A randomized, double-blind, placebo-controlled parallel arm dose titration study to assess the effects of SAR407899 in patients with microvascular angina and/or persistent stable angina despite angiographically successful percutaneous coronary intervention (PCI)

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Primary objective:* To assess the effects of SAR407899 on coronary vasomotor function using the coronary flow reserve (CFR) in patients with microvascular angina and/or persistent stable angina despite angiographically successful elective PCI....

Ethical review	Approved WMO
Status	Will not start
Health condition type	Cardiac disorders, signs and symptoms NEC
Study type	Interventional

Summary

ID

NL-OMON46635

Source
ToetsingOnline

Brief title
ACT14656

Condition

- Cardiac disorders, signs and symptoms NEC

Synonym
chestpain due to narrowed heart vessels, microvascular angina

Research involving
Human

Sponsors and support

Primary sponsor: Sanofi-aventis
Source(s) of monetary or material Support: Sanofi

Intervention

Keyword: angina, effectivity, microvascular, PCI

Outcome measures

Primary outcome

Change from baseline to Week 4 in uncorrected global CFR assessed by

13N-ammonia PET scan.

Secondary outcome

Secondary efficacy endpoint:

* Change from baseline to Week 4 on angina-induced physical limitation using

SAQ-PL (disease-specific health-related quality of life).

Exploratory endpoints:

* Rate of diary angina episodes at baseline and Week 4

* Rate of diary angina episodes requiring use of short-acting nitrates at

baseline and Week 4

* Change from baseline to Week 4 in the other dimensions of the SAQ.

* Change from baseline to Week 4 in the SAQ-7 score.

* Patients* perceptions of treatment and symptoms assessed at baseline and Week

4.

Safety:

* Adverse events (AEs) / treatment-emergent adverse events (TEAEs).

* Blood pressure and orthostatic blood pressure.

* Blood creatinine and cystatin C.

Pharmacokinetics:

* Peak and trough SAR407899 concentrations at specific timepoints.

Study description

Background summary

Patients who have microvascular dysfunction as demonstrated by a reduced CFR in the absence of obstructive CAD and who continue to have angina pectoris along with objective evidence of myocardial ischemia are an important group of patients with high unmet medical need as there is
no currently approved specific pharmacologic therapy. Low CFR is considered as a hallmark of microvascular dysfunction. An improvement in CFR observed after interventions in this patient population would suggest an improvement in the underlying causal vascular biological abnormalities.

Study objective

Primary objective:
* To assess the effects of SAR407899 on coronary vasomotor function using the coronary flow reserve (CFR) in patients with microvascular angina and/or persistent stable angina despite angiographically successful elective PCI.

Secondary objectives:
*To assess the effects of SAR407899 on quality of life using Seattle Angina Questionnaire physical limitation domain (SAQ-PL) in patients with microvascular angina and/or persistent stable angina despite angiographically successful elective PCI.
* To assess the safety of SAR407899 in patients with microvascular angina and/or persistent stable angina despite angiographically successful elective PCI with a focus on identified risks such as hypotension and orthostatic hypotension.
* To assess SAR407899 plasma concentrations in microvascular angina patients

and/or persistent stable angina despite angiographically successful elective PCI.

Study design

A Phase 2a, multi-center, randomized with 1:1 ratio, double-blind, placebo-controlled parallel group study with weekly titration up to maintenance dose, based on individual patient tolerability, particularly symptomatic or asymptomatic blood pressure (BP) decreases.

Intervention

Patients will receive the following interventions:
- Oral administration of SAR407899 or a placebo.
- Intravenous administration of a stressor (Adenosine or Regadenoson)

Study burden and risks

Risk are related to blood sampling, investigation procedures and possible side effects of the study drug.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Male or female patient not at childbearing potential *18 year-old or legal age of majority.;- Female patient if she has undergone sterilization at least 3 months earlier or is postmenopausal.;- Post-menopausal status is defined by having no menses for 12 months without an alternative medical cause.;- In females not treated with hormonal replacement therapy (HRT), menopausal status is confirmed by a high follicle stimulating hormone (FSH) level greater than 40 IU/L.;- In females on HRT and whose menopausal status is in doubt (ie, in women aged less than 45 years), a highly effective contraception methods will be required. Contraception should be used during the whole study and for at least seven days corresponding to time needed to eliminate study treatment.;- Symptomatic stable angina pectoris (typical or atypical symptoms with an average of at least biweekly episodes over the past month),;- 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 (SPECT), magnetic resonance imaging (MRI), positron emission tomography (PET)] within previous 12 months.;- Patients with *normal* or *subnormal* (<50% stenosis) coronary arteries or intermediate stenosis (between 50 and 70%) should have fractional flow reserve (FFR) >0.80 on angiogram documented within the previous 12 months. In patients with stenting, a minimum diameter stenosis of <10% is required.;or;Coronary computed tomography angiography (CCTA) without regional abnormal perfusion defects within 12 months in patients without previous PCI.
Or CCTA performed during screening period, with finding of non-obstructive coronary arteries, in patients diagnosed with MVA and stable angina without previous PCI who did not have a coronary angiogram or CCTA in the previous 24 months but between 24 months to 5 years. ;- Baseline global CFR (measured during the study) assessed by 13N-ammonia or 82rubidium PET scan <2.0.

Exclusion criteria

- Esophageal dysmotility or esophagitis.;- Any use of long-acting nitrates and/or calcium channel blockers (CCBs) and/or phosphodiesterase type 5 (PDE5) inhibitors within one week prior to baseline PET scan or anticipated to be used during the study.;- Patients with acute coronary syndrome (ACS) [myocardial infarction (MI) and/or unstable angina] in previous 3 months.;- Unsuccessful or incomplete coronary revascularization with residual obstructive stenosis or coronary artery disease (CAD) progression in native vessels as documented on invasive coronary angiography (*50% stenosis) within 12 months of enrollment.;- Patients with history of coronary artery bypass grafting (CABG).;- Percutaneous coronary intervention

performed at the time of an ACS (MI or unstable angina) in the previous 12 months.;- Recent elective PCI within the past 3 months.;- Contraindication to vasodilator stress PET scan and or CCTA if CCTA needed during screening.;- Regional local flow abnormal perfusion defects at baseline PET scan.;- Recent (*3 months) major surgery (ie, valvular surgery, surgery for congenital heart disease), stroke, transient ischemic attack (TIA), sustained ventricular arrhythmia, clinically significant structural heart disease (moderate-severe valvular disease, hypertrophic cardiomyopathy, congenital heart disease, pulmonary hypertension).;- Patients with cardiac conduction abnormalities (second or third degree atrioventricular [AV] block, sick sinus syndrome, symptomatic bradycardia, sinus node disease). Except in patients fitted with a functioning pacemaker.;- History or known carotid stenosis:
- carotid stenosis (>50%) or
- history of carotid stenosis in patient with previous symptoms;- Contraindication or known hypersensitivity to adenosine (or regadenoson).;- Contraindication to aminophylline.;- Ongoing dipyridamole treatment.;- Inability to discontinue treatment with methylxanthines treatment within 24 hours prior to PET scan.;- Patient unable to read, understand and fill a questionnaire without any help (eg, partially visually impaired or blind).;- Systolic Blood Pressure (SBP) <120 mmHg at baseline.;- Presence at baseline of symptomatic orthostatic hypotension (SBP decrease of 20 mmHg or more at Minute 3 and Minute 5 between seated and standing position), or asymptomatic orthostatic hypotension with a decrease in SBP equal or greater than 30 mmHg at Minute 3 and Minute 5 when changing from the seated to the standing position.;- Renal impairment [estimated glomerular filtration rate (eGFR) <50 milliliter (mL)/min/1.73m2 at screening and baseline].;- Drug-induced liver injury related criteria: ;- Underlying hepatobiliary disease, ;- ALT >3 times the upper limit of normal (ULN).

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	5

Type:	Anticipated

Ethics review

Approved WMO Date:	22-06-2017
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	30-10-2017
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-01-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-01-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-01-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-05-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-06-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2016-000629-38-NL
CCMO	NL62087.091.17
Other	Zie sectie J