2. SYNOPSIS

Study Number	IMR-SCD-301
Study Title	A Phase 2b Study to Evaluate the Safety and Efficacy of IMR-687 in Subjects with Sickle Cell Disease
Sponsor	IMARA, Inc. 116 Huntington Avenue, 6th Floor Boston, MA 02116
Clinical Trial Registry Identifiers	EudraCT: 2019-004471-39
IND Number	130549
Indication Studied	Treatment of sickle cell disease
Investigational Products	Finished Product: IMR-687 100, 150 and 200 mg tablet 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 Doses: 100, 150 or 200 mg once daily Mode of Administration: Oral Lot Numbers: M10901, M11155, M11196, M11251, M11490, and M11549 (100mg tablet); M11156, M11197, M11252, M11258, M11491, M11500, and M11550 (150 mg tablet); and M11057, M11058, M11492, and M11546 (200 mg tablet) Duration of Therapy: 52 weeks
Reference Therapy	The reference therapy in this study was placebo. Placebo consisted of tablets containing matrix absent IMR-687 and were identical in appearance to the IMR-687 tablets.
Investigators and Study Centers	Study subjects were enrolled at 28 sites in 11countries (United Kingdom, United States, Ghana, Greece, Kenya, Lebanon, Morocco, Oman, Senegal, Tunisia, Uganda)
Phase and Design	2b, safety, and efficacy
Conduct Period	Start Date: 20 July 2020 (First Subject Screened) Stop Date: 26 April 2022 (Last Subject Last Visit)
Number of Subjects (Planned and Analyzed)	A total of approximately 99 subjects with sickle cell anemia were planned for enrollment. A total of 115 subjects were enrolled and randomized.

Objectives

The primary efficacy objective of this study was to evaluate the effect of IMR-687 versus placebo on the annualized rate of vaso-occlusive crises (VOCs). The primary safety objective was to evaluate the safety and tolerability of IMR-687 versus placebo.

The secondary objectives of this study were as follows:

- To evaluate the effect of IMR-687 versus placebo on the time to the first occurrence of a VOC
- To evaluate the fetal hemoglobin (HbF) response to IMR-687 versus placebo
- To evaluate the effect of IMR-687 versus placebo on other measures of VOCs
- To evaluate the effect of IMR-687 versus placebo on percentage of cells positive for HbF (% F-cells) and total Hb
- To evaluate the effect of IMR-687 versus placebo on biomarkers of RBC hemolysis
- To evaluate the effect of IMR-687 versus placebo on quality of life (QoL) measures
- To evaluate the effect of IMR-687 versus placebo on biomarkers of adhesion, inflammation, and cardiac stress and on RBC indices
- To evaluate the PK exposure of IMR-687

Endpoints for Evaluation

The efficacy endpoints evaluated include the following:

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

- Change from baseline in biomarkers of cardiac stress such as N-terminal prohormone of brain natriuretic peptide (NT proBNP) at Week 24 and Week 52
- Change from baseline in RBC indices, such as mean corpuscular volume (MCV), at Week 24 and Week 52

The safety endpoints evaluated include the following:

- Incidence and severity of adverse events (AEs) and serious adverse events (SAEs)
- Clinically significant changes in 12-lead electrocardiogram (ECG) parameters, clinical laboratory tests, and vital signs

The secondary pharmacokinetic endpoint was as follows:

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

The exploratory endpointwas as follows:

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

Methodology

This was a phase 2b, randomized, double-blind, placebo-controlled, multicenter study of subjects aged 18 to 65 years with sickle cell disease (SCD; homozygous sickle hemoglobin [HbSS], sickle-β0 [HbSβ0] thalassemia, or sickle-β+ [HbSβ+] thalassemia) to evaluate the safety and efficacy of the phosphodiesterase type 9 inhibitor, IMR-687, administered once daily (qd) for 52 weeks. This study enrolled 115 subjects with SCD. This study consisted of a screening period (up to 4 weeks), a double-blind treatment period (52 weeks), and a safety follow-up period (4 weeks).

Screening

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

Treatment Period

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

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

Subjects returned to the investigational site at Week 1 for a safety assessment, and qualified site personnel contacted the subject by telephone at Week 2 and Week 6 to capture potential adverse events (AEs) and concomitant medications.

Subjects were seen at the investigational site approximately every 4 weeks through Week 24, then every 6 weeks through Week 36, and then every 8 weeks through Week 52 (end of treatment [EOT]), with a safety follow-up visit at Week 56 (end of study [EOS]). Safety was monitored throughout the study, and PK, PD, QoL, and clinical outcome measures were performed at the visits shown in the schedule of assessments. QoL assessments included the Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me®), Patient-Reported Outcomes Measurements Information System - Preference (PROMIS® 29 + 2 Profile v2.1 [PROPr]), and Sickle Cell Self-Efficacy Scale (SCSES).

Diagnosis and Main Criteria for Inclusion

Key Inclusion Criteria:

- A male or female ≥18 and ≤55 years of age.
- Confirmed diagnosis of SCD (HbSS, HbSβ0 thalassemia, or HbSβ+ thalassemia)) in the medical record; if not available, the diagnosis must be confirmed at the site's local laboratory instead.
- Subjects must have had at least 2 and no more than 12 documented episodes of VOC in the past 12 months at the time of ICF signing and at randomization (Day 1).
- Hb of >5.5 and <10.5 g/dL; Hb values within 21 days post-transfusion will be excluded.
- Subjects receiving HU must have received it continuously for at least 6 months prior to signing the ICF, and must have been on a stable dose for at least 3 months prior to signing the ICF, with no anticipated need for dose adjustments during the study including the screening period, in the opinion of the investigator.

Key Exclusion Criteria:

- Hospital discharge for sickle cell crisis or other vaso-occlusive event within the 4 days prior to randomization (Day 1).
- Subjects participating in a chronic/prophylactic RBC transfusion program (i.e., regularly scheduled RBC transfusions); any transfusions within 21 days of screening or baseline Hb measurements.
- Subjects with HbF >25% at screening.
- Subjects with known active hepatitis A, hepatitis B, or hepatitis C, with active or acute event of malaria, or who are known to be positive for human immunodeficiency virus (HIV).
- For female subjects of childbearing potential, a positive serum human chorionic gonadotropin (hCG) test (screening) or a positive urine hCG test at randomization (Day 1).
- Body mass index (BMI) <17.0 kg/m2 or >35 kg/m2; or total body weight <45 kg.
- History of a clinically significant allergic reaction or hypersensitivity, as judged by the investigator, to any drug or any component of the study drug formulations used in the study (see the Investigator's Brochure).
- On ECG testing at ICF signing and/or randomization (Day 1), a corrected QT interval, Fridericia's formula (QTcF) >450 ms in men and >470 ms in women on 2 or more of the triplicate ECGs, or the presence of clinically significant ECG abnormalities as determined by the investigator.
- Major surgery within 8 weeks or minor surgery within 2 weeks of randomization (Day 1).
- Prior exposure to IMR-687.
- History of crizanlizumab (Adakveo®) or voxelotor (Oxbryta®) use within 6 months prior to signing the ICF or anticipated need for such agents during the study.
- Participated in another clinical study of an investigational agent (or medical device) within 30 days or 5 half-lives of date of informed consent, whichever is longer, or is currently participating in another study of an investigational agent (or medical device).
- Receipt of erythropoietin, luspatercept (Reblozyl®), or other erythropoiesis-stimulating or erythroid maturation agent within 6 months prior to signing the ICF or anticipated need for such agents during the study.
- Prior gene therapy.
- Consumption/use of the following drugs or other substances within the specified time periods before randomization or plans to consume/use at any time during the study. If there is any question as to whether a substance is permitted, please review the product labeling (if applicable) and consult the medical monitor and/or sponsor.
    - Phosphodiesterase type 5 inhibitors (including but not limited to sildenafil, tadalafil, and vardenafil) within 7 days prior to randomization (Day 1) or plans to use during the study.
    - Grapefruit, grapefruit juice, grapefruit products, or herbal supplements with CYP-altering abilities within 1 week prior to randomization (Day 1) or plans to consume during the study.

- CYP3A-sensitive substrates, including the opioids fentanyl and alfentanil, or moderate to strong CYP3A inhibitors or inducers within 28 days prior to randomization (Day 1) or plans to use during the study
- Any drugs or substances known to be substrates or inhibitors of P-glycoprotein or breast cancer resistance protein within 28 days prior to randomization (Day 1) or plans to use during the study.

Statistical Methods

Safety Analyses:

Descriptive statistics were used to summarize all safety endpoints, by treatment group as appropriate. Data summaries were displayed for incidence of AEs, clinical laboratory variables, vital signs, and ECG parameters. Safety data summaries used the safety analysis set. All AEs were coded using MedDRA. Data was summarized using the preferred term and primary system organ class. AE summaries included AEs leading to study discontinuation and severity and frequency of AEs and SAEs.

Efficacy Analyses:

For all statistical analyses, adjustments were made for multiplicity at the planned Interim Analysis, p-values were adjusted, however, all rules of multiplicity were revoked with the execution of a SAP Addendum, then at which no adjustments were made of multiplicity for the final analysis, and nominal p-values are presented, and no level of significance (α) was set a priori. A conventional α of 0.05 was used as the cutoff for statistical significance.

Clinical Outcomes

Annualized rates were determined for VOCs. Median annualized rates were compared between IMR-687 200 mg/300 mg; 300 mg/400 mg; pooled IMR-687 and placebo groups using a stratified Wilcoxon Rank Sum Test. A separate analysis of annualized rate of VOC across stratification factors was performed.

Kaplan-Meier analysis for time to event was performed for the first VOC events. A log-rank test was used to compare the median time to VOC event between IMR-687 treatment groups and placebo.

HBF Responder Analysis

The proportion of HbF responders (defined as the proportion of subjects with an absolute increase of ≥3% in HbF from baseline) at Week 24 was calculated. A Cochran-Mantel Haenszel (CMH) analysis was performed and the summary of number of responders with difference in proportions was presented as odds ratios (OR) (treatment groups vs. placebo) including the corresponding 2-sided 95% CI and p-value.

Pharmacodynamics

The CFB in PD biomarkers were analyzed using a CFB with placebo for each PD biomarker at each time point.

Subject Disposition

A total of 115 subjects were enrolled and randomized to receive IMR-687 200 mg/300 mg (n=34), IMR-687 300 mg/400 mg (n=49), or placebo (n=32). Of these, a total of 113 subjects received treatment and were included in the safety analysis set (IMR-687 200 mg/300 mg (n=33), IMR-687 300 mg/400 mg (n=47), and placebo (n=32)). A total of 15 subjects (13.4%) completed the study treatment. Fewer subjects discontinued from treatment in the placebo group (65.6%) than in the IMR-687 200 mg/300 mg and 300 mg/400 mg groups (78.8% and 80.9%, respectively), although after accounting for subjects who discontinued early due to study termination, the groups were similar. Overall, the most common reasons for premature discontinuation of treatment were Study terminated by the Sponsor, adverse events, and other (each 53.6%, 4.5% and 4.5% respectively).

Summary of Results

Demographics and Baseline Characteristics

The overall median age was 23.0 (Q1, Q3: 20.0, 30.0) years and most subjects were female (55.7%); in terms of race, the majority were Black (60.0%). Among the placebo, IMR-687 200 mg/300 mg, and IMR-687 300 mg/400 mg treatment groups, the median age (23.0, 24.0, and 22.0 years), percentage of female subjects (43.8%, 41.2%, and 73.5%), and percentage of Black race subjects (62.5%, 44.1%, and 69.4%) were comparable.

Overall, the mean (SD) weight, body mass index (BMI), and % HbF were 57.7 (9.45) kg, 21.06 (3.308) kg/m^2, and 11.01% (6.384%), respectively. Among the placebo, IMR-687 200 mg/300 mg, and IMR-687 300 mg/400 mg treatment groups, mean weight (57.9, 58.2, and 57.3 kg) BMI (21.10, 21.03, and 21.04 kg/m^2), and% HbF(11.16%, 10.16, and 11.51%) were comparable.

Overall, the majority of subjects had HbSS genotype (92.0%) and had mean number of VOC events in the last 12 months of 2.5. Among treatment groups, the IMR-687 200 mg/300 mg group (93.9%) and IMR-687 300 mg/400 mg (93.6%) had a higher percentage of subjects with HbSS genotype than the placebo (87.5%). The mean number of VOC events in the last 12 months (Placebo: 2.6; IMR-687 200 mg/300 mg: 2.5; IMR-687 300 mg/400 mg: 2.5).

Clinical Outcomes Evaluation and Pharmacodynamics

Clinical Outcomes

The ITT analysis showed, the median annualized VOC rate was approximately 52% lower in IMR-687 200 mg/300 mg subjects with SCD than placebo (1.20 versus 2.48/year, respectively; p=0.146). The median annualized VOC rate was approximately 6% lower in IMR-687 300 mg/400 mg subjects with SCD than placebo (2.32 versus 2.48/year, respectively; p=0.930).

The median time to first VOC event was not statistically significant but showed longer delay to first VOC event in IMR-687 200 mg/300 mg subjects with SCD than placebo subjects (8.8 versus 2.7 months, respectively; p>0.05). There was no difference in time to first VOC event between IMR-687 300 mg/400 mg and placebo, as well as pooled IMR-687 and placebo.

Percentage of subjects with 0 VOC events throughout the study period was higher in IMR-687-treated subjects than placebo subjects (48% [IMR-687 200 mg/300 mg] versus 23% [IMR-687 300 mg/400 mg] versus 25% [placebo], respectively).

An increase from baseline of ≥3.0% in Mean HbF at Week 24, a total of 3, 3, and 5 responders were among placebo, IMR-687 200 mg/300 mg, and IMR-687 300 mg/400 mg, respectively, with an odds ratio difference from placebo, of 0.81 (p=0.82) and 1.14 (p=0.87) for, IMR-687 200 mg/300 mg, and IMR-687 300 mg/400 mg (ITT Analysis Set). No responders in increase from baseline of mean HbF was identified at Week 52 among IMR-687 treated subjects.

Pharmacodynamics

Little to no change from baseline and percent change from baseline were observed for hemoglobin F, hemoglobin, % F-cells, serum ferritin, hepcidin, total iron binding capacity, transferrin saturation, erythropoietin, soluble transferrin receptor, haptoglobin, lactate dehydrogenase, indirect bilirubin, absolute reticulocytes, % reticulocytes, NT-proBNP, C-reactive protein, E-selectin, P-selectin, intercellular adhesion molecule – 1, vascular cell adhesion molecule -1, erythrocytes distribution width, and erythrocytes mean corpuscular volume.

None of the other hemolysis, adhesion, inflammatory, or cardiac stress biomarkers evaluated showed a significant difference in mean CFB at EOT comparing IMR-687 treatment groups with placebo.

Safety

IMR-687 was well-tolerated in subjects with SCD. No deaths were reported during the study. One subject had an SAE assessed as related to IMR-687, the subject received the IMR-687 300 mg/400 mg dose, preferred term of headache. Four subjects had AEs leading to study discontinuation in IMR-687-treated subjects were assessed as related to IMR-687 [Preferred Terms included nausea, vomiting, insomnia, fatigue, dizziness, abdominal pain upper, agitation, and abdominal distension].

Overall, the incidence of subjects with any TEAE was similar between subjects who received IMR-687 200 mg/300 mg, IMR-687 300 mg/400 mg and those who received placebo (87.9%, 85.1% and 87.5%, respectively). The majority of TEAEs were mild, moderate, or severe in severity in all IMR-687 dosed groups.

The most frequently reported TEAE (27.6% of all subjects) was sickle cell anaemia with crisis. The incidence of subjects with sickle cell anaemia with crisis was lower for IMR-687-treated subjects compared to placebo (IMR-687 200 mg/300 mg: 27.3%; IMR-687 300 mg/400 mg: 25.5%; placebo: 31.3%).

Other frequently reported TEAEs (≥25% of subjects) in IMR-687 treated subjects included headache (both 16.1%). Regardless of the dose, the incidence of subjects with the TEAE headache was higher in the IMR-687 treated group (25.5 and 27.3%, respectively) compared to placebo (21.9%). Comparing placebo, IMR-687 200 mg/300 mg, and IMR-687 300 mg/400 mg treatment groups, the incidence of subjects with nausea (3.1% 21.2%, and 23.4%, respectively) appeared to increase with increasing IMR-687 dose.

A higher percentage of subjects had SAEs in the placebo group than the IMR-687 groups (37.5%; 36.4%; 36.2%, respectively). Reported SAEs in IMR-687 treated subjects included sickle cell anaemia with crisis. Only one of the SAEs in subjects who received IMR-687 were assessed as related to IMR-687 [headache].

Overall, no clinically meaningful trends regarding safety were observed from analysis of results in clinical laboratory evaluations (hematology, chemistry, coagulation, and urinalysis), vital signs, and ECGs. No TEAEs of neutropenia, reticulocytopenia, or thrombocytopenia were reported. Incidence of subjects with infections and infestations SOC TEAEs were similar among subjects treated with IMR-687 200 mg/300 mg and placebo but higher among subjects treated with IMR-687 300 mg/400 mg (43.8%, 36.4%, and 44.7%, respectively).

Conclusions

IMR-687 was well-tolerated in subjects with SCD, with or without HU background therapy. Clinical outcomes analysis showed prolongation of time to first VOC in IMR-687 200 mg/300 mg compared to placebo but not statistically significant, no prolongation was seen in IMR-687 300 mg/400 mg compared to placebo and reduction in annualized rate of VOCs though not statistically significant.

The data does not remain supportive for the continued development of IMR-687 as a therapeutic for SCD and the study was terminated.

Date of the Report: 27 June 2022