



Clinical trial results:

A Randomized, Double-blind, Placebo-Controlled Parallel Arm Dose Titration Study to Assess the Effects of SAR407899 in Patients With Microvascular Angina (MVA) and/or Persistent Stable Angina Despite Angiographically Successful Percutaneous Coronary Intervention (PCI) Summary

EudraCT number	2016-000629-38
Trial protocol	SE DK NL
Global end of trial date	23 July 2018

Results information

Result version number	v1 (current)
This version publication date	03 August 2019
First version publication date	03 August 2019

Trial information

Trial identification

Sponsor protocol code	ACT14656
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03236311
WHO universal trial number (UTN)	U1111-1182-1709

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1, Avenue Pierre Brossolette, Chilly Mazarin, France, 91385
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, contact-US@sanofi.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	22 November 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	23 July 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the effects of SAR407899 on coronary vasomotor function using the coronary flow reserve (CFR) in subjects with microvascular angina (MVA) and/or persistent stable angina despite angiographically successful percutaneous coronary intervention (PCI).

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy:

Non-investigational medicinal products (NIMPs): NIMPs were the medications used to assess the primary endpoint of the study, i.e., positron emission tomography (PET) radiopharmaceuticals (¹³N-ammonia and ⁸²Rubidium) and vasodilator stressors (adenosine and regadenoson). The NIMPs were used according to their approved labeling.

Evidence for comparator: -

Actual start date of recruitment	12 October 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Korea, Republic of: 1
Country: Number of subjects enrolled	United States: 3
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	Denmark: 4
Worldwide total number of subjects	10
EEA total number of subjects	6

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)	7
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in United States, South Korea, Sweden, Netherlands, and Denmark from 12 October 2017 to 23 July 2018.

Pre-assignment

Screening details:

A total of 10 subjects who met all of the inclusion criteria and none of the exclusion criteria were randomised and enrolled in the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Matching placebo for 4 weeks.

Arm type	Placebo
Investigational medicinal product name	SAR407899 matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to SAR407899 for 4 weeks.

Arm title	SAR407899
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Arm description:

SAR407899 with dose titration over 4 weeks administration (3 week titration phase + 1 week maintenance phase).

Arm type	Experimental
Investigational medicinal product name	SAR407899
Investigational medicinal product code	SAR407899
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

SAR407899 for 4 weeks. Dose was titrated individually.

Number of subjects in period 1	Placebo	SAR407899
Started	5	5
Completed	5	2
Not completed	0	3
Adverse event, non-fatal	-	1
Study terminated by sponsor	-	2

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description: Matching placebo for 4 weeks.	
Reporting group title	SAR407899
Reporting group description: SAR407899 with dose titration over 4 weeks administration (3 week titration phase + 1 week maintenance phase).	

Reporting group values	Placebo	SAR407899	Total
Number of subjects	5	5	10
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	64.8 ± 9.3	57.2 ± 8.5	-
Gender categorical Units: Subjects			
Female	4	4	8
Male	1	1	2
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	0	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	4	5	9
More than one race	0	0	0
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Matching placebo for 4 weeks.	
Reporting group title	SAR407899
Reporting group description: SAR407899 with dose titration over 4 weeks administration (3 week titration phase + 1 week maintenance phase).	

Primary: Change From Baseline in Uncorrected Global Coronary Flow Reserve at Week 4

End point title	Change From Baseline in Uncorrected Global Coronary Flow Reserve at Week 4 ^[1]
End point description: Absolute change from baseline to Week 4 in uncorrected global CFR, as assessed by the central core laboratory. The global CFR is the ratio of absolute myocardial blood flow (MBF) at stress over that at rest. The MBF was assessed by 13N-ammonia or 82Rubidium PET scan. Analysis was performed on modified intent-to-treat (mITT) population that included all randomised subjects analysed according to the treatment group allocated by randomisation; who received at least 1 dose or part of a dose of the investigational medicinal product (IMP) and with an evaluable primary efficacy endpoint.	
End point type	Primary
End point timeframe: Baseline, Week 4	

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 the number of subject randomised fell well below target (10 vs.78), hence no formal statistical analysis was performed.

End point values	Placebo	SAR407899		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	2		
Units: ratio				
arithmetic mean (standard deviation)	0.5 (± 0.6)	0.2 (± 0.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Angina-induced Physical Limitation Assessed Using Seattle Angina Questionnaire Physical Limitation Scale (SAQ-PL) at Week 4

End point title	Change From Baseline in Angina-induced Physical Limitation Assessed Using Seattle Angina Questionnaire Physical Limitation Scale (SAQ-PL) at Week 4
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End point description:

The SAQ-PL measures how common daily activities representing low, medium, and high exertional requirements were limited by angina (9 items). It was scored by assigning each response an ordinal value, beginning with 1 for the response that implied the 'lowest level of functioning' to 5 for 'not at all

limited', and summing across the 9 items. The score of 9 items was then transformed to 0-100 range by subtracting the lowest possible scale score, dividing by the range of the scale and multiplying by 100. The range of scores was 0 to 100, with higher scores indicates better functioning. A change of 10 points was considered to be clinically important. As the number of subjects randomised fell well below target (10 vs. 78), hence no data was collected and no analysis was performed.

End point type	Secondary
End point timeframe:	
Baseline, Week 4	

End point values	Placebo	SAR407899		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[2]	0 ^[3]		
Units: score on a scale				
number (not applicable)				

Notes:

[2] - Due to study termination, data was not collected and analysed.

[3] - Due to study termination, data was not collected and analysed.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Parameter: SAR407899 Plasma Concentration

End point title	Pharmacokinetic Parameter: SAR407899 Plasma Concentration
End point description:	
As the number of subjects randomised fell well below target (10 vs. 78), hence no data was collected and no analysis was performed.	
End point type	Secondary
End point timeframe:	
Day 1, 8, 15, 22, and Day 29	

End point values	Placebo	SAR407899		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[4]	0 ^[5]		
Units: nanograms per milliliter				
number (not applicable)				

Notes:

[4] - Due to study termination, data was not collected and analysed.

[5] - Due to study termination, data was not collected and analysed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AE) were collected from signature of the informed consent form up to the end of follow up (up to Week 5 post-treatment follow-up visit)

Adverse event reporting additional description:

Reported AEs are treatment-emergent adverse events i.e.AEs that developed/worsened during 'treatment emergent period'(time from first dose of study drug administration up to 7 days after last dose of study drug). Analysis was performed on safety population which included all randomised subjects who received at least one dose or part of dose of IMP.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Matching placebo for 4 weeks.

Reporting group title	SAR407899
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Reporting group description:

SAR407899 with dose titration over 4 weeks administration (3 week titration phase + 1 week maintenance phase).

Serious adverse events	Placebo	SAR407899	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Placebo	SAR407899	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 5 (80.00%)	5 / 5 (100.00%)	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Sports Injury			

subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 5 (0.00%) 0	
Cardiac disorders Angina Pectoris subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 5 (20.00%) 2	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Dizziness Postural subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Migraine subjects affected / exposed occurrences (all)	2 / 5 (40.00%) 2 0 / 5 (0.00%) 0 1 / 5 (20.00%) 1 0 / 5 (0.00%) 0	2 / 5 (40.00%) 5 1 / 5 (20.00%) 4 2 / 5 (40.00%) 2 1 / 5 (20.00%) 2	
General disorders and administration site conditions Non-Cardiac Chest Pain subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 5 (0.00%) 0	
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 2	0 / 5 (0.00%) 0	
Gastrointestinal disorders Abdominal Pain subjects affected / exposed occurrences (all) Abdominal Pain Lower subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0 0 / 5 (0.00%) 0	1 / 5 (20.00%) 1 1 / 5 (20.00%) 1	
Respiratory, thoracic and mediastinal disorders			

Dyspnoea subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 5 (20.00%) 1	
Skin and subcutaneous tissue disorders Dermatitis Allergic subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 5 (20.00%) 1	
Infections and infestations Hordeolum subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 2 1 / 5 (20.00%) 1	0 / 5 (0.00%) 0 1 / 5 (20.00%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 March 2017	Following amendment changes were made: The population of the study and its inclusion/exclusion criteria, modified to include both subjects with MVA and subjects with persistent stable angina despite angiographically successful elective PCI; the technique used to assess the primary endpoint, CFR: a non-invasive technique using PET scan replacing the invasive coronary angiogram; the statistical considerations including sample size calculation yielding more subjects to be randomised, stratification according to the sub-type of subject population and planned analyses, including those for the Data Monitoring Committee; the characterisation of female subjects pertaining to the potential for pregnancy that could be included in the study was further defined; biomarkers of endothelial dysfunction were deleted except the assessment of two biomarkers levels; the EQ-5D-5L questionnaire on quality of life was deleted as the study treatment duration was too short to allow detection of meaningful changes; change to the study title, inclusion/exclusion criteria, total expected number of subjects, study treatment, endpoints, statistical considerations, assessment of IMP, change to vital signs, and change to Appendix A.
05 December 2017	Amendment changes: Clarified inclusion criterion 01C: symptomatic stable angina pectoris (typical or atypical symptoms) with at least once weekly episodes will be required to be an average of at least weekly episodes over the past month; deletion of inclusion criterion 01D (i.e. electrocardiogram[ECG] evidence of ischemia with ST-segment depression during a symptom limited exercise test or non-invasive evidence of ischemia [echo, single photon emission computed tomography, magnetic resonance imaging, PET] within previous 12 months); change to inclusion criterion 01E, whereby the time until previous imaging for evidence of non-obstructive coronary artery disease was changed from 12 to 24 months. In subjects with stenting, minimum diameter stenosis of <10% was required. Coronary computed tomography angiography without regional abnormal perfusion defects within 12 months in subjects without previous elective PCI). Use of instantaneous wave-free ratio as an alternative to fractional flow reserve was allowed; change to exclusion criterion 03 to allow calcium channel blockers (CCBs) during the study (any use of long-acting nitrates and/or CCBs and/or PDE-5 inhibitors within one week prior to baseline PET scan or anticipated to be used during the study); precisions of exclusion criterion 12 (i.e., regional local flow abnormal perfusion defects at baseline PET scan) were given; deletion of exclusion criterion 13 (subjects with any ECG abnormalities preventing the interpretation of ischemia); change to exclusion criterion 25 as systolic blood pressure <110 mmHg from <120 mmHg at baseline; addition of exclusion criterion for breast-feeding subjects; expansion of window period up to the Day 1 visit for the baseline PET assessment from 3 to 7 days; changes to prohibited medications and authorized concomitant medications; assessment methods and activity parameters; clarified vital signs and ECG methodology; addition of NIMP; changed storage conditions and shelf life; deletion of Appendix A.
18 April 2018	Following amendment changes were made: Opened the subject recruitment to subjects with MVA and stable symptoms who did not have recent coronary artery imaging with a special focus on those from large sites having access to existing registries of coronary microvascular dysfunction subjects; altered the study protocol so that it fits better with clinical practice at academic sites and previous guidelines on management of acute coronary syndrome; provided guidance on how to handle subjects who undergo premature study drug discontinuation; cancellation of "elective"; change to the inclusion/exclusion criteria; change to duration of study participation; change to safety endpoints; change to sample blood volume; change to pharmacokinetic endpoint; change to screening visit, assessment methods and activity parameters; change to baseline/randomisation/Day 1 visit, visits 2, 3, 4, and 6, change to definition of source data; and handling of subjects after permanent treatment discontinuation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was prematurely terminated due to small number of subjects entering randomisation.
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Notes: