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

Summary

EudraCT number	2017-000653-39
Trial protocol	GB
Global end of trial date	28 August 2020

Results information

Result version number	v1 (current)
This version publication date	12 September 2021
First version publication date	12 September 2021

Trial information

Trial identification

Sponsor protocol code	IMR-SCD-102

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03401112
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Imara Inc.
Sponsor organisation address	116 Huntington Avenue, 6th Floor, Boston, MA, United States, 02116
Public contact	Imara Clinical Operations , Imara Inc., 617 206-2020, info@imaratx.com
Scientific contact	Imara Clinical Operations , Imara Inc., 617 206-2020, info@imaratx.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 November 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 August 2020
Global end of trial reached?	Yes
Global end of trial date	28 August 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

This study was conducted in accordance with consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines; applicable International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines; and applicable laws and regulations, including the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 January 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 31
Country: Number of subjects enrolled	United Kingdom: 69
Worldwide total number of subjects	100
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	100
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study participants were enrolled at 13 sites in 2 countries (United Kingdom and United States).

Pre-assignment

Screening details:

IMR-687 was administered in 2 populations of participants with SCA: those who were not receiving HU and those who were receiving a stable dose of HU according to standard of care. Participants on HU must have been on a stable dose for at least 60 days prior to Screening.

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	IMR-687 50 mg/100 mg (Without HU)

Arm description:

A starting dose of IMR-687 50 milligrams (mg) with dose escalation after 4 or 12 weeks, up to 100 mg was administered to participants who were not receiving daily HU.

Arm type	Experimental
Investigational medicinal product name	IMR-687
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral administration of IMR-687 once daily. Duration of administration was 24 weeks (Week 25).

Arm title	IMR-687 100 mg/200 mg (Without HU)

Arm description:

A starting dose of IMR-687 100 mg with dose escalation after 4 or 12 weeks, up to 200 mg was administered to participants who were not receiving daily HU.

Arm type	Experimental
Investigational medicinal product name	IMR-687
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral administration of IMR-687 once daily. Duration of administration was 24 weeks (Week 25).

Arm title	Placebo (Without HU)

Arm description:

Matching placebo was administered to participants who were not receiving daily HU.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral administration of matching placebo once daily. Duration of administration was 24 weeks (Week 25).

Arm title	IMR-687 50 mg/100 mg (With HU)

Arm description:

A starting dose of IMR-687 50 mg with dose escalation after 4 or 12 weeks, up to 100 mg was administered to participants who were receiving daily HU. HU doses ranged from 500 to 2000 mg.

Arm type	Experimental
Investigational medicinal product name	IMR-687
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral administration of IMR-687 once daily. Duration of administration was 16 (Week 17) or 24 weeks (Week 25).

Arm title	Placebo (With HU)

Arm description:

Matching placebo was administered to participants who were receiving daily HU. HU doses ranged from 500 to 2000 mg.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral administration of matching placebo once daily. Duration of administration was 16 (Week 17) or 24 weeks (Week 25).

Number of subjects in period 1	IMR-687 50 mg/100 mg (Without HU)	IMR-687 100 mg/200 mg (Without HU)	Placebo (Without HU)
Started	15	26	22
Received at Least 1 Dose of Study Drug	12	26	20
Completed	10	19	11
Not completed	5	7	11
Consent withdrawn by subject	-	3	2
Physician decision	-	-	-
Adverse event, non-fatal	1	2	3
Did not Meet Inclusion Criteria	1	-	-
Study was Terminated by Sponsor	-	-	-
Not Dosed	-	-	1

Missed Clinical Visit	-	-	1
Lost to follow-up	1	-	-
Day 1 Assessment not Done	1	-	-
Missed Doses	-	-	1
Noncompliance	1	2	3

Number of subjects in period 1	IMR-687 50 mg/100 mg (With HU)	Placebo (With HU)
Started	27	10
Received at Least 1 Dose of Study Drug	25	10
Completed	21	10
Not completed	6	0
Consent withdrawn by subject	1	-
Physician decision	2	-
Adverse event, non-fatal	2	-
Did not Meet Inclusion Criteria	-	-
Study was Terminated by Sponsor	1	-
Not Dosed	-	-
Missed Clinical Visit	-	-
Lost to follow-up	-	-
Day 1 Assessment not Done	-	-
Missed Doses	-	-
Noncompliance	-	-

Baseline characteristics

Reporting groups	
Reporting group title	IMR-687 50 mg/100 mg (Without HU)
Reporting group description:	
A starting dose of IMR-687 50 milligrams (mg) with dose escalation after 4 or 12 weeks, up to 100 mg was administered to participants who were not receiving daily HU.	
Reporting group title	IMR-687 100 mg/200 mg (Without HU)
Reporting group description:	
A starting dose of IMR-687 100 mg with dose escalation after 4 or 12 weeks, up to 200 mg was administered to participants who were not receiving daily HU.	
Reporting group title	Placebo (Without HU)
Reporting group description:	
Matching placebo was administered to participants who were not receiving daily HU.	
Reporting group title	IMR-687 50 mg/100 mg (With HU)
Reporting group description:	
A starting dose of IMR-687 50 mg with dose escalation after 4 or 12 weeks, up to 100 mg was administered to participants who were receiving daily HU. HU doses ranged from 500 to 2000 mg.	
Reporting group title	Placebo (With HU)
Reporting group description:	
Matching placebo was administered to participants who were receiving daily HU. HU doses ranged from 500 to 2000 mg.	

Reporting group values	IMR-687 50 mg/100 mg (Without HU)	IMR-687 100 mg/200 mg (Without HU)	Placebo (Without HU)
Number of subjects	15	26	22
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	15	26	22
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	36.33	32.04	35.68
standard deviation	± 8.608	± 9.349	± 8.150
Gender categorical Units: Subjects			
Female	9	17	12
Male	6	9	10

Reporting group values	IMR-687 50 mg/100 mg (With HU)	Placebo (With HU)	Total
Number of subjects	27	10	100

Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	27	10	100
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	32.33	28.80	
standard deviation	± 8.788	± 7.084	-
Gender categorical Units: Subjects			
Female	17	9	64
Male	10	1	36

End points

End points reporting groups

Reporting group title	IMR-687 50 mg/100 mg (Without HU)
Reporting group description:	
A starting dose of IMR-687 50 milligrams (mg) with dose escalation after 4 or 12 weeks, up to 100 mg was administered to participants who were not receiving daily HU.	
Reporting group title	IMR-687 100 mg/200 mg (Without HU)
Reporting group description:	
A starting dose of IMR-687 100 mg with dose escalation after 4 or 12 weeks, up to 200 mg was administered to participants who were not receiving daily HU.	
Reporting group title	Placebo (Without HU)
Reporting group description:	
Matching placebo was administered to participants who were not receiving daily HU.	
Reporting group title	IMR-687 50 mg/100 mg (With HU)
Reporting group description:	
A starting dose of IMR-687 50 mg with dose escalation after 4 or 12 weeks, up to 100 mg was administered to participants who were receiving daily HU. HU doses ranged from 500 to 2000 mg.	
Reporting group title	Placebo (With HU)
Reporting group description:	
Matching placebo was administered to participants who were receiving daily HU. HU doses ranged from 500 to 2000 mg.	
Subject analysis set title	All IMR-687
Subject analysis set type	Full analysis
Subject analysis set description:	
All participants who received IMR-687.	
Subject analysis set title	All Placebo
Subject analysis set type	Full analysis
Subject analysis set description:	
All participants who received placebo.	
Subject analysis set title	Pooled IMR-687 (Without HU)
Subject analysis set type	Full analysis
Subject analysis set description:	
All participants administered IMR-687 who were not receiving HU.	

Primary: Number Of Participants With Treatment-emergent Adverse Events (TEAEs) And Serious Adverse Events (SAEs)

End point title	Number Of Participants With Treatment-emergent Adverse Events (TEAEs) And Serious Adverse Events (SAEs)[1]
End point description:	
An adverse event (AE) was defined as any untoward medical occurrence in a clinical study participant administered a pharmaceutical product and which did not necessarily have to have a causal relationship with this treatment. An SAE was defined as any AE that resulted in 1 or more of the following outcomes: death, required or prolonged hospitalization, life-threatening, persistent or significant disability/incapacity, congenital anomaly or birth defect, or other medically important event. A summary of serious and all other non-serious AEs, regardless of causality, is located in the Reported Adverse Events module.	
End point type	Primary
End point timeframe:	
Day 1 (after dosing) through up to Week 24	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As per protocol, descriptive summary statistics are presented.

End point values	IMR-687 50 mg/100 mg (Without HU)	IMR-687 100 mg/200 mg (Without HU)	Placebo (Without HU)	IMR-687 50 mg/100 mg (With HU)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	26	20	25
Units: participants				
number (not applicable)				
TEAEs	12	24	18	23
SAEs	4	7	8	5

End point values	Placebo (With HU)	All IMR-687	All Placebo	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	10	63	30	
Units: participants				
number (not applicable)				
TEAEs	10	59	28	
SAEs	3	16	11	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK) Of Participants Who Did Not Concomitantly Receive HU: Maximum Plasma Concentration (Cmax) Of IMR-687

End point title	Pharmacokinetics (PK) Of Participants Who Did Not Concomitantly Receive HU: Maximum Plasma Concentration (Cmax) Of IMR-687[2]

End point description:

For PK assessments of participants who did not concomitantly receive HU, serial blood samples for IMR-687 plasma concentrations were drawn predose at 0.5, 1, 1.5, 2, 4, 6, and 8 hours after administration of study drug; and at 24 hours after administration of study drug. Day 1 (single-dose) and steady-state (Week 25) assessments are presented.

End point type	Secondary

End point timeframe:

Day 1 and Week 25

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK analyses of IMR-687 was not conducted for placebo groups. The IMR-687 50 mg/100 mg (without HU) and IMR-687 100 mg/200 mg (without HU) groups are presented.

End point values	IMR-687 50 mg/100 mg (Without HU)	IMR-687 100 mg/200 mg (Without HU)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[3]	13[4]		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Day 1: Single Dose	512 (± 30.1)	1130 (± 33.5)		

Week 25: Steady State	1290 (± 36.4)	2180 (± 24.1)		

Notes:

[3] - Week 25: n= 8

[4] - Week 25: n= 8

Statistical analyses

No statistical analyses for this end point

Secondary: PK Of Participants Who Did Not Concomitantly Received HU: Area Under The Concentration-time Curve (AUC) From Time 0 To 24 Hours Postdose (AUC0-24h) Of IMR-687

End point title	PK Of Participants Who Did Not Concomitantly Received HU: Area Under The Concentration-time Curve (AUC) From Time 0 To 24 Hours Postdose (AUC0-24h) Of IMR-687[5]

End point description:

For PK assessments of participants who did not concomitantly receive HU, serial blood samples for IMR-687 plasma concentrations were drawn predose at 0.5, 1, 1.5, 2, 4, 6, and 8 hours after administration of study drug; and at 24 hours after administration of study drug. Day 1 (single-dose) and steady-state (Week 25) assessments are presented.

End point type	Secondary

End point timeframe:

Day 1 and Week 25

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: PK analyses of IMR-687 was not conducted for placebo groups. The IMR-687 50 mg/100 mg (without HU) and IMR-687 100 mg/200 mg (without HU) groups are presented.

End point values	IMR-687 50 mg/100 mg (Without HU)	IMR-687 100 mg/200 mg (Without HU)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11[6]	10[7]		
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)				
Day 1: Single Dose	2850 (± 12.5)	6590 (± 17.7)		
Week 25: Steady State	8420 (± 24.1)	15000 (± 22.3)		

Notes:

[6] - Week 25: n=7

[7] - Week 25: n=6

Statistical analyses

No statistical analyses for this end point

Secondary: PK Of Participants Who Concomitantly Received HU: Cmax Of IMR-687

End point title	PK Of Participants Who Concomitantly Received HU: Cmax Of IMR-687[8]

End point description:

For PK assessments of participants who concomitantly received HU, serial blood samples for IMR-687 PK were drawn predose at 0.5, 1, 1.5, 2, 4, 6, and 8 hours after administration of study drug; and at 24 hours after administration of study drug. Day 1 (single-dose) and steady-state (Week 17) assessments are presented.

End point type	Secondary

End point timeframe:

Day 1 and Week 17

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK analyses of IMR-687 was not conducted for placebo groups. The IMR-687 50 mg/100 mg (with HU) group is presented.

End point values	IMR-687 50 mg/100 mg (With HU)			
Subject group type	Reporting group			
Number of subjects analysed	13[9]			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Day 1: Single Dose	657 (± 24.7)			
Week 17: Steady State	1370 (± 18.6)			

Notes:

[9] - Week 17: n=8

Statistical analyses

No statistical analyses for this end point

Secondary: PK Of Participants Who Concomitantly Received HU: AUC0-24h Of IMR-687

End point title	PK Of Participants Who Concomitantly Received HU: AUC0-24h Of IMR-687[10]

End point description:

For PK assessments of participants who concomitantly received HU, serial blood samples for IMR-687 plasma concentrations were drawn predose at 0.5, 1, 1.5, 2, 4, 6, and 8 hours after administration of study drug; and at 24 hours after administration of study drug. Day 1 (single-dose) and steady-state (Week 17) assessments are presented.

End point type	Secondary

End point timeframe:

Day 1 and Week 17

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK analyses of IMR-687 was not conducted for placebo groups. The IMR-687 50 mg/100 mg (with HU) group is presented.

End point values	IMR-687 50 mg/100 mg (With HU)			
Subject group type	Reporting group			
Number of subjects analysed	12[11]			
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)				
Day 1: Single Dose	3090 (± 34.0)			
Week 17: Steady State	7300 (± 16.1)			

Notes:

[11] - Week 17: n=8

Statistical analyses

No statistical analyses for this end point

Secondary: PK Of Participants Who Concomitantly Received HU: Cmax of HU

End point title	PK Of Participants Who Concomitantly Received HU: Cmax of HU[12]

End point description:

For PK assessments of participants who concomitantly received HU, serial blood samples for HU PK were drawn predose and at 0.5, 1, 1.5, 3, 6, 8, and 10 hours after self-administration of the prescribed dose of HU. HU in the presence (end of treatment [EOT]: Week 17) or absence of IMR-687 (Baselines 1 and 2) are presented. HU concentration data were not sorted with respect to HU dose.

End point type	Secondary

End point timeframe:

Baseline (1 and 2) and Week 17

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The IMR-687 50 mg/100 mg (with HU) and placebo (with HU) groups are presented.

End point values	IMR-687 50 mg/100 mg (With HU)	Placebo (With HU)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14[13]	6[14]		
Units: µg/mL				
geometric mean (geometric coefficient of variation)				
Baseline 1	25.3 (± 36.7)	20.6 (± 87.8)		
Baseline 2	24.8 (± 38.1)	25.4 (± 98.6)		
Week 17	24.5 (± 55.2)	20.5 (± 127)		

Notes:

[13] - Week 17: n=10

[14] - Week 17: n=5

Statistical analyses

No statistical analyses for this end point

Secondary: PK Of Participants Who Concomitantly Received HU: AUC0-24h Of HU

End point title	PK Of Participants Who Concomitantly Received HU: AUC0-24h Of HU[15]

End point description:

For PK assessments of participants who concomitantly received HU, serial blood samples for HU PK were drawn predose and at 0.5, 1, 1.5, 3, 6, 8, and 10 hours after self-administration of the prescribed dose of HU. HU in the presence (EOT: Week 17) or absence of IMR-687 (Baselines 1 and 2) are presented. HU concentration data were not sorted with respect to HU dose.

End point type	Secondary

End point timeframe:

Baseline (1 and 2) and Week 17

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The IMR-687 50 mg/100 mg (with HU) and placebo (with HU) groups are presented.

End point values	IMR-687 50 mg/100 mg (With HU)	Placebo (With HU)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[16]	5[17]		
Units: h*µg/mL				
geometric mean (geometric coefficient of variation)				
Baseline 1	99.2 (± 32.4)	113 (± 87.7)		
Baseline 2	103 (± 30.7)	129 (± 71.7)		
Week 17	122 (± 23.0)	91.4 (± 127)		

Notes:

[16] - Baseline 1: n=11
Week 17: n=8
[17] - Baseline 1: n=4
Week 17: n=4

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline In F-Cells

End point title	Change From Baseline In F-Cells

End point description:

Absolute least squares (LS) mean change from Baseline at EOT is presented. Change from Baseline in pharmacodynamic (PD) biomarkers was analyzed using mixed models for repeated measures with covariate of treatment, visit, treatment-by-visit interaction, and baseline value.

End point type	Other pre-specified

End point timeframe:

Baseline, EOT (Week 25 for participants without HU and Weeks 17 or 25 for participants with HU)

End point values	IMR-687 50 mg/100 mg (Without HU)	IMR-687 100 mg/200 mg (Without HU)	Placebo (Without HU)	IMR-687 50 mg/100 mg (With HU)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	13	7	5
Units: Percentage				
least squares mean (standard error)	3.97 (± 4.07)	5.66 (± 2.87)	-6.00 (± 3.77)	-2.49 (± 6.00)

End point values	Placebo (With HU)	Pooled IMR-687 (Without HU)		

Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	1	20		
Units: Percentage				
least squares mean (standard error)	7.38 (± 15.54)	4.81 (± 2.48)		

Statistical analyses

No statistical analyses for this end point

Post-hoc: Percentage Of Participants With Vaso-occlusive Crisis (VOCs)

End point title	Percentage Of Participants With Vaso-occlusive Crisis (VOCs)

End point description:

VOCs include the events of acute painful crisis and acute chest symptoms (includes fever, cough, sputum production, shortness of breath, tachypnea, hypoxia, and chest pain).

End point type	Post-hoc

End point timeframe:

Day 1 (after dosing) through up to Week 24

End point values	IMR-687 50 mg/100 mg (Without HU)	IMR-687 100 mg/200 mg (Without HU)	Placebo (Without HU)	IMR-687 50 mg/100 mg (With HU)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	26	20	25
Units: percentage of participants				
number (not applicable)	50	54	70	40

End point values	Placebo (With HU)	All IMR-687	All Placebo	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	10	63	30	
Units: percentage of participants				
number (not applicable)	70	48	70	

Statistical analyses

No statistical analyses for this end point

Post-hoc: Time To First VOC Event

End point title	Time To First VOC Event

End point description:

VOCs include the events of acute painful crisis and acute chest symptoms (includes fever, cough, sputum production, shortness of breath, tachypnea, hypoxia, and chest pain). Time to first VOC event was assessed by Kaplan Meier analysis in the pooled analysis of all IMR-687 and placebo populations.

End point type	Post-hoc

End point timeframe:

Day 1 (after dosing) through up to Week 24

End point values	All IMR-687	All Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	63[18]	30		
Units: days				
median (confidence interval 95%)	169.00 (80.00 to 9999)	87.00 (26.00 to 167.00)		

Notes:

[18] - The upper confidence limit was non-estimable due to insufficient number of participants.

Statistical analyses

Statistical analysis title	Time To First VOC Event
Comparison groups	All IMR-687 v All Placebo
Number of subjects included in analysis	93
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0294
Method	Logrank

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 (after dosing) through up to Week 24

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	IMR-687 50 mg/100 mg (Without HU)

Reporting group description:

A starting dose of IMR-687 50 mg with dose escalation after 4 or 12 weeks, up to 100 mg was administered to participants who were not receiving daily HU.

Reporting group title	IMR-687 100 mg/200 mg (Without HU)

Reporting group description:

A starting dose of IMR-687 100 mg with dose escalation after 4 or 12 weeks, up to 200 mg was administered to participants who were not receiving daily HU.

Reporting group title	Placebo (Without HU)

Reporting group description:

Matching placebo was administered to participants who were not receiving daily HU.

Reporting group title	IMR-687 50 mg/100 mg (With HU)

Reporting group description:

A starting dose of IMR-687 50 mg with dose escalation after 4 or 12 weeks, up to 100 mg was administered to participants who were receiving daily HU. HU doses ranged from 500 to 2000 mg.

Reporting group title	Placebo (With HU)

Reporting group description:

Matching placebo was administered to participants who were receiving daily HU.

Reporting group title	All IMR-687

Reporting group description:

All participants who received IMR-687.

Reporting group title	All Placebo

Reporting group description:

All participants who received placebo.

Serious adverse events	IMR-687 50 mg/100 mg (Without HU)	IMR-687 100 mg/200 mg (Without HU)	Placebo (Without HU)
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 12 (33.33%)	7 / 26 (26.92%)	8 / 20 (40.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			

subjects affected / exposed[1]	1 / 8 (12.50%)	0 / 17 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Multiple injuries			
subjects affected / exposed	0 / 12 (0.00%)	0 / 26 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 12 (0.00%)	0 / 26 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Sickle cell anaemia with crisis			
subjects affected / exposed	3 / 12 (25.00%)	7 / 26 (26.92%)	7 / 20 (35.00%)
occurrences causally related to treatment / all	0 / 4	0 / 8	0 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 26 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 26 (3.85%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed[2]	0 / 8 (0.00%)	0 / 17 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			

Hepatic lesion			
subjects affected / exposed	1 / 12 (8.33%)	0 / 26 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash generalised			
subjects affected / exposed	0 / 12 (0.00%)	0 / 26 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	IMR-687 50 mg/100 mg (With HU)	Placebo (With HU)	All IMR-687
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 25 (20.00%)	3 / 10 (30.00%)	16 / 63 (25.40%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed[1]	0 / 15 (0.00%)	0 / 9 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Multiple injuries			
subjects affected / exposed	1 / 25 (4.00%)	0 / 10 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 25 (4.00%)	0 / 10 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Sickle cell anaemia with crisis			
subjects affected / exposed	3 / 25 (12.00%)	3 / 10 (30.00%)	13 / 63 (20.63%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 15
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 25 (4.00%)	0 / 10 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 10 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed[2]	1 / 15 (6.67%)	0 / 9 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic lesion			
subjects affected / exposed	0 / 25 (0.00%)	0 / 10 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash generalised			
subjects affected / exposed	0 / 25 (0.00%)	0 / 10 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	All Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 30 (36.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed[1]	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Injury, poisoning and procedural complications			
Multiple injuries			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Sickle cell anaemia with crisis			
subjects affected / exposed	10 / 30 (33.33%)		
occurrences causally related to treatment / all	0 / 14		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed[2]	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic lesion			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Skin and subcutaneous tissue disorders			
Rash generalised			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: The adverse event occurs in female participants only.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: The adverse event occurs in female participants only.

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	IMR-687 50 mg/100 mg (Without HU)	IMR-687 100 mg/200 mg (Without HU)	Placebo (Without HU)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)	22 / 26 (84.62%)	16 / 20 (80.00%)
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 12 (0.00%)	1 / 26 (3.85%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 12 (16.67%)	8 / 26 (30.77%)	4 / 20 (20.00%)
occurrences (all)	2	11	6
Dizziness			
subjects affected / exposed	0 / 12 (0.00%)	0 / 26 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Lethargy			
subjects affected / exposed	0 / 12 (0.00%)	0 / 26 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	3
Blood and lymphatic system disorders			
Sickle cell anaemia with crisis			
subjects affected / exposed	5 / 12 (41.67%)	9 / 26 (34.62%)	9 / 20 (45.00%)
occurrences (all)	15	15	14
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 12 (8.33%)	2 / 26 (7.69%)	2 / 20 (10.00%)
occurrences (all)	1	2	2

Influenza like illness			
subjects affected / exposed	2 / 12 (16.67%)	2 / 26 (7.69%)	2 / 20 (10.00%)
occurrences (all)	2	3	2
Pain			
subjects affected / exposed	2 / 12 (16.67%)	1 / 26 (3.85%)	1 / 20 (5.00%)
occurrences (all)	2	2	2
Oedema peripheral			
subjects affected / exposed	0 / 12 (0.00%)	0 / 26 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 26 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 12 (16.67%)	8 / 26 (30.77%)	0 / 20 (0.00%)
occurrences (all)	3	14	0
Abdominal pain			
subjects affected / exposed	0 / 12 (0.00%)	3 / 26 (11.54%)	1 / 20 (5.00%)
occurrences (all)	0	4	1
Abdominal pain upper			
subjects affected / exposed	1 / 12 (8.33%)	2 / 26 (7.69%)	0 / 20 (0.00%)
occurrences (all)	1	2	0
Vomiting			
subjects affected / exposed	1 / 12 (8.33%)	2 / 26 (7.69%)	0 / 20 (0.00%)
occurrences (all)	1	2	0
Diarrhoea			
subjects affected / exposed	1 / 12 (8.33%)	0 / 26 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Hepatobiliary disorders			
Ocular icterus			
subjects affected / exposed	1 / 12 (8.33%)	2 / 26 (7.69%)	0 / 20 (0.00%)
occurrences (all)	1	2	0
Jaundice			
subjects affected / exposed	0 / 12 (0.00%)	0 / 26 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal			

disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 12 (8.33%)	1 / 26 (3.85%)	2 / 20 (10.00%)
occurrences (all)	1	1	2
Cough			
subjects affected / exposed	0 / 12 (0.00%)	0 / 26 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
Rhinorrhoea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 26 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 12 (0.00%)	0 / 26 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 12 (0.00%)	6 / 26 (23.08%)	2 / 20 (10.00%)
occurrences (all)	0	7	2
Arthralgia			
subjects affected / exposed	0 / 12 (0.00%)	4 / 26 (15.38%)	1 / 20 (5.00%)
occurrences (all)	0	5	1
Pain in extremity			
subjects affected / exposed	1 / 12 (8.33%)	2 / 26 (7.69%)	2 / 20 (10.00%)
occurrences (all)	1	2	2
Musculoskeletal pain			
subjects affected / exposed	1 / 12 (8.33%)	1 / 26 (3.85%)	1 / 20 (5.00%)
occurrences (all)	1	1	1
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	3 / 12 (25.00%)	1 / 26 (3.85%)	2 / 20 (10.00%)
occurrences (all)	5	1	2
Nasopharyngitis			
subjects affected / exposed	2 / 12 (16.67%)	2 / 26 (7.69%)	1 / 20 (5.00%)
occurrences (all)	2	2	1

Non-serious adverse events	IMR-687 50 mg/100 mg (With HU)	Placebo (With HU)	All IMR-687
Total subjects affected by non-serious			

adverse events subjects affected / exposed	23 / 25 (92.00%)	10 / 10 (100.00%)	57 / 63 (90.48%)
Vascular disorders Hot flush subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 10 (10.00%) 1	1 / 63 (1.59%) 1
Nervous system disorders Headache subjects affected / exposed occurrences (all)	12 / 25 (48.00%) 18	4 / 10 (40.00%) 6	22 / 63 (34.92%) 31
Dizziness subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	1 / 10 (10.00%) 1	2 / 63 (3.17%) 2
Lethargy subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 10 (0.00%) 0	0 / 63 (0.00%) 0
Blood and lymphatic system disorders Sickle cell anaemia with crisis subjects affected / exposed occurrences (all)	10 / 25 (40.00%) 14	6 / 10 (60.00%) 23	24 / 63 (38.10%) 44
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	4 / 25 (16.00%) 6	2 / 10 (20.00%) 2	7 / 63 (11.11%) 9
Influenza like illness subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 5	0 / 10 (0.00%) 0	6 / 63 (9.52%) 10
Pain subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	0 / 10 (0.00%) 0	4 / 63 (6.35%) 5
Oedema peripheral subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 10 (10.00%) 1	0 / 63 (0.00%) 0
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	1 / 10 (10.00%) 1	1 / 63 (1.59%) 1
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	4 / 25 (16.00%)	5 / 10 (50.00%)	14 / 63 (22.22%)
occurrences (all)	4	5	21
Abdominal pain			
subjects affected / exposed	2 / 25 (8.00%)	0 / 10 (0.00%)	5 / 63 (7.94%)
occurrences (all)	3	0	7
Abdominal pain upper			
subjects affected / exposed	2 / 25 (8.00%)	0 / 10 (0.00%)	5 / 63 (7.94%)
occurrences (all)	2	0	5
Vomiting			
subjects affected / exposed	2 / 25 (8.00%)	1 / 10 (10.00%)	5 / 63 (7.94%)
occurrences (all)	2	4	5
Diarrhoea			
subjects affected / exposed	2 / 25 (8.00%)	1 / 10 (10.00%)	3 / 63 (4.76%)
occurrences (all)	2	1	3
Hepatobiliary disorders			
Ocular icterus			
subjects affected / exposed	4 / 25 (16.00%)	1 / 10 (10.00%)	7 / 63 (11.11%)
occurrences (all)	4	1	7
Jaundice			
subjects affected / exposed	1 / 25 (4.00%)	2 / 10 (20.00%)	1 / 63 (1.59%)
occurrences (all)	2	3	2
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 25 (4.00%)	0 / 10 (0.00%)	3 / 63 (4.76%)
occurrences (all)	1	0	3
Cough			
subjects affected / exposed	0 / 25 (0.00%)	1 / 10 (10.00%)	0 / 63 (0.00%)
occurrences (all)	0	1	0
Rhinorrhoea			
subjects affected / exposed	0 / 25 (0.00%)	1 / 10 (10.00%)	0 / 63 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 25 (0.00%)	0 / 10 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0

Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 25 (4.00%)	2 / 10 (20.00%)	7 / 63 (11.11%)
occurrences (all)	1	2	8
Arthralgia			
subjects affected / exposed	2 / 25 (8.00%)	1 / 10 (10.00%)	6 / 63 (9.52%)
occurrences (all)	2	1	7
Pain in extremity			
subjects affected / exposed	2 / 25 (8.00%)	2 / 10 (20.00%)	5 / 63 (7.94%)
occurrences (all)	3	2	6
Musculoskeletal pain			
subjects affected / exposed	1 / 25 (4.00%)	1 / 10 (10.00%)	3 / 63 (4.76%)
occurrences (all)	1	1	3
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	2 / 25 (8.00%)	2 / 10 (20.00%)	6 / 63 (9.52%)
occurrences (all)	3	2	9
Nasopharyngitis			
subjects affected / exposed	1 / 25 (4.00%)	1 / 10 (10.00%)	5 / 63 (7.94%)
occurrences (all)	1	1	5

Non-serious adverse events	All Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 30 (86.67%)		
Vascular disorders			
Hot flush			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 30 (26.67%)		
occurrences (all)	12		
Dizziness			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Lethargy			

subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Sickle cell anaemia with crisis			
subjects affected / exposed	15 / 30 (50.00%)		
occurrences (all)	37		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	4		
Influenza like illness			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Pain			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	2		
Oedema peripheral			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences (all)	5		
Abdominal pain			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Abdominal pain upper			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	4		

Diarrhoea subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2		
Hepatobiliary disorders Ocular icterus subjects affected / exposed occurrences (all) Jaundice subjects affected / exposed occurrences (all)	 1 / 30 (3.33%) 1 2 / 30 (6.67%) 3		
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) Rhinorrhoea subjects affected / exposed occurrences (all)	 2 / 30 (6.67%) 2 3 / 30 (10.00%) 3 2 / 30 (6.67%) 2		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	 2 / 30 (6.67%) 2		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) Musculoskeletal pain	 4 / 30 (13.33%) 4 2 / 30 (6.67%) 2 4 / 30 (13.33%) 4 		

subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2		
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all)	 4 / 30 (13.33%) 4 2 / 30 (6.67%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 September 2017	Clarified that participants who experience VOC should receive all appropriate interventions and that the assessment and treatment of participants, as well as the decision to unblind, solely depended on the clinical judgement of the Investigator.
09 October 2017	Change in wording from compliance to compliance/adherence.
27 October 2017	Increased number of planned study sites. Updated the timing of blood draws for HU PK assessment (Population B). Removed blood draws for assessment of trough IMR-687 PK (Population A) and the 12-hour blood draw from serial sampling for IMR-687 PK (Populations A and B).
19 December 2017	Modification of the exclusion criteria to decrease the required reticulocyte count for enrollment in Population B to account for bone marrow suppression from HU use. Removal of exclusion criterion 4 because the opiate limits were too restrictive per site clinicians and key opinion leaders. Addition of 12 lead ECG assessments to Week 14, 17, and 21 visits for Population A.
26 March 2018	Several on-site visits were changed to telephonic visits (with on-site visit required only if AEs were identified) to reduce participant burden.
10 August 2018	Updated the exclusion criteria to (1) increase the upper limit of allowable hemoglobin (Hb) because participants on HU may have higher baseline Hb levels; and (2) increase the number of hospitalizations allowed within the past year for VOCs to assess a wider range of participants.
19 December 2018	Increased number of study sites. Updated the timing of blood draws for HU PK assessment. Removed all blood draws for assessment of trough IMR-687 PK and 1 additional IMR-687 PK blood draw.
07 January 2019	The treatment and study durations were clarified, and the extension phase of the study was removed. Baseline HU PK profiling in Population B1 (participants concomitantly received HU) was reduced from 2 samples to 1 sample. Also, modifications were made schedule of assessment tables.
09 January 2019	Further modifications were made to schedule of assessment tables, particularly for quality of life assessments.
17 January 2019	In Population A1, Week 4 was converted from a telephonic visit to an on-site visit, and 12-lead electrocardiogram collection was added to the Week 9 Visit. Updates were made to Appendix C to approximate the volume of blood drawn at each visit.
28 June 2019	Increased allowable enrollment from 70 to 90 participants based on the study withdrawal rates, which were similar to other studies in SCD. Provided discretion to the Principal Investigator regarding participant discontinuation based on study drug treatment compliance. Allowed for Sponsor to review unblinded interim analysis data.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported