A Phase 2a, Randomised, Double-Blind, Placebo-Controlled Study of IMR-687 in Adult Patients with Sickle Cell Anaemia (Homozygous HbSS or Sickle-β^0 Thalassemia)

Unique Protocol ID:	IMR-SCD-102
NCT Number:	NCT03401112
EudraCT Number:	2017-000653-39
Date of Protocol:	28 June 2019

CLINICAL TRIAL PROTOCOL

Study Title:	A Phase 2a, Randomised, Double-Blind, Placebo-Controlled Study of IMR-687 in Adult Patients with Sickle Cell Anaemia (Homozygous HbSS or Sickle-β^0 Thalassemia)
Study Number:	IMR-SCD-102
Study Phase:	2a
Product Name:	IMR-687
IND Number:	130549
EudraCT Number:	2017-000653-39
Protocol Version:	United States: 008 United Kingdom: 011
Protocol Date:	28 June 2019
Indication:	Sickle Cell Anaemia (Homozygous sickle HbSS or Sickle-β^0 Thalassemia)
Sponsor:	Imara 700 Technology Square, 3rd Floor Cambridge, MA 02139
Sponsor Contact:	PPD Imara PPD

SIGNATURE PAGE

Sponsor's Approval

The protocol has been approved by Imara, Inc.

Sponsor's Authorized Officer:

PPD

Imara, Inc.

PPD

28 Jun 2019

Date

INVESTIGATOR'S AGREEMENT

I have read the Protocol IMR-SCD-102 and agree to conduct the study in compliance with the approved protocol and will adhere to Good Clinical Practice (GCP) and all applicable laws and regulatory requirements. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

KEY ROLES AND RESPONSIBILITIES

Emergency Contact Information

Role in Study	Name	Telephone number
Responsible Physician	PPD	
Medical Advisor		

Safety Review Committee

A Safety Review Committee (SRC) will review all available clinical safety data approximately every 2 weeks (with additional ad hoc meetings, if necessary) throughout the study. The SRC must approve any intra-patient dose escalations as well as the initiation of treatment in Population B (patients receiving a stable dose of hydroxyurea). The minutes from all SRC meetings will be documented in writing and retained in the study files.

The composition of the SRC as well as specific governing procedures (e.g., convening meetings, executing responsibilities) will be described in the SRC charter, which is maintained as a separate document.

1. PROTOCOL SUMMARY

1.1. Synopsis

Name of Sponsor/Company: Imara	
Name of Investigational Product: IMR-687	
Name of Active Ingredient: 6-[(3S,4S)-4-methyl-1-(pyrimidin-2-ylmethyl)pyrrolidin-3-yl]-3-tetrahydropyran-4-yl-7H-imidazo[1,5-a]pyrazin-8-one	
Title of Study: A Phase 2a, Randomised, Double-Blind, Placebo-Controlled Study of IMR-687 in Adult Patients with Sickle Cell Anaemia (Homozygous HbSS or Sickle-β^0 Thalassemia)	
Study centre(s): This study will be conducted at approximately 10 study sites in the United States (US) and up to 10 study sites in the United Kingdom (UK).	
Studied period (years): Estimated date first patient enrolled: January 2018 Estimated date last patient completed: December 2019	**Phase of development:** 2a

Objectives:

Primary Objectives:

- To assess the safety and tolerability of IMR-687 in adult patients with sickle cell anaemia (SCA), defined as homozygous sickle haemoglobin (HbSS) or sickle-β^0 thalassemia, who are not receiving hydroxyurea (HU) and in adult SCA patients who are receiving a stable dose of HU

Secondary Objectives:

- To characterise the pharmacokinetic (PK) profile of IMR-687 in adult patients with SCA who are/are not receiving a stable dose of HU
- To characterise the PK profile of HU in adult patients with SCA before and after receiving IMR-687 to determine whether there is a clinically relevant PK interaction.

Exploratory Objectives:

- To assess the pharmacodynamic (PD) effects of IMR-687 in adult patients with SCA who are/are not receiving stable HU
- To assess the potential efficacy of IMR-687 on SCA-related clinical outcome measures in adult patients with SCA who are/are not receiving stable HU

Methodology:

This is a randomised, double-blind, placebo-controlled study to evaluate the safety, tolerability, PK, and exploratory PD and clinical outcomes of the phosphodiesterase (PDE) type 9 (PDE9) inhibitor, IMR-687, administered once daily for 16 to 24 weeks in 2 populations of patients with SCA: those who are not receiving HU (Populations A and A1) and those who are currently receiving a stable dose of HU according to standard of care (Populations B and B1). Approximately 60 patients will be enrolled in Populations A and A1 combined and approximately 30 patients will be enrolled in Population B and B1 combined.

Population A is composed of those patients already enrolled at the time of this amendment who are not receiving HU. These patients will attend site visits at the time points specified in the Schedule of Assessments (SOA) provided in Table 1 (Population A). Population A1 is composed of patients who are not receiving HU and will be enrolled after this amendment. These patients will attend site visits at the time points specified in the SOA provided in Table 2. Population B consists of those patients already enrolled at the time of this amendment who are receiving stable doses of HU. These patients will attend site visits at time points specified in the SOA provided in Table 3. Population B1 consists of patients who are receiving stable doses of HU and will be enrolled after this amendment. These patients will attend site visits at the time points specified in the SOA provided in Table 4. In addition, for the first 4 weeks for each population, patients will be seen in person once a week for an abbreviated physical examination and collection of adverse events (AEs) and vital signs; thereafter, telephone-based check-

ins may be performed on weeks where there are no scheduled assessments. Safety and concomitant medications will be monitored throughout the study, while PK, PD, and clinical outcome measures will be performed at selected site visits.

All available clinical data from all patients in all populations will be collated and submitted to a Safety Review Committee (SRC) for review approximately every 2 weeks throughout the course of the entire study.

The study designs for Populations A, A1, B, and B1 are depicted graphically in Figure 1, Figure 2, Figure 3, and Figure 4, respectively.

Population A

Following a Screening period of up to 4 weeks, eligible patients in Population A (i.e., those enrolled prior to this amendment and not receiving HU) will receive either IMR-687 or placebo for a total of 24 weeks. On Day 1, patients will be randomised 1:1:1 to receive oral IMR-687 50 mg, IMR-687 100 mg, or placebo daily for the first 12 weeks; for the second 12 weeks (Weeks 13-24), each patient's dose may be doubled (i.e., from 50 mg to 100 mg; from 100 mg to 200 mg; or placebo). (*Note:* Because placebo and all dose levels of IMR-687 are the same in appearance, dose escalation will not affect study medication blinding.)

Throughout the study, all available clinical data will be reviewed approximately every 2 weeks by the SRC, and dose escalation will occur on an individual-patient basis on Day 85 only if approved by the SRC based on review of each patient's individual clinical safety data.

Safety, PK, PD, and efficacy assessments will be performed at the time points shown in Table 1.

Population A1

Following a Screening period of up to 4 weeks, eligible patients in Population A1 (i.e., those enrolled after this amendment and not receiving HU) will receive either IMR-687 or placebo for a total of 24 weeks. On Day 1, patients will be randomised 2:1 to receive oral IMR-687 100 mg or placebo daily for 4 weeks; for the subsequent 20 weeks (Weeks 5-24), each patient's dose may be doubled (i.e., from 100 mg to 200 mg; or placebo). (*Note:* because placebo and all dose levels of IMR-687 are the same in appearance, dose escalation will not affect study medication blinding.)

Throughout the study, all available clinical data will be reviewed approximately every 2 weeks by the SRC, and dose escalation will occur on an individual-patient basis on Day 29 only if approved by the SRC based on review of each patient's individual clinical safety data.

Safety, PK, PD, and efficacy assessments will be performed at the time points shown in Table 2.

Population B

Following a Screening period of up to 4 weeks, eligible patients in Population B (i.e., those enrolled prior to this amendment and receiving stable HU) will enter an approximately 8-week lead-in period and will have blood samples drawn to characterise the PK profile of the patient's prescribed dose of HU in the absence of IMR-687 (i.e., to characterise the patient's baseline HU PK profile). Two full baseline HU PK profile (with blood samples drawn over a 10-hour period) will be determined.

IMR-687 dosing in Population B will not begin until at least 4 weeks of safety data from 6 patients in Population A have been reviewed by the SRC and the SRC has determined that it is safe and appropriate to begin dosing in Population B. Following SRC approval to initiate dosing in Population B and once the baseline HU PK blood draw are complete, patients will be randomised 2:1 on Day 1 to receive oral IMR-687 50 mg or placebo for 16 weeks. For the first 4 weeks (Weeks 1-4), patients will receive study medication according to their randomised treatment assignment; for the following 12 weeks (Weeks 5-16), each patient's dose may be doubled (i.e., from 50 mg to 100 mg; or placebo). Dose escalation will occur on Day 29 only if approved by the SRC based on review of each patient's individual clinical safety data. (*Note:* because placebo and all dose levels of IMR-687 are the same in appearance, dose escalation will not affect study medication blinding.)

Safety, PK, PD, and efficacy assessments will be performed at the time points shown in Table 3.

Population B1

Following a Screening period of up to 4 weeks, eligible patients in Population B1 (i.e., those enrolled after this amendment and receiving stable HU) will enter an approximate 4-week lead-in period and will have a single set of blood samples drawn to characterise the patient's baseline HU PK profile.

Once the baseline HU PK blood draw is complete, patients will be randomised 2:1 on Day 1 to receive oral IMR-687 or placebo for 24 weeks. For the first 4 weeks (Weeks 1-4), patients will receive study medication according to their randomised treatment assignment (i.e., 50 mg or placebo); for the following 20 weeks (Weeks 5-24), each patient's dose may be doubled (i.e., from 50 mg to 100 mg; or remain on placebo). Dose escalation will occur on Day 29 only if approved by the SRC based on review of each patient's individual clinical safety data. (*Note:* because placebo and all dose levels of IMR-687 are the same in appearance, dose escalation will not affect study medication blinding.)

Safety, PK, PD, and efficacy assessments will be performed at the time points shown in Table 4.

Study Design Rationale

This is the first study in a patient population (patients with SCA), and as such, is designed to examine the safety, tolerability, and PK, as well as the potential PD effects and clinical efficacy, of IMR-687 across a range of doses in adult patients with SCA. Given the possibility that IMR-687, if approved, could be administered as a single agent or co-administered with HU, the effects of IMR-687 will be evaluated in SCA patients who are not receiving HU or any other treatment known to modulate foetal haemoglobin (HbF) levels (Populations A and A1), as well as in those who are currently receiving a stable dose of HU (Populations B and B1).

Available nonclinical and healthy volunteer clinical data suggest that IMR-687 will be safe and well tolerated at once daily doses of 50, 100, and 200 mg and that a potentially clinical beneficial PD effect is likely to be observed when a dose of at least 100 mg is administered for at least 24 weeks. Therefore, Populations A and A1 are designed to explore the PD dose response in patients as well as the tolerability of the 200 mg dose level in sickle cell patients who have tolerated the 100 mg dose well.

Results from Populations B and B1 are intended to provide information on IMR-687 when administered concomitantly with HU, both of which increase HbF levels through alternative biochemical pathways that increase intracellular cyclic guanosine monophosphate (cGMP). Because there are no clinical data to support administration of IMR-687 concomitantly with HU, patients in Population B will initiate IMR-687 dosing at the low dose (50 mg) and will only escalate to the 100 mg dose if the 50 mg dose has been safe and tolerated for 4 weeks. In addition, although available nonclinical data do not suggest that concomitant administration of HU with IMR-687 would increase IMR-687 exposure, dosing in Population B will not initiate until 4 weeks of safety data are available from Population A in2 patients each at 50 mg (starting dose in Population B) and at 100 mg (twice the starting dose) as well as placebo.

Number of patients (planned):

A total of approximately 90 evaluable patients are expected to enroll in this study.

- In Populations A and A1, approximately 60 adult patients with a confirmed diagnosis of SCA who have not received HU for at least 90 days prior to Screening and who are not planning to take HU within the next 6 months will be enrolled.
- In Populations B and B1, approximately 30 adult patients with a confirmed diagnosis of SCA who have received HU for at least 6 months, have been on a stable dose for at least 60 days prior to Screening, and are not planning to change the dose or discontinue HU within the next 6 months will be enrolled.

Diagnosis and main criteria for inclusion:

Inclusion Criteria:

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

1. Male or female ≥18 or ≤55 years of age.
2. Confirmed diagnosis of SCA (HbSS or sickle-B^0 thalassemia). *Note:* If not already documented in the

patient's record, the diagnosis of SCA must be confirmed via electrophoresis, high-performance liquid chromatography (HPLC), and/or genotyping.

3. Use of HU:
   - For patients in Populations A and A1: Have not received HU within 90 days prior to Screening and are not planning to take HU while on the study.
   - For patients in Populations B and B1: Have received HU for at least 6 months, have been on a stable dose for at least 60 days prior to Screening, and are not planning to change the dose level, dose regimen, or discontinue HU within the next 6 months.
4. Female patients must not be pregnant and be highly unlikely to become pregnant. Male patients must be unlikely to impregnate a partner. Male or female patients must meet at least one of the following criteria:
   - A female patient who is not of reproductive potential is eligible without requiring the use of contraception. A female patient 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 local 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 male patient who is not of reproductive potential is eligible without requiring the use of contraception. A male patient 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 patient who is of reproductive potential agrees to remain truly abstinent or use (or have their partner use) acceptable methods of highly effective contraception starting from the time of consent through 3 months after the completion of study therapy. True abstinence is defined as abstinence that is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of the trial and withdrawal are not acceptable methods of contraception. Acceptable methods of highly effective birth control are combined or progestogen-only hormonal contraception that is associated with inhibition of ovulation, intrauterine device, and intrauterine hormone-releasing system.
5. Be capable of giving informed consent and reading and signing the informed consent form after the nature of the study has been fully explained by the investigator or investigator designee.
6. Be willing and able to complete all study assessments and procedures and to communicate effectively with the investigator and site staff.

Exclusion Criteria:

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

1. Total haemoglobin (Hb) at Screening >12.5 g/dL or <6 g/dL.
2. Reticulocyte count <100 x 10^9/L for Populations A and A1, or <80 x 10^9/L for Populations B and B1.
3. Greater than 7 hospitalizations (for at least 24 hours) for vaso-occlusive crises (VOC), including acute chest syndrome and priapism, within the prior year.
4. *(Intentionally left blank.)*
5. Blood transfusion or donation of blood or any blood product within 60 days of Day 1 or on chronic transfusion therapy regimen.
6. Positive for human immunodeficiency virus (HIV), hepatitis C (HCV) antibodies (unless the patient has successfully completed drug therapy that results in cure/clearance of HCV), or hepatitis B surface antigen.
7. For female patients of childbearing potential, a positive serum human chorionic gonadotropin (hCG) test

(Screening) or a positive urine hCG test on Day 1.

8. Estimated glomerular filtration rate (eGFR) <50 mL/min as calculated by the equation from the Modification of Diet in Renal Disease Study using creatinine, age, sex, and ethnicity.
9. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3x the upper limit of normal (ULN).
10. Body mass index (BMI) <17.5 or >35 kg/m^2; a total body weight <50 kg.
11. Use of PDE type 5 (PDE5) inhibitors (including but not limited to sildenafil, tadalafil, vardenafil) within 7 days prior to the first dose of study drug, or planning to use any time during study.
12. A history of drug or alcohol abuse as judged by the investigator within the past 1 year, or a positive alcohol (breathalyser) test (Screening or Day -1).
13. A cancer that has not been in complete remission for at least 5 years. Patients with squamous cell or basal cell carcinoma of the skin, localised cervical cancer, or localised prostate cancer are eligible if, in the opinion of the investigator, the condition has been adequately diagnosed, and is determined to be clinically in remission, and the patient's participation in the study would not represent a safety concern.
14. A history of a clinically significant allergic reaction or hypersensitivity, as judged by the investigator, to any drug or any component of the study drug formulations used in the study.
15. On electrocardiogram (ECG), a corrected QT interval, Fridericia's formula (QTcF) >450 ms in men and >470 ms in women or the presence of clinically significant abnormalities as determined by the investigator.
16. A history of major surgery within 4 weeks or minor surgery within 2 weeks of Day 1.
17. Any flu-like syndrome or other respiratory infection within 2 weeks of Day 1 or vaccination with attenuated live virus within 4 weeks of Day 1.
18. Participation in an investigational drug or device study within 30 days prior to Day 1.
19. Use within 30 days prior to Day 1, or planning to use during the study, of any drugs or substances that are known to strongly inhibit or induce cytochrome P450 (CYP) enzymes, including but not limited to cimetidine, cyclosporine, erythromycin, omeprazole, rifampin, ritonavir, and St. John's wort. If there is any question as to whether a substance is permitted, please review the product labelling (if applicable) and consult the Sponsor.
20. Consumption of grapefruit, grapefruit juice, or grapefruit products within 24 hours prior to Day 1 or planning to consume grapefruit products during the study.
21. Use within 30 days prior to Day 1, or planning to use during the study, of any CYP3A-sensitive substrates (excluding opioids), including but not limited to alfentanil, avanafil, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, ebastine, eletriptan, eplerenone, everolimus, felodipine, ibrutinib, indinavir, lomitapide, lurasidone, maraviroc, midazolam, naloxegol, nisoldipine, quetiapine, saquinavir, sirolimus, tacrolimus, ticagrelor, tipranavir, tolvaptan, and triazolam. If there is any question as to whether a substance is permitted, please review the product labelling (if applicable) and consult the Sponsor.
22. Use within 30 days prior to Day 1, or planning to use during the study, of any drugs or substances known to be significant substrates or inhibitors of P-glycoprotein (P-gp), including but not limited to cyclosporine, lovastatin, propranolol, quinidine, and simvastatin. If there is any question as to whether a substance is permitted, please review the product labelling (if applicable) and consult the Sponsor.
23. Other prior or ongoing medical condition, physical findings, or laboratory abnormality that, in the investigator's opinion, could adversely affect the safety of the patient, make it unlikely that the course of treatment or follow-up would be completed, or impair the assessment of study results.
24. In the opinion of the investigator, the patient is unable to meet the requirements of the study.

Investigational product, dosage and mode of administration:

IMR-687 will be supplied as 50, 100, or 200 mg white tablets and will be administered orally with food. The different doses of IMR-687 are visually identical in tablet form.

Reference therapy, dosage and mode of administration:

Placebo will consist of tablets containing matrix absent IMR-687 and will be identical in appearance to the IMR-687 tablets. Placebo will be administered orally with food.

Duration of study participation and treatment:

The total duration of the study is approximately 32 weeks for Populations A and A1, including a Screening period of up to 4 weeks, a treatment period of 24 weeks, and a 4-week safety follow-up assessment after the last dose of study drug is administered.

The total duration of the study is approximately 32 weeks for Population B, including a Screening period of up to 4 weeks, a lead-in period of approximately 8 weeks, a treatment period of 16 weeks, and a 4-week safety follow-up assessment after the last dose of study drug is administered.

The total duration of the study is approximately 36 weeks for Population B1, including a Screening Period of up to 4 weeks, a lead-in period of approximately 4 weeks, a treatment period of 24 weeks, and a 4-week safety follow-up assessment after the last dose of study drug is administered.

Endpoints:

The endpoints for Populations A, A1, B, and B1 are the same except where noted otherwise.

Primary Endpoints

- IMR-687 safety and tolerability as measured by:
  - Incidence and severity of adverse events (AEs) and serious adverse events (SAEs);
  - Change from baseline in 12-lead ECG parameters, clinical laboratory tests (chemistry, haematology, coagulation, urinalysis), and vital signs
  - Physical examination findings

Secondary Endpoints

- The plasma PK profile of IMR-687 after oral administration to adult patients with SCA (Populations A, A1, B, and B1)
- The plasma PK profile of HU before and after oral administration of IMR-687 to adult patients with SCA (Populations B and B1 only)

Exploratory Endpoints

- IMR-687 PD as measured by the following (additional exploratory biomarkers may also be tested):
  - Total Hb levels
  - HbF value (%)
  - Percent erythrocytes containing HbF (%F cells)
  - Indices of red cell haemolysis (unconjugated bilirubin, reticulocyte count, lactase dehydrogenase [LDH], and haptoglobin levels)
  - Soluble E-selectin (sE-sel), soluble P-selectin (sP-sel), and soluble intercellular adhesion molecule 1 (sICAM-1)
  - High-sensitivity C-reactive protein (hs-CRP)
- IMR-687 clinical outcomes as measured by pain-related measures (frequency, severity, and duration of pain; impact of pain/fatigue on work/school and on activities of daily living; need for/use of pain medication; SCA-related events requiring professional medical or health care, including events requiring hospitalization or therapies, such as transfusions) and in the physical, social, and emotional impact of SCA as measured by the Adult Sickle Cell Quality-of-Life Measurement Information System (ASCQ-Me)

In addition, a separate blood sample will be collected for confirmation of diagnosis by electrophoresis, HPLC, and/or deoxyribonucleic acid (DNA) sequencing (as needed) as well as for possible pharmacogenomic analyses of genes that may affect treatment response (including but not limited to alpha globin and BCL11A).

Statistical Methods:

General Considerations:

Descriptive summary statistics will be provided for demographics, disposition, and IMR-687 exposure (and HU for patients in Populations B and B1). The number and percentage of patients who discontinue from the study, along with reasons for discontinuations will be tabulated and described in listings.

Continuous data will be summarised using descriptive statistics (number of patients, mean, standard deviation [SD], median, minimum, and maximum) and, where appropriate, coefficient of variation (%CV) and graphic representation. Categorical data will be summarised by sample size and proportions. Data will be summarised by population (A, A1, B, and B1) and dose cohort at each time point as appropriate. Graphs of actual values and changes over time may also be created as appropriate.

Analysis Datasets:

The safety analysis set, defined as all patients who have received any amount of study drug and from whom informed consent has been obtained, will be used to summarise all safety and tolerability data.

The PK concentration set, defined as a subset of the safety analysis set that includes all patients who are enrolled in the study, have received one dose of IMR-687, and have any measurable IMR-687 concentration-time data, will be used to generate IMR-687 (and HU for patients in Populations B and B1) PK concentration profiles.

The PK evaluable set, defined as a subset of the PK concentration set that includes all patients who have provided sufficient concentration data without protocol deviations or events that would be expected to affect the PK analysis, will be used to generate IMR-687 (and HU for patients in Populations B and B1) PK parameter data.

The PD evaluable set, defined as a subset of the safety analysis set that includes all patients who have provided samples for PD analysis sufficient to obtain at least one valid PD observation and who are without protocol deviations or events that would be expected to affect the PD analysis, will be used to generate PD observation and parameter data.

The per protocol set, defined as a subset of the safety analysis set that includes all patients who have completed at least one valid clinical outcomes assessment without protocol deviations or events that would be expected to affect the analysis, will be used to generate clinical outcomes data.

Safety Analyses:

Descriptive statistics will be computed for safety parameters, as appropriate. The number and percentage of patients who discontinued from the study because of AEs will be tabulated; severity and frequency of AEs and SAEs will also be summarised. Absolute and, where appropriate, change from baseline in clinical laboratory values, vital signs, and ECG results will also be summarised. All safety data will be provided in listings.

Further statistical evaluations will be applied for select safety endpoints, if warranted.

Pharmacokinetic Analyses:

PK analysis parameters will be estimated using non-compartmental analysis methods. Graphs of individual and mean IMR-687 (and HU for patients in Populations B and B1) plasma concentrations over time will be generated by population and dose cohort as appropriate. The following PK parameters will be determined, as appropriate: maximum concentration (C_{max}); time to maximum concentration (t_{max}); apparent terminal half-life ($t_{½}$); and area under the concentration-time curve (AUC) from time 0 to 12 hours (AUC_{0-12}), from 0 to 24 hours (AUC_{0-24}), from 0 to the last measurable time point (AUC_{last}), and extrapolated to infinity ($AUC_{0-\infty}$). Other PK parameters may be determined as appropriate. PK parameters will be summarised descriptively using the number of non-missing values (n), mean, median, SD, minimum, maximum, %CV, geometric mean, and geometric %CV. Dose proportionality will be assessed.

To assess the potential drug interaction for HU with IMR-687 (test) and HU without IMR-687 (reference) in Populations B and B1, log-transformed PK parameters (C_{max}, AUC) will be analysed using analysis of variance (ANOVA), including terms for visit as a fixed effect and patient as a random effect. Based on this analysis, point estimates and two-sided 90% confidence intervals (CI) for the ratios "IMR-687+HU/HU" will be calculated by back-transformation of the logarithmic data. Within-subject variability will be estimated.

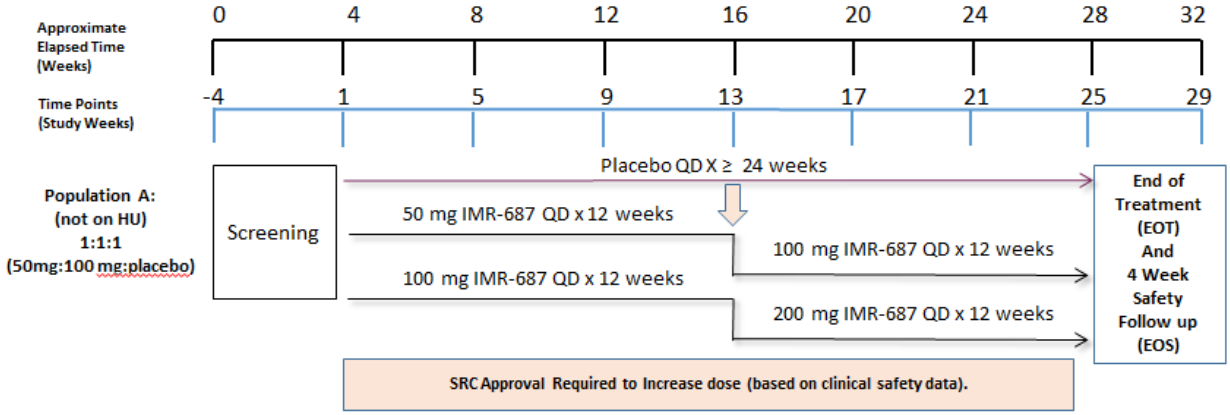
Analyses of Exploratory Endpoints:

Exploratory PD and clinical outcomes data for each time point will be listed by patient and summarised by population and dose cohort as appropriate. Correlations between PK and the exploratory endpoints may be assessed. Descriptive statistics will be computed as appropriate.

1.2. Protocol Schema

The study design for Populations A, A1, B, and B1 are depicted graphically in Figure 1, Figure 2, Figure 3, and Figure 4, respectively.

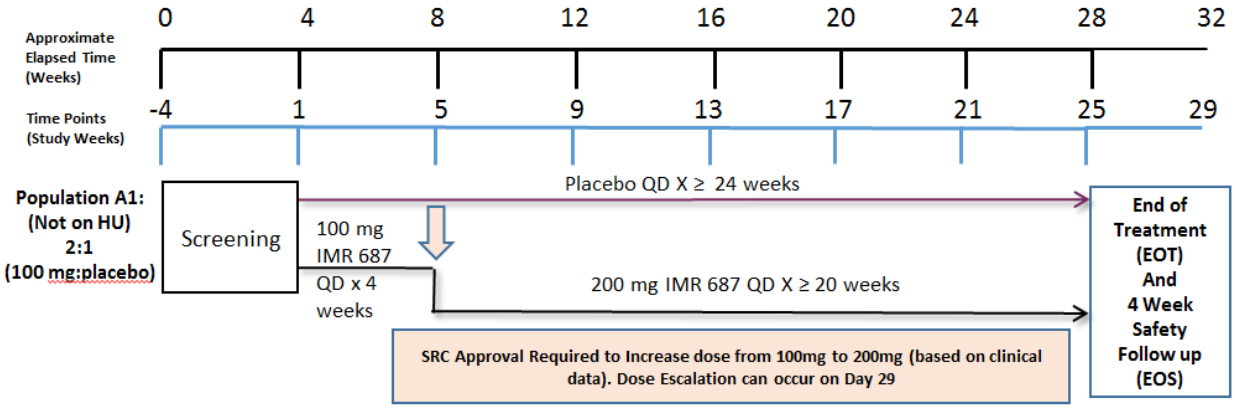
Figure 1: Study Design Schema for Population A



HU = hydroxyurea; QD = once daily; SRC = Safety Review Committee

Note: The SRC reviews all available collated and individual data every other week throughout the study and has jurisdiction over decisions to continue dosing, dose escalate individual patients, initiate dosing in Populations B and B1, and to terminate dosing.

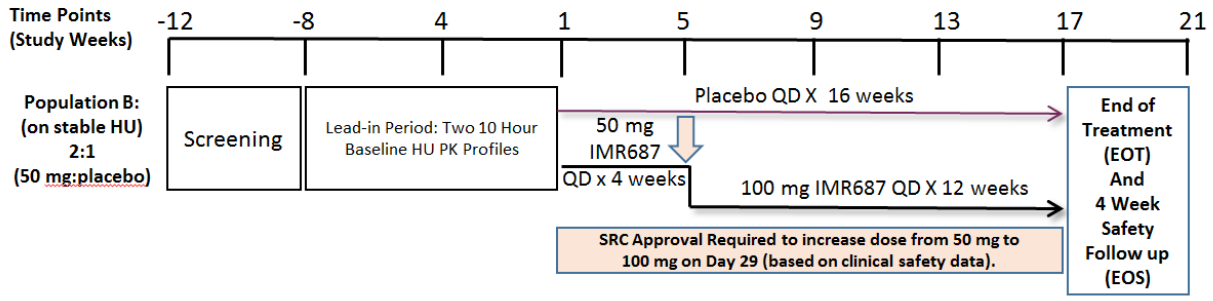
Figure 2: Study Design Schema for Population A1



HU = hydroxyurea; QD = once daily; SRC = Safety Review Committee

Note: The SRC reviews all available collated and individual data every other week throughout the study and has jurisdiction over decisions to continue dosing, dose escalate individual patients, initiate dosing in Populations B and B1, and to terminate dosing.

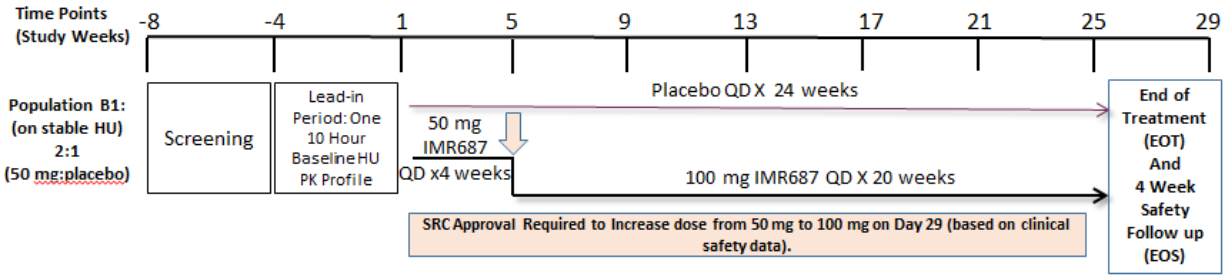
Figure 3 Study Design Schema for Population B



HU = hydroxyurea; QD = once daily; SRC = Safety Review Committee

Note: The SRC reviews all available collated and individual data every other week throughout the study and has jurisdiction over decisions to continue dosing, dose escalate individual patients, initiate dosing in Populations B and B1, and to terminate dosing.

Figure 4 Study Design Schema for Population B1



HU = hydroxyurea; QD = once daily; SRC = Safety Review Committee

Note: The SRC reviews all available collated and individual data every other week throughout the study and has jurisdiction over decisions to continue dosing, dose escalate individual patients, initiate dosing in Populations B and B1, and to terminate dosing.

1.3. Schedule of Assessments

The Schedule of Assessments is provided in Table 1, Table 2, Table 3, and Table 4 below for Populations A, A1, B, and B1, respectively.

Table 1: Schedule of Assessments: Population A (not receiving HU)

	Screening	Double-Blind, Placebo-Controlled Treatment													End of Study (Safety FU)
Study Week(s)		**1**	**2**	**3**	**4**	**5**	**9**	**13**	**14**	**15**	**16**	**17**	**21**	**25[b] (EOT)**	**29 (EOS)**
Study Day(s)	**-28 to -1**	**1[a]**	**8 ± 2**	**15 ± 2**	**22 ± 2**	**29 ± 2**	**57 ± 2**	**85 ± 2**	**92 ± 2**	**99 ± 2**	**106 ± 2**	**113 ± 2**	**141 ± 2**	**169 ± 2**	**197± 5**
Informed Consent	X														
Demographic Information	X														
Medical/Disease History	X														
Inclusion/Exclusion Criteria	X														
Blood for Dx Confirmation & Pharmacogenomics[c]	X														
Randomization		X													
Telephonic Visits [d]				X	X					X	X				
Vital Signs[e]	X	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														
Physical Examination[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG[g]		X						X	X			X	X	X	
Safety Laboratory Assessments	X	X	X			X	X	X				X	X	X	X
Pregnancy Testing[h]	X	X				X	X	X				X	X	X	X
Exploratory PD Markers[i]		X				X	X	X				X	X	X	
IMR-687 Plasma PK[j]		X						X						X	
QOL Assessments (ASCQ-Me)		X						X						X	
App-based Pain Questionnaire		Daily													
Study Drug Administration		Once Daily Oral Administration IMR-687[k]													
AEs & Concomitant Medications		Continuous[l]													

Abbreviations: % F cells = percent of red blood cells containing foetal haemoglobin; AEs = adverse events; ASCQ-Me = Adult Sickle Cell Quality-of-Life Measurement Information System; BL = baseline; Dx = disease; FU = follow-up; ECG = electrocardiogram; EOT = end of treatment; PD = pharmacodynamics; PE = physical examination; PK = pharmacokinetic; QOL = quality of life; SFU = safety follow-up.

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

[a] The first day study drug is taken is considered "Day 1".

[b] The last day of dosing will be the end of Week 24 (Day 169 ± 2); patient should consume their last dose of study drug on site, after pre-dose assessments have been completed. During the study visit Day 169 ± 2, assessments should be collected from any patient who discontinues study drug or study prematurely. The week 25 visit will also be the EOT visit.

[c] Pharmacogenomic evaluation is optional and may be performed at any point during the study if patient provides informed consent.

[d] Site will contact the patient telephonically during Weeks 3, 4, 15, and 16. If any AEs of significant clinical concern are identified during the telephonic visit, the patient will be requested to come into the site to be assessed by targeted PE and vital sign measurements. Physical examinations and vital signs will not be assessed at these time points if patients do not have AEs of concern.

[e] On Days 1, 85, and the last day of dosing (End of Week 24 [Day 169 ± 2]), vital signs will be taken pre-dose and 2 hours (± 15 minutes) post-dose. At all other time points, vital signs will be taken pre-dose only. Vital sign measurements on Weeks 3, 4, 15, and 16 are obtained only if the patient is brought into the site after identification of AEs of significant clinical concern during the telephonic visits. Vital signs should be measured in the sitting or semi-supine position.

[f] At the Screening and Day 1 visits, the PE will include a general examination of the body including the abdomen, heart, chest, lungs, lymph nodes, dentition, back/neck, neurological system, skin, extremities, head, ears, eyes, nose, and throat. Subsequent PEs will be symptom directed; symptom-directed PEs on Weeks 3, 4, 15, and 16 are obtained only if the patient is brought into the site after identification of AEs of significant clinical concern during the telephonic visits.

[g] On Days 1, 85, and the last day of dosing (End of Week 24 [Day 169 ± 2]), ECGs will be obtained in triplicate at pre-dose and 2 hours (± 30 minutes) post-dose.

[h] Females of childbearing potential only. A serum pregnancy test will be performed at screening; all subsequent tests will be urine.

[i] Includes total haemoglobin (Hb), haemoglobin F (% HbF levels and % F cells), indices of red cell haemolysis (unconjugated bilirubin, reticulocyte counts, lactate dehydrogenase [LDH], haptoglobin, soluble E-selectin [sE-sel], soluble P-selectin [sP-sel], soluble intercellular adhesion molecule 1 [sICAM-1], and high-sensitivity C-reactive protein [hsCRP]). Blood samples should be obtained within 30 minutes prior to administration of study drug.

[j] On Days 1, 85, and the last day of dosing (End of Week 24 [Day 169 ± 2]), serial blood samples for IMR-687 plasma concentrations will be drawn pre-dose (within 30 minutes); at 0.5, 1, 1.5, 2, 4, 6, and 8 hours (± 5 minutes) after administration of study drug; and at 24 hours (± 1 hour) after administration of study drug.

[k] At each study visit, patients should be reminded to bring their study medication to their next site visit and to not take study drug on the day of the next visit until instructed to do so by the site during the visit. The last day of dosing will be the end of Week 24 (Day 169 ± 2); patient should consume the last dose on site after pre-dose assessments have been completed.

[l] Adverse events will be recorded throughout the study from Screening through the safety follow-up. In addition to the specified study time points in the Schedule of Assessments, patients will be followed weekly by the investigator for safety. Telephone-based check-ins may be performed on weeks where there are no scheduled site visits.

Table 2 Schedule of Assessments: Population A1 (not receiving HU)

	Screening	Double-Blind, Placebo-Controlled Treatment													End of Study (Safety FU)
Study Week(s)		**1**	**2**	**3**	**4**	**5**	**9**	**13**	**14**	**15**	**16**	**17**	**21**	**25[b] EOT**	**29 (EOS)**
Study Day(s)	**-28 to -1**	**1[a]**	**8 ± 2**	**15 ± 2**	**22 ± 2**	**29 ± 2**	**57 ± 2**	**85 ± 2**	**92 ± 2**	**99 ± 2**	**106 ± 2**	**113 ± 2**	**141 ± 2**	**169 ± 2**	**197± 5**
Informed Consent	X														
Demographic Information	X														
Medical/Disease History	X														
Inclusion/Exclusion Criteria	X														
Blood for Dx Confirmation & Pharmacogenomics[c]	X														
Randomization		X													
Telephonic Visits [d]				X						X	X				
Vital Signs[e]	X	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														
Physical Examination[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG[g]		X				X	X	X	X			X	X	X	
Safety Laboratory Assessments	X	X	X		X	X	X	X				X	X	X	X
Pregnancy Testing[h]	X	X			X	X	X	X				X	X	X	X
Exploratory PD Markers[i]		X				X	X	X				X	X	X	
IMR-687 Plasma PK[j]		X				X								X	
QOL Assessments (ASCQ-Me)		X						X						X	
App-based Pain Questionnaire		Daily													
Study Drug Administration		Once Daily Oral Administration IMR-687[k]													
AEs & Concomitant Medications		Continuous[l]													

Abbreviations: % F cells = percent of red blood cells containing foetal haemoglobin; AEs = adverse events; ASCQ-Me = Adult Sickle Cell Quality-of-Life Measurement Information System; BL = baseline; Dx = disease; FU = follow-up; ECG = electrocardiogram; EOT = end of treatment; PD = pharmacodynamics; PK = pharmacokinetic; QOL = quality of life; SFU = safety follow-up.

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

[a] The first day study drug is taken is considered "Day 1".

[b] The last day of dosing will be the end of Week 24 (Day 169 ± 2); patient should consume their last dose of study drug on site, after pre-dose assessments have been completed. During the study visit Day 169 ± 2, assessments should be collected from any patient who discontinues study drug or study prematurely.

[c] Pharmacogenomic evaluation is optional and may be performed at any point during the study if patient provides informed consent.

[d] Site will contact the patient telephonically during Weeks 3, , 15, and 16. If any AEs of significant clinical concern are identified during the telephonic visit, the patient will be requested to come into the site to be assessed by targeted PE and vital sign measurements. Physical examinations and vital signs will not be assessed at these time points if patients do not have AEs of concern.

[e] On Days 1, 29, and the last day of dosing (End of Week 24 [Day 169 ± 2]), vital signs will be taken pre-dose and 2 hours (± 15 minutes) post-dose. At all other time points, vital signs will be taken pre-dose only. Vital sign measurements on Weeks 3, 15, and 16 are obtained only if the patient is brought into the site after identification of AEs of significant clinical concern during the telephonic visits. Vital signs should be measured in the sitting or semi-supine position.

[f] At the Screening and Day 1 visits, the PE will include a general examination of the body including the abdomen, heart, chest, lungs, lymph nodes, dentition, back/neck, neurological system, skin, extremities, head, ears, eyes, nose, and throat. Subsequent PEs will be symptom directed; symptom-directed PEs on Weeks 3, 15, and 16 are obtained only if the patient is brought into the site after identification of AEs of significant clinical concern during the telephonic visits.

[g] On Days 1, 29, and the last day of dosing (End of Week 24 [Day 169 ± 2]), ECGs will be obtained in triplicate at pre-dose and 2 hours (± 30 minutes) post-dose.

[h] Females of childbearing potential only. A serum pregnancy test will be performed at screening; all subsequent tests will be urine.

[i] Includes total haemoglobin (Hb), haemoglobin F (% HbF levels and % F cells), indices of red cell haemolysis (unconjugated bilirubin, reticulocyte counts, lactate dehydrogenase [LDH], haptoglobin, soluble E-selectin [sE-sel], soluble P-selectin [sP-sel], soluble intercellular adhesion molecule 1 [sICAM-1], and high-sensitivity C-reactive protein [hsCRP]). Blood samples should be obtained within 30 minutes prior to administration of study drug.

[j] On Days 1, 29, and the last day of dosing (End of Week 24 [Day 169 ± 2]), serial blood samples for IMR-687 plasma concentrations will be drawn pre-dose (within 30 minutes); at 0.5, 1, 1.5, 2, 4, 6, and 8 hours (± 5 minutes) after administration of study drug; and at 24 hours (± 1 hour) after administration of study drug. If well-tolerated, dose escalation from 100 mg to 200 mg will occur after 4 weeks of treatment.

[k] At each study visit, patients should be reminded to bring their study medication to their next site visit and to not take study drug on the day of the next visit until instructed to do so by the site during the visit. The last day of dosing will be the end of Week 24 (Day 169 ± 2); patient should consume the last dose on site after pre-dose assessments have been completed.

[l] Adverse events will be recorded throughout the study from Screening through the safety follow-up. In addition to the specified study time points in the Schedule of Assessments, patients will be followed weekly by the investigator for safety. Telephone-based check-ins may be performed on weeks where there are no scheduled site visits.

Table 3: Schedule of Assessments: Population B (receiving stable dose of HU)

			Double-Blind, Placebo-Controlled Treatment											End of Study (Safety FU)
Study Week(s)	**Screening Period[a]**	**Lead-in Period[b]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**13**	**17[d] (EOT)**	**21(EOS)**
Study Day(s)			**1[c]**	**8 ± 2**	**15 ± 2**	**22 ± 2**	**29 ± 2**	**36 ± 2**	**43 ± 2**	**50 ± 2**	**57 ± 2**	**85 ± 2**	**113 ± 2**	**141 ± 5**
Informed Consent	X													
Demographic Information	X													
Medical/Disease History	X													
Inclusion/Exclusion Criteria	X													
Blood for Dx Confirmation & Pharmacogenomics[e]	X													
Randomization			X											
Telephonic Visits[f]					X	X		X	X	X				
Vital Signs[g]	X		X	X	X	X	X	X	X	X	X	X	X	X
Weight	X		X				X				X	X	X	
Height	X													
Physical Examination[h]	X		X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG[i]			X				X						X	
Safety Laboratory Assessments	X		X	X			X				X	X	X	X
Pregnancy Testing[j]	X		X				X				X	X	X	
Exploratory PD Markers[k]			X				X				X	X	X	
IMR-687 Plasma PK[l]			X				X						X	
HU PK[m]		X					X						X	
QOL Assessments (ASCQ-Me)			X				X						X	
App-based Pain Questionnaire			Daily											
Study Drug Administration			Once Daily Oral Administration IMR-687 and HU[n]											
AEs & Concomitant Medications			Continuous[o]											

Abbreviations: % F cells = percent of red blood cells containing foetal haemoglobin; AEs = adverse events; App = application; BL = baseline; Dx = disease; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; FU = follow-up; HU = hydroxyurea; PD = pharmacodynamic; PE = physical examination; PK = pharmacokinetic; QOL = quality of life; SRC = safety review committee.

Note: Unless otherwise specified, all assessments should be completed prior to dosing.

[a] Screening should occur within a 4-week period and can begin approximately 12 weeks prior to the anticipated first dose of study medication in Population B.

[b] Once all Screening assessments have been performed and the patient is eligible for the study, the patient will enter the lead-in period and will have serial blood samples drawn for 2 complete baseline HU PK profiles. For each profile, samples will be drawn pre-dose (within 30 minutes); at 0.5, 1, 1.5, 3, 6, 8, and 10 hours (± 5 minutes) after self-administration of the prescribed dose of HU. The duration of the lead-in period is up to approximately 8 weeks, depending on when at least 4 weeks of safety data from at least 6 patients in Population A are available for SRC review.

[c] The first day study drug is taken is considered "Day 1"; unless otherwise specified. Administration of study medication (Day 1) in Population B will not begin until at least 4 weeks of safety data from at least 6 patients in Population A have been reviewed by the SRC and the SRC has determined that it is safe and appropriate to begin dosing in Population B.

[d] The last day of dosing will be the end of Week 16 (Day 113 ± 2), patient should consume the last dose on site after pre-dose assessments have been completed. During study visit Day 113 ± 2, assessments should be collected from any patient who discontinues study drug or study prematurely.

[e] Assessments are optional and may be performed at any point during the study if the patient consents.

[f] Site will contact the patient telephonically during study week 3, 4, 6, 7, and 8. If any AEs of significant clinical concern are identified during the telephonic visit, the patient will be requested to come into the site to be assessed by targeted PE and vital sign measurements. Physical examinations and vital signs will not be assessed at these time points if patients do not have AEs of concern.

[g] On Days 1, 29, and the last day of dosing [End of Week 16 (Day 113 ± 2)], vital signs will be taken pre-dose and 2 hours (± 15 minutes) post-dose. At all other time points, vital signs will be taken pre-dose only. Vital sign measurements on Weeks 3, 4, 6, 7, and 8 are obtained only if the patient is brought into the site after identification of AEs of significant clinical concern during the telephonic visits. Vital signs should be measured in the sitting or semi-supine position.

[h] At the Screening and Day 1 visits, the PE will include a general examination of the body including the abdomen, heart, chest, lungs, lymph nodes, dentition, back/neck, neurological system, skin, extremities, head, ears, eyes, nose, and throat. Subsequent PEs will be symptom-directed; symptom-directed PEs on Weeks 3, 4, 6, 7, and 8 are obtained only if the patient is brought into the site after identification of AEs of significant clinical concern during the telephonic visits.

[i] On Days 1, 29, and the last day of dosing (End of Week 16 [Day 113 ± 2]), ECGs will be obtained in triplicate at pre-dose and 2 hours (± 30 minutes) post-dose.

[j] Females of childbearing potential only; a serum pregnancy test will be performed at screening; all subsequent tests will be urine.

k Includes total haemoglobin (Hb), haemoglobin F (% HbF levels and % F cells), indices of red cell haemolysis (unconjugated bilirubin, reticulocyte counts, lactate dehydrogenase [LDH], haptoglobin, soluble E selectin [sE-sel], soluble P-selectin [sP-sel], soluble intercellular adhesion molecule 1 [sICAM-1], and high-sensitivity C-reactive protein [hsCRP]). Blood samples should be obtained within 30 minutes prior to administration of study drug.

[l] On Days 1, 29, and 113, serial blood samples for IMR-687 PK will be drawn pre-dose (within 30 minutes); at 0.5, 1, 1.5, 2, 4, 6, and 8 hours (± 5 minutes) after administration of study drug; and at 24 hours (± 1 hour) after administration of study drug.

[m] Baseline blood samples for HU PK will be drawn as described in footnote 'b'. On Days 29 and 113, serial blood samples for HU PK will be drawn pre-dose (within 30 minutes) and at 0.5, 1, 1.5, 3, 6, 8, and 10 hours (± 5 minutes) after self-administration of the prescribed dose of HU.

[n] At each study visit, patients should be reminded to bring their study medication and their HU to their next site visit and to not take either medication on the day of the next visit until instructed to do so by the site during the visit.

[o] Adverse events will be recorded throughout the study from Screening to end of Follow-up. In addition to the specified study time points in the Schedule of Assessments, patients will be followed weekly by the investigator for safety. Telephone-based check-ins may be performed on weeks where there are no scheduled site visits.

Table 4 Schedule of Assessments: Population B1 (receiving stable dose of HU)

			Double-Blind, Placebo-Controlled Treatment													End of Study (Safety FU)
Study Week(s)	**Screening Period[a]**	**Lead-in Period[b]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**13**	**17**	**21**	**25[d] (EOT)**	**29 (EOS)**
Study Day(s)			**1[c]**	**8 ± 2**	**15 ± 2**	**22 ± 2**	**29 ± 2**	**36 ± 2**	**43 ± 2**	**50 ± 2**	**57 ± 2**	**85 ± 2**	**113 ± 2**	**141 ± 2**	**169 ± 2**	**197± 5**
Informed Consent	X															
Demographic Information	X															
Medical/Disease History	X															
Inclusion/Exclusion Criteria	X															
Blood for Dx Confirmation & Pharmacogenomics[e]	X															
Randomization			X													
Telephonic Visits[f]					X	X		X	X	X						
Vital Signs[g]	X		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															
Physical Examination[h]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG[i]			X				X								X	
Safety Laboratory Assessments	X		X	X			X				X	X	X	X	X	X
Pregnancy Testing[j]	X		X				X				X	X	X	X	X	
Exploratory PD Markers[k]			X				X				X	X	X	X	X	
IMR-687 Plasma PK[l]			X				X								X	
HU PK[m]		X					X								X	
QOL Assessments (ASCQ-Me)			X				X						X		X	
App-based Pain Questionnaire			Daily													
Study Drug Administration			Once Daily Oral Administration IMR-687 and HU[n]													
AEs & Concomitant Medications			Continuous[o]													

Abbreviations: % F cells = percent of red blood cells containing foetal haemoglobin; AEs = adverse events; App = application; BL = baseline; Dx = disease; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; FU = follow-up; HU = hydroxyurea; PD = pharmacodynamic; PE = physical examination; PK = pharmacokinetic; QOL = quality of life; SRC = safety review committee.

Note: Unless otherwise specified, all assessments should be completed prior to dosing.

[a] Screening should occur within a 4-week period and can begin approximately 8 weeks prior to the anticipated first dose of study medication in Population B.

[b] Once all Screening assessments have been performed and the patient is eligible for the study, the patient will enter the lead-in period and will have serial blood samples drawn for 1 complete baseline HU PK profile. For the baseline HU PK profile, samples will be drawn pre-dose (within 30 minutes); at 0.5, 1, 1.5, 3, 6, 8, and 10 hours (± 5 minutes) after self-administration of the prescribed dose of HU. The duration of the lead-in period is approximately 4 weeks.

[c] The first day study drug is taken is considered "Day 1"; unless otherwise specified.

[d] The last day of dosing will be the end of Week 24 (Day 169 ± 2); patient should consume the last dose on site after pre-dose assessments have been completed. During study visit Day 169 ± 2, assessments should be collected from any patient who discontinues study drug or study prematurely.

[e] Assessments are optional and may be performed at any point during the study if the patient consents.

[f] Site will contact the patient telephonically during study week 3, 4, 6, 7, and 8. If any AEs of significant clinical concern are identified during the telephonic visit, the patient will be requested to come into the site to be assessed by targeted PE and vital sign measurements. Physical examinations and vital signs will not be assessed at these time points if patients do not have AEs of concern.

[g] On Days 1, 29, and the last day of dosing (End of Week 24 [Day 169 ± 2]), vital signs will be taken pre-dose and 2 hours (±15 minutes) post-dose. At all other time points, vital signs will be taken pre-dose only. Vital sign measurements on Weeks 3, 4, 6, 7, and 8 are obtained only if the patient is brought into the site after identification of AEs of significant clinical concern during the telephonic visits. Vital signs should be measured in the sitting or semi-supine position.

[h] At the Screening and Day 1 visits, the PE will include a general examination of the body including the abdomen, heart, chest, lungs, lymph nodes, dentition, back/neck, neurological system, skin, extremities, head, ears, eyes, nose, and throat. Subsequent PEs will be symptom-directed; symptom-directed PEs on Weeks 3, 4, 6, 7, and 8 are obtained only if the patient is brought into the site after identification of AEs of significant clinical concern during the telephonic visits.

[i] On Days 1, 29, and the last day of dosing (End of Week 24 [Day 169 ± 2]), ECGs will be obtained in triplicate at pre-dose and 2 hours (±30 minutes) post-dose.

[j] Females of childbearing potential only; a serum pregnancy test will be performed at screening; all subsequent tests will be urine.

k Includes total haemoglobin (Hb), haemoglobin F (% HbF levels and % F cells), indices of red cell haemolysis (unconjugated bilirubin, reticulocyte counts, lactate dehydrogenase [LDH], haptoglobin, soluble E selectin [sE-sel], soluble P-selectin [sP-sel], soluble intercellular adhesion molecule 1 [sICAM-1], and high-sensitivity C-reactive protein [hsCRP]). Blood samples should be obtained within 30 minutes prior to administration of study drug.

[l] On Days 1, 29, and 169, serial blood samples for IMR-687 PK will be drawn pre-dose (within 30 minutes); at 0.5, 1, 1.5, 2, 4, 6, and 8 hours (± 5 minutes) after administration of study drug; and at 24 hours (± 1 hour) after administration of study drug.

[m] Baseline blood samples for HU PK will be drawn as described in footnote 'b'. On Days 29 and 169, serial blood samples for HU PK will be drawn pre-dose (within 30 minutes) and at 0.5, 1, 1.5, 3, 6, 8, and 10 hours (± 5 minutes) after self-administration of the prescribed dose of HU.

[n] At each study visit, patients should be reminded to bring their study medication and their HU to their next site visit and to not take either medication on the day of the next visit until instructed to do so by the site during the visit.

[o] Adverse events will be recorded throughout the study from Screening to end of Follow-up. In addition to the specified study time points in the Schedule of Assessments, patients will be followed weekly by the investigator for safety. Telephone-based check-ins may be performed on weeks where there are no scheduled site visits

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Abbreviation	Definition
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
API	active pharmaceutical ingredient
ARC	absolute reticulocyte count
ASCQ-Me	Adult Sickle Cell Quality-of-Life Measurement Information System
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-12}	area under the concentration-time curve from time 0 to 12 hours
AUC_{0-24}	area under the concentration-time curve from time 0 to 24 hours
AUC_{0-inf}	area under the concentration-time curve extrapolated to infinity
AUC_{last}	area under the concentration-time curve from time 0 to the last measurable time point
cGMP	cyclic guanosine monophosphate
CI	confidence interval
CIOMS	Council for International Organisations of Medical Sciences
C_{max}	maximum concentration
CNS	central nervous system
CRO	contract research organisation
CTCAE	Common Terminology Criteria for Adverse Events
%CV	coefficient of variation
CYP	cytochrome P450
DNA	deoxyribonucleic acid
eCRF	electronic case report form
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
FE	food effect

Abbreviation	Definition
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
Hb	haemoglobin
HbF	foetal haemoglobin
HbSS	homozygous sickle haemoglobin
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HPLC	high-performance liquid chromatography
HU	hydroxyurea
IC_{50}	concentration that produces 50% of maximal response
ICF	informed consent form
ICH	International Council on Harmonisation
IMP	investigational medicinal product
IRB	Institutional Review Board
LDH	lactate dehydrogenase
MAD	multiple ascending dose
MDR1	multidrug-resistant protein 1
MHRA	Medicines and Healthcare Products Regulatory Agency
MPO	myeloperoxidase
mRNA	messenger ribonucleic acid
NIMP	non-investigational medicinal product
NO	nitric oxide
NOAEL	no-observed-adverse-effect level
OECD	Organisation for Economic Cooperation and Development
PD	pharmacodynamic(s)
PDE	phosphodiesterase
P-gp	P-glycoprotein
PK	pharmacokinetic(s)

Abbreviation	Definition
QTc	corrected QT interval
QTcF	corrected QT interval, Fridericia's formula
RBC	red blood cell
REC	Research Ethics Committee
SAD	single ascending dose
SAE	serious adverse event
SCA	sickle cell anaemia
SCD	sickle cell disease
SD	standard deviation
sE-sel	soluble E-selectin
sICAM-1	soluble intercellular adhesion molecule-1
sP-sel	soluble P-selectin
SRC	Safety Review Committee
SUSAR	suspected unexpected serious adverse reaction
sVCAM	soluble vascular cell adhesion molecule
$t_{½}$	apparent terminal half-life
TEAE	treatment-emergent adverse event
t_{max}	time to maximum concentration
ULN	upper limit of normal
US	United States
VOC	vaso-occlusive crisis
WBC	white blood cell

4. INTRODUCTION

4.1. Background

The Sponsor is developing IMR-687 for the treatment of patients with the most severe forms of sickle cell disease (SCD), which include homozygous sickle haemoglobin (HbSS) and sickle-β^0 thalassemia, collectively referred to as sickle cell anaemia (SCA).

With a neonatal incidence of 294,000 to 330,000 patients worldwide (Piel 2013), SCA is a rare inherited disorder of red blood cells (RBCs) that is both serious and life threatening. The most common manifestations of SCA include vaso-occlusive crisis (VOC), chronic and acute severe pain, acute chest syndrome, stroke, priapism, acute anaemia (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, though many patients succumb to the disease much earlier (Platt 1994; Lanzkron 2013; Paulukonis 2016).

SCA is caused by a specific point mutation in the gene encoding haemoglobin subunit beta that results in the substitution of a hydrophobic valine residue for glutamic acid in the 6th position from the N terminus of the β chain and leads to the production of abnormal haemoglobin ("sickle haemoglobin" or HbS), which polymerises when in the deoxygenated conformation. Under conditions of hypoxia, acidity, and/or dehydration, the intracellular concentration of deoxyHbS increases thereby favouring polymerization and causing RBCs to deform (i.e., sickle) or become rigid, leading to a complex cascade of haemolysis, inflammation, elevated cell adhesion, leucocytosis, oxidative stress, and endothelial dysfunction that culminates in the vascular obstruction and ischemia responsible for much of the observed morbidity.

Prior to July 2017, the only drug specifically approved for the treatment of SCA was hydroxyurea (HU), a small molecule inhibitor of ribonucleotide reductase that was originally developed for the treatment of myeloproliferative disorders. HU is also known as hydroxycarbamide and has been approved to treat SCA since 1998 in the United States (US) and since 2001 in Europe. In SCA, HU reduces painful crises and the need for blood transfusions (Charache 1995), at least in part by increasing levels of foetal haemoglobin (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 2008).

In July 2017, L-glutamine oral powder (Endari™) was approved in the US to reduce complications of SCD; however, the data available to date are limited primarily to the results from 230 patients (158 who received L-glutamine oral powder and 78 who received placebo) in the phase 3 pivotal trial. In this study, the median number of sickle cell crises through Week 48 (primary endpoint) was 3 in patients who received L-glutamine oral powder compared with 4 in patients who received placebo. Thus, additional novel, safe, and effective treatments to prevent the morbid complications of SCA in patients of all ages are still urgently needed.

4.1.1. IMR-687

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

By inhibiting PDE9, IMR-687 is intended to increase cGMP levels and in doing so, stimulate the production of HbF, which reduces the cellular concentration of abnormal haemoglobin within RBCs and its associated sequelae. The importance of increasing HbF in treating SCD is evidenced by large studies like the Cooperative Study of Sickle Cell Disease 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 haematological parameters of SCA (Akinsheye 2011; Alsultan 2013; Barbosa 2013; Sheehan 2013).

PDE9 is highly expressed in hematopoietic cells and is also widely distributed in brain, with the highest expression measured in cerebellar Purkinje cells of rodents (van Staveren 2002). A potential advantage of IMR-687 for the SCA indication is that it does not readily distribute to the brain and, therefore, is less likely to result in the central nervous system (CNS) effects observed with other, brain-penetrating PDE9 inhibitors (Schwam 2014; Hutson 2011; Van der Staay 2008).

4.1.2. Nonclinical Data

The IMR-687 nonclinical program supports its potential safety and efficacy for the treatment of SCA.

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 SCA 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 Good Laboratory Practice (GLP)/Organisation for Economic Cooperation and Development (OECD)-compliant safety pharmacology studies, IMR-687 had no test article-related adverse effects on respiratory function in the rat at doses <1000 mg/kg, no test article-related adverse effects on CNS/behavioural function in the rat at doses ≤250 mg/kg, and no test article-related adverse effects on cardiac function in conscious dogs at doses ≤25 mg/kg. The no observed adverse effect level (NOAEL) for IMR-687 in a GLP/OECD 13-week repeat-dose toxicity study in the rat was the maximum oral dose of 200 mg/kg/day, which resulted in an area under the concentration-time curve (AUC) from time 0 to 24 hours post dose (AUC_{0-24}) of 352,000 and 454,000 ng•h/mL in males and females, respectively. In a GLP/OECD 13-week study in the dog, the NOAEL for orally administered IMR-687 was 25 mg/kg/day, which resulted in an AUC_{0-24} of 83,200 and 81,200 ng•h/mL in males and females, respectively. IMR-687 was negative in GLP/OECD

bacterial mutation, chromosome aberration, and Ames mutagenicity studies as well as in rat micronucleus assays. In addition, a 6-month toxicology study in the rat and a 9-month toxicology study in the dog are ongoing; draft results for the 6-month rat toxicology study and the 6-month in-life findings from the 9-month dog toxicology study will be available prior to the start of this study and a draft, unaudited report will be available prior to dosing any patient beyond 12 weeks.

IMR-687 exhibited low plasma protein binding in mouse, rat, dog, monkey, and humans; no competitive inhibition for the 7 major human cytochrome P450 (CYP) isoforms up through concentrations of 100 µM; and no notable induction of CYP1A2 or CYP2B6 messenger ribonucleic acid (mRNA) expression in human hepatocytes. However, IMR-687 did show the potential for induction of CYP3A4 mRNA expression at high doses and was found to be a multidrug-resistant protein 1 (MDR1) substrate (human P-glycoprotein [P-gp]) in a study to evaluate MDR1-mediated efflux of IMR-687 in MDCK MDR1 cell monolayers. In addition, in a rat study to evaluate the potential for interactions between IMR-687 and HU that used high doses of both, the maximum plasma concentration (C_{max}) and AUC_{0-24} of HU were 65% lower when given in combination with 250 mg/kg/day IMR-687 than when given in isolation, while IMR-687 exposure was similar when administered either in isolation or with HU. There were no deaths or clinical signs in groups given IMR-687 and HU in combination or in isolation, and weight gains and food intake were similar across groups.

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

4.1.3. Clinical Data

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

A first-in-human, randomised, double-blind, placebo-controlled study to evaluate the safety, tolerability, and pharmacokinetics (PK) of IMR-687 in up to 66 healthy male and female adults between the ages of 18 and 55 years, inclusive, has been conducted (IMR-SCD-101). The study was divided into 3 parts: a single ascending dose (SAD) study (Part A), a food effect (FE) study (Part B), and a multiple ascending dose (MAD) study (Part C). The last subject's last visit has occurred for all 3 study parts and draft, unaudited, unblinded data are available for all cohorts except for the highest dose in Part C, which is still blinded.

4.1.3.1.1. IMR-SCD-101: Part A (SAD)

Part A sequentially evaluated single oral doses of 0.3, 1, 3, 4.5, and 6 mg/kg in 5 cohorts of subjects; in each cohort, 6 subjects were randomised to receive either IMR-687 (N=4) or placebo (N=2) in double-blind fashion. Study drug (IMR-687 or placebo) was administered following an overnight fast on Day 1 and subjects returned to the study unit on Day 5 for an end-of-study visit.

All subjects completed Part A; there were no serious adverse events (SAEs) and all adverse events (AEs) were mild to moderate in severity, transient, self-limited, and easily monitorable. The most commonly occurring treatment-related AE was nausea, which was noted in 7 subjects who received IMR-687: 1 in the 1 mg/kg group and 3 each in the 4.5 and 6 mg/kg groups. At the highest dose level of 6 mg/kg, 2 of these subjects also experienced emesis, which was considered a

dose-limiting toxicity. Therefore, the maximum tolerated dose of IMR-687 in Part A was 4.5 mg/kg (equivalent to a dose of 225 mg in a 50 kg patient, the minimum permitted weight for inclusion in this study).

Assessments for vital signs (heart rate, blood pressure, temperature) and serial electrocardiograms (ECGs) did not demonstrate any clinically significant, dose-dependent findings. Review of selected safety labs, including white blood cell (WBC) count, absolute neutrophil count, haemoglobin/haematocrit, platelets, serum creatinine, and liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin, and alkaline phosphatase) did not reveal any clinically significant findings, either for individual subjects or in the assessments of group mean values for these parameters.

IMR-687 geometric mean exposure ($AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and C_{max}) increased in an approximately dose-proportional fashion and terminal 24-hour concentrations remained at or above the half-maximal concentration (IC_{50}) for inhibition of PDE9 (10 nM or 5.8 ng/mL). Geometric mean half-life ($t_{½}$) ranged from 3.55 to 5.72 hours across all dose levels, and median time to maximum concentration (t_{max}) ranged from 1.0 to 3.0 hours.

4.1.3.1.2. IMR-SCD-101: Part B (Food Effect)

In Part B, 12 healthy volunteers were administered two single oral doses of IMR-687 at 1 mg/kg. The FE part was open-label; all subjects received their first dose of IMR-687 in the fasted state (Period 1) and the second dose in the fed state (Period 1) after a 1-week washout between doses.

All subjects completed both study periods in Part B; there were no serious adverse events (SAEs) and all adverse events (AEs) were mild in severity, transient, self-limited, and easily monitorable. Oral administration of IMR-687 to fasted subjects (Period 1) resulted in the following treatment-emergent adverse events (TEAEs) that were considered by the Investigator to be possibly related to study drug: nausea (n=1), dyspepsia (n=1), and headache (n=4). In Period 2, oral administration of IMR-687 to fed subjects did not result in any treatment-related TEAEs.

Review of vital signs, serial ECGs, and laboratory parameters did not reveal any clinically significant findings.

At a single oral dose of 1 mg/kg, the effect of food on the PK profile of IMR-687 was a delay in t_{max} (median delay of 3 hours), an approximately 26% decrease in C_{max}, and a <10% decrease in $AUC_{(0\text{-inf})}$. Thus, the high-fat meal had no notable impact on systemic exposure to IMR-687 despite a mild delay in the rate of absorption.

4.1.3.1.3. IMR-SCD-101: Part C (MAD)

Part C sequentially evaluated oral doses of 1, 3, and 4.5 mg/kg administered once daily for 7 days; in each dose cohort, 8 subjects were randomised to receive either IMR-687 (N=6) or placebo (N=2) in double-blind fashion. Based on the improved safety and tolerability profile of IMR-687 in the fed state in Part B, all subjects in the MAD part received IMR-687 or placebo immediately after a meal.

At the 1 and 3 mg/kg dose levels, the most common AEs were associated with phlebotomy (thirst, sensation of warmth, and mild dizziness on Day 1 contemporaneous to phlebotomy [n=1,

1 mg/kg]; superficial thrombophlebitis [n=2, placebo]) or were headaches (n=1, 3 mg/kg; n=1, placebo).

At the 4.5 mg/kg dose level (results are still blinded), TEAEs included hematoma at the phlebotomy site (n=1); nausea (n=1) that occurred 45 minutes after dosing on Day 7 and was transient and self-limiting; headache (n=1) on Day 1 that resolved the same day following treatment with acetaminophen; and mild nausea on Days 6 and 7 with a single bout of mild emesis on Day 7 (n=1).

Review of vital signs, serial ECGs, and laboratory parameters did not reveal any clinically significant findings for subjects in the 1 or 3 mg/kg dose cohorts. Full results are pending for Cohort 3 (4.5 mg/kg); however, preliminary review of vital signs and ECG data did not demonstrate any clinically significant findings.

On Days 1 and 7, increases in geometric mean C_{max} were trending less than dose proportional, while increases in geometric mean AUC_{0-24} (or AUC_{0-t}) and $AUC_{0-\infty}$ were closer to dose proportional. With a 4.5-fold increase in dose from 1 to 4.5 mg/kg, the geometric mean C_{max} increased ~3.3-fold while the geometric mean AUC_{0-24} and geometric mean $AUC_{0-\infty}$ increased 4.3- and 4.2-fold, respectively, on Day 1. On Day 7, the geometric mean C_{max} increased ~3.6-fold while the geometric mean AUC_{0-24} increased ~4.1-fold. Trough concentrations indicated steady state was achieved by or before Day 7 with once daily dosing. The geometric mean accumulation ratio for $AUC_{(0-24)}$ was ≤1.125 for all three dose levels, indicating no notable accumulation at steady state with once daily dosing.

4.1.3.2. Phase 2 Study of IMR-687 in Adult Patients with Sickle Cell Anaemia (IMR-SCD-102)

4.1.3.2.1. IMR-SCD-102: Interim Analysis Summary

A pre-specified blinded interim analysis was performed after at least 18 subjects in Population A had ≥4 weeks of available data for soluble adhesion markers. In addition, 3-month RBC data were available for a subset of 13 of these Population A subjects. To maintain the study blind, summary tables were prepared by an independent unblinded statistician who is not affiliated with the ongoing conduct of the study. In addition, no unblinded data were presented on individual subjects, and all data except for safety were pooled by randomized assignment.

As of the cut-off date (01 October 2018), safety measures (SAEs, AEs, vital signs) were analysed for 24 subjects enrolled in the study. Blinded safety evaluation found 58 AEs, with 4/58 events (7%) determined to be possibly related (2), probably related (1), or definitely related (1) to study drug. All these events were Grade 1 mild events that resolved without sequelae. No clinically relevant changes in vital signs were observed. Five SAEs were reported; all were categorized as sickle cell pain crises or VOCs.

Nineteen subjects (9 male and 10 female), were evaluated after 5 weeks of treatment, with a focus on WBC and adhesion biomarkers. A PK assessment following the first dose of IMR-687 indicated that 50 mg PK concentrations were below the target exposure indicated by preclinical mouse concentration-time data and time above the IC_{90} (Table 5 and Figure 5). The 100 mg dose level demonstrated drug concentrations expected to be effective, but at the lower end of the predicted

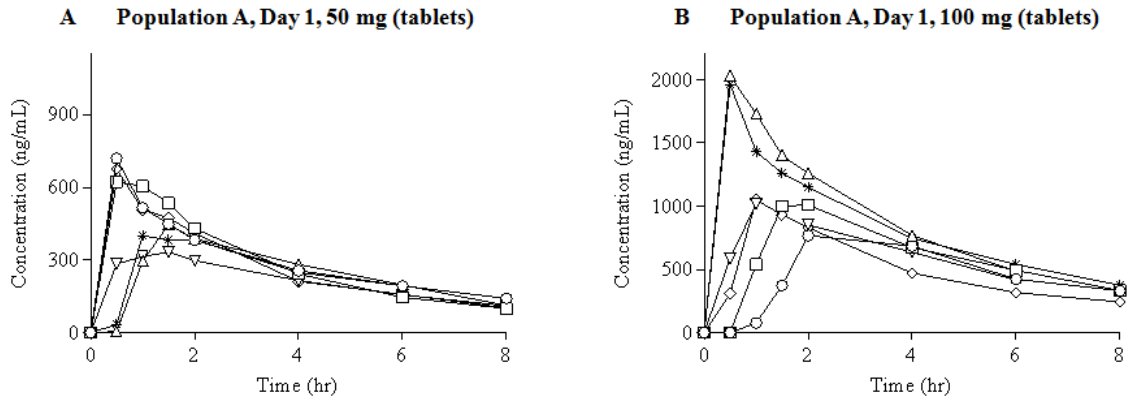
therapeutic window. In line with these findings, in the 100 mg dose group, there was a trend to reduced soluble P-selectin (sP-sel), soluble E-selectin (sE-sel), soluble vascular cell adhesion molecule (sVCAM), and myeloperoxidase compared to placebo treatment. In addition, RBC parameters were assessed in 13 subjects after 13 weeks of treatment and the 100 mg dose showed a consistent increase in the percentage of F cells over time, an increase in total Hb, and a reduction in both absolute reticulocytes counts (ARCs) and % reticulocyte counts. There was no obvious decrease in sE-sel, sP-sel, sVCAM, ARC, or % reticulocytes, or increases in % F cells, HbF, or Hb with the 50 mg dose vs. placebo.

Table 5 Summary of PK Parameters in Fed Patients After a Single Dose of IMR-687 (IMR-SCD-102 Part A Interim Analyses)

	50 mg	**100 mg**
Mean $t_{½}$ (hr)	4.83	4.83
Mean t_{max} (hr)	NR	NR
Mean C_{max} (ng/mL)	533	1310
Mean AUC_{0-t} (hr*ng/mL)	2610	6730
Mean AUC_{0-24} (hr*ng/mL)	2790	7060
Mean $AUC_{0-\infty}$ (hr*ng/mL)	2900	7340
CL/F (L/hr)	17/5	14.1
V_z/F (L)	119	97.7

AUC = area under the time-concentration curve; CL/F = apparent total clearance; C_{max} = maximum concentration; NR = not reported; PK = pharmacokinetic; $t_{½}$ = half-life; t_{max} = time to C_{max}; Vz/F = apparent volume of distribution
Note: N=6 for both dose groups and all PK parameters.

Figure 5 Individual Pharmacokinetic Concentrations After a Single Dose of IMR-687 (IMR-SCD-102 Part A Interim Analysis)



In summary, daily dosing of IMR-687 was safe and well tolerated in the 24 subjects enrolled in the study as of the 01 Oct 2018 data cut. Results of the interim analysis provide preliminary clinical evidence that IMR-687 may provide beneficial effects on both RBC and WBC biomarkers in SCD. Exposure data from the interim PK of the IMR-687 50 mg and IMR-687 100 mg dose groups and clinically relevant biomarkers suggest the planned 200 mg dose has the potential to achieve improved target coverage to mediate more profound changes in RBC and WBC biology.

4.2. Rationale for Conducting the Study

This is the first study in patients with SCA. The purpose of this study is to evaluate the safety, tolerability, PK, exploratory pharmacodynamics (PD), and clinical outcomes of IMR-687 in adult patients with SCA. Given that approximately 25% of patients with SCA are currently prescribed HU, it is possible that IMR-687, should it be approved, will be administered as a single agent or co-administered with HU. Therefore, the effects of IMR-687 will be evaluated in patients with SCA who are not receiving HU (Populations A and A1) as well as those who are currently receiving a stable dose of HU according to standard of care (Populations B and B1).

4.3. Benefit/Risk Assessment

The proposed doses in this study are 50, 100, and 200 mg daily, which are anticipated to be in the pharmacologically active range based on available nonclinical data (see Section 6.2 for dose selection rationale). The minimum weight for an eligible patient to enter this study is 50 kg; thus, the maximum possible per kilogram doses of IMR-687 are 1, 2, and 4 mg/kg. Based on the observed safety and tolerability of IMR-687 in the first-in-human study (Section 4.1.3), these dose levels should be well tolerated and may have a clinical beneficial PD effect in patients with SCA. The potential benefits and risks are summarized below.

4.3.1. Potential Benefits

This is the first study of IMR-687 in patients; therefore, the primary objective of this study is to determine the safety and tolerability of once daily oral doses of IMR-687 across a range of doses

anticipated to be pharmacologically active. However, potential benefits include the production of increased levels of HbF, which is associated with the decreased RBC sickling and improved bloodflow, and decreases in WBC adhesion molecules; individually and together these PD changes may lead to fewer painful SCA-associated crises and less need for blood transfusions.

4.3.2. Potential Risks

The potential risks of IMR-687 are inferred from the relevant nonclinical findings and the results of the first-in-human study in healthy volunteers. These potential risks are briefly summarized in the sections below. Further details are provided in the Investigator's Brochure.

4.3.2.1. 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, particularly when administered in the fasted state. Nausea observed thus far was transient and self-limited. Emesis has occurred at 6 mg/kg when administered in the fasted state, and after multiple-dose administration at 4.5 mg/kg in the fed state (on Day 7). Administration of IMR-687 with food mitigates nausea significantly and should be recommended. No correlate changes in liver function tests in any healthy volunteers administered IMR-687, or specifically in those subjects with nausea, with or without emesis, were observed.

4.3.2.2. Central Nervous System

Mild headaches (self-limiting or treatable with acetaminophen) were observed in the first-in-human study in healthy normal volunteers, and appeared to occur with nausea.

4.3.2.3. 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. At doses of 75 mg/kg in the safety pharmacology study, statistically significant heart rates were observed in dogs. In the 14-day dog toxicology study, the highest heart rates were noted in dogs at the highest dose level of 75 mg/kg, but did not reach statistical significance. In healthy volunteers in the first-in-human study, at doses between 0.3 to 6 mg/kg, sporadic observations of sinus tachycardia (i.e., heart rates >100 bpm) occurred in various subjects, including a subject in the MAD on placebo. The contribution of concomitant AEs such as headache to the rise in heart rate could not be excluded. No dose dependency or dose-duration dependency was noted for these heart rate observations. No signs of prolongation of QTcF were noted in any cohort of healthy volunteers at any dose of IMR-687.

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

5. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

5.1. Primary Objective and Endpoint(s)

The primary objective of this (second-in-human) study is:

- To assess the safety and tolerability of IMR-687 in adult patients with SCA, defined as HbSS or sickle-β^0 thalassemia, who are not receiving HU and in adult SCA patients who are receiving a stable dose of HU

The safety and tolerability of IMR-687 will be assessed by the following endpoints:

- Incidence and severity of AEs and SAEs
- Observed values and changes from baseline in 12-lead ECG parameters, clinical laboratory tests (chemistry, haematology, coagulation, urinalysis), and vital signs
- Physical examination findings
- Use of concomitant medications and therapies

5.2. Secondary Objectives and Endpoints

The secondary objectives of this study are:

- To characterise the PK profile of IMR-687 in adult patients with SCA who are/are not receiving a stable dose of HU
- To characterise the PK profile of HU in adult patients with SCA before and after receiving IMR-687 to determine whether there is a clinically relevant PK interaction

The PK profiles of IMR-687 and HU (administered alone and concomitantly with IMR-687) will be evaluated by the determination of PK parameters based on drug concentration levels in plasma obtained over time.

5.3. Exploratory Objectives and Endpoints

The exploratory objectives of this study are:

- To assess the PD effects of IMR-687 in adult patients with SCA who are/are not receiving stable HU
- To assess the potential efficacy of IMR-687 in adult patients with SCA who are/are not receiving stable HU

The following endpoints will be evaluated to assess the PD activity of IMR-687 (additional exploratory PD biomarkers may also be tested):

- Total haemoglobin (Hb) level
- HbF value (%)
- % F cells
- Indices of red cell haemolysis (unconjugated bilirubin, reticulocyte count, lactate dehydrogenase [LDH], and haptoglobin levels)

- sE-sel, sP-sel, and sICAM-1
- High-sensitivity C-reactive protein (hs-CRP)

The following SCA-related clinical outcome measures will be evaluated to assess the potential efficacy of IMR-687:

- Pain-related measures, including
  - Frequency, severity, and duration of pain
  - Impact of pain/fatigue on work/school and on activities of daily living (ADL)
  - Need for/use of pain medication
  - SCA-related events requiring professional medical or health care, including events requiring hospitalization or therapies, such as transfusions
- The physical, social, and emotional impact of SCA as measured by the ASCQ-Me

6. STUDY DESIGN

6.1. Overall Design

This is a randomised, double-blind, placebo-controlled study to evaluate the safety, tolerability, PK, and exploratory PD and clinical outcomes of the PDE9 inhibitor, IMR-687, administered once daily for 16 to 24 weeks in 2 populations of patients with SCA: those who are not receiving HU (Populations A and A1) and those who are currently receiving a stable dose of HU according to standard of care (Populations B and B1). Approximately 60 patients will be enrolled in Populations A and A1 combined and approximately 30 patients will be enrolled in Populations B and B1 combined.

The overall study design is depicted in Figure 1, Figure 2, Figure 3, and Figure 4, for Populations A, A1, B, and B1, respectively.

6.1.1. Population A

Following a Screening period of up to 4 weeks, eligible patients in Population A (i.e., those enrolled prior to this amendment and not receiving HU) will receive either IMR-687 or placebo once daily for a total of 24 weeks. On Day 1, patients will be randomised 1:1:1 to receive oral IMR-687 50 mg, IMR-687 100 mg, or placebo; the first 6 patients (sentinel patients to initiate dosing in Part B) will be randomized as a separate block. For the first 12 weeks (Weeks 1-12), all patients will receive study medication once daily according to their randomised treatment assignment; if well tolerated for 12 weeks, each patient's dose may be doubled (i.e., from 50 mg to 100 mg; from 100 mg to 200 mg; or placebo) for the next 12 weeks (Weeks 13-24). *Note*: Because placebo and all dose levels of IMR-687 are the same in appearance, dose escalation will not affect study medication blinding.

Throughout the study, all available clinical safety data will be reviewed approximately every 2 weeks by a Safety Review Committee (SRC; see Safety Review Committee). Dose escalation

will occur on an individual-patient basis on Day 85 patients enrolled in Population Aonly if approved by the SRC based on review of each patient's individual clinical safety data.

Safety, PK, PD, and efficacy assessments will be performed at the time points shown in Table 1.

6.1.2. Population A1

A pre-planned interim analysis of the data from the first 24 patients (Section 4.1.3.2.1) showed that daily dosing of IMR-687 was safe and well tolerated. In the 19 patients who had PK and PD biomarkers analysed, the 50 mg dose was considered to be subtherapeutic, and data indicated the planned 200 mg dose would likely achieve improved target coverage to mediate more profound changes in RBC and WBC biology. Subsequent patients (approximately 12 subjects) will not be randomized to the 50 mg dose level.

Following a Screening period of up to 4 weeks, eligible patients in Population A1 (i.e., those enrolled after this amendment and not receiving HU) will receive either IMR-687 or placebo once daily for a total of 24 weeks. On Day 1, patients will be randomised 2:1 to receive oral IMR-687 100 mg or placebo. For the first 4 weeks (Weeks 1-4), all patients will receive study medication once daily according to their randomised treatment assignment; if well tolerated for 4 weeks, each patient's dose may be doubled (i.e., from 100 mg to 200 mg; or placebo) for the next 20 weeks (Weeks 5-24). *Note*: Because placebo and all dose levels of IMR-687 are the same in appearance, dose escalation will not affect study medication blinding.

Throughout the study, all available clinical safety data will be reviewed approximately every 2 weeks by a SSRC; see Safety Review Committee). Dose escalation will occur on an individual-patient basis on Day 29 for patients enrolled on this amendment (version 005, 07 Jan 2019) only if approved by the SRC based on review of each patient's individual clinical safety data.

Safety, PK, PD, and efficacy assessments will be performed at the time points shown in Table 2.

6.1.3. Population B

Following a Screening period of up to 4 weeks, eligible patients in Population B (i.e., those enrolled prior to this amendment and receiving stable HU) will have blood samples drawn to characterise the PK profile of the patient's prescribed dose of HU in the absence of IMR-687 (i.e., to characterise the patient's baseline HU PK profile).

Following completion of the Screening and lead-in periods, eligible patients in Population B will receive their standard-of-care, stable dose of HU in addition to either IMR-687 or placebo once daily for 16 weeks. Dosing in Population B will not begin until at least 4 weeks of safety data from at least 6 patients in Population A have been reviewed by the SRC and the SRC has determined that it is safe and appropriate to begin dosing in Population B. Following SRC approval to initiate dosing in Population B and once the lead-in period is complete, patients will be randomised 2:1 on Day 1 to receive either IMR-687 50 mg or placebo. For the first 4 weeks (Weeks 1-4), patients will receive study medication once daily according to their randomised treatment assignment; for the following 12 weeks (Weeks 5-16), each patient's dose may be doubled (i.e., from 50 mg to 100 mg; or placebo). *Note*: Because placebo and all dose levels of IMR-687 are the same in appearance, dose escalation will not affect study medication blinding.

Throughout the study, all available clinical safety data (from Populations A, A1, B, and B1 will be reviewed approximately every 2 weeks by the SRC. Dose escalation in Population B will occur on an individual-patient basis on Day 29 only if approved by the SRC based on review of each patient's individual clinical safety data.

Safety, PK, PD, and efficacy assessments will be performed at the time points shown in Table 3.

6.1.4. Population B1

Following a Screening period of up to 4 weeks, eligible patients in Population B1 (i.e., those enrolled after this amendment and receiving stable HU) will enter a 4-week lead-in period and will have a single set of blood samples drawn to characterise the patient's baseline HU PK profile.

Once the baseline HU PK blood draws are complete, patients will be randomised 2:1 on Day 1 to receive oral IMR-687 50 mg or placebo for 24 weeks. For the first 4 weeks (Weeks 1-4), patients will receive study medication once daily according to their randomised treatment assignment; for the following 20 weeks (Weeks 5-24), each patient's dose may be doubled (i.e., from 50 mg to 100 mg; or placebo). Dose escalation will occur on Day 29 only if approved by the SRC based on review of each patient's individual clinical safety data.

Safety, PK, PD, and efficacy assessments will be performed at the time points shown in Table 4.

6.2. Dose Selection Rationale

The starting dose for this study of 50 and 100 mg correlates with an approximately 0.7 mg/kg and 1.4 mg/kg dose for an average 70 kg adult, while the maximum planned dose of 200 mg correlates to an approximately 2.9 mg/kg dose for an average 70 kg adult. The minimum acceptable weight in this study is 50 kg. Therefore, the corresponding doses of 50, 100, and 200 mg are equivalent to maximum doses of approximately 1, 2, and 4 mg/kg.

In nonclinical mouse models of sickle cell disease, IMR-687 at a dose of 30 mg/kg/day was effective at increasing the number of HbF+ RBCs, decreasing the percentage of sickled RBCs, and decreasing microvascular stasis after induced transient hypoxia/reperfusion. Based on the exposure of IMR-687 in these models, the target pharmacologically active range of IMR-687 in humans is expected to be between 0.3 to 3 mg/kg per day.

Based on the observed safety and tolerability of IMR-687 in the first-in-human study, once daily doses of 50, 100, and 200 mg should be well tolerated, especially if taken with food, as administration with food appears to reduce the incidence of nausea. The most likely potential AEs of nausea and emesis are easily monitorable and are self-limiting if dosing is stopped. Furthermore, following once daily dosing for 7 days, minimal accumulation was observed and steady state was achieved by or before Day 7; therefore, the safety and tolerability profile observed in the MAD part of the first-in-human study can likely be extrapolated to longer-term dosing. Exposure (AUC) increased in a near dose-proportional manner (a 4.1-fold increase for a 4.5-fold change in dose [see Section 4.1.3.1.3]), and the mean exposure (AUC_{0-24}) at 4.5 mg/kg on Day 7 was 25.6 µg•h/mL, which is approximately 3.6-fold below the Day 14 exposure (AUC_{0-24}) in the dog (most conservative species) at the NOAEL in the repeat-dose toxicology study.

6.3. Scientific Rationale for Study Design

This is a phase 2a study intended to explore the potential use of IMR-687 to treat patients with SCA. This is the first study in a patient population (patients with SCA), and as such, is designed to examine the safety, tolerability, and PK, as well as the potential PD effects and clinical efficacy, of IMR-687 across a range of doses in adult patients with SCA. Given the possibility that IMR-687, if approved, could be administered as a single agent or co-administered with HU, the effects of IMR-687 will be evaluated in SCA patients who are not receiving HU (Populations A and A1) as well as in those who are currently receiving a stable dose of HU (Populations B and B1).

Available nonclinical and healthy volunteer clinical data suggest that IMR-687 will be safe and well tolerated at once daily doses of 50, 100, and 200 mg and that these doses, if administered for at least 12 weeks, may demonstrate HbF induction and potential beneficial effects on markers of WBC adhesion (including sE-sel, sP-sel, and sICAM-1). Each test dose level (50, 100, and 200 mg in Population A and 100 mg in Population B) is planned to be administered for at least 12 weeks. In addition, given that the induction of HbF is directly and mechanistically related to relief from symptoms in SCA patients, the greatest likelihood to see a clinical effect is expected if IMR-687 is administered for at least 24 weeks at a dose of at least 100 mg. Therefore, Population A is also designed to provide at least 12 weeks of data (and at most 24 weeks of data) at a dose of at least 50 mg, as well as to assess the tolerability of the 200 mg dose level in sickle cell patients who have tolerated the 100 mg dose well. Population A1 is designed to provide at least 20 weeks of data at a dose of 200 mg. Population B1 is designed to provide at least 20 weeks data at a dose of 100 mg and to assess the tolerability and PD effects of IMR-687 in sickle cell patients.

To minimise potential confounding factors and increase the interpretability of the findings, the study is randomised, double blind, and placebo controlled. As only approximately 25% of patients with SCA receive treatment with HU and concomitant use of HU is permitted in Populations B and B1, the use of a concurrent placebo control provides scientific rigor without affecting standard of care.

Safety will be monitored intensively at regular site visits and, in addition to ongoing oversight of the study by the SRC, all patients will be seen in person once weekly for the first 4 weeks following initiation of treatment and dose escalation. Because there are no safety data on the administration of IMR-687 in patients with SCA, administration of IMR-687 will begin in Population A (patients not on HU).

Results from Populations B and B1 are intended to provide information on IMR-687 when administered concomitantly with HU, both of which increase HbF levels through alternative biochemical pathways that increase intracellular cGMP. Furthermore, because there are no clinical data to support administration of IMR-687 concomitantly with HU, patients in Populations B and B1will initiate dosing at the low IMR-687 dose (50 mg) used in Population A and will escalate to the 100 mg dose only if the 50 mg dose has been safe and tolerated for 4 weeks. In addition, although available nonclinical data do not suggest that concomitant administration of HU with IMR-687 would increase IMR-687 exposure, dosing in Population B will not initiate until 4 weeks of safety data are available from Population A in 2 patients each at 50 mg (starting dose in Population B) and 100 mg (twice the starting dose), as well as 2 patients at placebo.

6.4. End of Study Definition

6.4.1. Participant Completion

The length of a patient's participation in the study will be from the time informed consent is signed until the patient completes the end-of-study/follow-up visit and will be approximately 32 weeks for Populations A, A1, and B and approximately 36 weeks for Population B1.

A patient is considered to have completed the study if he/she has completed the end-of-study/follow-up visit as shown in schedules of assessments in Table 1 (Population A), Table 2 (Population A1), Table 3 (Population B), and Table 4 (Population B1).

6.4.2. Study Completion

Study completion is defined as the final date on which data are collected (i.e., the last patient's last visit or the last patient's last scheduled assessment).

7. STUDY POPULATION

A total of 90 evaluable patients are expected to enrol in this study, approximately 60 patients in Populations A and A1 combined (patients not receiving HU) and approximately 30 patients in Populations B and B1 combined (patients on a stable dose of HU).

7.1. Patient Inclusion Criteria

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

1. Be a male or female ≥18 and ≤55 years of age.
2. Have a confirmed diagnosis of SCA (HbSS or sickle-B^0 thalassemia). *Note*: If not already documented in the patient's record, the diagnosis of SCA must be confirmed via electrophoresis, high performance liquid chromatography (HPLC), and/or genotyping.
3. Use of HU:
   a. For patients in the Populations A and A1: Have not received HU within 90 days prior to Screening and are not planning to take HU while on the study.
   b. For patients in Populations B and B1: Have received HU for at least 6 months, have been on a stable dose for at least 60 days prior to Screening, and are not planning to change the dose level, dose regimen, or discontinue HU within the next 6 months.
4. Female patients must not be pregnant and be highly unlikely to become pregnant. Male patients must be unlikely to impregnate a partner. Male or female patients must meet at least one of the following criteria:
   c. A female patient who is not of reproductive potential is eligible without requiring the use of contraception. A female patient 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

local 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).

d. A male patient who is not of reproductive potential is eligible without requiring the use of contraception. A male patient 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.

e. A male or female patient who is of reproductive potential agrees to remain truly abstinent or use (or have their partner use) acceptable methods of highly effective contraception starting from the time of consent through 3 months after the completion of study therapy. True abstinence is defined as abstinence that is line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of the trial and withdrawal are not acceptable methods of contraception. Acceptable methods of highly effective birth control are combined or progestogen-only hormonal contraception that is associated with inhibition of ovulation, intrauterine device, and intrauterine hormone-releasing system.

5. Be capable of giving informed consent and reading and signing the informed consent form after the nature of the study has been fully explained by the investigator or investigator designee.

6. Be willing and able to complete all study assessments and procedures and to communicate effectively with the investigator and site staff.

7.2. Patient Exclusion Criteria

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

1. Total Hb at Screening >12.5 g/dL or <6 g/dL.

2. Reticulocyte count <100 x 10^9/L for Populations A and A1, or <80 x 10^9/L for Populations B and B1.

3. Greater than 7 hospitalizations (for at least 24 hours) for VOC, including acute chest syndrome and priapism, within the prior year.

4. *(intentionally left blank)*

5. Blood transfusion or donation of blood or any blood product within 60 days of Day 1 or on chronic transfusion therapy regimen.

6. Positive for human immunodeficiency virus (HIV), hepatitis C (HCV) antibodies (unless the patient has successfully completed drug therapy that results in cure/clearance of HCV), or hepatitis B surface antigen.

7. For female patients of childbearing potential, a positive serum human chorionic gonadotropin (hCG) test (Screening) or a positive urine hCG test on Day 1.

8. Estimated glomerular filtration rate (eGFR) <50 mL/min as calculated by the equation from the Modification of Diet in Renal Disease Study using creatinine, age, sex, and ethnicity.
9. ALT or AST >3x the upper limit of normal (ULN)
10. Body mass index (BMI) <17.5 or >35 kg/m^2; a total body weight <50 kg
11. Use of PDE type 5 (PDE5) inhibitors (including but not limited to sildenafil, tadalafil, vardenafil) within 7 days prior to the first dose of study drug, or planning to use any time during study
12. A history of drug or alcohol abuse as judged by the investigator within the past 1 year, or a positive alcohol (breathalyser) test (Screening or Day -1).
13. A cancer that has not been in complete remission for at least 5 years. Patients with squamous cell or basal cell carcinoma of the skin, localised cervical cancer, or localised prostate cancer are eligible if, in the opinion of the investigator, the condition has been adequately diagnosed, and is determined to be clinically in remission, and the patient's participation in the study would not represent a safety concern.
14. A history of a clinically significant allergic reaction or hypersensitivity, as judged by the investigator, to any drug or any component of the study drug formulations used in the study.
15. On ECG, a corrected QT interval (QTc), Fridericia's formula (QTcF) >450 ms in men and >470 ms in women or the presence of clinically significant abnormalities as determined by the investigator.
16. A history of major surgery within 4 weeks or minor surgery within 2 weeks of Day 1.
17. Any flu-like syndrome or other respiratory infection within 2 weeks of Day 1 or vaccination with attenuated live virus within 4 weeks of Day 1.
18. Participation in an investigational drug or device study within 30 days prior to Day 1.
19. Use within 30 days prior to Day 1, or planning to use during the study, of any drugs or substances that are known to strongly inhibit or induce CYP enzymes, including but not limited to cimetidine, cyclosporine, erythromycin, omeprazole, rifampin, ritonavir, and St. John's wort. If there is any question as to whether a substance is permitted, please review the product labelling (if applicable) and consult the Sponsor.
20. Consumption of grapefruit, grapefruit juice, or grapefruit products within 24 hours prior to Day 1 or planning to consume grapefruit products during the study.
21. Use within 30 days prior to Day 1, or planning to use during the study, of any CYP3A sensitive substrates (see Appendix A). If there is any question as to whether a substance is permitted, please review the product labelling (if applicable) and consult the Sponsor.
22. Use within 30 days prior to Day 1, or planning to use during the study, of any drugs or substances known to be significant substrates or inhibitors of P-gp (see Appendix B). If there is any question as to whether a substance is permitted, please review the product labelling (if applicable) and consult the Sponsor.

23. Other prior or ongoing medical condition, physical findings, or laboratory abnormality that, in the investigator's opinion, could adversely affect the safety of the patient, make it unlikely that the course of treatment or follow-up would be completed, or impair the assessment of study results.
24. In the opinion of the investigator, the patient is unable to meet the requirements of the study.

7.3. Screen Failures

Any patient who consents to participate in the study but is not randomised is considered a screen failure. Demographic data, eligibility criteria, reason not randomised (if other than failed 1 or more inclusion or exclusion criterion), and – if applicable – any SAEs will be recorded and reported for patients who are screen failures.

8. STUDY INTERVENTION

8.1. Name and Description

8.1.1. Test Therapy (IMR-687)

IMR-687 is the active investigational medicinal product (IMP) being tested in this clinical study. It is a novel organic compound that inhibits the cGMP-degrading enzyme, PDE9A. IMR-687 is in clinical development and is not authorised for marketing in any country. In earlier development studies, the active pharmaceutical ingredient (API) was alternately referred to as AF68722. The API is a white to off-white powder that is highly soluble in water. IMR-687 drug product will be supplied as 50, 100, or 200 mg white tablets for oral administration. The different doses of IMR-687 are visually identical in tablet form. Information on the IMP is provided in Table 6.

Product characteristics, including Reference Safety Information, are provided in the Investigator's Brochure.

Table 6: IMR-687 Active Investigational Medicinal Product

Chemical Name:	6-[(3S,4S)-4-methyl-1-(pyrimidin-2-ylmethyl)pyrrolidin-3-yl]-3-tetrahydropyran-4-yl-7H-imidazo[1,5-a]pyrazin-8-one
Other Names or Designations:	AF68722, 68722, and CK1598
CAS RN:	Not listed
Molecular Formula:	$C_{21}H_{26}N_6O_2$
Molecular Weight:	CCI [redacted]
Dosage Form:	CCI [redacted]
Strength:	CCI [redacted]
Route of Administration	CCI [redacted]
Excipients:	CCI [redacted]
Manufacturer	CCI [redacted]

CAS RN = Chemical Abstracts Service Registry Number; EP = European Pharmacopoeia; NF = National Formulary

8.1.2. Reference Therapy (Placebo)

The reference IMP in this study is placebo. Placebo will consist of tablets containing matrix absent IMR-687 and will be identical in appearance to the IMR-687 tablets.

8.2. Packaging and Labelling

CCI [redacted]

8.3. Preparation, Handling, Storage, and Accountability

Upon receipt of the study medication, an inventory must be performed and a drug receipt log filled out 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. Any damaged or unusable study medication must be documented, and the site must notify the Sponsor.

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

The study site must maintain accurate records demonstrating dates and quantity of study medication received, to whom dispensed (patient-by-patient accounting), any amount returned, and accounts of any study medication that was accidentally or deliberately destroyed. At the end of the study, a final reconciliation must be made between the quantity of study medication supplied, dispensed, and subsequently destroyed or returned to the Sponsor. A written explanation must be provided for any discrepancies.

Any unused study medication remaining at the end of the study will be returned to the Sponsor or destroyed after accountability has been performed by the Sponsor or Sponsor's designee.

8.4. Randomization and Blinding

8.4.1. Randomization

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

On Day 1, eligible patients in Populations A, A1, B, and B1 will be assigned a unique number (randomization number) in sequential order. The randomization number codes the patient's initial treatment assignment to IMR-687 50 mg, IMR-687 100 mg, or placebo for Population A, IMR-687 100 mg or placebo for Population A1, or IMR-687 50 mg or placebo for Populations B and B1, according to the randomization schedule generated prior to the study. Randomization for Population A will be 1:1:1 for each of the 3 groups; randomization for Population A1 will be 2:1 for IMR-687 100 mg and placebo, and randomization for Populations B and B1 will be 2:1 for IMR-687 50 mg and placebo. In Population A, the first 6 patients (sentinel patients to initiate dosing for Population B) will be randomized as a separate block.

Randomization numbers will not be re-used once assigned. In the event that a patient is replaced, the replacement patient will receive the same treatment as the replaced patient and will be assigned a randomization number incremented by PPD (e.g., PPD would replace PPD).

8.4.2. Blinding

To ensure that the patient and site are blinded with respect to each patient'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 placebo, IMR-687 50 mg, IMR-687 100 mg, or IMR-687 200 mg. At each site visit, as needed, an unblinded study pharmacist will select a bottle containing the correct IMP and, if applicable, dose level and will provide the blinded study medication to the patient.

Every attempt should be made to preserve the integrity of study drug blinding. Except for cases of emergency unblinding, as described in Section 8.4.3, the randomization code will remain unbroken

for patients and study personnel at the site until the database has been locked for each study population.

8.4.3. Emergency Unblinding

Unblinding is not always necessary to provide effective medical intervention and patient management in the event a patient experiences a VOC, an SAE, or an event that results in cessation of treatment (see Section 9.2). However, in the exceptional circumstance where the investigator believes that knowledge of the study drug assignment is essential to provide appropriate medical management, the treatment assignment for that patient will be provided to the investigator according to standard operating procedures at the contract research organisation (CRO). The Medical Monitor and Sponsor are available to the Investigator as needed for any considerations of unblinding a specific patient; however, the decision to unblind a specific patient relies solely on the clinical judgement of the Investigator and there is no requirement to discuss with the Medical Monitor and/or Sponsor prior to unblinding a specific patient by the Investigator.

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 electronic case report form (eCRF) pages.

8.5. Administration

Patients will take IMR-687 or matched placebo tablets orally with food once per day for 24 weeks (Populations A, A1, and B1) or 16 weeks (Population B).

8.6. Compliance/Adherence

The investigator or designee must ensure that all patients 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; all study drug administration will be documented on the appropriate pages of the eCRF.

8.7. Concomitant Medications/Therapies

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

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

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.

8.7.1. Non-investigational Medicinal Products

A non-investigational medicinal product (NIMP) is a product that is not under investigation, but will be used in the trial; a NIMP may include any background medication(s) administered to all participants.

There are no NIMPs administered to Populations A and A1.

HU is administered as a NIMP to patients in Populations B and B1. Patients in Populations B and B1 will take HU as prescribed by their treating physician according to their current, stable, standard-of-care dose.

8.7.2. Prohibited Concomitant Medications/Therapies

The following are not permitted at any time during the study. If any of the following are determined to be necessary for the well-being of the patient, the patient will be withdrawn from the study.:

- PDE5 inhibitors (including but not limited to sildenafil, tadalafil, vardenafil).
- Any drugs or substances, including grapefruit juice, that are known to strongly inhibit or induce CYP enzymes, including but not limited to cimetidine, cyclosporine, erythromycin, grapefruit or grapefruit juice, omeprazole, rifampin, ritonavir, and St. John's wort. If there is any question as to whether a substance is permitted, please review the product labelling (if applicable) and consult the Sponsor.
- Any drug or substance that is a CYP3A-sensitive substrate (other than opioids), including but not limited to alfentanil, avanafil, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, ebastine, eletriptan, eplerenone, everolimus, felodipine, ibrutinib, indinavir, lomitapide, lurasidone, maraviroc, midazolam, naloxegol, nisoldipine, quetiapine, saquinavir, sirolimus, tacrolimus, ticagrelor, tipranavir, tolvaptan, triazolam. If there is any question as to whether a substance is permitted, please review the product labelling (if applicable) and consult the Sponsor.
- Any drugs or substances that are significant substrates or inhibitors of P-gp, including but not limited to cyclosporine, lovastatin, propranolol, quinidine, and simvastatin. If there is any question as to whether a substance is permitted, please review the product labelling (if applicable) and consult the Sponsor.
- Concomitant use of L-glutamine and erythropoietin (e.g., Procrit, Epogen). For erythropoietin, a washout period of at least 6 weeks is required before starting on study.
- Any other investigational drug or device.

Medications prohibited prior to study entry are described in the exclusion criteria in Section 7.2.

8.8. Dose Modification

If the SRC determines that it is safe to do so, each patient's dose will be increased during the study. Patients in Population A will receive their randomised dose for the first 12 weeks of the study; beginning at Week 13, each patient's dose may be doubled (i.e., from 50 mg to 100 mg; from 100 mg to 200 mg; or placebo). Patients in Population A1 will receive their randomised dose for

the first 4 weeks of the study; beginning at Week 5, each patient's dose may be doubled (i.e., from 100 mg to 200 mg or placebo). Patients in Population B will receive their randomized dose for the first 4 weeks of the study; beginning on Week 5, each patient's dose may be doubled (i.e., from 50 mg to 100 mg or placebo). Patients in Population B1 will receive their randomised dose for the first 4 weeks of the study; beginning at Week 5, each patient's dose may be doubled (i.e., from 50 mg to 100 mg; or placebo).

To maintain the blind, placebo and all dose levels of IMR-687 are identical in appearance.

The SRC will decide whether or not to dose escalate on a patient-by-patient basis once it has reviewed all available safety data for a given patient. The SRC may decide to continue a patient on his or her initial randomized dose (i.e., not to dose escalate) or to double the patient's blinded dose (i.e., dose escalate). Dose escalation will occur only at Week 13 for patients in Population A or at Week 5 for patients in Populations A1, B, and B1, and only once approved by the SRC.

Dose reductions are not permitted during the study, including after a patient's dose has been escalated. If, in his/her clinical judgement, the investigator believes that continued administration of study medication may pose an unacceptable safety risk to the patient, study drug should be discontinued (see also Section 9.2).

9. STUDY, SITE, OR PARTICIPANT DISCONTINUATION

9.1. Criteria for Study or Site Termination or Study Suspension

The Sponsor may terminate this study or investigational site participation in this study at any time for any reason. Conditions that may warrant termination of the study or investigational site participation in this study include, but are not limited to:

- Decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of IMR-687
- Failure of the investigator to comply with the approved protocol, pertinent guidelines, and/or regulations
- Submission of knowingly false information from the investigator to the Sponsor and/or regulatory authorities

In addition, the Sponsor or the SRC may suspend the study (i.e., instruct cessation of IMP dosing in all patients) if, in their opinion, emerging data at that time indicate that the risk of continued dosing outweighs any possible benefit from study continuation. In the case of study suspension, dosing of further patient volunteers cannot restart without a positive opinion from the Medicines and Healthcare Products Regulatory Agency (MHRA) and Ethics' Committee to recommence the study.

9.2. Treatment Discontinuation/Stopping Rules

After consultation between the investigator and the sponsor CRO medical monitor, dosing of any individual patient may be stopped and the patient withdrawn from the study if any of the following arises:

- The patient becomes pregnant
- The patient misses ≥5 days of dosing within a 28-day period for any reason
- For Population A and A1 patients – the patient has started, or will be started on HU during the period of the study for any reason (e.g., recurrent VOCs)
- ALT or AST >5x ULN upon repeat testing
- eGFR <30 mL/min upon repeat testing with suspicion of renal parenchymal damage
- Any other clinical event or finding that in the clinical judgement of the investigator would pose an unacceptable safety risk to the patient to continue in the study

Note: Patients who experience VOC(s) or other SCA-related events may remain in the study and continue to receive IMP, unless the investigator deems that continued treatment would pose an unacceptable safety risk to the patient. Patients who experience VOCs or other SCA-related events should not be unblinded (even if treatment is discontinued) unless the investigator believes that knowledge of the study drug assignment is essential to provide appropriate medical management of the patient (see Section 8.4.3). Patients who experience a VOC should receive all appropriate interventions as per local standard of care. These include hydration (oral and/or intravenous), rapid and adequate pain control (nonsteroidal anti-inflammatory drugs and/or opioids as appropriate), and rest (hospital admission may be necessary). Supplemental oxygen may also be of benefit. Assessment and treatment of a SCD patient with a new VOC depend solely on the clinical judgement of the Investigator, and should include management of potential sequelae of the VOC, such as renal failure or stroke.

In patients who are not already on HU, dosing of HU is typically not initiated in the acute phase of a VOC. Consideration of starting HU in any given patient takes into account the patient's prior response to SCD management, potential compliance/adherence for serial follow-up, and other potential clinical issues (e.g., likelihood for pregnancy in the future). The decision for starting HU in a previously naïve SCD patient is at the clinical discretion of the Investigator. Patients already on HU should remain on their stable outpatient dose, unless considered by the Investigator to require modulation of their dosing. Changes in dosing of HU is at the clinical discretion of the Investigator.

In the event that treatment is prematurely discontinued, if possible, patients in Populations A, A1, or B1 should complete all assessments scheduled at the Week 25 study visit before being withdrawn from the study. Patients in Population B should complete all assessments scheduled at the Week 17 study visit before being withdrawn from the study.

The investigator will document the reason(s) for treatment or study discontinuation on the eCRF. The Sponsor and the CRO medical monitor should be informed when a patient is withdrawn from the study.

9.3. Participant Discontinuation/Withdrawal

All patients who receive study drug should remain in the study whenever possible. However, patients are free to withdraw consent and/or discontinue participation in the study at any time, without providing a reason and without prejudice to further medical care. If the patient withdraws from the study, he/she must be provided with a point of contact to obtain further information about the study, if desired. Data and samples collected to the point of withdrawal may only be used after withdrawal if the patient consented to this. A patient who withdraws from the study may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

A patient's treatment and participation in the study may also be discontinued at any time at the discretion of the investigator, the CRO medical monitor, or the Sponsor. Justifiable reasons to discontinue a patient from treatment and the study may include, but are not limited to the following:

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

In the event that a patient withdraws or is withdrawn from the study, if possible, the patient should complete all assessments scheduled at the Week 25 (Populations A, A1, and B1 [Table 1, Table 2, and Table 4, respectively]) or Week 17 (Population B, Table 3) study visit before being withdrawn from the study.

A patient will be considered "discontinued due to an AE" if he or she withdraws from the study due to any AE, regardless of whether or not the AE is considered related to study drug. If the patient withdraws from the study due to an AE, the investigator should arrange for the patient to be followed appropriately until the AE has resolved or stabilised (in the opinion of the investigator).

The investigator will document the reason(s) for treatment or study discontinuation on the eCRF. The Sponsor and the CRO medical monitor should be informed when a patient is withdrawn from the study.

9.4. Lost to Follow-up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

If a patient fails to return to the clinic for a required study visit, the site must:

- Attempt to contact the patient and reschedule the missed visit as soon as possible

- Counsel the patient on the importance of maintaining the assigned visit schedule
- Ascertain whether or not the patient wishes to and/or should continue in the study.

Before a patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.

Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.

9.5. Patient Replacement

To ensure an adequate number of patients to evaluate the safety and PK of IMR-687, any patient who is randomised but does not receive study drug may be replaced. In addition, any patient who discontinues prior to the Week 13 study visit (Populations A, A1, B, and B1) may be replaced subject to SRC agreement. Available data for all patients will be reported in data listings.

9.6. Patient Telephonic Visits

Patients enrolled in Populations A will have telephonic visits during Weeks 3, 4, 15, and 16. Patients enrolled in Populations A1 will have telephonic visits during Weeks 3, 15, and 16. Similarly, for patients enrolled in Populations B and B1, telephonic visits will occur during Weeks 3, 4, 6, 7, and 8. The telephonic visit should collect information on any AEs of significant clinical concern, as well as remind patients to continue to take study drug orally with food once a day, and to complete their daily app-based symptom questionnaire in a timely manner.

If any AEs of significant clinical concern are identified during the telephonic visit, the patient will be requested to come into the site to be assessed by targeted physical exam and vital signs measurement. Physical exams and vital signs will not be measured at these time points if patients do not have AEs of concern.

10. STUDY ASSESSMENTS AND PROCEDURES

Study assessments and their timing are outlined in the Schedules of Assessments (Population A, Table 1; Population A1, Table 2; Population B, Table 3; and Population B1, Table 4).

All eligibility (inclusion/exclusion) assessments must be completed at Screening (and, for Group B, prior to obtaining blood samples for the 24-hour baseline HU PK profile) and reviewed on Day 1 to confirm that potential patients meet all eligibility criteria. All eligibility criteria must be recorded on the eCRF, including reasons for screen failure or other exclusion from the study, if applicable.

10.1. Pharmacokinetic and Pharmacodynamic Assessments

10.1.1. Blood Sample Collection

Blood samples will be collected from all patients at the time points indicated in Table 1 (Population A), Table 2 (Population A1), Table 3 (Population B), and Table 4 (Population B1) for the determination of IMR-687 and HU plasma concentrations and for determination of PD biomarker levels.

On study days, when post-dose blood samples are drawn for IMR-687 or for HU PK, the exact date and time of IMR-687/placebo or HU, respectively, dose administration must be recorded on the eCRF. The exact date and time (actual) for each blood draw must also be recorded on the eCRF.

The accepted window of time for blood draws for PK and PD parameters is shown in Table 7. The actual date and time of each sample will be recorded. The approximate total volume of blood to be withdrawn in shown in Appendix C.

Table 7: Accepted Time Window for PK and PD Blood Draws

Procedure	Time Point (Relative Time)	Window Allowance
PK and PD	Pre dose	Within 30 minutes prior to dose
PK	Post-dose time points up through 10 hours post dose	± 5 minutes for each time point
	24 hours post dose	± 1 hour at each time point

PD = pharmacodynamics; PK = pharmacokinetics

Refer to the Study Laboratory Manual for details on the collection, handling, and processing of blood samples.

10.1.2. Analytical Methodology

Plasma PK (IMR-687 and HU) concentrations and all PD biomarkers will be quantified using validated assays. Details of the method validation will be documented (for each assay) in a method validation report.

10.2. Exploratory Clinical Outcome Assessments

In this phase 2a study, the potential efficacy of IMR-687 will be evaluated by assessing measures related to pain and SCA-related events that require professional medical or health care attention. In addition, patient quality of life will also be evaluated. The same assessments will be performed in Population A, Population A1, Population B, and Population B1 at the time points indicated in Table 1, Table 2, Table 3, and Table 4, respectively.

10.2.1. Pain-related Measures

An app-based pain questionnaire (completed daily) will be used to evaluate the following pain-related measures:

- Frequency, severity, and duration of pain

- Impact of pain/fatigue on work/school and on activities of daily living
- Need for professional medical or health care
- Need for pain medication

In addition, the details of all opiate- and non-opiate-based pain medication use will be recorded on the eCRF, including the start date/time, dose, frequency, route of administration, and stop date/time; any change during the study must be recorded as a new record.

If pain or any other SCA-related event results in the need for professional medical or health care, the details will also be recorded, including the event(s) that required care (e.g., VOCs), the need for hospitalization (start and stop dates/times for each hospitalization), and any therapies administered (e.g., transfusions).

10.2.2. Quality of Life Measurement

The ASCQ-Me will be administered to evaluate the potential effects of IMR-687 on the physical, social, and emotional impacts of SCA.

10.3. Disease Confirmation and Pharmacogenomics

If the study-prescribed genotype for a patient has not been previously confirmed, a 2-mL blood sample will be drawn at Screening for confirmation of diagnosis by electrophoresis, HPLC, and/or deoxyribonucleic acid (DNA) sequencing (as needed). An additional 3-mL sample may also be collected for possible pharmacogenomic analyses of genes that may affect treatment response (including but not limited to alpha globin and BCL11A). DNA sequencing will be performed only on samples collected from patients who have consented to genetic analysis.

10.4. Safety Assessments

Safety will be assessed by the incidence of AEs and SAEs, and evaluation of vital signs, physical examination findings, and ECG and clinical laboratory test results.

10.4.1. Adverse Event and Serious Adverse Event Collection

10.4.1.1. Time Period Adverse Event Collection

Any AE, including any SAE, that occurs after the patient has signed informed consent but prior to assignment of a patient identification number will be recorded on the medical history page of the eCRF. AEs that occur following assignment of a patient identification number (randomization), including those that may occur prior to administration of study drug, will be recorded on the AE page(s) of the eCRF. AEs that occur following administration of study drug will be considered TEAEs. Adverse events (related and unrelated), including SAEs, will be recorded from the signing of informed consent through the end-of-study safety follow-up visit.

All SAEs will be recorded and reported to the Sponsor or Sponsor's designee within 24 hours, as indicated in Section 10.4.2.3. The investigator will also submit any updated SAE data to the Sponsor within 24 hours of it being available.

10.4.1.2. Follow-up

After the initial AE/SAE report, the investigator is required to proactively follow each patient at subsequent visits and phone contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 9.4).

10.4.2. Adverse Event Recording and Reporting

10.4.2.1. Definitions

10.4.2.1.1. Definition of an Adverse Event

An AE is defined as any untoward medical occurrence in a clinical study patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable 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.

10.4.2.1.2. Definition of a Serious Adverse Events

An SAE is any AE that results in 1 or more of the following outcomes:

- **Death**
- **Requires or prolongs hospitalization** (In general, hospitalization signifies that the patient 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 patient 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, diarrhoea, influenza, or accidental trauma [e.g., sprained ankle] that may interfere or prevent everyday life functions, but do not constitute a substantial disruption.)
- **Congenital anomaly or birth defect** (that occurs in the offspring of a patient exposed to the investigational product.)

- **Other medically important event** (In general, this means an AE that, based on appropriate medical judgment, is considered to jeopardise the patient'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 10.4.2.3.

10.4.2.1.3. Definition of a Suspected Unexpected Serious Adverse Reaction

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

Reporting requirements for SUSARs are described in Section 10.4.2.4.

10.4.2.2. Evaluation of Adverse Events / Serious Adverse Events

10.4.2.2.1. Assessment of Severity

AE severity (intensity) will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The CTCAE is a descriptive terminology utilised 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 activities of daily living (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. 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 (see Section 10.4.3.1).

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 10.4.2.1.2).

10.4.2.2.2. Assessment of Causality

The investigator will assess the potential relatedness of each AE to the investigational product. An investigator causality assessment (Unrelated, Unlikely, Possible, Probable, or Definite) 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.

Not Related/Unrelated:	Suggests that there is no causal association between the investigational product and the reported event. That is, another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the exposure to investigational product and/or causal relationship is considered biologically implausible.
Unlikely Related:	Suggests that the clinical picture is highly consistent with a cause other than the investigational product; however, the AE cannot be attributed with absolute certainty to another cause and a relationship between the investigational product and AE cannot be excluded with complete confidence.
Possibly Related:	Suggests that treatment with the investigational product may have caused or contributed to the AE (i.e., the event follows a reasonable temporal sequence from the time of drug administration and/or follows a known response pattern to the investigational product), but could also have been produced by other factors.
Probably Related:	Suggests a likely causal association of the AE with administration of the investigational product. This may be based on the known pharmacological action of the investigational product, known or previously reported adverse reactions to the investigational product or class of drugs, reasonable temporal association between administration of the investigational product and onset of the AE, or judgment based on the investigator's clinical experience.

Definitely Related:	Suggests that there is strong evidence of a causal relationship between exposure to the investigational product and the AE, such as other conditions (concurrent illness, concurrent medication reaction, or progression/expression of disease state) do not appear to explain the AE, the AE corresponds with the known pharmaceutical profile of the investigational product, the AE improves upon discontinuation of the investigational product and/or re-appears upon re-challenge.

10.4.2.2.3. 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.

10.4.2.3. Recording and Reporting Adverse Events and Serious Adverse Events

All non-serious AEs 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 is initially notified by telephone, the phone call is to be immediately followed with by notification on study-specific SAE forms. 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.

SAE Reporting:

Email: PPD

Fax: PPD

Initial SAE reports must be followed by detailed descriptions. These should include copies of 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.

SAEs occurring up to and including the patient'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 patient has been discharged from the study, and he/she considers the event to be *reasonably related* to the study medication 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 time frame detailed above

- Causality of the SAE(s)
- Outcome of the SAE(s)
- Medical records and laboratory/diagnostic information

10.4.2.4. Regulatory Reporting Requirements

Sponsor's Reporting Requirements

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

Investigator's Reporting Requirements

The investigator must fulfil all local regulatory obligations required of investigators for the study. It is the investigator's responsibility to notify the Ethics Committee 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.

10.4.2.5. Exposure During Pregnancy

Pregnancy data will be collected during this study for all patients. 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 patient must be followed until the outcome of the pregnancy is known (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) even though the patient will be withdrawn from the study per Section 9.2.

If a patient within this study or a patient'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.

10.4.3. Other Safety Parameters

10.4.3.1. Clinical Laboratory Tests

Samples for haematology, clinical chemistry (including liver function tests and lipid panel), coagulation panel, and urinalysis will be collected as outlined in the Schedules of Assessments in Table 1 (Population A), Table 2 (Population A1), Table 3 (Population B), and Table 4 (Population B1). Laboratory tests may be repeated at any visit if there was an abnormal finding at the most recent previous evaluation or if additional information is clinically necessary to appropriately evaluate the patient's current condition, follow up, and/or manage an AE.

See Table 8 for a list of parameters to be measured. The approximate total volume of blood to be drawn at each visit is shown in Appendix C.

Table 8: Safety Laboratory Parameters to be Measured

Chemistry:	Sodium, potassium, calcium, chloride, bicarbonate, magnesium, phosphate, glucose, BUN, creatinine, CPK, total protein, ALP, LDH, albumin, bilirubin (total; direct; indirect), ALT, AST, and GGT
Haematology:	Absolute and differential WBC count, erythrocyte count, reticulocyte count, Hb (including HbF), haematocrit, platelet count, and RBC indices (mean corpuscular volume, mean corpuscular haemoglobin, and mean corpuscular haemoglobin concentration)
Coagulation:	Prothrombin time (PT) and activated partial thromboplastin time (aPTT)
Urinalysis:	Specific gravity, pH, protein, glucose, bilirubin, urobilinogen, ketones, and blood

ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Hb = haemoglobin; HbF = fetal haemoglobin; LDH = lactate dehydrogenase; PT = prothrombin time; RBC = red blood cell; WBC = white blood cell

10.4.3.2. Vital Signs

Vital signs should be measured in the sitting or semi-supine position, on the days and time points indicated in the Schedules of Assessments in Table 1 (Population A), Table 2 (Population A1) Table 3 (Population B), and Table 4 (Population B1). Additional vital sign measurements may be taken at the investigator's discretion to evaluate symptoms or assess possible trends or patterns. Vital signs will include systolic and diastolic blood pressure (mmHg), heart rate (beats/minute), respiratory rate (breaths/minute), and temperature (°C). Any value outside of the current reference ranges will be flagged on the results (e.g., H [high] or L [low]). The investigator will score all abnormal assessment results as either clinically significant or not clinically significant based on his or her medical judgement.

Any clinically significant change from baseline in vital signs will be documented as an AE on the AE eCRF. Screening/baseline events will be documented in the Medical History eCRF. Clinical significance is defined as any variation in vital signs that has medical relevance and may result in an alteration in medical care. The investigator will continue to monitor the patient until the finding is resolved or, in the judgment of the investigator, follow-up is no longer medically necessary.

10.4.3.3. Electrocardiograms

A standard 12-lead ECG will be performed in triplicate predose and postdose on the days and time points indicated in the Schedules of Assessments in Table 1 (Population A), Table 2 (Population A1), Table 3 (Population B), and Table 4 (Population B1). Consecutive replicate ECGs will be obtained at approximately 1-minute intervals. ECGs may be obtained at additional times, if deemed clinically necessary. Collection of more replicates than expected at a particular time point is allowed if needed to ensure high-quality records.

ECGs will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible to evaluate the need for immediate patient management, should any clinically relevant findings be identified.

After enrolment, if a clinically significant increase in the QT/QTc interval from baseline or another clinically significant quantitative or qualitative change from baseline is identified, the patient will be assessed by the investigator for symptoms (for example, palpitations, near syncope, syncope). The investigator or qualified designee is responsible for determining whether any change in patient management is needed and must document his/her review of the ECG printed at the time of evaluation from at least 1 of the replicate ECGs at each time point. The investigator will continue to monitor the patient until the finding is resolved or, in the judgment of the investigator, follow-up is no longer medically necessary.

10.4.3.4. Physical Examinations

A complete physical examination will be performed at the Screening and Day 1 visits as outlined in the Schedules of Assessments in Table 1 (Population A), Table 2 (Population A1), Table 3 (Population B), and Table 4 (Population B1). These examinations will include height and weight plus the following assessments: general appearance; skin; head, ear, eye, nose, and throat; neck; lymph node; chest; heart; abdominal cavity; limb; CNS; and musculoskeletal. Clinically significant findings prior to Day 1 will be recorded on the Medical History eCRF.

Subsequent physical examinations as indicated in the schedule of assessments will be symptom-based, and only changes from baseline will be recorded. Any clinically significant change from baseline will be documented as an AE on the AE eCRF. Clinical significance is defined as any variation in physical findings that has medical relevance and may result in an alteration in medical care. The investigator will continue to monitor the patient until the finding is resolved or, in the judgment of the investigator, follow-up is no longer medically necessary.

11. STATISTICS

11.1. General Considerations

Data analysis will be performed for each population (A, A1, B, and B1) separately. Descriptive summary statistics will be provided for demographics, disposition, and IMR-687 exposure (and HU exposure for patients in Populations B and B1). The number and percentage of patients who discontinue from the study, along with reasons for discontinuations, will be tabulated and listed.

Continuous data will be summarised using descriptive statistics (number of patients, mean, standard deviation [SD], median, minimum, maximum) and, where appropriate, coefficient of variation (%CV) and graphic representation. Categorical data will be summarised by sample size, number of events, and proportions. Data will be summarised by population (A and B) and dose cohort at each time point as appropriate. Graphs of actual values and changes over time may also be created as appropriate.

Details of the statistical analyses/summaries described below will be provided in a statistical analysis plan prior to the database lock and study unblinding.

11.2. Analysis Datasets:

Safety Analysis Set: is defined as all patients who have received any amount of study drug and from whom informed consent has been obtained, and will be used to summarise all safety and tolerability data. The Safety Analysis Set will be used for listings of all data, including safety, tolerability, and PK/PD concentrations and parameters.

PK Concentration Set: is a subset of the safety analysis set and includes all patients who are enrolled in the study, have received one dose of IMR-687, and have any measurable IMR-687 concentration-time data, without protocol deviations or events expected to affect PK. Pharmacokinetic IMR-687 (and HU for patients in Populations B and B1) concentration profiles will be summarised based on the PK concentration set.

PK Evaluable Set: is a subset of the PK concentration set and includes all patients who have provided sufficient concentration data without protocol deviations or events that would be expected to affect the PK analysis. PK parameter data will be summarised based on the PK Evaluable Set.

PD Evaluable Set: is a subset of the safety analysis set and includes all patients who have provided samples for PD analysis sufficient to obtain at least one valid PD observation, without protocol deviations or events that would be expected to affect the PD analysis. PD observation and parameter data will be summarised based on the PD Evaluable Set.

11.3. Safety Analyses

Descriptive statistics will be computed for safety parameters, as appropriate. The number and percentage of patients who discontinue from the study because of AEs will be tabulated; severity and frequency of AEs and SAEs will also be summarised. Absolute and, where appropriate, change from baseline in clinical laboratory values, vital signs, and ECG results will also be summarised. All safety data will be provided in listings.

Further statistical evaluations will be applied for select endpoints, if warranted.

11.4. Pharmacokinetic Analyses

PK analysis parameters will be estimated using non-compartmental analysis methods. Patients will be analysed by actual dose received.

Graphs of individual and mean IMR-687 (and HU for patients in Populations B and B1) plasma concentration over time will be generated by population and dose cohort as appropriate. The following PK parameters will be determined, as appropriate: C_{max}, t_{max}, $t_{½}$, AUC_{0-12}, AUC_{0-24}, AUC_{last}, and AUC_{0-inf}. Other PK parameters may be determined as appropriate. All AUC parameters will be calculated by the linear up/log down method. PK parameters will be summarised descriptively using the number of non-missing values (n), mean, median, SD, minimum, maximum, %CV, geometric mean, and geometric %CV. Dose proportionality will be assessed.

To assess the potential drug interaction for HU with IMR-687 (test) and HU without IMR-687 (reference) in Populations B and B1, log-transformed HU PK parameters (C_{max}, AUC) will be analysed using analysis of variance (ANOVA), including terms for visit as a fixed effect and patient

as a random effect. Based on this analysis, point estimates and two-sided 90% confidence intervals (CI) for the ratios "IMR-687+HU/HU" will be calculated by back-transformation of the logarithmic data. Within-subject variability will be estimated.

11.5. Analyses of Exploratory Endpoints

Exploratory PD and clinical outcomes data for each time point will be listed by patient and summarised by population and dose cohort as appropriate. Correlations between PK and the exploratory endpoints may be assessed. Descriptive statistics will be computed as appropriate.

11.6. Interim Analysis

Two interim analyses are planned to review pooled data for specific biomarkers. The first analysis will be performed once at least 18 patients in Population A have at least 1 month of available data for sE-sel, sP-sel, and sICAM-1; the second analysis will be performed once at least 18 patients in Population A have at least 3 months of available data for HbF (%HbF and %F cells), sE-sel, and sP-sel. An additional planned interim analysis may be performed when approximately 12 patients have been dosed with 200 mg for 13 weeks.

To maintain the study blind, summary tables will be prepared by a separate unblinded statistician/programmer who is not affiliated with the study team responsible for the ongoing conduct of the study. In addition, no unblinded data will be presented for individual patients. All data will be pooled by randomized assignment for each of the biomarkers. Additional details may be provided in a statistical analysis plan.

Based on business reasons, the sponsor may decide to conduct the second and subsequent interim analyses as unblinded at the patient level. In this situation, a dedicated team at the sponsor will be unblinded and all personnel directly involved in the conduct of the study at both the sponsor and the vendors, including the CRO, will remain blinded to treatment allocation. All site personnel and patients will also remain blinded to treatment allocation. Details to define the process for unblinding and to ensure that no study related personnel will be unblinded to treatment allocation will be captured in a separate study-specific plan.

11.7. Determination of Sample Size

The sample sizes for Populations A, A1, B, and B1 were not based on formal statistical considerations. However, the number of subjects involved in this placebo-controlled study is considered sufficient to achieve the principal objectives of this exploratory study.

Based on available data, it is expected that 12 to 24 patients treated at each dose of IMR-687 (50, 100, and 200 mg) for at least 12 weeks compared with 12 placebo patients would be sufficient to assess the safety, tolerability, and PK of IMR-687 in Populations A and A1. In addition, based on the study design in Populations B and B1 (i.e., determination of a separate baseline HU PK profile prior to administration of IMP), it is expected that 12 active and 6 placebo subjects would be sufficient to assess the potential for a drug-drug interaction (e.g., a change in safety, HbF or other PD biomarkers, or HU [PK] exposure compared to HU administered alone) when HU and IMR-687 are administered concomitantly for at least 24 weeks.

11.8. Computer Systems

Statistical analyses will be performed using SAS, and PK analyses will be performed using WinNonlin.

12. DATA MANAGEMENT

12.1. Data Collection Tools and Source Document Identification

12.1.1. Source Data

Source data are defined as "All information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies)."

12.1.2. Source Documents

Source documents are defined as "Original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries of 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, patient files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial)."

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

12.1.3. Case Report Forms

All patient data relating to the study will be recorded on an eCRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator is responsible for verifying that data entries are accurate and correct by signing the CRF.

12.2. Audits and Inspections

The investigator must permit audits, Research Ethics Committee (REC) / Institutional Review Board (IRB) review, and regulatory agency inspections and provide direct access to source data documents.

The purpose of an audit or inspection by the Sponsor is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP) guidelines of the International Council on Harmonisation (ICH), and any applicable regulatory requirements.

The investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

12.3. Archiving

Records and documents, including signed informed consent forms (ICFs), pertaining to the conduct of this study must be retained by the investigator for a period of 2 years after the last marketing application approval, or, if not approved, 2 years following the discontinuance of the test article for investigation unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

12.4. Data Monitoring

The sponsor or designee is responsible for the data management of this study, including quality checking of the data. The investigator must permit study-related monitoring and provide direct access to source data documents. Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements. The monitor will be available between site visits if the investigator(s) or other staff needs information or advice.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Compliance

This study will be conducted in accordance with the protocol. Prospective, planned deviations or waivers to the protocol are not permitted, and patients who do not meet all eligibility criteria may not be enrolled. In the event of accidental protocol deviations, the deviation(s) must be documented and reported to the principal investigator and the Sponsor.

This study will also be conducted in accordance with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable laws and regulations, including the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments

The protocol, protocol amendments, informed consent form, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an REC/IRB by the investigator and reviewed and approved by the REC/IRB; the investigator must submit written approval to the

Sponsor before he or she can enrol any patient into the study. In addition, no patients will be enrolled in the UK until Clinical Trial Authorisation is obtained from the MHRA.

Substantial amendments to the protocol will require REC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the REC/IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the local health authorities and the REC/IRB, including (if applicable) a final report within 1 year of the end of the study
- Notifying the REC/IRB of SAEs or other significant safety findings as required by REC/IRB procedures
- Notifying the REC/IRB of the end of the studyz
- Providing oversight of the conduct of the study at the site and adherence to requirements of US Code of Federal Regulations Title 21, ICH guidelines, the REC/IRB, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

13.2. Serious Breaches to GCP or the Protocol

A “serious breach” is a breach which is likely to effect to a significant degree either the safety or physical or mental integrity of the patients of the trial; or the scientific value of the trial.

The site will immediately notify the sponsor of any case where the above definition applies during the conduct of the study. The sponsor will notify the licensing authority in writing of any *serious* breach of the conditions and principles of GCP in connection with this trial; or the protocol.

13.3. Written Informed Consent

The investigator or qualified designee will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Patients must be informed that their participation is voluntary and that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient’s signed and dated informed consent must be obtained before conducting any study procedures. The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

The site must maintain the original, signed ICF. A copy of the signed and dated ICF must be given to the patient.

13.4. Data Protection and Patient Confidentiality

All investigators and trial site staff must comply with all applicable local laws and regulations regarding the collection, storage, processing and disclosure of personal information.

Patients will be assigned a unique identifier by the sponsor. Any patient records or datasets that are transferred to the sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate REC/IRB members, and by inspectors from regulatory authorities.

13.5. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities.

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15. APPENDICES

Appendix A: Sample List of Prohibited CYP3A-Sensitive Substrates

Note: This list is not intended to be exhaustive. If there is any question as to whether or not a substance is permitted, please review the product labelling (if applicable) and consult the Sponsor.

Appendix B: Sample List of Prohibited P-gp Substrates and Inhibitors

Note: This list is not intended to be exhaustive. If there is any question as to whether or not a substance is permitted, please review the product labelling (if applicable) and consult the Sponsor.

Appendix C: Approximate Volume of Blood to be Drawn at Each Study Visit

Appendix A: Sample List of Prohibited CYP3A Sensitive Substrates

Drug (oral)	**Therapeutic Class**	**Max AUC ratio**	**Inhibitor**	**Inhibitor Dose (oral)**	**Accession or NDA #**	**Published**
ABT-384	Diabetes Treatments	**17.8**	ketoconazole	400 mg QD (10 days)	23431112	2013 May
alfentanil	Opioids	**36.5**	indinavir/ ritonavir[1]	800 mg/100 mg BID (1 day)	19225389	2009 Mar
alisporivir	Antivirals	**7.9**	ketoconazole	400 mg QD (23 days)	25008118	2014 Oct 15
almorexant	Hypnotics - Sedatives	**10.7**	ketoconazole	400 mg QD 14 days	24604243	2014 May
alpha-dihydroergocryptine	Dopaminergic Agonists	**13.3**	erythromycin	500 mg TID (4 days)	11503008	2001 Aug
aplaviroc	CCR5 Receptor Antagonists	**7.7**	lopinavir/ ritonavir[1]	400/100 mg BID (21 days)	16934050	2006 Sep
aprepitant	Neurokinin-1 Receptor Antagonists	**5.0**	ketoconazole	400 mg QD (5-10 days)	Emend® Prescribing Info	2007 Nov
atazanavir	Protease Inhibitors	**25.9**	ritonavir[1]	100 mg QD (2 days)	22288567	2012 Aug
atorvastatin	Statins [a]	**9.4**	tipranavir/ ritonavir[1]	500 mg/200 mg BID (8 days)	19667285	2009 Oct
avanafil	Erectile Dysfunction Treatments	**12.8**	ketoconazole	400 mg QD (5 days)	NDA # 202276	2012
BIRL 355	NNRTIs	**30.6**	ritonavir[1]	100 mg x 2	18824608	2008 Dec
bosutinib	Kinase Inhibitors	**8.1**	ketoconazole	400 mg QD (4.5 days)	21148045	2011 Dec
brecanavir	Protease Inhibitors	**19.1**	ritonavir[1]	100 mg single dose	16723584	2006 Jun
brotizolam	Benzodiazepines	**5.1**	itraconazole	200 mg QD (4 days)	15521894	2004 Nov
budesonide	Corticosteroids	**6.8**	ketoconazole	200 mg QD (4 days)	10945311	2000 Jul
buspirone | CYP3A *in vivo Probe*	Anxiolytics	**19.2**	itraconazole	100 mg BID (4 days)	9333111	1997 Sep
capravirine	Antivirals	**9.3**	ritonavir[1]	100 mg QD (14 days)	15205383	2004 Jul
casopitant	Neurokinin-1 Receptor Antagonists	**12.1**	ketoconazole	400 mg QD (7 days)	20124517	2010 Aug
cobimetinib	Kinase Inhibitors	**6.6**	itraconazole	200 mg QD (14 days)	NDA # 206192	2015
conivaptan	Vasopressin Antagonists	**10.8**	ketoconazole	200 mg BID (3 days)	NDA # 021697	2005
danoprevir	Antivirals	**6.0**	ritonavir[1]	100 mg BID (10 days)	22624502	2012 Jul
darifenacin	Anticholinergics	**5.3-11.6**	ketoconazole	400 mg QD (8 days)	Enablex® Prescribing Info	2004 Dec
darunavir	Protease Inhibitors	**10.7**	ritonavir[1]	100 mg BID (9 days)	19131522	2009 Apr
dasatinib	Kinase Inhibitors	**5.0**	ketoconazole	200 mg BID (6 days)	NDA # 021986	2006
dronedarone	Antiarrhythmics	**24.8**	ketoconazole	200 mg QD (8 days)	NDA # 022425	2009
ebastine	H1 Receptor Antagonists	**42.5**	ketoconazole	400 mg QD (8 days)	15752381	2005 Mar
eletriptan | CYP3A *in vivo Probe*	Triptans	**5.9**	ketoconazole	not available	Relpax® Prescribing Info	2004 May
eliglustat (in subjects CYP2D6 PMs)	Glucosylceramide Synthase Inhibitors	**6.2** (in CYP2D6 PMs)	ketoconazole	400 mg QD - PBPK Modeling	NDA # 205494	2014
elvitegravir	HIV-Integrase Strand Transfer Inhibitors	**19.9**	ritonavir[1]	100 mg BID (10 days)	NDA # 203100	2012
eplerenone	Diuretics	**5.4**	ketoconazole	200 mg BID (6 days)	15204695	2004 Mar
everolimus	Immunosuppressants	**14.7**	ketoconazole	200 mg BID (8 days)	15831774	2005 May
felodipine | CYP3A *in vivo Probe*	Calcium Channel Blockers	**6.3**	itraconazole	200 mg QD (4 days)	9129558	1997 Apr
ibrutinib	Kinase Inhibitors	**23.9**	ketoconazole	400 mg QD (6 days)	NDA # 205552	2013
indinavir	Protease Inhibitors	**5.5**	ritonavir[1]	400 mg BID (15 days)	9797204	1998 Nov
isavuconazole	Antifungals	**5.2**	ketoconazole	200 mg BID (24 days)	NDA # 207500	2015
ivacaftor	Miscellaneous Agents	**8.5**	ketoconazole	400 mg QD (10 days)	NDA # 203188	2012
L-771,688	Alpha/Beta Adrenergic Antagonists	**60**	ketoconazole	400 mg QD (10 days)	15901753	2005 Jun
levomethadyl (LAAM)	Drug Addiction Treatments	**5.5**	ketoconazole	400 mg single dose	15289792	2004 Aug

Drug (oral)	Therapeutic Class	Max AUC ratio	Inhibitor	Inhibitor Dose (oral)	Accession or NDA #	Published
lomitapide	Other Antilipemics	**27.3**	ketoconazole	200 mg BID (9 days)	NDA # 203858	2012
lopinavir	Protease Inhibitors	**up to 30**	ritonavir[1]	RIT adm. as booster	Kaletra® Prescribing Info	2004 Oct
lovastatin | CYP3A *in vivo Probe*	Statins [a]	**36.4**	itraconazole	200 mg QD (4 days)	8689812	1996 Jul
lumefantrine	Antimalarials	**5.7**	lopinavir/ritonavir[1]	400/100 mg BID (> 1 month)	22316571	2012 May
lurasidone	Antipsychotics	**9.3**	ketoconazole	400 mg QD (7 days)	NDA # 200603	2010
maraviroc	CCR5 Receptor Antagonists	**10**	saquinavir / ritonavir[1]	400/100 mg BID (7 days)	18333864	2008 April
midazolam | CYP3A *in vivo Probe*	Benzodiazepines	**26.4**	ritonavir[1]	100 mg x 3	20002087	2009 Dec
midostaurin	Kinase Inhibitors	**10.4**	ketoconazole	400 mg QD (10 days)	24085261	2013 Dec
naloxegol	Gastrointestinal Agents	**12.4**	ketoconazole	400 mg QD (5 days)	204760	2014
neratinib	Kinase Inhibitors	**5.2**	ketoconazole	400 mg QD (4.5 days)	21395644	2011 Apr
nisoldipine	Calcium Channel Blockers	**25.3**	ketoconazole	200 mg QD (5 days)	10206086	1999 Mar
paritaprevir[4]	Antivirals	**6.1**	lopinavir/ritonavir[1]	400/100 mg BID (14 days)	NDA # 206619	2014
perospirone	Antipsychotics	**6.8**	itraconazole	200 mg QD (5 days)	16418697	2006 Feb
quetiapine	Antipsychotics	**6.2**	ketoconazole	200 mg QD (4 days)	16390352	2006 Jan
ridaforolimus	Kinase Inhibitors	**8.5**	ketoconazole	400 mg QD (14 days)	22290273	2012 May
saquinavir	Protease Inhibitors	**236.6**	ritonavir[1]	100 mg single dose	23381882	2013 Jun
sildenafil | CYP3A *in vivo Probe*	Erectile Dysfunction Treatments	**9.9**	ritonavir[1]	300-500 mg BID (7 days)	10930961	2000 Aug
simeprevir	Protease Inhibitors	**6.5**	erythromycin	500 mg TID (7 days)	NDA # 205123	2013
simvastatin | CYP3A *in vivo Probe*	Statins [a]	**16.1**	grapefruit juice DS	200 mL TID (2 days)	9834039	1998 Nov
sirolimus	Immunosuppressants	**10.9**	ketoconazole	200 mg QD (10 days)	Rapamune® Prescribing Info	
tacrolimus	Immunosuppressants	**78.0**	telaprevir[2]	750 mg TID (13 days)	21618566	2011 Jul
terfenadine	H1 Receptor Antagonists	**5.6**	nefazodone	200-300 mg BID (8 days)	11240972	2001 Mar
ticagrelor	Anticoagulants and Antiplatelets	**7.3**	ketoconazole	200 mg BID (10 days)	NDA # 022433	2011
tilidine[3]	Treatments of Pain and Inflammation	**20.3**	voriconazole	400 mg single dose	19916995	2009 Nov
tipranavir	Protease Inhibitors	**13.4**	ritonavir[1]	200 mg BID (21 days)	15682350	2004 Nov-Dec
tolvaptan	Vasopressin Antagonists	**5.4**	ketoconazole	200 mg QD (3 days)	NDA # 022275	2009
triazolam | CYP3A *in vivo Probe*	Benzodiazepines	**40.7**	ritonavir[1]	200 mg BID (1 day)	16513448	2006 Mar
ulipristal	Hormones	**5.9**	ketoconazole	400 mg QD (7 days)	Ella® Prescribing Info	2014 Jul
vardenafil	Erectile Dysfunction Treatments	**49.1**	ritonavir[1]	300-600 mg BID (8 days)	NDA # 021400	2003
vicriviroc	CCR5 Receptor Antagonists	**5.4**	ritonavir[1]	100 mg QD (14 days)	21348539	2011 Apr
voclosporin	Immunosuppressants	**18.1**	ketoconazole	400 mg QD (10 days)	24330024	2014 Jun

Notes:

- The present list includes CYP3A substrates with AUC ratios of at least 5 fold.
- Some known substrates of the enzyme may not be listed because they do not have changes in exposure reaching that level, or may not have DDI studies with AUC/CL changes available.
- Example of substrate with no changes in AUC available: fluticasone—multiple case reports of Cushing's Syndrome with ritonavir
- CYP3A Inhibition may not be the sole mechanism for the observed interactions. Many substrates of CYP3A are also substrates of P-glycoprotein (P-gp)

[1] Ritonavir also inhibits multiple transporters, including P-gp
[2] Telaprevir also inhibits multiple transporters, including P-gp
[3] Tilidine is a substrate of CYP3A and CYP2C19 and inhibition of both enzymes by voriconazole may contribute to the change in AUC
[4] Paritaprevir is also a substrate of multiple transporters, including P-gp DS= double strength
[a] Statins, particularly atorvastatin, may be administered concomitantly at the discretion of the Investigator, because any decrease in their exposure is not likely to pose significant risk over the short term course of this study

Appendix B: Sample List of Prohibited P-gp Substrates and Inhibitors

Inhibitor[a]	Therapeutic Class	Inhibitor Dose (oral)	Substrate[b]	Max AUC ratio	Accession or NDA #	Published
alogliptin	Dipeptidyl Peptidase-4 Inhibitors	100 mg QD (7 days)	fexofenadine	**1.26**	NDA # 022271	2013
amiodarone	Antiarrhythmics	400 mg/day (5 days)	digoxin (IV)	**-26.5% (CL)**	3964797	1985 Jan
		800 mg/day (7 days)	digoxin	**1.68**	2487521	1989 Mar
AZD5672	CCR5 Receptor Antagonists	150 mg QD (13 days)	digoxin	**1.33**	21075975	2011 Feb
azithromycin	Antibiotics	250 mg QD (5 days)	fexofenadine	**1.72**	11318079	2001 Mar
canagliflozin	Sodium-dependent Glucose Cotransporter 2 Inhibitors	300 mg QD (7 days)	digoxin	**1.20**	NDA # 204042	2013
captopril	ACE Inhibitors	12.5 mg TID (7 days)	digoxin	**1.39**	11471775	2001 Jul
carvedilol	α/β Adrenergic Antagonists	6.25 mg BID (7 days)	digoxin	**1.57**	16767433	2006 Jul
clarithromycin	Antibiotics	500 mg BID (7 days)	digoxin	**1.68**	18214850	2008 Jul
		500 mg BID (4 days)	dabigatran[c]	**1.49**	23210726	2013 Jul
clopidogrel	Anticoagulants and Antiplatelets	300 mg single dose	dabigatran	**1.35**	22782539	2013 Mar
conivaptan	Diuretics	40 mg BID (10 days)	digoxin	**1.43**	NDA # 021697	2005
cremophor EL	Transporter Modulators	1440 mg SD	fexofenadine	**1.28**	25882073	2015 Jun
cremophor RH40	Transporter Modulators	600 mg TID (9 days)	digoxin	**1.21**	12732840	2003 May
curcumin	Food Products	1000 mg QD (14 days)	talinolol	**1.54**	22725663	2012 Dec
diltiazem	Calcium Channel Blockers	60 mg TID (10 days)	digoxin	**1.44**	12070557	2002 Jun
dronedarone	Antiarrhythmics	400 mg BID (10 days)	digoxin	**2.33**	NDA # 022425	2009
eliglustat	Glucosylceramide Synthase Inhibitors	100 mg (PMs) and 150 mg (others) (7 days)	digoxin	**1.49**	NDA # 205494	2014
erythromycin	Antibiotics	500 mg TID (7days)	fexofenadine	**2.09**	NDA # 021963	1996
		2 g single dose	talinolol	**1.52**	10783825	2000 Apr
felodipine	Calcium Channel Blockers	2.5 mg single dose	digoxin	**1.49**	3443063	1987
fostamatinib	Anti-inflammatory Drugs	0.25 mg QD (15 days)	digoxin	**1.37**	26514315	2015 Dec
fluvoxamine	Selective Serotonin Reuptake Inhibitors	50 mg QD (7 days)	fexofenadine	**1.78**	22367658	2012 Apr
ginkgo	Herbal Medications	120 mg TID (14 days)	talinolol	**1.25**	19280523	2009 Mar
indinavir	Protease Inhibitors	80 mg TID (21 days)	fexofenadine	**3.31**	22273859	2012 Feb
indinavir/ritonavir	Protease Inhibitors	800 mg/100 mg BID (1 day)	fexofenadine	**4.84**	19225389	2009 Mar
itraconazole	Antifungals	200 mg QD (5 days)	digoxin	**1.68**	9421099	1997 Dec
		100 mg BID (5 days)	fexofenadine	**3.01**	16084853	2006 May
isavuconazole	Antifungals	Not Provided	digoxin (not provided)	**1.25**	NDA # 207500	2015
ivacaftor	Other	150 mg (9 days)	digoxin	**1.32**	25103957	2015 Jan
ketoconazole	Antifungals	400 mg QD (7 days)	fexofenadine	**2.74**	Allegra® Product Label	1996
lapatinib	Kinase Inhibitors	1500 mg QD (8 days)	digoxin	**1.63**	Embase # 20160047065	2015 Nov
		Not Provided	digoxin (IV)	**2.80**	Tykerb® Product Label	2007
lopinavir/ritonavir	Protease Inhibitors	400 mg/100 mg BID (14 days)	digoxin	**1.81**	18183034	2008 Jul
		400 mg/100 mg single dose	fexofenadine	**4.14**	16809801	2006 July
mibefradil	Calcium Channel Blockers	150 mg QD (7 days)	digoxin	**1.31**	7669484	1995 May
milk thistle	Herbal Medications	140 mg TID (14 days)	talinolol	**1.30**	19555315	2009 Sep
mirabegron	Beta3-Adrenoreceptor Agonist	100 mg QD (14 days)	digoxin	**1.16**	NDA # 202611	2012
nelfinavir	Protease Inhibitors	1250 mg BID (14 days)	digoxin	**1.35**	22190694	2012 Mar
nifedipine	Calcium Channel Blockers	10 mg TID (7 days)	digoxin	**1.23**	3943268	1986 Jan
nitrendipine	Calcium Channel Blockers	20 mg QD (7 days)	digoxin	**1.16**	3816917	1986
paritaprevir/ritonavir/ombitasvir	Antivirals	150/100/25 mg QD (19 days)	digoxin	**1.35**	26459906	2015 Jan

paroxetine	Selective Serotonin Reuptake Inhibitors	20 mg QD (7 days)	fexofenadine	**1.38**	22367658	2012 Apr
Inhibitor[a]	**Therapeutic Class**	**Inhibitor Dose** (oral)	**Substrate**[b]	**Max AUC ratio**	**Accession or NDA #**	**Published**
propafenone	Antiarrhythmics	300 mg TID (3 days)	digoxin (IV)	**1.29**	2708548	1989 Jan
		600 mg QD (7 days)	digoxin	**-31% (CL)**	2911842	1989
		250-500 mg/kg QD (7 days)	digoxin	**-67% (CL)**[d]	2299507	1990 Feb
quercetin	Food Product	500 mg TID (7days)	fexofenadine	**1.56**	19221726	2009 Jun
quinidine	Antiarrhythmics	200 mg QID (6 days)	digoxin (IV)	**-64% (CL)**	7309901	1981 Oct
		600 mg BID (8 days)	digoxin	**2.66**	3997300	1985 Mar
		25 mg single dose	fexofenadine	**2.14**	24722393	2014 Sep

Appendix C: Approximate Volume of Blood to be Drawn at Each Study Visit

Time Point	All Pops mL	IMR-687 PK				HU PK		PD Parameters				Safety Parameters	Total Sample			
		Pop A mL	Pop A1 mL	Pop B mL	Pop B1 mL	Pop B mL	Pop B1 mL	Pop A mL	Pop A1 mL	Pop B mL	Pop B1 mL	ALL POP mL	Pop A mL	Pop A1 mL	Pop B mL	Pop B1 mL
Screening	5	—		—	—	—		—	—	—	—	18	23	23	23	23
Lead-in (Pops B and B1 only)	—	—		—	—	16 x 2 [a]	16 x 1	—	—	—	—	—	—	—	32	16
Day 1	—	18	18	18	18	—	—	12	12	12	12	18	48	48	48	48
Week 2	—	—		—	—	—	—	—	—	—	—	18	18	18	18	18
Week 5	—		18	18	18	16	16	12	12	12	12	18	30	48	64	64
Week 9	—	—	—	—	—	—	—	12	12	12	12	18	30	30	30	30
Week 13	—	18	—	—	—	—	—	12	12	12	12	18	48	30	30	30
Week 17	—	—	—	18	—	16	—	12	12	12	12	18	30	30	64	30
Week 21	—	—	—	—	—	—	—	12	12	—	12	18	30	30	18	30
Week 25 (Pop A/A1/B1 only)	—	18	18	—	18	—	16	12	12	—	12	18	48	48	—	64
Week 29 (Pop A/A1 only)	—	—	—	—	—	—	—	—	—	—	—	18	18	18	—	18
	Study Total mL												**323**	**323**	**327**	**371**

[a] One full HU PK profile will be obtained at baseline.

Abbreviations: — = not applicable/not done; HU = hydroxyurea; PD = pharmacodynamics; PK = pharmacokinetics; Pop = population.