assessments (Table 1).

The **A**dult **S**ickle **C**ell **Q**uality of **L**ife **Me**asurement Information System (ASCQ-Me®) is a systematic, reliable, and valid method for documenting adult SCD patient-reported outcomes. The questions are grouped into 3 domains (physical, social, and emotional) encompassing 7 subdomains, of which the following 5 will be measured: emotional impact, pain impact, sleep impact, social functioning impact, and stiffness impact. (Note: pain episodes and frequency, and SCD medical history checklist will not be evaluated). Each subdomain includes 5 to 9 items. Recall periods vary by subdomain and even question, with most of the periods being from 7 days to 30 days (Keller 2014).

The **P**atient-**R**eported **O**utcomes **M**easurement **I**nformation **S**ystem (PROMIS®), is a National Institutes of Health initiative to develop state-of-the-science self-report measures to assess functioning and well-being in physical, mental, and social domains of health. The **PRO**MIS - **Pr**eference (PROMIS® 29 + 2 Profile v 2.1 [PROPr]) score can be estimated using the following 7 PROMIS domains: cognitive function, emotional distress, fatigue, pain interference, physical function, ability to participate in social roles and activities, and sleep disturbance. Each domain is rated on a 5-point Likert scale. Recall periods vary by subdomain with most periods being in the past 7 days (Hanmer 2018). The translated QoL assessments from PROPr will be used when available.

The **S**ickle **C**ell **S**elf-**E**fficacy **S**cale (SCSES) is a 9-item QoL measure for adults with SCD. This measure is a self-appraisal of an SCD patient's ability to engage in daily functional activities and to manage SCD symptomatology. Response choices range from "not at all sure" to "very sure" (Edwards 2000).

11.3. Safety Assessments

11.3.1. Telephone Visits

Qualified site personnel will contact the subject by telephone at Week 2 and Week 6 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 and should be consistently measured in either the sitting or semi-supine position. Vital signs will be collected at every on-site visit (Table 1).At the Day 1 and Week 4 visits, 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 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 selected study visits as shown in the schedule of assessments.

11.3.4. Physical Examination

A complete PE will be conducted at selected study visits (including screening) as shown in the schedule of assessments (Table 1); at other visits, a symptom-driven PE may be conducted. The complete PE 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.

During the course of the study, PEs will be symptom directed (except where indicated otherwise); symptom-directed PEs will be obtained after identification of AEs deemed by the investigator to be of significant clinical concern.

Clinically significant findings that were present prior to the signing of informed consent must be included on 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 AEs 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) at selected study visits as shown in the schedule of assessments.

At the Baseline (Day 1), Week 1, and Week 4 visits, ECGs will be obtained pre-dose and 2 hours (±30 minutes) post-dose. At all other timepoints, ECG 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 12.1.1.

11.3.6. Laboratory Assessments

Blood and urine samples will be collected for routine clinical safety laboratory assessments according to the schedule of assessments. Clinical safety tests will be assessed to evaluate IMR-687 safety and tolerability. Some of these tests are also considered efficacy assessments.

For both safety and efficacy evaluations, laboratory tests specified in the protocol will be performed by a central laboratory. Because knowledge of certain laboratory assessments (HbF, % F-cells, MCV, total and unconjugated [indirect] bilirubin, and absolute and % reticulocyte count) may unblind the treatment assignment, these measurements will be blinded at the central laboratory. Based on predefined safety laboratory alerts, these blinded laboratory assessments may be communicated to the investigator.

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 (MCV, mean corpuscular Hb, and mean corpuscular Hb concentration), hematocrit (Hct), Hb, HbF, platelets, absolute WBC count (with differential: basophils, eosinophils, neutrophils, monocytes, and lymphocytes), erythrocyte count, reticulocyte count, and reticulocyte percentage. Some of these assessments are also considered efficacy/PD endpoints (refer to Section 11.2).

11.3.6.2. Coagulation

Coagulation assessments will include prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR).

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, eGFR, and gamma-glutamyl transferase (GGT). FSH is added for post-menopausal women at screening. Some of these assessments are also considered efficacy/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). Urine creatinine, Pr:Cr ratio, and microalbumin will be completed with each analysis.

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. AEs 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. Pharmacokinetics Assessments

Serial blood samples will be collected at the timepoints indicated in the schedule of assessments for the determination of IMR-687 plasma concentrations (including metabolites and HU, if applicable). Trough blood samples (pre-dose) will be drawn at the specified timepoints (Table 1). The date/time of the last administered 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 EOS safety follow-up visit. 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 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, the following:

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

Additionally, AEs 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 Event

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., is 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

AE severity (intensity) will be graded using National Cancer Institute Common Terminology for Adverse Events (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

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

Telephone: +49 621 878 2154

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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.

SAEs 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 IB 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 fulfill 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 8.4.

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 the following:

- 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 AE(s), is captured as an AE.

13. STATISTICS

13.1. General Considerations

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

Continuous variables will be summarized using descriptive statistics (number of subjects, mean, standard deviation [SD], median, first quartile [Q1], third quartile [Q3], minimum, and maximum) and, where appropriate, coefficient of variation (%CV) and graphic representation. Categorical data will be summarized by sample size and proportions.

An IA will be performed after all randomized subjects have reached Week 24 or terminated early. Alpha spending will be needed based on the results of these analyses. A final analysis (FA) will be conducted at study completion (i.e., when all subjects have reached Week 56 or terminated early).

13.2. Analysis Datasets

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

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 any measurable IMR-687 concentration-time data; this set will be used to generate the corresponding PK concentration summaries and plots.

The PK evaluable set will be defined as a subset of the safety analysis set that received at least 1 dose of IMR-687 and has at least 4 consecutive non-zero post-dose IMR-687 concentration-time data points. The PK Evaluable Set will be used to generate the corresponding PK exposure (parameter) assessments.

The intent-to-treat (ITT) set will include all randomized subjects. The ITT set will be used as the primary analysis set to summarize efficacy, PD, and clinical outcome parameters. Subjects will be analyzed according to their randomized treatment assignment.

The modified intent-to-treat (mITT) set will include all randomized subjects who had at least 1 VOC in the 12 months prior to randomization and have received at least 1 dose of study drug. The mITT set will be used for sensitivity analyses of efficacy, PD, and clinical outcome parameters. Subjects will be analyzed according to their randomized treatment assignment.

The per protocol (PP) set will include all subjects of the safety analysis set who had at least 1 VOC in the 12 months prior to randomization, completed at least 1 valid clinical outcomes assessment without major protocol deviations or events that would be expected to affect the analysis and did not discontinue prior to Week 24 for reasons other than AEs. The PP set will be identified based on blinded data prior to unblinding the mITT dataset. The PP set will be used for sensitivity analyses of efficacy, PD, and clinical outcome parameters.

13.3. Safety Analyses

Descriptive statistics will be used to summarize all safety endpoints, by 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 the Medical Dictionary for Regulatory Activities (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. Efficacy Analyses

Primary Efficacy Analysis

The primary efficacy endpoint, annualized rate of VOCs, will be analyzed using a stratified Wilcoxon rank-sum test based on stratification factors of region (North America/Europe versus Africa/Middle East) and HU use (Yes versus No) to compare the treatment effect of the highest tolerated dose of IMR-687 to placebo. VOCs are defined for this study in Inclusion Criterion 3 (Section 8.1).An IA will be performed after all randomized subjects have reached Week 24 or terminated early. A Lan-DeMets alpha spending function will be used to determine the significance levels for the IA to maintain an overall type I error rate of 5% for 2-sided tests.

Secondary Efficacy Analyses

The first key secondary efficacy endpoint, time to first VOC, will be analyzed using a stratified log rank test (stratification factors of HU use and region) and stratified Cox regression model to compare the treatment effect of the highest tolerated dose of IMR-687 to placebo.

The second key secondary efficacy endpoint, proportion of HbF responders (defined as the proportion of subjects with an absolute increase of ≥3% in HbF from baseline) at Week 24, will be analyzed using a stratified Cochran-Mantel-Haenszel (CMH) test based on stratification factors of HU use and region to compare the highest tolerated dose of IMR-687 to placebo.

Other secondary endpoints that will be tested at the highest tolerated dose include the following:

- Proportion of VOC-free subjects
- Annualized rate of hospitalizations for VOCs
- Time to second VOC
- Proportion of HbF responders (defined as the proportion of subjects with an absolute increase of ≥3% in HbF from baseline) at Week 52
- Change from baseline in HbF (%) and F-cells (%) at Week 24 and Week 52
- Proportion of Hb responders (defined as the proportion of subjects with an increase of ≥1.0 g/dL in total Hb from baseline) at Week 24 and Week 52
- Change from baseline in total Hb (g/dL) at Week 24 and Week 52

- Change from baseline in biomarkers of RBC hemolysis (% and absolute reticulocytes, unconjugated [indirect] bilirubin, and LDH) at Week 24 and Week 52
- Change from baseline in each measured subdomain of the ASCQ-Me® questionnaire at Week 24 and Week 52
- Change from baseline in total preference score and individual domain scores of the PROPr questionnaire at Week 24 and Week 52
- Change from baseline in overall score of the SCSES at Week 24 and Week 52
- Change from baseline in biomarkers of adhesion such as soluble E-sel, P-sel, ICAM-1, and VCAM-1 at Week 24 and Week 52
- Change from baseline in biomarkers of inflammation such as hsCRP and MPO at Week 24 and Week 52
- Change from baseline in biomarkers of cardiac stress such as NT-proBNP at Week 24 and Week 52
- Change from baseline in RBC indices, such as MCV, at Week 24 and Week 52

The secondary endpoints of proportion of HbF responders at Week 52 and proportion of Hb responders at Week 24 and Week 52 will each be analyzed in a similar manner as the second key secondary efficacy endpoint using a stratified CMH test based on stratification factors of HU use and region.

The annualized rate of hospitalizations for VOCs will be analyzed using a stratified Wilcoxon rank-sum tests based on stratification factors of HU use and region.

Change from baseline endpoints for continuous variables will be analyzed using mixed models for repeated measures (MMRM) with treatment, visit, and treatment-by-visit interaction as fixed effects, and baseline value, HU use, and region as covariates. Unstructured covariance matrices will be used. If there are convergence problems, then the use of other covariance matrices will be considered as appropriate.

Time-to-event endpoints will be analyzed using log-rank tests, and Kaplan-Meier plots will be provided.

An FA will be conducted at study completion (i.e., when all subjects have reached Week 56 or terminated early). A Lan-DeMets alpha spending function will be used to determine the significance levels for the IA and FA to maintain an overall type I error rate of 5% for 2-sided tests. At the FA endpoints will be tested in a sequential hierarchical order at the highest tolerated dose.

13.5. Pharmacokinetic Analyses

Summary statistics for trough (C_{trough}) and other plasma concentration 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 the PK data from other clinical studies for a population PK analysis, as appropriate.

13.6. Analyses of Exploratory Endpoint

Change from baseline in renal function as measured by the urine Pr:Cr ratio and microalbumin at Week 24 and Week 52 will be summarized with descriptive statistics by treatment group.

The statistical analysis plan will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

13.7. Sample Size Calculation

The sample size of this study was previously determined based on HbF responder rate, comparing the highest tolerated dose of IMR-687 to placebo, as the primary endpoint:

The sample size was determined assuming that the percentage of subjects who are HbF responders (i.e., have an HbF increase of ≥3% from baseline) at Week 24 is 5% in the placebo arm and 35% in either of the IMR-687 arms, with a 20% dropout rate prior to Week 24. Based on these assumptions, 26 subjects/arm at Week 24 is sufficient to achieve 80% power to detect a difference between the highest tolerated IMR-687 dose and placebo in the HbF responders at Week 24 at a 2-sided significance level of 0.05.

Based on regulatory feedback, annualized rate of VOCs was elevated from a key secondary endpoint to the primary endpoint, with a corresponding change in statistical methodology:

Assuming that the actual data distribution is normal when the significance level (alpha) of the test is 0.05, the standard deviation is 2.7 in both groups, and there are no dropouts, there will be 88% power to detect a difference between the medians of 5.0 and 3.0 for the placebo and the IMR-687 highest tolerated dose groups, respectively (i.e., a 40% difference), using a 2-sided Wilcoxon rank-sum test.

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 will 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 MedDRA 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), and the progress of enrollment. The monitors will also ensure that study drug 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 or a notice informing the subject of the following:

- The sponsor's (i.e., Data Controller's) identity.
- The European Union 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.

  Note: 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. 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 or Independent Ethics Committee

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 International Council for Harmonisation (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, the following:

- US CFR
- 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 who 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 1 year of the end of the study (worldwide).

The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor.

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 ET 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, IB, 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

17.1. Appendix 1: 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.

17.2. Appendix 2: National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, version 5.0)

AEs will be graded according to NCI CTCAE, version 5.0.

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

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