



NCT Number: NCT03236311

AMENDED CLINICAL TRIAL PROTOCOL NO 03

COMPOUND: SAR407899

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

STUDY NUMBER: ACT14656

VERSION DATE / STATUS: Approval date (18-Apr-2018) / Approved

Protocol Amendment 04	Version number: 1 (electronic 1.0)	Date : 18-Apr-2018
Amended Clinical Trial Protocol 03 (local for Sweden)	Version number: 1 (electronic 3.0)	Date : 05-Dec-2017
Amended Clinical Trial Protocol 02	Version number: 1 (electronic 3.0)	Date : 05-Dec-2017
Protocol Amendment 03	Version number: 1 (electronic 2.0)	Date : 05-Dec-2017
Amended Clinical Trial Protocol 02 (local for Sweden)	Version number: 1 (electronic 1.0)	Date : 11-Sep-2017
Protocol Amendment 02 (local for Sweden)	Version number: 1 (electronic 1.0)	Date : 11-Sep-2017
Amended Clinical Trial Protocol 01	Version number: 1 (electronic 1.0)	Date : 31-Mar-2017
Protocol Amendment 01	Version number: 1 (electronic 1.0)	Date : 31-Mar-2017
Clinical Trial Protocol	Version number: 1 (electronic 1.0)	Date : 07-Jul-2016
Version Number: 1	EudraCT Number: 2016-000629-38	
	IND Number: 129855	
	WHO Universal Trial Number: U1111-1182-1709	
Date: 18-Apr-2018	Total number of pages: 108	

Any and all information presented in this document shall be treated as confidential and shall remain the exclusive property of Sanofi (or any of its affiliated companies). The use of such confidential information must be restricted to the recipient for the agreed purpose and must not be disclosed, published or otherwise communicated to any unauthorized persons, for any reason, in any form whatsoever without the prior written consent of Sanofi (or the concerned affiliated company); 'affiliated company' means any corporation, partnership or other entity which at the date of communication or afterwards (i) controls directly or indirectly Sanofi, (ii) is directly or indirectly controlled by Sanofi, with 'control' meaning direct or indirect ownership of more than 50% of the capital stock or the voting rights in such corporation, partnership or other entity

NAMES AND ADDRESSES OF

COORDINATING INVESTIGATOR

Name:
Address:

Tel:
Fax:
E-mail:

MONITORING TEAM'S REPRESENTATIVE

Name:
Address:

Tel:
Fax:
E-mail:

To be filled in by each CSU participating in the study

SPONSOR

Company:
Address:

sanofi-aventis Recherche & Développement
1, Avenue Pierre Brossolette
91385 Chilly Mazarin - France



OTHER EMERGENCY TELEPHONE NUMBERS

CLINICAL TRIAL SUMMARY

COMPOUND: SAR407899	STUDY No.: ACT14656
TITLE	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).
INVESTIGATOR/TRIAL LOCATION	Europe, Asia and US
PHASE OF DEVELOPMENT	Phase 2a
STUDY OBJECTIVE(S)	<p>Primary objective:</p> <ul style="list-style-type: none"> Assess the effects of SAR407899 on coronary vasomotor function using coronary flow reserve (CFR) in patients with microvascular angina and/or persistent stable angina despite angiographically successful PCI. <p>Secondary objectives:</p> <ul style="list-style-type: none"> Assess the effects of SAR407899 on quality of life using SAQ-PL in patients with microvascular angina and/or persistent stable angina despite angiographically successful PCI. Assess the safety of SAR407899 in patients with microvascular angina and/or persistent stable angina despite angiographically successful PCI with a focus on identified risks such as hypotension and orthostatic hypotension. Assess SAR407899 plasma concentrations in microvascular angina patients and/or persistent stable angina despite angiographically successful 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.
STUDY POPULATION	Male and female patients with microvascular angina and/or persistent stable angina despite angiographically successful PCI.
Main selection criteria	<p>Main Inclusion criteria:</p> <ul style="list-style-type: none"> 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. <ul style="list-style-type: none"> 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.

	<p>Contraception should be used during the whole study and for at least seven days corresponding to time needed to eliminate study treatment.</p> <ul style="list-style-type: none">• Symptomatic stable angina pectoris (typical or atypical symptoms with an average of at least bi-weekly episodes over the past month),• Patients with non-obstructive (<50% stenosis) coronary arteries or intermediate stenosis (between 50 and 70%) should have fractional flow reserve (FFR) >0.80 or instantaneous wave-free ratio (iFR) >0.89 on angiogram documented within the previous 24 months*. In patients with stenting, a minimum diameter stenosis of <10% is required. <p>or</p> <p>Coronary computed tomography angiography (CCTA) with finding of non-obstructive coronary arteries within the past 24 months* in patients without previous PCI.</p> <p>*Note: in cases of clinically suspected progression of atherosclerosis as per the Investigator, a more contemporary (ie, 6 months) evidence should be provided.</p> <p>or</p> <p>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.</p> <ul style="list-style-type: none">• Baseline global CFR (measured during the study) assessed by ¹³N-ammonia or ⁸²Rubidium PET scan <2.0. <p>Main Exclusion criteria:</p> <ul style="list-style-type: none">• Esophageal dysmotility or esophagitis.• Any use of nitrates (except short-acting nitrates) and/or dipyridamole 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 24 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 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*. <p>*Note: if contemporary evidence with invasive coronary</p>
--	---

	angiography or CCTA demonstrates non-obstructive coronary arteries or if the regional local flow abnormal perfusion defect on PET scan is consistent with previous studies then patient qualifies for the study.
	<ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> - Carotid stenosis ($>50\%$) or - History of carotid stenosis in patients with previous symptoms. • Contraindication or known hypersensitivity to adenosine (or regadenoson). • Contraindication to aminophylline. • 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) <110 mmHg at baseline. • Presence at baseline of symptomatic orthostatic hypotension (SBP decrease of 20 mmHg or more at Minute 3 or 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 or 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: <ul style="list-style-type: none"> - Underlying hepatobiliary disease, - ALT >3 times the upper limit of normal (ULN).
Total expected number of patients:	78 patients to be randomized (39 per arm).
Expected number of sites:	Approximately 20 sites. Stratification on the presence of angiographically successful PCI (YES/NO) will be performed.
STUDY TREATMENT(s)	
Investigational medicinal product(s)	SAR407899, 2.5 mg and 5mg capsules. SAR407899 matching placebo.
Formulation:	Capsules.
Route(s) of administration:	Oral administration, twice per day: in the morning and at bedtime. Dose may be taken with or without food as per preference of the patient.

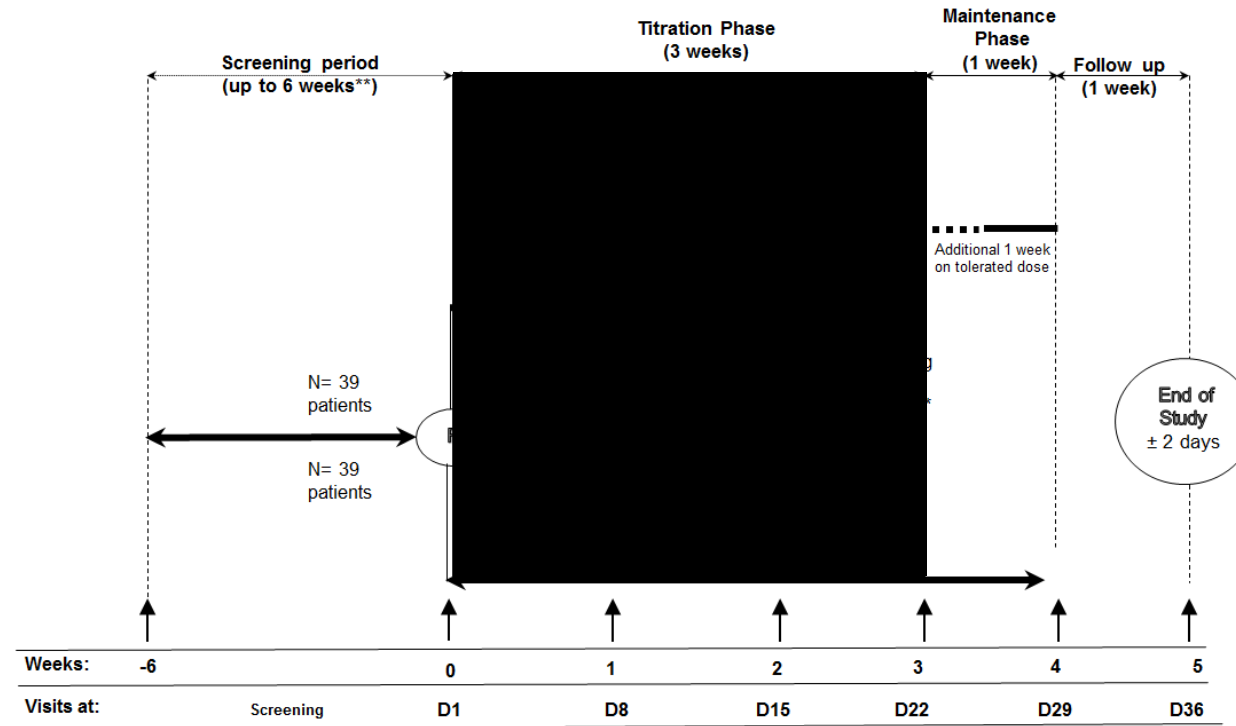
<p>Dose regimen:</p>	<p>Starting dose: [REDACTED].</p> <p>Individual dose titration based on BP tolerability at scheduled visits with the following rules:</p> <ul style="list-style-type: none"> • [REDACTED] if well tolerated over a period of 3 weeks followed by a maintenance period of 1 week (total duration of treatment 4 weeks including titration).
	<p>[REDACTED]</p> <p>[REDACTED]</p>
	<ul style="list-style-type: none"> • If [REDACTED] dose is not tolerated, the study drug will be discontinued. <p>Stopping criterion based on creatinine level:</p> <ul style="list-style-type: none"> • Stop study drug if creatinine blood level >150 µmol/L and increase from baseline >30%. <p>[REDACTED]. When 19 patients will have completed first week after randomization, the Data Monitoring Committee (DMC) will review the clinical safety data including adverse events of special interests (AESIs). During the safety evaluation of the first 19 enrolled patients, these patients will continue to receive IMPs as per the titration schedule described above and enrolment will continue.</p>
<p>Non investigational medicinal product(s)</p>	<ul style="list-style-type: none"> • PET radiopharmaceuticals (¹³N-ammonia and ⁸²Rubidium). • Vasodilator stressors (adenosine and regadenoson). <p>The NIMPs for PET scan should be used according to their approved labeling.</p>
<p>ENDPOINTS</p>	<p>Primary efficacy endpoint:</p> <ul style="list-style-type: none"> • Change from baseline to Week 4 in uncorrected global CFR assessed by ¹³N-ammonia or ⁸²Rubidium PET scan. <p>Secondary efficacy endpoint:</p> <ul style="list-style-type: none"> • Change from baseline to Week 4 on angina-induced physical limitation using SAQ-PL (disease-specific health-related quality of life). <p>Exploratory endpoints:</p> <ul style="list-style-type: none"> • 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.

	<p>Safety:</p> <ul style="list-style-type: none"> • Adverse events (AEs) / treatment-emergent adverse events (TEAEs). • Blood pressure and orthostatic blood pressure. • Blood creatinine and cystatin C. <p>Pharmacokinetics:</p> <ul style="list-style-type: none"> • Peak and trough SAR407899 concentrations at specific time points.
<p>ASSESSMENT SCHEDULE</p>	<p>Coronary Flow Reserve assessed by ¹³N-ammonia or ⁸²Rubidium PET scan and SAQ will be assessed at baseline and the end of Week 4.</p> <p>Safety will be monitored during the whole study with special focus on BP and renal function (creatinine and Cystatin C).</p> <p>Pharmacokinetics: sparse sampling will be performed on Day 1 at 1 hour and 3 hour post-dosing, pre-dose on Day 8, Day 15 and Day 22, and pre-dose and in the 1-3 hour interval post-dose on Day 29.</p> <p>Number of angina episodes and short acting NTG intake per week using a diary from baseline to Week 4.</p>
<p>STATISTICAL CONSIDERATIONS</p>	<p>Sample size determination:</p> <p>Estimated as 78 patients (39 per group). Based on a large study of 2783 patients referred for rest/stress PET (1) which suggested a SD of 0.65 for CFR at baseline. Under the hypothesis of a correlation of 0.6 between baseline assessment and week 4-assessment the SD for the change from baseline to Week 4 could be estimated at 0.58.</p> <p>35 patients per group will be needed to detect with 1 sided test alpha 0.05 and 80% power, a clinically significant relevant difference versus placebo of 0.35 in the change from baseline in PET CFR to Week 4.</p> <p>To reach this number of patients 78 patients need to be included in this study with the hypothesis of 10% inevaluable.</p> <p>Analysis population:</p> <p>The efficacy population will be the modified intend-to-treat population, defined as all randomized patients analyzed according to the treatment group allocated by randomization, receiving at least one dose or part of a dose of the investigational medicinal product and having a baseline PET scan CFR assessment available.</p> <p>The safety population will include all randomized patients who received at least one dose or part of a dose of the IMP. In the safety analysis, patients will be analyzed in the treatment group as actually received.</p> <p>Primary analysis: efficacy analyses will be performed on ITT population.</p> <p>The change in CFR from baseline to week 4 will be analyzed using an ANCOVA model. The model will include the two fixed categorical effect of treatment group (pooled SAR407899 doses versus placebo) and of the presence of angiographically successful PCI (YES/NO) as well as a continuous fixed covariate of baseline CFR. The corresponding interaction of order two will be also included in the model.</p> <p>The final model will provide adjusted least-squares means (LS means)</p>

	<p>estimates of the change from baseline to Week 4 in both treatment groups and their corresponding 95% confidence intervals. The difference of these estimates will be tested at the 5% 1-sided alpha level and the 95% confidence interval of the difference will be provided.</p> <p>To evaluate the impact of missing values on treatment effect estimation, a multiple imputation method will be used.</p>
	<p>Analysis of the key secondary endpoint:</p> <p>The secondary analysis will use a similar model as primary analysis applied to the change from baseline to Week 4 in SAQ PL. The final model will provide adjusted least-squares means (LS means) estimates of the change from baseline to Week 4 in both treatment groups and their corresponding 95% confidence intervals. The difference of these estimates will be tested at the 10% 1-sided alpha level and the 95% confidence interval of the difference will be provided.</p> <p>A safety review with a DMC meeting will start as soon as the first 19 patients will have been randomized and have finished the first week of treatment. Additional analyses for safety may be performed in this study.</p> <p>Safety analysis:</p> <p>Safety analyses will be descriptive, based on the safety population with a focus on BP, creatinine and cystatin C.</p> <p>The safety analysis will focus on the TEAE period. This period is defined as the time from the first administration of the IMP to the last administration of the IMP +5 times the half-life. The half-life being from 20 to 31 hours depending on the age of the patients, a conservative estimate of 31 hours is used for all patients (thus 5 times the half-life corresponds to 5 times 31 hours ie, approximately 7 days).</p> <p>Pharmacokinetic analysis:</p> <p>Descriptive statistics will be provided by SAR407899 dose and time-point for observed concentrations.</p> <p>Pharmacokinetic/pharmacodynamic analysis:</p> <p>Scatter plots of concentrations versus primary/secondary endpoints will be provided. If relevant, some models will be provided to fit the relationship between concentrations and endpoint(s).</p>
<p>DURATION OF STUDY PERIOD (per patient)</p>	<ul style="list-style-type: none"> • Screening: up to 4 weeks before the first dosing (Day -28 to Day -1) and up to 6 weeks in patients diagnosed with MVA and stable angina without previous PCI who did not have a coronary artery angiography or CCTA in the previous 24 months but between 24 months and 5 years prior to screening and requiring CCTA in this screening period. • Titration phase: 3 weeks. • Maintenance phase: 1 week. • Total duration of treatment: 4 weeks (including titration). • Follow-up: 1 week. • Total study duration: 9 weeks (+/- 2 days) and up to 11 weeks (+/- 2 days) in patients requiring CCTA in screening period.

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



* See titration rules in next pages.
** For patients with stable angina due to MVA without PCI, who need CCTA during screening period, additional 2 weeks of screening are allowed thus having a maximal screening period of up to 6 weeks.

R: randomization On-site visits

1.2 POTENTIAL TITRATION SCHEDULES & DECISION RULES STUDY

- 1.
- 2.
- 3.
- 4.
- 5.
- 6.
- 7.
- 8.



In case a patient does not tolerate a dose, he/she call the investigator to have an on-site visit. Based on the tolerability assessed at this visit, the investigator could decide to stop or modify study drug dose. Dose titration based on BP tolerability at visits as per [Section 9.2.4.3](#) with the following recommendations:



Stopping criterion based on creatinine level:

- Stop study drug if creatinine blood level $>150 \mu\text{mol/L}$ and increase from baseline $>30\%$. In specific circumstances where creatinine blood level can be obtained only in the afternoon the day of the visit, the patient will be titrated according to titration scheme and if creatinine blood level meets stopping rules, the investigator will need to contact the patient before bedtime study drug intake as study drug should be permanently discontinued and a premature study drug discontinuation visit will be planned as per [Section 8.1.1](#).

1.3 STUDY FLOW CHARTS

1.3.1 Study flow chart for patients with previous coronary artery angiography or CCTA within 24 months prior to screening

Phase	Screening D-28 to D-1	Titration Phase				Maintenance Phase D29 (+2days) EOT/early discontinuation	End-of-study D36 (+/-2days)
		D1 (see separate flow chart for this visit)	D8 (+/-2days)	D15 (+/-2days)	D22 (+/-2days)		
Informed consent	X						
Visit at clinical site	X	X ^a	X	X	X	X ^a	X
Data of previous coronary artery angiography or CCTA	X ^b						
Inclusion/exclusion criteria	X	X					
Medical/surgical history	X						
Prior/concomitant medications ^c	<---	----	----	----	----	----	--->
IVRS/IWRS	X ^o	X ^p	X ^p	X ^p	X ^p	X	
Randomization		X					
IMP administration ^d		<---	----	----	----	--->	
IMP dispensation		X	X	X	X	X ^q	
Safety							
Physical examination	X	X				X	
Height	X						
Body weight	X	X				X	
Vital signs ^e (including search for orthostatic BP), ECGs	X	X ^{f,g}	X ^f	X ^f	X ^f	X ^{f,g}	X
Body temperature		X				X	
Hematology, biochemistry, urinalysis	X	X	X ^s	X ^{ns}	X ^{ns}	X	X ^s
Renal function (blood creatinine and cystatin C)	X	X	X	X	X	X	X
Plasma FSH ^m	X						
Adverse event collection	<---	----	----	----	----	----	--->
Pharmacodynamics							
Data of previous CFR assessment whatever the method	X ^b						
CFR assessed by vasodilator stress PET		X ⁱ				X ⁱ	

Phase	Screening	Titration Phase				Maintenance Phase	End-of-study
		D1 (see separate flow chart for this visit)	D8 (+/-2days)	D15 (+/-2days)	D22 (+/-2days)		
scan ^h							
NIMP administration		X ^{i,r}				X ^r	
Patient's diary dispensation and/or review (angina episodes and short-acting nitroglycerin intakes)	X	X	X	X	X	X	X
SAQ ^j		X				X	
Resources Utilization ^k		X					
Patients' perception of treatment and symptoms ^l		X				X	
Pharmacokinetics							
SAR407899 pharmacokinetic plasma samples		X ^l	X ^l	X ^l	X ^l	X ^l	
DNA							
Pharmacogenetic DNA sample		X					
Biomarkers							
Blood samples for [REDACTED] and [REDACTED]		X					
Future use of samples							
Blood sample if specific consent signed		X					

ECG = electrocardiogram; EOT = End of Treatment; FSH = follicle-stimulating hormone; IMP = investigational medicinal product; CCTA: Coronary Computed Tomography Angiography.

- a Whole day stay due to assessment duration process.
- b If assessment done within 24 months prior to screening.
- c Concomitant medication (if those are not allowed during the study, see exclusion criterion 3 in [Section 7.2.1](#)) needs to be stopped 1 week before baseline CFR assessed by PET scan and during the whole study.
- d Capsules in the morning and at bedtime. If PET assessment on Day 29 no administration at bedtime. If PET assessment delayed, last IMP administration should be done in the morning of the PET assessment.
- e Vital signs: BP & heart rate measurements including search of hypotension (orthostatic or not).
- f Before morning administration, vital signs should be assessed by the investigator or designee except on Day 1 which requires before morning administration, at T1H and T3H. For any safety reasons additional physical examination, vital signs, ECG may be performed at the investigator's discretion.
- g At Day 1 & Day 29 PET assessments, continuous monitoring of heart rate, BP and ECG should be performed throughout the stressor infusion.
- h Restriction rules for CFR assessed by vasodilator stress PET scan (detailed in [Section 10.1.2](#) and [Section 10.1.4](#)) to follow.
- i On Day 1 (or, if not otherwise possible, up to 14 days prior to Day 1) CFR assessed by vasodilator stress PET scan should be performed before the IMP administration. On Day 29 or up to 2 days after (if not otherwise possible) CFR assessed by vasodilator stress PET scan should be performed approximately 1 to 2 hours after morning IMP intake. Prior to baseline PET assessment (on day 1 or up to 14 days prior to day 1), the eligibility criteria must be carefully reviewed (including review of the screening labs), and if the patient no longer qualifies for the study, then he/she should not undergo the PET assessment.
- j To be completed before any other assessment and without any help.

- k Health care resources will include number of out-patients visits by type physician (specialists, general practitioner, other) and impact on working status.
- l Two PK samplings on Day 1 (1h and 3 h post-dose), one PK sampling (pre-dose) at Day 8, Day 15 and Day 22, two PK samplings on Day 29 (pre-dose and 1-3 hours post-dose). The patient will have to come at the site without having taken his morning dose of IMP if the visit occurs in the morning.
- m Only in post-menopausal female patient not receiving hormone replacement therapy.
- n Except hematology.
- o To assign patient number.
- p To obtain the treatment number after specifying the chosen titration.
- q Only if not enough IMP for PET scan scheduled on Day 30 or Day 31.
- r Only for PET scan.
- s Except urinalysis.

1.3.2 Study flow chart for patients diagnosed with MVA and stable angina without previous PCI and with previous coronary artery angiography or CCTA between 24 months and 5 years prior to screening, who need CCTA during screening period

Phase	Screening	Titration Phase				Maintenance Phase	End-of-study
		D1 (see separate flow chart for this visit)	D8 (+/-2days)	D15 (+/-2days)	D22 (+/-2days)		
Informed consent	X						
Visit at clinical site	X	X ^a	X	X	X	X ^a	X
Data of previous coronary artery angiography or CCTA	X ^b						
CCTA	X ^s						
Inclusion/exclusion criteria	X	X					
Medical/surgical history	X						
Prior/concomitant medications ^c	<---	---	---	---	---	---	--->
IVRS/IWRS	X ^o	X ^p	X ^p	X ^p	X ^p	X	
Randomization		X					
IMP administration ^d		<---	---	---	---	--->	
IMP dispensation		X	X	X	X	X ^q	
Safety							
Physical examination	X	X				X	
Height	X						
Body weight	X	X				X	
Vital signs ^e (including search for orthostatic	X	X ^{f,g}	X ^f	X ^f	X ^f	X ^{f,g}	X

Phase	Screening	Titration Phase				Maintenance Phase	End-of-study
		D1 (see separate flow chart for this visit)	D8 (+/-2days)	D15 (+/-2days)	D22 (+/-2days)		
BP), ECGs							
Body temperature		X				X	
Hematology, biochemistry, urinalysis	X	X	X ^t	X ^{nt}	X ^{nt}	X	X ^t
Renal function (blood creatinine and cystatin C)	X	X	X	X	X	X	X
Plasma FSH ^m	X						
Adverse event collection	<---	----	----	----	----	----	--->
Pharmacodynamics							
Data of previous CFR assessment whatever the method	X ^u						
CFR assessed by vasodilator stress PET scan ^h	X ⁱ					X ⁱ	
NIMP administration	X ^r					X ^r	
Patient's diary dispensation and/or review (angina episodes and short-acting nitroglycerin intakes)	X	X	X	X	X	X	X
SAQ ^j		X				X	
Resources Utilization ^k		X					
Patients' perception of treatment and symptoms ⁱ		X				X	
Pharmacokinetics							
SAR407899 pharmacokinetic plasma samples		X ^l	X ^l	X ^l	X ^l	X ^l	
DNA							
Pharmacogenetic DNA sample		X					
Biomarkers							
Blood samples for [REDACTED] and [REDACTED]		X					
Future use of samples							
Blood sample if specific consent signed		X					

ECG = electrocardiogram; EOT = End of Treatment; FSH = follicle-stimulating hormone; IMP = investigational medicinal product; CCTA: Coronary Computed Tomography Angiography.

a Whole day stay due to assessment duration process.

b If assessment done between 24 months and 5 years prior to screening.

- c* Concomitant medication (if those are not allowed during the study, see exclusion criterion 3 in [Section 7.2.1](#)) needs to be stopped 1 week before baseline CFR assessed by PET scan and during the whole study.
- d* Capsules in the morning and at bedtime. If PET assessment on Day 29 no administration at bedtime. If PET assessment delayed, last IMP administration should be done in the morning of the PET assessment.
- e* Vital signs: BP & heart rate measurements including search of hypotension (orthostatic or not).
- f* Before morning administration, vital signs should be assessed by the investigator or designee except on Day 1 which requires before morning administration, at T1H and T3H. For any safety reasons additional physical examination, vital signs, ECG may be performed at the investigator's discretion.
- g* At Day 1 & Day 29 PET assessments, continuous monitoring of heart rate, BP and ECG should be performed throughout the stressor infusion.
- h* Restriction rules for CFR assessed by vasodilator stress PET scan (detailed in [Section 10.1.2](#) and [Section 10.1.4](#)) to follow.
- i* Up to 4 weeks before Day 1, CFR assessed by vasodilator stress PET scan should be performed before the IMP administration. On Day 29 or up to 2 days after (if not otherwise possible) CFR assessed by vasodilator stress PET scan should be performed approximately 1 to 2 hours after morning IMP intake. Prior to baseline PET assessment, the eligibility criteria must be carefully reviewed (including review of the screening labs), and if the patient no longer qualifies for the study, then he/she should not undergo the PET assessment or CCTA.
- j* To be completed before any other assessment and without any help.
- k* Health care resources will include number of out-patients visits by type physician (specialists, general practitioner, other) and impact on working status.
- l* Two PK samplings on Day 1 (1h and 3 h post-dose), one PK sampling (pre-dose) at Day 8, Day 15 and Day 22, two PK samplings on Day 29 (pre-dose and 1-3 hours post-dose). The patient will have to come at the site without having taken his morning dose of IMP if the visit occurs in the morning.
- m* Only in post-menopausal female patient not receiving hormone replacement therapy.
- n* Except hematology.
- o* To assign patient number.
- p* To obtain the treatment number after specifying the chosen titration.
- q* Only if not enough IMP for PET scan scheduled on Day 30 or Day 31.
- r* Only for PET scan.
- s* CCTA after PET scan (if CFR <2.0) in order to have CCTA results available for inclusion.
- t* Except urinalysis.
- u* If assessment done within 24 months prior to screening.

1.4 DAY 1 FLOW CHART

1.4.1 Flow chart with PET scan on Day 1 (not applicable for patients diagnosed with MVA and stable angina without previous PCI and with previous coronary artery angiography or CCTA between 24 months and 5 years prior to screening, who need CCTA during screening period)

Day	D1						
Time (hour/minute) ^a	-4H	-3H	-2H30	-0H30	0H	1H	3H
Visit start	X						
End of visit							X ⁱ
Concomitant medications ^b	←-----→						
SAQ	X						
Resources Utilization	X						
Patients' perception of treatment and symptoms	X						
Patient's diary	←-----→						
Inclusion/Exclusion criteria		X			X		
CFR assessed by vasodilator stress PET scan ^c			X ^d				
NIMP administration			X ^h				
IVRS/IWRS					X		
Randomization					X		
IMP administration					X		
Safety^e							
Physical examination		X					
Body temperature		X					
Body weight		X					

Day	D1						
	-4H	-3H	-2H30	-0H30	0H	1H	3H
Time (hour/minute)^a							
Vital signs ^g , 12 lead-ECG ^f		X		X		X	X
Hematology, biochemistry, urinalysis		X					
Renal function (blood creatinine ⁱ , and cystatin C)		X					
Adverse event collection	←----->						
Pharmacokinetics							
SAR407899 plasma samples						X	X
DNA							
Pharmacogenetic DNA sample			X				
Biomarkers							
Blood samples for [REDACTED] and [REDACTED]			X				
Future use of samples							
Blood sample if specific consent signed			X				

DME = drug metabolizing enzymes; ECG = electrocardiogram; IMP = investigational medicinal product.

Note: when several items take place at the same time, the following order should be respected: questionnaires, ECG, vital signs, blood sampling, pharmacodynamics, drug administration, meal.

In order to respect exact timing of pharmacokinetic samples, the other measures will be done ahead of the scheduled time.

- a Time (hour/minute) is expressed in reference to the first administration of SAR407899 (T0H). The times expressed prior to T0H are approximate.
- b Concomitant medication (if those are not allowed during the study, see exclusion criterion 3 in [Section 7.2.1](#)) needs to be stopped 1 week before CFR assessed by PET scan.
- c Restriction rules for CFR assessed by vasodilator stress PET scan (detailed in [Section 10.1.2](#)) to follow.
- d Prior to the Day 1 PET assessment, the eligibility criteria must be carefully reviewed (including review of the screening labs), and if the patient no longer qualifies for the study, then he/she should not undergo the PET assessment.
- e Refer to Safety [Section 9.2](#) for detailed safety investigations.
- f Vital signs should be performed by the investigator or designee. Continuous monitoring of heart rate, BP and 12-lead ECG should be performed throughout the stressor infusion.
- g Vital signs: BP & heart rate measurements including search of hypotension (orthostatic or not).
- h Only for PET scan.
- i The patient may be discharged later on Day 1 to guarantee patient's safety based upon the opinion of the Investigator.
- j Mandatory to check criterion E 25. Alternatively for practical reasons, blood creatinine results should be obtained within 2 days prior to Day 1 to check the exclusion criterion E25.

1.4.2 Flow chart with PET scan prior to Day 1

This flow chart is displayed as follows:

- PET scan up to 28 days if patient with MVA and stable angina without previous PCI and with previous coronary artery angiography or CCTA between 24 months and 5 years prior to screening
- or PET scan up to 14 days prior to D1 if previous coronary artery angiography or CCTA within 24 months prior to screening

Day	PET scan up to 28 days or up to 14 days	D1			
		Prior dosing	0H	1H	3H
Time (hour/minute) ^a					
Visit start	X	X			
End of visit	X				X ^j
Concomitant medications ^b	←-----→				
SAQ		X			
Resources Utilization		X			
Patients' perception of treatment and symptoms		X			
Patient's diary	←-----→				
Inclusion/Exclusion criteria	X		X		
CFR assessed by vasodilator stress					
PET scan ^{c,f}	X ^d				
NIMP administration	X ^h				
IVRS/IWRS			X		
Randomization			X		
IMP administration			X		

Day	PET scan up to 28 days or up to 14 days	D1			
		Prior dosing	0H	1H	3H
Time (hour/minute)^a					
Safety^e					
Physical examination		X			
Body temperature		X			
Body weight		X			
Vital signs ^g , 12 lead-ECG ^f		X ^k		X	X
Hematology, biochemistry, urinalysis		X			
Renal function (blood creatinine ^j , and cystatin C)		X			
Adverse event collection	←----->				
Pharmacokinetics					
SAR407899 plasma samples				X	X
DNA					
Pharmacogenetic DNA sample		X			
Biomarkers					
Blood samples for [redacted] and [redacted]		X			
Future use of samples					
Blood sample if specific consent signed		X			

DME = drug metabolizing enzymes; ECG = electrocardiogram; IMP = investigational medicinal product.

Note: when several items take place at the same time, the following order should be respected: questionnaires, pharmacodynamics, ECG, vital signs, blood sampling, drug administration, meal.

In order to respect exact timing of pharmacokinetic samples, the other measures will be done ahead of the scheduled time.

a Time (hour/minute) is expressed in reference to the first administration of SAR407899 (T0H). Prior dosing at the arrival on site, if it takes eg. 3 hours to get creatinine result after the blood sampling, to check that the patients do not meet the exclusion criterion E25, vital signs and 12-lead ECG may have to be repeated closer before dosing. Otherwise, blood creatinine result may be obtained within 2 days prior to Day 1.

b Concomitant medication (if those are not allowed during the study, see exclusion criterion 3 in [Section 7.2.1](#)) needs to be stopped 1 week before CFR assessed by PET scan.

c Restriction rules for CFR assessed by vasodilator stress PET scan (detailed in [Section 10.1.2](#)) to follow.

- d* Prior to the PET assessment, the available eligibility criteria must be carefully reviewed (including review of the screening labs), and if the patient no longer qualifies for the study, then he/she should not undergo the PET assessment.
- e* Refer to Safety Section 9.2 for detailed safety investigations.
- f* Vital signs should be performed by the investigator or designee. Continuous monitoring of heart rate, BP and 12-lead ECG should be performed throughout the stressor infusion.
- g* Vital signs: BP & heart rate measurements including search of hypotension (orthostatic or not).
- h* Only for PET scan.
- i* The patient may be discharged later on Day 1 to guarantee patient's safety based upon the opinion of the Investigator.
- j* Mandatory before dosing to check criterion E 25.
- k* To be repeated as close as possible and before to the study drug administration if the turnaround time to get the results of creatinine before dosing is approximately 3 hours.

1.5 DAY 29 FLOW CHART SUGGESTED TIME FRAME (CAN BE ADAPTED BY SITE)

Day	D29					
	At arrival at the site	0H Study drug intake	1H	2H	3H before leaving the site	Additional hours at Investigator's discretion
Visit start	X					
End of visit					X ^j	
Concomitant medications	←----->					
SAQ	X					
Patients' perception of treatment and symptoms	X					
Patient's diary	←----->					
IMP administration		X ^g				
CFR assessed by vasodilator stress PET scan ^{b, e}				X ^c		
NIMP administration				X ^h		
Safety^d						
Physical examination	X					
Body temperature	X					

Day	D29					
	At arrival at the site	0H Study drug intake	1H	2H	3H before leaving the site	Additional hours at Investigator's discretion
Body weight	X					
Vital signs ^f , 12 lead-ECG ^e	X					
Hematology, biochemistry, urinalysis,	X					
Renal function (blood creatinine and cystatin C)	X					
Adverse event collection	←----->					
Pharmacokinetics						
SAR407899 plasma samples	X		<i>x^j</i>			

DME = drug metabolizing enzymes; ECG = electrocardiogram; IMP = investigational medicinal product.

Note: when several items take place at the same time, the following order should be respected: questionnaires, ECG, vital signs, blood sampling, drug administration, pharmacodynamics, meal.

In order to respect exact timing of pharmacokinetic samples, the other measures will be done ahead of the scheduled time.

a Time (hour/minute) is expressed in reference to the last administration of SAR407899 (T0H).

b Restriction rules for CFR assessed by vasodilator stress PET scan (detailed in [Section 10.1.4](#)) to follow.

c On Day 29 or up to 2 days after (at the latest if not otherwise possible) CFR assessed by vasodilator stress PET scan should be performed approximately 1 to 2 hours after morning IMP intake.

d Refer to Safety section for detailed safety investigations.

e Vital signs should be performed by the investigator or designee. Continuous monitoring of heart rate, BP and 12-lead ECG should be performed throughout the stressor infusion.

f Vital signs: BP & Heart rate measurements including search of hypotension (orthostatic or not).

g IMP administration should be continued until the day of the CFR assessment by vasodilator PET scan.

h Only for PET scan.

i Based on Investigator's judgement, the patient may be discharged later for safety reasons.

j To be performed 1 to 3 hours after dosing.

2 TABLE OF CONTENTS

1	FLOW CHARTS	9
1.1	GRAPHICAL STUDY DESIGN	9
1.2	POTENTIAL TITRATION SCHEDULES & DECISION RULES STUDY.....	10
1.3	STUDY FLOW CHARTS.....	11
1.3.1	Study flow chart for patients with previous coronary artery angiography or CCTA within 24 months prior to screening	11
1.3.2	Study flow chart for patients diagnosed with MVA and stable angina without previous PCI and with previous coronary artery angiography or CCTA between 24 months and 5 years prior to screening, who need CCTA during screening period	13
1.4	DAY 1 FLOW CHART	16
1.4.1	Flow chart with PET scan on Day 1 (not applicable for patients diagnosed with MVA and stable angina without previous PCI and with previous coronary artery angiography or CCTA between 24 months and 5 years prior to screening, who need CCTA during screening period)	16
1.4.2	Flow chart with PET scan prior to Day 1.....	18
1.5	DAY 29 FLOW CHART SUGGESTED TIME FRAME (CAN BE ADAPTED BY SITE).....	20
2	TABLE OF CONTENTS	22
2.1	LIST OF TABLES.....	27
2.2	LIST OF FIGURES.....	27
3	LIST OF ABBREVIATIONS	28
4	INTRODUCTION AND RATIONALE	30
4.1	GENERAL BACKGROUND	30
4.1.1	Background on patient population	30
4.1.1.1	Patients with persistent angina despite angiographically successful PCI	30
4.1.1.2	Patients with microvascular angina (MVA)	30
4.1.1.3	Pathophysiology and purported beneficial mechanism of Rho-Kinase inhibition:	30
4.2	BACKGROUND ON SAR407899	32
4.3	RATIONALE FOR THE STUDY.....	32
4.4	DESIGN RATIONALE AND RISK ASSESSMENT	32
5	STUDY OBJECTIVES	36
5.1	PRIMARY	36

5.2	SECONDARY	36
6	STUDY DESIGN	37
6.1	DESCRIPTION OF THE STUDY	37
6.2	DURATION OF STUDY PARTICIPATION	37
6.2.1	Duration of study participation for each patient	37
6.2.2	Determination of end of clinical trial (all patients)	37
6.3	INTERIM ANALYSIS.....	37
6.4	STUDY COMMITTEES.....	38
6.4.1	Data Monitoring Committee	38
7	SELECTION OF PATIENTS.....	39
7.1	INCLUSION CRITERIA.....	39
7.2	EXCLUSION CRITERIA	40
7.2.1	Exclusion criteria related to study methodology	40
7.2.2	Additional exclusion criteria during or at the end of screening before randomization	42
8	STUDY TREATMENTS	43
8.1	INVESTIGATIONAL MEDICINAL PRODUCT(S) / NON INVESTIGATIONAL MEDICINAL PRODUCT(S).....	43
8.1.1	INVESTIGATIONAL MEDICINAL PRODUCT(S)	43
8.1.2	NON INVESTIGATIONAL MEDICINAL PRODUCT(S)	44
8.1.2.1	¹³ N-ammonia and ⁸² Rubidium	44
8.1.2.2	Adenosine and regadenoson	44
8.2	BLINDING PROCEDURES.....	44
8.2.1	Methods of blinding	44
8.2.2	Randomization code breaking during the study.....	44
8.3	METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP	45
8.4	PACKAGING AND LABELING	45
8.5	STORAGE CONDITIONS AND SHELF LIFE	46
8.6	RESPONSIBILITIES	46
8.6.1	Treatment accountability and compliance.....	46
8.6.2	Return and/or destruction of treatments	47
8.7	CONCOMITANT MEDICATION.....	47
9	ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT	49

9.1	EFFICACY ENDPOINTS	49
9.1.1	Primary efficacy endpoint.....	49
9.1.2	Secondary efficacy endpoint.....	49
9.1.3	Exploratory endpoints	49
9.1.4	Assessment methods and activity parameters	49
9.1.4.1	¹³ N-ammonia or ⁸² Rubidium PET scan	49
9.1.4.2	Analysis of rest and stress myocardial perfusion PET images	50
9.1.4.3	Angina episodes and short-acting nitrates:.....	51
9.1.4.4	Patient Reported Outcomes.....	51
9.1.4.5	Coronary computed tomography angiography	53
9.2	SAFETY ENDPOINTS	53
9.2.1	Adverse events	53
9.2.2	Physical examination	53
9.2.3	Laboratory safety variables	54
9.2.4	Vital signs	54
9.2.4.1	Technical aspects	54
9.2.4.2	Screening visit (determination of reference arm).....	55
9.2.4.3	Measurements for assessing presence or not of orthostatic hypotension.....	55
9.2.5	Electrocardiogram variables	55
9.3	PHARMACOKINETIC ENDPOINT	56
9.3.1	Pharmacokinetics	56
9.3.1.1	Sampling time	56
9.3.1.2	Pharmacokinetics handling procedure.....	56
9.3.1.3	Bioanalytical method	56
9.3.1.4	Pharmacokinetics parameters	57
9.3.2	Pharmacogenetic assessment.....	57
9.3.2.1	Drug metabolizing enzymes DNA sample	57
9.3.2.2	Optional stored DNA sample	57
9.4	BIOMARKER ENDPOINTS	57
9.4.1	Sampling / handling procedures	58
9.4.2	Biomarker assay methods	58
9.5	FUTURE USE OF SAMPLES FOR BIOMARKER SAMPLES	58
9.6	SAMPLE BLOOD VOLUME.....	59
9.7	APPROPRIATENESS OF MEASUREMENTS	59
10	STUDY PROCEDURES	61
10.1	VISIT SCHEDULE.....	61
10.1.1	Visit 0: Screening visit.....	61

10.1.2	Visit 1: Baseline / Randomization / Day 1	62
10.1.3	Visits 2, 3, and 4: Days 8, 15, and 22 (+/- 2 days).....	65
10.1.4	Visit 5: End of treatment: Day 29 (or up to 2 days after at the latest) even in case of early IMP discontinuation.....	65
10.1.5	Visit 6: End of study: Day 36 (+/- 2 days)	67
10.2	DEFINITION OF SOURCE DATA.....	67
10.3	HANDLING OF PATIENT TEMPORARY OR PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION.....	68
10.3.1	Temporary treatment discontinuation with investigational medicinal product(s)	68
10.3.2	Permanent treatment discontinuation with investigational medicinal product(s)	68
10.3.3	Handling of patients after permanent treatment discontinuation	69
10.3.4	Procedure and consequence for patient withdrawal from study.....	70
10.4	OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING	70
10.4.1	Definitions of adverse events	70
10.4.1.1	Adverse event	70
10.4.1.2	Serious adverse event	71
10.4.1.3	Adverse event of special interest	72
10.4.2	Serious adverse events waived from expedited regulatory reporting to regulatory authorities.....	73
10.4.3	General guidelines for reporting adverse events	73
10.4.4	Instructions for reporting serious adverse events	73
10.4.5	Guidelines for reporting adverse events of special interest.....	74
10.4.6	Guidelines for management of specific laboratory abnormalities	74
10.5	OBLIGATIONS OF THE SPONSOR	75
10.6	SAFETY INSTRUCTIONS	76
10.7	ADVERSE EVENTS MONITORING	76
11	STATISTICAL CONSIDERATIONS	77
11.1	DETERMINATION OF SAMPLE SIZE.....	77
11.2	DISPOSITION OF PATIENTS	77
11.3	ANALYSIS POPULATIONS.....	78
11.3.1	Efficacy populations	78
11.3.1.1	Modified intent-to-treat population	78
11.3.2	Safety population	78
11.3.3	Pharmacokinetic and biomarker analysis population.....	78
11.4	STATISTICAL METHODS	78

11.4.1	Extent of study treatment exposure and compliance	78
11.4.1.1	Extent of investigational medicinal product exposure	78
11.4.1.2	Compliance	79
11.4.2	Analyses of efficacy endpoints	79
11.4.2.1	Analysis of primary efficacy endpoint	79
11.4.2.2	Analyses of secondary efficacy endpoints	80
11.4.2.3	Multiplicity considerations	80
11.4.3	Analyses of safety data	80
11.4.3.1	Adverse events	81
11.4.3.2	Laboratory data	82
11.4.3.3	Potential drug-induced liver injury	82
11.4.3.4	Vital signs data	83
11.4.3.5	Electrocardiogram data	83
11.4.4	Analyses of pharmacokinetic and pharmacodynamic variables	83
11.5	INTERIM ANALYSIS	83
12	ETHICAL AND REGULATORY CONSIDERATIONS	84
12.1	ETHICAL AND REGULATORY STANDARDS	84
12.2	INFORMED CONSENT	84
12.3	HEALTH AUTHORITIES AND INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)	84
13	STUDY MONITORING	86
13.1	RESPONSIBILITIES OF THE INVESTIGATOR(S)	86
13.2	RESPONSIBILITIES OF THE SPONSOR	86
13.3	USE AND COMPLETION OF CASE REPORT FORMS (CRFS) AND ADDITIONAL REQUEST	87
13.4	USE OF COMPUTERIZED SYSTEMS	87
14	ADDITIONAL REQUIREMENTS	88
14.1	CURRICULUM VITAE	88
14.2	RECORD RETENTION IN STUDY SITES	88
14.3	CONFIDENTIALITY	88
14.4	PROPERTY RIGHTS	89
14.5	DATA PROTECTION	89
14.6	INSURANCE COMPENSATION	89

14.7	SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES	90
14.8	PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE	90
14.8.1	By the Sponsor.....	90
14.8.2	By the Investigator	91
14.9	CLINICAL TRIAL RESULTS	91
14.10	PUBLICATIONS AND COMMUNICATIONS	91
15	CLINICAL TRIAL PROTOCOL AMENDMENTS	92
16	BIBLIOGRAPHIC REFERENCES.....	93
17	APPENDICES.....	96
APPENDIX A	GENERAL GUIDANCE FOR THE FOLLOW-UP OF LABORATORY ABNORMALITIES BY SANOFI.....	97
APPENDIX B	PROCEDURE FOR COLLECTION, HANDLING, STORAGE, AND SHIPMENT OF SAR407899 SPECIMENS FOR PHARMACOGENETIC SAMPLES.....	102
APPENDIX C	PATIENT REPORTED OUTCOMES	105

2.1 LIST OF TABLES

Table 1 - Summary of sampling/handling procedures for [REDACTED]	58
Table 2 - Summary of sampling/handling procedures for [REDACTED]	58
Table 3 - Summary of sampling/handling procedures for future use of samples.....	58
Table 4 - Sampled blood volume.....	59
Table 5 - Summary of adverse event reporting instructions.....	75

2.2 LIST OF FIGURES

Figure 1 - Rho kinase pathway.....	31
------------------------------------	----

3 LIST OF ABBREVIATIONS

ACS:	acute coronary syndrome
AE:	adverse event
AESI:	adverse event of special interest
AV:	atrioventricular
BP:	blood pressure
CABG:	coronary artery bypass grafting
CAD:	coronary artery disease
CCBs:	calcium channel blockers
CCTA:	coronary computed tomography angiography
CFR:	coronary flow reserve
CVR:	coronary vascular resistance
DBTP:	double blind treatment package
DMC:	data monitoring committee
eGFR:	estimated glomerular filtration rate
eNOS:	endothelial nitric oxide synthase
FFR:	fractional flow reserve
FSH:	follicle stimulating hormone
HRT:	hormonal replacement therapy
IAG:	imaging acquisition guidelines
IEC:	independent ethics committee
iFR:	instantaneous wave-free ratio
IMP:	investigational medicinal product
IRB:	institutional review board
IRT:	interactive response technology
LAD:	left anterior descending
LCX:	left circumflex
LV:	left ventricle
LVEF:	left ventricular ejection fraction
MAPK:	mitogen-activated protein kinases
MBF:	myocardial blood flow
MI:	myocardial infarction
mL:	milliliter
NIMP:	non investigational medicinal product
OCT2:	organic cation transporter-2
PCI:	percutaneous coronary intervention
RCA:	right coronary artery
[REDACTED]	[REDACTED]
SAE:	serious adverse event
SBP:	systolic blood pressure
TEAE:	treatment-emergent adverse events

TIA: transient ischemic attack
TPD: total perfusion deficit

4 INTRODUCTION AND RATIONALE

4.1 GENERAL BACKGROUND

4.1.1 Background on patient population

Patients who have microvascular dysfunction as demonstrated by a reduced CFR in the absence of obstructive CAD and who continue to have angina pectoris are an important group of patients with high unmet medical need as there is no currently approved specific pharmacologic therapy.

4.1.1.1 Patients with persistent angina despite angiographically successful PCI

Coronary revascularization procedures by means of PCI are performed routinely for the symptomatic treatment of patients with myocardial ischemia. Percutaneous coronary intervention has not been shown to reduce mortality in patients with stable CAD. Data from large trials investigating the use of PCI in patients with stable CAD show that angina is still experienced in a large number of patients one year after the procedure and that this proportion increases over time. In a select group of these patients who have no current obstructive CAD but with evidence of myocardial ischemia, are thought to be due coronary microvascular dysfunction as a possible cause of persistent stable angina (2, 3).

4.1.1.2 Patients with microvascular angina (MVA)

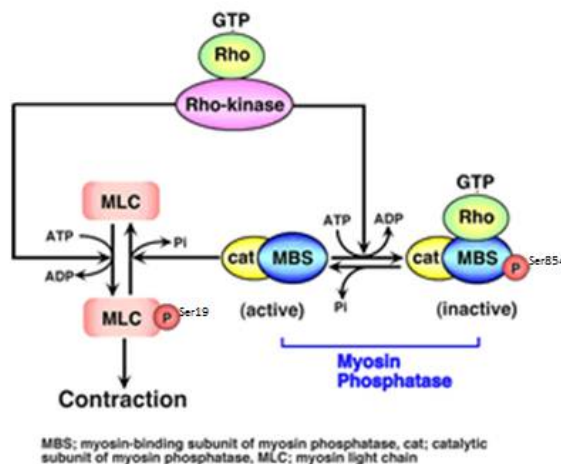
Patients who present with angina and a positive noninvasive test may undergo a diagnostic coronary angiography. The yield of elective coronary angiography in such patients is unsatisfactory with no coronary artery disease (defined as <20% stenosis in all vessels) reported in close to 40% of the patients (4). Amongst them a significant proportion of patients have coronary microvascular dysfunction (CMD), a disease that affects the walls and inner lining of tiny coronary artery blood vessels that branch off from the larger coronary arteries (5). Accordingly, this type of angina is categorized as microvascular angina (MVA). Irrespective of the degree of coronary artery disease, higher angina episodes frequencies are associated with lower physical functioning, quality of life (QoL) (6), angina stability, treatment satisfaction and higher prevalence of anxiety and depression, hospital re-admission (7, 8) and repeat coronary angiography (9).

4.1.1.3 Pathophysiology and purported beneficial mechanism of Rho-Kinase inhibition:

Abnormalities in vascular smooth muscle cell (VSMC) as well as vascular endothelial cells in the heart's smallest arterioles have been widely discussed as major contributor in the pathophysiology of MVA (10, 11). The finding that a reduced coronary blood flow response to direct arteriolar dilator agents like adenosine, dipyridamole or papaverine has been shown in patients with angina pectoris and normal coronary angiograms suggests abnormalities of smooth muscle cell relaxation in MVA (12, 13, 14). In addition, an impairment of endothelium-dependent coronary microvascular dilation is also described in patients with MVA (13, 14, 15).

Physiologic levels of rho-kinase activity are important for vascular homeostasis, whereas on the opposite, enhanced rho-kinase activity could causes vascular diseases through VSMC hypercontractility/proliferation, endothelial cell damage and promotion of pro-inflammatory pathways (16).

Figure 1 - Rho kinase pathway



Myosin-binding subunit myosin light chain phosphatase (MBS) is one of the major endogenous substrates for Rho-kinase, and its phosphorylation is acknowledged as a marker for Rho-kinase activity in various tissues including kidney (17), vasculature (18) and cardiac tissue (19). Thus using a pMBS/totMBS, a statistically significant 1.5-fold higher Rho kinase activity was considered in circulating neutrophils of patients with pulmonary arterial hypertension (PAH) compared to healthy controls (20) and a 1.9-fold higher activity in patients with cardiovascular diseases compared healthy controls (21). Moreover, a statistically significant reduction from baseline of pMBS/totMBS ratio was observed in patients with vasospastic angina after treatment with CCBs (22).

SAR407899 is a potent ATP-competitive rho-kinase inhibitor (23) and has, based on this MoA, the potential to improve patient conditions with MVA through endothelium dependent [prevention of ROCK induced inhibition of endothelial nitric oxide synthase (eNOS) expression] and endothelium independent effects (prevention of hypervasoconstriction) (24). Such beneficial effects could therefore potentially lead to an improvement in symptoms and quality of life, and a decreased burden of CV procedures/hospitalization for patients with microvascular dysfunction and/or non-obstructive coronary artery disease.

Based on the above described patient needs and the therapeutic potential of SAR407899, patients with microvascular angina and/or persistent angina despite successful PCI will be evaluated in the POC-study ACT14656.

4.2 BACKGROUND ON SAR407899

SAR407899 is an inhibitor of Rho kinase (ROCK), a broadly expressed serine/threonine protein kinase.

SAR407899 has already been studied in healthy adult volunteers, healthy elderly subjects, patients with chronic kidney disease (CKD) and patients with erectile dysfunction. Although SAR407899 was generally well-tolerated, dose-related symptomatic orthostatic hypotension occurred in some subjects, primarily after administration of the first dose, and particularly in patients who had renal dysfunction and who were treated with concomitant anti-hypertensive drugs. Orthostatic hypotension is considered to be a mechanism-related effect and will be mitigated in the current study by using an individual dose titration approach. In healthy young subjects, a few cases of serum creatinine increase >30% were observed however the values remain within normal range. This effect was not observed in elderly subjects or in patients with CKD.

4.3 RATIONALE FOR THE STUDY

This study will evaluate SAR407899 compared with placebo in a population of patients with microvascular angina and/or persistent angina despite angiographically successful PCI (typical or atypical symptoms of angina pectoris), non-obstructive (<50% stenosis) coronary arteries on angiogram or intermediate stenosis with FFR >0.80 or iFR >0.89, and microvascular dysfunction documented by a global CFR <2.0 measured by PET. Angiographically successful balloon angioplasty with a reduction of a minimum stenosis diameter to <50% or for coronary stents a minimum diameter stenosis of <10%, with a final TIMI flow Grade 3 (visually assessed by angiography) without side branch loss, flow-limiting dissection, distal embolization, or angiographic thrombus.

This study will assess whether SAR407899 improves PET scan global CFR (25) before and after administration of a pharmacologic stressor (ie, vasodilator). 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. Assessment of patient-reported outcome using the Seattle Angina Questionnaire physical limitation scale (SAQ-PL) due to its sensitivity will be used as secondary endpoint.

Change in angina episodes and short-acting nitrate intakes will be collected in the patient's diary.

4.4 DESIGN RATIONALE AND RISK ASSESSMENT

- This study will be placebo-controlled as no treatment is currently approved in the population with microvascular angina and/or persistent stable angina despite angiographically successful PCI. The drug will be tested on top of standard treatments for angina excluding nitrates (except short-acting nitrates) and PDE 5 inhibitors that should be discontinued at least one week before baseline PET assessment and not used during the study in order to avoid masking the effects of SAR407899 while increasing the risk of orthostatic hypotension.
- Beta-blockers act directly on the heart to reduce heart rate, contractility, AV conduction and ectopic activity. Additionally, they may increase perfusion of ischemic areas by

prolonging the diastole and increasing vascular resistance in non-ischemic areas this is why beta-blockers are currently first-line anti-anginal therapy in stable CAD patients without contraindications according to ESC 2013 guidelines on stable CAD (26). Hence, beta-blockers should be kept at the same dose, as it could potentially impact the assessment of efficacy.

- SAR407899 will be administered in the morning and at bedtime. As no relevant food-effect was demonstrated, dose may be taken with or without food as per preference of the patient. Twice a day (BID) regimen has been chosen in order to minimize peak concentration effects while maintaining sufficient trough levels.
- Decrease in BP (hypotension, orthostatic dysregulation) is considered as a mechanism-related effect and will be mitigated by using a dose titration approach.

[REDACTED]

A safety review will be performed by the DMC when 19 patients will have completed the first week of treatment. The DMC will review the clinical safety data including AESIs. During the safety evaluation of the first 19 enrolled patients, these patients will continue to receive IMPs as per the titration schedule described above and enrolment will continue.

- If patient does not tolerate a dose level due to hypotension, symptomatic orthostatic hypotension with SBP decrease ≥ 20 mmHg, at Minute 3 or Minute 5 after changing position from seated to standing, the investigator will decrease the dose level of the investigational product to the previous tolerated dose level for the remaining duration of the study.
- Overall, the exposure to the study drug should last for 4 weeks in total (3 weeks for the titration phase and 1 week for the maintenance phase) for all patients. Patients will be followed one week after the end of the study treatment to collect any potential AEs during the washout period.
- Serum creatinine will be monitored. Creatinine is filtered in glomerulus and also partly eliminated in urine via an active secretion mediated by organic cation transporter-2 (OCT2). These observed increases in adults could then possibly be explained by inhibition of its active secretion by SAR407899 which is a weak in vitro OCT2 inhibitor. Serum cystatin C, which is filtered in glomerulus but not subject to tubular secretion, will be measured in parallel to serum creatinine to assess glomerular filtration rate.

Specific parameters rationale

Primary endpoint:

- **Coronary flow reserve (CFR)**, represents blood flow to the myocardium; the critical factor in angina. It is the endpoint with the most abundant clinical data in MVA patients. CFR is the ratio of the maximal myocardial blood flow (MBF) after a hyperemic stimulus (such as intravenous adenosine injection) to baseline resting blood flow. In patients with

normal endothelial function, adenosine increases MBF by a factor of 2.5 or more while in patients with endothelial dysfunction the increase is less than 2.0 (27).

Secondary endpoints:

- **The Seattle Angina Questionnaire (SAQ) (28)** was used in pilot MVA studies. It is currently used in clinical trials in MVA populations for ranolazine and thus provided a basis for statistical calculations. The SAQ is a self-report instrument with 19 items designed to quantify the physical and emotional effects of coronary artery disease. The questionnaire has a 4-week recall period. It yields five dimensions, each scored separately: physical limitation, angina stability, angina frequency, treatment satisfaction, and disease perception. A SAQ-7 summary score can also be derived using 7 items from the physical limitation, angina frequency and disease perception domains. The physical limitation (SAQ-PL) dimension is the most relevant for defining treatment benefit in this trial and was thus specified as a secondary objective. The SAQ-PL dimension measures how common daily activities representing low, medium, and high exertional requirements are limited by angina (9 items). It is scored by assigning each response an ordinal value, beginning with 1 for the response that implies the lowest level of functioning, and summing across the 9 items. The score is 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 possible range of scores is therefore 0 to 100, with higher scores better. A change of 10 points is considered to be clinically important.
- **Safety** will be assessed during the whole study on adverse events with a special focus on BP, laboratory data and renal function.

Exploratory endpoints:

Assessment of angina episodes with or without short-acting nitrate intakes

Angina episodes and short-acting nitrate intakes collected by the patients in a diary will be measured. This will allow assessing the number of angina episodes (and their severity).

Assessment of other dimensions of the SAQ and SAQ-7 score (29)

The SAQ yields five dimensions, each scored separately: physical limitation, angina stability, angina frequency, treatment satisfaction, and disease perception. All the dimensions except SAQ-PL will be assessed.

The SAQ-7 summary score can also be derived using 7 items from the physical limitation, angina frequency and disease perception domains.

Assessment of patient's perceptions of treatment and symptoms

The patient qualitative self-assessment aims to better understand the patient's views on their treatment and symptoms at baseline and at the end of the study. Three questions assessing the patient's perception will be asked and a free-text box will be provided for patients to give qualitative answers. This assessment should take between 5-10 minutes, and the text will later be

analyzed using qualitative data analysis software to perform content analysis using text mining. The patient will be asked to complete these three questions. The questions are:

- Day 1 and at the end of treatment visit/permanent treatment discontinuation or Day 29: “Please think back over the **past week**. In your own words, please describe the symptoms you have experienced because of your **angina without obstructive coronary artery disease**.”
- End of treatment visit/permanent treatment discontinuation or Day 29 only: “Please think about the study you have been part of. In your own words, please list the pros and cons of study treatment”.
- End of treatment visit/permanent treatment discontinuation or Day 29 only: “Please give your overall thoughts on the study treatment you have received as part of this study”.

[REDACTED]

[REDACTED]

[REDACTED]

5 STUDY OBJECTIVES

5.1 PRIMARY

- Assess the effects of SAR407899 on coronary vasomotor function using CFR in patients with microvascular angina and/or persistent stable angina despite angiographically successful PCI.

5.2 SECONDARY

- Assess the effects of SAR407899 in patients with microvascular angina and/or persistent stable angina despite angiographically successful PCI using SAQ-PL.
- Assess the safety of SAR407899 in patients with microvascular angina and/or persistent stable angina despite angiographically successful PCI with a focus on identified risks such as hypotension and orthostatic hypotension.
- Assess SAR407899 plasma concentrations in microvascular angina patients and/or persistent stable angina despite angiographically successful PCI.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

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 BP decreases.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

- Screening: up to 4 weeks before the first dosing (Day -28 to Day -1) and up to 6 weeks in patients diagnosed with MVA and stable angina without previous PCI who did not have a coronary artery angiography or CCTA in the previous 24 months but between 24 months and 5 years prior to screening and requiring CCTA in this screening period.
- Titration phase: 3 weeks.
- Maintenance phase: 1 week.
- Total duration of treatment: 4 weeks (including titration).
- Follow-up: 1 week.
- Total study duration: 9 weeks (± 2 days) and up to 11 weeks (± 2 days) in patients requiring CCTA in screening period.

6.2.2 Determination of end of clinical trial (all patients)

The end of the clinical trial is defined as the day when the last patient completes her/his last visit planned in the protocol.

6.3 INTERIM ANALYSIS

A safety review with a DMC meeting will start as soon as the first 19 patients will have been randomized and have finished the first week of treatment. Additional analyses for safety may be performed in this study.

Refer to [Section 11.5](#) and to [Section 6.4.1](#) for details on interim analyses.

6.4 STUDY COMMITTEES

6.4.1 Data Monitoring Committee

A Data Monitoring Committee (DMC) will be charged with monitoring the safety of the patients participating in this clinical trial. This committee is comprised of externally-based individuals with expertise in the diseases under study, biostatistics, or clinical research. The DMC will review all serious adverse events (SAEs), death, and adverse events of special interest (AESIs), in due time. The DMC will give appropriate recommendations to the Sponsor on safety aspects during the conduct of the study, if needed. The DMC is justified by the early stage of development of SAR407899 that has not gathered safety information in patients with microvascular angina or persistent angina despite angiographically successful PCI and the identified risk of hypotension. The DMC responsibilities and the data review processes are fully described in the DMC charter that will be developed prior to study start.

In the above capacities, the DMC is advisory to the Sponsor. The Sponsor is responsible for promptly reviewing and for taking into account in a timely manner the recommendations of the DMC in terms of trial continuation with or without alterations or of potential trial termination.

Following DMC review of the safety data (of the first 19 patients who will have completed first week after randomization) and their recommendations, the Sponsor may have to adjust titration schedules and dosing regimen.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

- I 01. MVA and/or persistent stable angina despite angiographically successful PCI male or female patients with:
- A) Male and female patients not at childbearing potential ≥ 18 year-old or legal age of majority.
 - B) 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 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.
 - C) Symptomatic stable angina pectoris (typical or atypical symptoms with an average of at least bi-weekly episodes over the past month).
 - D) Patients with non-obstructive (<50% stenosis) coronary arteries or intermediate stenosis (between 50 and 70%) should have FFR >0.80 or iFR >0.89 on angiogram, documented within the previous 24 months*. In patients with stenting, a minimum diameter stenosis of <10% is required.
or
Coronary computed tomography angiography with finding of non-obstructive coronary arteries within the past 24 months* in patients without previous PCI.

*Note: in cases of clinically suspected progression of atherosclerosis as per the Investigator, a more contemporary (i.e., 6 months) evidence should be provided.
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 .
 - E) Baseline global CFR (measured during the study) assessed by ^{13}N -ammonia or $^{82}\text{Rubidium}$ PET scan <2.0.
- I 02. Signed written informed consent.
- I 03. Not under any administrative or legal supervision.

7.2 EXCLUSION CRITERIA

Patients who have met all the above inclusion criteria listed in [Section 7.1](#) will be screened for the following exclusion criteria which are sorted and numbered in the following 4 subsections:

7.2.1 Exclusion criteria related to study methodology

- E 01. Any patient who, in the judgment of the Investigator, is likely to be noncompliant during the study, or unable to cooperate because of a language problem or poor mental development, or cannot be contacted in case of emergency.
- E 02. Patient who has taken other investigational drugs or SAR407899 for this study within 3 months or 5 half-lives from screening or randomization, whichever is longer.
- E 03. Any use of nitrates (except short-acting nitrates) and/or dipyridamole and/or PDE 5 inhibitors within one week prior to baseline PET scan or anticipated to be used during the study.
- E 04. Conditions/situations such as:
- Patients with a short life expectancy (including heart failure New York Heart Association [NYHA] III or IV).
 - Presence or history of drug hypersensitivity that in the opinion of the investigator would compromise patient's safety.
 - Any history or presence of clinically relevant pulmonary, gastrointestinal, hepatic, renal, metabolic, hematological, neurological, osteomuscular, articular, psychiatric, systemic, ocular, gynecologic (if female), or infectious disease, or signs of acute illness that according to Investigator's judgment, would adversely affect the patient's participation in the study.
- E 05. Esophageal dysmotility or esophagitis.
- E 06. Patients with acute coronary syndrome (ACS) (MI and/or unstable angina) in previous 3 months.
- E 07. Unsuccessful or incomplete coronary revascularization with residual obstructive stenosis or coronary artery disease progression in native vessels as documented on invasive coronary angiography ($\geq 50\%$ stenosis) within 24 months of enrollment.
- E 08. Percutaneous coronary intervention performed at the time of an ACS (MI or unstable angina) in the previous 12 months.
- E 09. Recent PCI within the past 3 months.
- E 10. Patients with history of coronary artery bypass grafting (CABG).
- E 11. Recent (≤ 3 months) major surgery (ie, valvular surgery, surgery for congenital heart disease), stroke, TIA, sustained ventricular arrhythmia, clinically significant structural heart disease (moderate-severe valvular disease, hypertrophic cardiomyopathy, congenital heart disease, pulmonary hypertension).

- E 12. Regional local flow abnormal perfusion defects at baseline PET scan*.
- *Note: if contemporary evidence with invasive coronary angiography or CCTA demonstrates non-obstructive coronary arteries or if the regional local flow abnormal perfusion defect on PET scan is consistent with previous studies then patient qualifies for the study.
- E 13. Patients with cardiac conduction abnormalities (second or third degree AV block, sick sinus syndrome, symptomatic bradycardia, sinus node disease) except in patients fitted with a functioning pacemaker.
- E 14. History or known carotid stenosis:
- Carotid stenosis (>50%)
 - or
 - History of carotid stenosis in patients with previous symptoms.
- E 15. Contraindication or known hypersensitivity to adenosine or regadenoson.
- E 16. Contraindication to aminophylline.
- E 17. Contraindication to vasodilator stress PET scan and/or CCTA if CCTA needed during screening.
- E 18. Inability to discontinue treatment with methylxanthines treatment within 24 hours prior to PET scan.
- E 19. Patient unable to read, understand and fill a questionnaire without any help (eg, partially visually impaired or blind).
- E 20. Blood donation (blood volume to be defined if needed depending on the country), any volume, within 2 months before inclusion (duration to be checked according to local regulations).
- E 21. Impossibility to meet specific protocol requirements.
- E 22. Patient is the Investigator or any Sub-investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol.
- E 23. SBP <110 mmHg at baseline.
- E 24. Presence at baseline of **symptomatic** orthostatic hypotension (SBP decrease of 20 mmHg or more at Minute 3 or 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 or Minute 5 when changing from the seated to the standing position.
- E 25. Renal impairment with estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m² at screening and baseline.
- E 26. Male patient having a female partner of childbearing potential not protected by highly-effective method(s) of birth control (as defined in a local protocol amendment in case of specific local requirement).
- E 27. Women who are breast feeding.

E 28. Drug-induced liver injury related criteria:

- Underlying hepatobiliary disease.
- ALT >3 times the upper limit of normal (ULN).

7.2.2 Additional exclusion criteria during or at the end of screening before randomization

E 29. Patient who has withdrawn consent before randomization (starting from signed informed consent form).

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S) / NON INVESTIGATIONAL MEDICINAL PRODUCT(S)

8.1.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

Investigational medicinal products:

- SAR407899, 2.5 mg and 5 mg capsules.
- SAR407899 matching placebo.

Formulation: Capsules.

Route and method of administration: Oral administration, twice per day, in the morning and at bedtime, with or without a meal.

Dose regimen: 2 capsules in the morning and at bedtime. Dose may be taken with or without food as per preference of the patient.

Starting dose: [REDACTED].

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

Stopping criterion based on creatinine level:

- Stop study drug if creatinine level >150 µmol/L and increase from baseline >30%. In specific circumstances where creatinine blood level can be obtained only in the afternoon the day of the visit, the patient will be titrated according to titration scheme and if creatinine blood level meets stopping rules, the investigator will need to contact the patient before bedtime intake to permanently discontinue the study drug and schedule a premature study drug discontinuation visit.

[REDACTED]

When 19 patients will have completed first week of treatment, the DMC will review the clinical safety data. During the safety evaluation of the first 19 enrolled patients, these patients will continue to receive IMPs as per the titration schedule described above and enrolment will continue.

Dosing of SAR407899 is limited to 31 days.

8.1.2 NON INVESTIGATIONAL MEDICINAL PRODUCT(S)

The following classes of drugs are identified as non-investigational medicinal products (NIMP) because the medications are used to assess the primary endpoint of the study:

- PET radiopharmaceuticals (¹³N-ammonia and ⁸²Rubidium).
- Vasodilator stressors (adenosine and regadenoson).

The NIMPs should be used according to their approved labeling.

8.1.2.1 ¹³N-ammonia and ⁸²Rubidium

¹³N-ammonia and ⁸²Rubidium are PET radiopharmaceuticals. These NIMPs are administered to the patients to assess their primary endpoint using PET scan.

8.1.2.2 Adenosine and regadenoson

Adenosine and regadenoson are vasodilator stressors. These NIMPs are given to the patient to assess the primary endpoint using PET scan.

8.2 BLINDING PROCEDURES

8.2.1 Methods of blinding

For the double blind treatment package (DBTP), each double-blind SAR407899 treatment kit, either SAR407899 or placebo for SAR407899, will be prepared to contain 1 weekly (7 days +2 extra days) “child resistant” wallet of 36 capsules in each. In order to protect the blind, all SAR407899 double-blind treatment kit boxes (SAR407899 whatever the dose or Placebo for SAR407899) will have the same look and feel (identical capsules, same amount of capsules whatever the dose, packaging) and therefore will be labeled with a double-blind label.

8.2.2 Randomization code breaking during the study

In case of an adverse event (AE), the code should only be broken in circumstances when knowledge of the investigational medicinal product (IMP) is required for treating the patient.

If possible, a contact should be initiated with the Sponsor's monitoring team or medical expert before breaking the code.

Code breaking can be performed at any time by using the proper module of the interactive response technology (IRT) and/or by calling any other phone number provided by the Sponsor for that purpose. If the blind is broken, the Investigator should document the date, time of the day and the reason for code breaking.

If the code is broken, the patient must discontinue IMP administration but he/she continues the study.

Refer to [Section 10.5](#) for suspected unexpected serious adverse drug reaction requiring unblinding by the Sponsor.

8.3 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

At the screening visit, patients who will sign the informed consent form will be assigned an incremental subject number according to chronological order. The subject number remains unchanged during the study and allows the patient to be identified during the whole study. Stratification on the presence of angiographically successful PCI (YES/NO) will be performed.

The randomized treatment kit number list is generated centrally by Sanofi.

The IMPs are packaged in accordance with this list. The randomization and the treatment allocation (1:1) are performed centrally by an interactive voice/web response system (IVRS/IWRS). The IVRS/IWRS allocates treatment kits to the patient according to a prespecified randomization list, generated by the company in charge of the IVRS/IWRS.

A patient is considered as randomized as soon as the IVRS/IWRS has assigned a patient to active or placebo and indicated a treatment kit to be allocated to the patient, regardless whether the treatment kit was used or not (ie, patient registered by the IVRS/IWRS).

A patient cannot be randomized more than once in the study.

- All screening-failed patients will be entered in database with their subject number allocated at screening.

8.4 PACKAGING AND LABELING

For the double-blind treatment package (DBTP), each double-blind SAR407899 treatment kit, containing either SAR407899 or matching placebo, will be prepared to contain 1 weekly (7 days +2 extra days) "child resistant" wallets of 36 capsules in each.

In order to protect the blind, all SAR407899 double-blind treatment kit boxes (*SAR407899 whatever the dose or Placebo for SAR407899*) will have the same look and feel and therefore will be labeled with a double-blind label.

Packaging is in accordance with the administration schedule. One kit will be dispensed for first week of treatment. Then several kits will be dispensed according to the number of treatment weeks.

The content of the labeling is in accordance with the local regulatory specifications and requirements.

8.5 STORAGE CONDITIONS AND SHELF LIFE

The SAR407899 and Placebo kits will be stored at ambient temperature by the site. The temperature of the site storage room should be checked at least daily and recorded on a log sheet.

The IMP that will be stored at the investigational site should be kept in an appropriate locked room, under the responsibility of the Investigator or designee.

8.6 RESPONSIBILITIES

The Investigator, the hospital pharmacist, or other personnel allowed to store and dispense the IMP will be responsible for ensuring that the IMP used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements.

All IMPs will be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of IMP issued and returned is maintained.

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) should be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure.

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall the IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

8.6.1 Treatment accountability and compliance

Compliance of IMP:

- The first IMP intake (morning dosing) of each on-site visit will be performed under direct medical supervision at each on site visit.
- The Investigator or designee records the dosing information on the appropriate page(s) of the case report form.

- The investigator keeps all used/ unused IMPs for monitoring purposes until notice by the Sponsor is given to destroy them.
- Compliance will be checked by the investigator or designee, through patient's interview and counting of capsules returned by the patient at each study visit versus the number of capsules dispensed at the previous visit.

IMP accountability:

- Treatment units are returned by the patient at each visit.
- The Investigator or designee counts the number of capsules remaining in the returned treatment kits, and fills in the Treatment Log Form.
- The monitoring team in charge of the study then checks the CRF data by comparing them with the IMP which he/she has retrieved and treatment log forms.

8.6.2 Return and/or destruction of treatments

Investigational medicinal product reconciliation must be performed on a daily basis at the site by the Investigator and the monitoring team using treatment log forms and documented on center IMP inventory countersigned by the Investigator and the monitoring team.

A written authorization for destruction will be given by the clinical trial team once the IMP reconciliation is achieved. This destruction can be performed at site depending on IMP specificities and local requirements or IMP can be returned to the Sponsor for destruction if kits destruction on site is not authorized.

8.7 CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the patient concomitantly to any IMP(s).

An accurate record of all prescription medications must be kept on the appropriate record form, including the name of the medication (international nonproprietary name), start of administration, daily dosage, and duration for such use.

Prohibited medication:

- Nitrates (except short-acting nitrates) should not be used at least one week before screening PET scan and during the study as they may mask the vasodilating effects of SAR407899 and could increase the risk of hypotension and orthostatic hypotension.
- Phosphodiesterase type 5 (PDE5) inhibitors should not be used at least one week before screening PET scan and during the study as they may mask the vasodilating effects of SAR407899 and could increase the risk of hypotension and orthostatic hypotension.
- Dipyridamole should not be used at least one week before screening PET scan and during the study as its use is associated with a drug interaction with the vasodilator stressor that is utilized during the PET assessment.

Authorized concomitant medication:

- Beta-blockers administered at the recommended dosage for at least four weeks prior to the randomization (baseline). No change is permitted unless the patient develops an AE or based on the investigator's judgment. Dose and any change will be recorded on the patient e-CRF. Beta-blockers cannot be started during the course of the study.
- Calcium channel blockers (CCBs) administered at the recommended dosage for at least four weeks prior to the randomization (baseline). No change is permitted unless the patient develops an AE or based on the investigator's judgment. Dose and any change will be recorded on the patient e-CRF. CCBs cannot be started during the course of the study.
- Short-acting nitrates intakes are authorized as rescue medication at the recommended dosage. The use of this medication should be reported in e-CRF.
- Any other standard treatments at the recommended dosage for at least one week prior to the randomization (baseline). No change is permitted unless the patient develops an AE. Dose and any change will be recorded on the patient e-CRF.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 EFFICACY ENDPOINTS

9.1.1 Primary efficacy endpoint

- Change from baseline to Week 4 in uncorrected global CFR assessed by ¹³N-ammonia or ⁸²Rubidium PET scan.

9.1.2 Secondary efficacy endpoint

- Change from baseline to Week 4 in physical limitation as assessed by SAQ-PL.

9.1.3 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.
- [REDACTED]

9.1.4 Assessment methods and activity parameters

9.1.4.1 ¹³N-ammonia or ⁸²Rubidium PET scan

Coronary Flow Reserve is assessed by PET scan in the morning at baseline (Day 1 or up to 14 days prior to first day of study drug administration and up to 4 weeks before in patients diagnosed with MVA and stable angina without previous PCI and whose coronary angiogram or CCTA was not performed in the previous 24 months but between 24 months to 5 years) and end of treatment Day 29 visit (or up to Day 31), approximately one or two hours after last IMP intake.

PET scan CFR procedure is described hereafter. Details on the procedure are contained in the imaging acquisition guidelines (IAG).

9.1.4.1.1 Positron emission tomography (PET):

Regional and global MBF will be assessed using PET imaging in accordance with the study-specific acquisition protocol (see IAG). PET scans will be performed using a whole body PET scanner.

Anti-hypertensives, beta-blockers and calcium channel blockers will be withheld 24 hours prior to

PET scan. Patients will be allowed to continue using sublingual nitroglycerin as needed. Studies will be performed after 4 hours of fasting and 24 hours of abstinence from caffeine-containing products. The PET scan will take approximately 2.5 hours, including patient preparation.

Myocardial blood flow (MBF) will be measured at rest and during maximal hyperemia using adenosine or regadenoson infusion, and using ^{13}N -ammonia or ^{82}Rb as the flow tracer. After transmission imaging and beginning with the intravenous (IV) administration of the flow tracer, list mode images are acquired. Then, patients will undergo a standard infusion of adenosine or bolus injection regadenoson. At peak hyperemia, a second dose of the flow tracer will be injected IV, and images recorded in the same manner. The heart rate, BP, and 12-lead ECG will be recorded at baseline and throughout the infusion of adenosine or regadenoson, and at recovery. All PET scans will be done for research (non-clinical) purposes only. For safety reasons, all PET scans will be reviewed at the sites by site investigators for clinically important findings. No reports or analyses will be provided to sites from the PET core laboratory and studies will not be assessed in real-time.

9.1.4.1.2 Risks and discomforts from the PET scans

The risks and discomforts to the patients associated with the PET scan include those associated with administration of the vasodilator and potentially aminophylline that may be utilized to reverse the side effects due to vasodilator administration. Also, there are radiation risks related to the procedure and the radioactive flow tracers. These risks are detailed in the patient consent form.

9.1.4.2 Analysis of rest and stress myocardial perfusion PET images

A complete analysis of rest and stress myocardial perfusion PET images will be performed. It will include:

- Quantitative analysis of all PET studies will be performed at the central core laboratory. The following analyses will be performed:
- Semi-Quantitative Analysis:
 1. Total Perfusion Deficit (TPD): it measures the total left ventricular perfusion deficit at rest (reflecting scarred myocardium) and during stress (reflecting both scarred + ischemic myocardium), as well as the difference between stress and rest (reflecting ischemic myocardium). TPD scores will be processed using standard software (CSI software, Cedars Sinai Medical Center, Los Angeles, CA).
 2. For each patient, the following variables will be obtained at baseline and during the follow-up scans:
 1. Rest TPD
 2. Stress TPD
 3. Difference TPD
- Quantification of left ventricular function: rest and post-stress left ventricular ejection fraction (LVEF) will be calculated from the gated myocardial perfusion images using

commercially available software (Corridor4DM, INVIA Medical Imaging Solutions, Ann Arbor, MI).

For each patient, the following variables will be obtained at baseline and during the follow-up scans: (1) rest LVEF, and (2) post-stress LVEF

- Quantification of myocardial blood flow and CFR: Absolute myocardial blood flow (MBF, in mL/g/min) will be computed from the dynamic rest and stress imaging series using commercially available software (Corridor4DM; Ann Arbor, MI) and previously validated methods (30, 31, 32). Automated regions of interest will be used to generate blood pool (arterial input function) and tissue time-activity curves. A validated 2-compartment tracer kinetic model for ¹³N-ammonia or ⁸²Rubidium will be used to quantify absolute MBF at rest and during peak hyperemic-stress. Per-patient regional and global CFR will be calculated as the ratio of absolute MBF at stress over that at rest. Finally, a regional and global index of coronary vascular resistance (CVR) will be generated by dividing the mean arterial pressure by MBF (both at rest and during peak hyperemic-stress).

For each patient, the following variables will be obtained at baseline and during the follow-up scans:

1. Rest MBF: individual values will be obtained for each of the coronary vascular territories (left anterior descending, LAD; left circumflex, LCX; and right coronary artery, RCA) and also for the entire LV (global rest MBF).
2. Peak hyperemic-stress MBF: individual values will be obtained for each of the coronary vascular territories (LAD, LCX, and RCA) and also for the entire LV (global stress MBF).
3. Coronary flow reserve (CFR): individual values will be obtained for each of the coronary vascular territories (LAD, LCX, and RCA) and also for the entire LV (global CFR).
4. Rest CVR: individual values will be obtained for each of the coronary vascular territories (LAD, LCX, and RCA) and also for the entire left ventricle, LV (global rest CVR).
5. Peak hyperemic-stress CVR: individual values will be obtained for each of the coronary vascular territories (LAD, LCX, and RCA) and also for the entire LV (global stress CVR).

9.1.4.3 Angina episodes and short-acting nitrates:

A diary is provided to the patient to collect the number and severity (requiring short-acting nitrate intakes) of angina episodes that he/ she will experience in between site's visits. This patient's diary will be reviewed by the investigator or designee at each on-site visit.

9.1.4.4 Patient Reported Outcomes

- Change from baseline to end of study treatment/Week 4 in the other dimensions of the SAQ (see [Appendix C](#)).
- Change from baseline to end of study treatment/Week 4 in the SAQ-7 score.

- Change from baseline to end of study treatment/Week 4 in Patients' perception of treatment and symptoms.

Assessment of the other dimensions of the SAQ

- Angina stability: measures whether angina has changed in frequency when patient performs his or her most strenuous level of activity (1 question).
- Angina frequency: measures frequency of angina over the previous 4 weeks (2 questions).
- Treatment satisfaction: measures patient satisfaction with current angina treatment (4 questions).
- Disease perception: measures concern about angina in relation to quality of life and possibility of death (3 questions).

Each SAQ dimension is scored from 0-100 with higher scores better (as per the SAQ-PL; see [Section 4.4](#)). A change of 10 points is considered to be clinically important for any dimension.

Assessment of the SAQ-7 (29)

An SAQ summary score, called the SAQ-7, can be derived using the “best” 7 items from the three dimensions that directly measure patients' current health status: Physical Limitation, Angina Frequency, and Disease Perception (“best” defined as the items that had the highest levels of concordance with the overall domain score). Scores for each of the three dimensions were calculated using methodology analogous to that of the full SAQ, so that scores ranged from 0 to 100 for each dimension (although the number of items is smaller). The SAQ-7 score is derived as the average of the three domain scores.

Patient's perception of treatment and symptoms

The patient qualitative self-assessment aims to better understand the patient's views on their treatment and symptoms at baseline and at the end of the treatment. Three questions assessing the patient's perception will be asked and a free-text box will be provided for patients to give qualitative answers. This assessment should take between 5-10 minutes, and the text will later be analyzed using qualitative data analysis software to perform content analysis using text mining. The patient will be asked to complete these three questions. The questions are:

- Day 1 and at the end of study treatment visit/Day 29: “Please think back over the **past week**. In your own words, please describe the symptoms you have experienced because of your **angina without obstructive coronary artery disease**.”
- End of study treatment visit/Day 29 only: “Please think about the study you have been part of. In your own words, please list the pros and cons of study treatment”.
- End of study treatment visit/Day 29 only: “Please give your overall thoughts on the study treatment you have received as part of this study”.

Resources utilization

To assess the economic burden of MVA and/or persistent stable angina despite angiographically successful PCI, health care resources will be collected retrospectively at baseline within the year before study inclusion:

- Number of out-patients visits by type (cardiologists, general practitioner, other).
- Working status (activity, number of day off).

9.1.4.5 Coronary computed tomography angiography

A CCTA will be performed only in patients without previous PCI and whose coronary angiogram or CCTA was not performed in the previous 24 months but between 24 months to 5 years in whom screening PET scan results and CFR < 2.0 qualify for the study. This additional investigation will be performed according to common practice.

9.2 SAFETY ENDPOINTS

9.2.1 Adverse events

Refer to [Section 10.4](#) to [Section 10.7](#) for details.

Adverse events, serious adverse events, and adverse events of special interest: spontaneously reported to the Investigator (see [Section 10.4](#)) will be collected from signed informed consent until the End of Study at Day 36.

To ensure the continuing safety of patients in this study, an independent DMC will be responsible for reviewing the safety data on a periodic basis throughout the course of the study as outlined in [Section 6.4.1](#).

9.2.2 Physical examination

Physical examination including smoking habits and vital signs will be performed at Screening, Day 1 and Day 29.

In addition:

- Body weight (kg) will be measured at Screening, Day 1 and Day 29 by using the same calibrated scale.
- Body temperature (°C) will be measured using the same method for a given patient (oral/rectal/ tympanic) at Day 1 and Day 29.

9.2.3 Laboratory safety variables

The clinical laboratory data are collected in accordance with the study schedule ([Section 1.3](#) and [Section 1.4](#)) and consist of:

- Blood count: red blood cell count (RBC - with morphology if blood cell count is abnormal), hematocrit (Hct), hemoglobin (Hb), white blood cell count (WBC) with differential (neutrophils, eosinophils, basophils, monocytes and lymphocytes), platelets.
- Serum Biochemistry:
 - Plasma/serum electrolytes: glucose, sodium, potassium, chloride, calcium, bicarbonate, BUN, creatinine (with estimated glomerular filtration rate), uric acid, total protein, albumin, creatine phosphokinase (CPK), LDH and cystatin C,
 - Lipid profile: total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides,
 - Liver function: AST, ALT, alkaline phosphatases, gamma-glutamyl transferase (GGT), total and conjugated bilirubin.
- Urinalysis: dipstick for proteins, glucose, blood, leucocytes, ketone bodies, pH, bilirubin, urobilinogen, nitrite, specific gravity. If positivity of this test, microscopic analysis has to be considered.

Clinical laboratory values will be analyzed after conversion into standard international units. International units will be used in all listings and tables.

Decision trees for the management of some laboratory abnormalities are provided in [Appendix A](#).

9.2.4 Vital signs

Vital signs include: heart rate (HR), systolic and diastolic BP. The measurements will commence after 10 minutes have elapsed in seated resting position and continue at Minute 3 and Minute 5 in standing position.

9.2.4.1 Technical aspects

Blood pressure will be measured using an electronic device (ie, Omron[®] or equivalent, if possible, with the same device for a selected patient applied consistently throughout the study). The BP cuff should be placed over the arm at the heart level with the patient's arm extended and supported comfortably on a table or arm rest (for seated measurements) or the arm should be supported by the site staff (during standing measurements). A standard bladder (12-13 cm width and 35 cm long) or larger or smaller depending on the patient's arm circumference should be used. Blood pressure should be measured in the seated position after at least 10 minutes of wait. Heart rate will be measured concomitantly with BP measurements using the electronic device, if available or with the same methodology applied consistently throughout the study.

9.2.4.2 Screening visit (determination of reference arm)

Blood pressure will be measured seated in both arms to detect possible differences. The arm with the higher value will be used as a reference and all subsequent BP measurements will occur on this arm.

9.2.4.3 Measurements for assessing presence or not of orthostatic hypotension

In seated position, three BP measurements spaced 1-2 min apart should be done, if an automated device is available preferably in absence of the investigator. The average of the 3 readings is considered the seated BP value for comparison with standing BPs. The investigator or designee will be present. The patient will be instructed to stand and then a single BP and HR measurement will be obtained at Minute 3 and Minute 5 in the standing position. The lower BP value of the two standing BP values, regardless of whether at Minute 3 or Minute 5, will be used for assessing any orthostatic effect. Symptoms will not be elicited but rather spontaneously reported by the patient during this time. The Vital signs data are collected in accordance with the study schedule ([Section 1.3](#) and [Section 1.4](#)).

- Heart rate and BP to check for orthostatic hypotension will be performed by the investigator or designee before morning administration on visit days except on Day 1 which requires before morning administration, at T1h and T3h.

Of note:

- No increase and maintenance of the dose at the same level in case of **asymptomatic** orthostatic hypotension with SBP decreases at Minute 3 or Minute 5 between seated and standing position ≥ 30 mmHg,
- Decrease of the dose to the previous level in case of **symptomatic** orthostatic hypotension with SBP decreases at Minute 3 or Minute 5 between seated and standing position ≥ 20 mmHg or hypotension with SBP < 90 mmHg. If the starting dose of 5 mg BID is not tolerated, based on investigator's judgment, the dose could be decreased to 2.5 mg BID dose,
- If 2.5 mg BID dose is not tolerated, the study drug will be discontinued.

9.2.5 Electrocardiogram variables

Electrocardiogram data will be assessed by the Investigator.

Twelve-lead ECGs recorded after at least 10 minutes rest will be performed in accordance with the study schedule ([Section 1.3](#) and [Section 1.4](#)).

Measurements of ECG parameters are initially made automatically by a computerized electrocardiograph and further interpreted by the investigator.

The printout includes the date, time, initials and patient number as well as an automatic measurement of heart rate in beats per minute, PR interval (msec), QRS interval (msec), QT interval (msec), and QTc interval (msec) corrected for heart rate using Fridericia's (QTcF) formula. If the printout doesn't include either one of the corrected QT, it will be calculated by the investigator using Fridericia's formula.

Note: Any abnormal ECG parameter is immediately rechecked for confirmation before making a decision of permanent discontinuation of IMP for the concerned patient. ECG parameters include: heart rate, PR, QRS, QT, QTc automatic correction evaluation (by the ECG device).

Please note that due to different scenarios related to the visit window of the D1 PET assessment, the following ECG schedule should be followed:

- If PET assessment done at D1 visit:
 - ECG recorded prior PET (T-3H) and monitored during the PET (up to the end of PET [T-0H30]).
- If PET assessment done during screening period and not at D1 visit:
 - ECG recorded prior PET and monitored during the PET (up to the end of PET [T-0H30]).
 - ECG recorded on D1 prior 1st dosing (could be repeated just before dosing according to creatinine results availability).

Please note that the following ECG schedule should be followed on Day 29 or Day 30 or Day 31:

- ECG recorded at arrival on site (before dosing) and monitored during the PET (up to the end of PET [T-0H30]).

9.3 PHARMACOKINETIC ENDPOINT

9.3.1 Pharmacokinetics

9.3.1.1 Sampling time

A total of seven pharmacokinetic samples will be collected in all patients as follow: 1 hour and 3 hours post-dose on Day 1, pre-dose on Day 8, Day 15 and Day 22, and pre-dose and 1 to 3 hours post-dose on Day 29 (see [Section 1.3](#)). In case of premature study drug discontinuation a pharmacokinetic blood sample will be collected as soon as possible and no later than 3 days after the last study drug intake.

9.3.1.2 Pharmacokinetics handling procedure

Special procedures for collection, storage and shipping of plasma will be described in a separate laboratory manual.

9.3.1.3 Bioanalytical method

Concentrations of SAR407899 in plasma samples will be measured using a validated liquid chromatography method coupled with tandem mass spectrometry (LC-MS/MS) with a lower limit of quantification of 1 ng/mL (DOH1425) under the responsibility of Covance Laboratories.

9.3.1.4 Pharmacokinetics parameters

Observed SAR407899 concentrations will be reported in the clinical study report. A population pharmacokinetic analysis may be conducted and will be reported in a separated report.

9.3.2 Pharmacogenetic assessment

9.3.2.1 Drug metabolizing enzymes DNA sample

Not applicable.

9.3.2.2 Optional stored DNA sample

For those patients who signed the optional pharmacogenetic informed consent form, a blood sample will be collected at the study visit as specified in the study flow chart and this sample will be stored for up to 15 years after completion of the final study report of the main clinical trial.

This sample may be used to determine a possible relationship between genes and response to treatment with SAR407899, how the body processes SAR407899, and possible side effects to SAR407899. Genes that may be studied include those related to ROCK pathway and/or endothelial dysfunction. This blood sample will be transferred to a site that will, on behalf of Sanofi, extract DNA from the sample and that is managed by Covance.

This blood sample, and the DNA that is extracted from it, will be assigned a second number, a genetic ID (deidentification code) that is different from the patient ID. This “double coding” is performed to separate a subject’s medical information and DNA data.

The clinical study data (coded by subject ID) will be stored in the clinical data management system (CDMS), which is a distinct database in a separate environment from the database containing the pharmacogenetic data (coded by genetic ID). The key linking subject ID and genetic ID will be maintained by a third party, under appropriate access control. The matching of clinical data and pharmacogenetic data, for the purpose of data analysis, will be possible only by using this key, which will be under strict access control. All data will be reported only in coded form in order to maintain confidentiality.

The DNA will be stored for up to 15 years from the completion of the clinical study report.

Special procedures for storage and shipping of pharmacogenetic samples are described in a separate laboratory manual and in [Appendix B](#).

[REDACTED]

9.4.1 Sampling / handling procedures

Table 1 - Summary of sampling/handling procedures for [REDACTED]

Sample volume	10 mL blood
Matrix	Serum
Anticoagulant	None
Handling procedures	See laboratory manual
Aliquot split	4 aliquots with 1 mL serum for the first three aliquots, at each timepoint
Storage conditions	-20°C
Shipment conditions	In dry ice

Table 2 - Summary of sampling/handling procedures for [REDACTED]

Sample volume	10 mL blood
Matrix	Serum
Anticoagulant	None
Handling procedures	See laboratory manual
Aliquot split	4 aliquots with 1 mL serum for the first three aliquots, at each timepoint
Storage conditions	-20°C
Shipment conditions	In dry ice

Special procedures for collection, storage and shipping of blood/plasma/serum will be described in a separate laboratory manual.

9.4.2 Biomarker assay methods

The methods are still under development. Methods will be described in a separate laboratory manual.

9.5 FUTURE USE OF SAMPLES FOR BIOMARKER SAMPLES

Table 3 - Summary of sampling/handling procedures for future use of samples

Sample volume	4 mL blood
Matrix	Serum
Anticoagulant	None
Handling procedures	See laboratory manual
Aliquot split	8 aliquot of 0.250 mL serum at each timepoint
Storage conditions	-20°C
Shipment conditions	In dry ice

For patients who have consented to it, one sample will be collected at the visits specified in the study flow chart and these samples will be stored for up to 15 years after completion of the final study report. These samples may be used for other research purposes (excluding genetic analysis) related to endothelial dysfunction and/or microvascular angina.

These other research analyses will help to understand either disease subtypes or drug response, or to develop and/or validate a bioassay method, or to identify new drug targets or biomarkers.


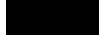
These samples will remain labelled with the same identifiers than the one used during the study (ie, subject ID). They will be transferred to a Sanofi site (or a subcontractor site) which can be located outside of the country where the study is conducted. The Sponsor has included safeguards for protecting subject confidentiality and personal data.

Special procedures for storage and shipping are described in a separate laboratory manual.

9.6 SAMPLE BLOOD VOLUME

Sample blood volume is presented in the table below.

Table 4 - Sampled blood volume

Type	Volume per sample	Sample number	Total
Laboratory	5 mL	7	35 mL
	10 mL	1	10 mL
	10 mL	1	10 mL
Future use of sample	2.5 mL	1	2.5 mL
Pharmacogenetics	6 mL	1	6 mL
Pharmacokinetics	2 mL	7	14 mL
Total for male patient			Approximately up to 80 mL
FSH	10 mL	1	10 mL
Total for female patient			Approximately up to 90 mL

9.7 APPROPRIATENESS OF MEASUREMENTS

Please refer to [Section 4](#).

Primary endpoint:

Change from baseline to end of study treatment/Week 4, in uncorrected global CFR assessed by ¹³N-ammonia or ⁸²Rubidium PET scan will be the primary endpoint as CFR represents the increase in blood flow to the myocardium in response to metabolic or pharmacological stimulations, the critical factor in angina. CFR is the endpoint with the most abundant clinical data in MVA patients. An abnormal CFR is <2.0.

The standard deviation and the mean of the placebo group of a study published by (1), using a noninvasive measures of coronary flow reserve based on rest/stress PET in 2783 patients with known or suspected coronary artery disease, were used in sample size calculation.

Secondary endpoints:

Change from baseline to end of study treatment/Week 4 in physical limitation as assessed by the SAQ-PL will be the secondary endpoint as it relates to patients' physical activity. The Seattle Angina Questionnaire (SAQ) is widely used to understand patients' perceptions of cardiovascular disease and symptoms. It was used in pilot MVA studies. Although data will be collected on multiple dimensions of the SAQ, the physical limitation (PL) dimension is the most relevant for defining treatment benefit in this population.

SAR407899 peak and trough concentrations will also be assessed as secondary endpoint as no data on microvascular angina patient and/or persistent stable angina despite angiographically successful PCI population are available with this compound.

10 STUDY PROCEDURES

10.1 VISIT SCHEDULE

10.1.1 Visit 0: Screening visit

The screening visit has to be performed 4 weeks to one day before scheduled (first) dosing (Day 1) and up to 6 weeks in patients before scheduled (first) dosing with CCTA during screening.

Informed Consent

Information on the study will be given to and discussed with the patient. The patient will sign the informed consent for the current trial before any procedure. When the consent has been obtained, full identification of patient and personal physician will be recorded for the Investigator's record, and a subject number will be assigned as described in [Section 8.3](#).

Also the informed consents have to be obtained for the optional DNA banking and future use of samples for possible later further analyses.

Collection of adverse events has to be started from the time of signing informed consent. The patient has to be registered with the IVRS/IWRS.

After the informed consent has been signed, the following measurements have to be performed:

- Call IVRS/IWRS to assign patient number.
- Demographic information.
- Collection of prior/concomitant medications.
- Begin AEs reporting.
- Medical/surgical history.
- Data of previous (if done 24 months prior to screening) coronary artery angiography or CCTA.
- Data of previous (if done between 24 months and 5 years prior to screening) coronary artery angiography or CCTA.
- Data of previous (if done 24 months prior to screening) CFR assessment whatever the method.
- Assessment of inclusion and exclusion criteria.
- Physical examination (including smoking habits).
- Body weight and height.
- Vital signs, resting 12 lead-ECG.

Patients who do not meet inclusion criteria and/or met at least one exclusion criterion will be considered a screening failure and will not perform the following measurements:

- Blood sampling for hematology, biochemistry and plasma FSH (For post-menopausal female patients not treated with HRT).
- Blood sampling for renal function (blood creatinine and cystatin C).
- Collection of urine for urinalysis.
- A patient diary will be dispensed to the eligible patients in order to record their angina episodes and the short-acting nitrates intakes.
- Patients who meet all the inclusion criteria and none of the exclusion will be potentially eligible for inclusion into the study depending on PET scan CFR value assessed at baseline visit or if not otherwise possible up to 14 days prior to Day 1 (except for patients described below where PET scan will be performed up to 4 weeks prior to Day 1). A visit within the next 4 weeks will be scheduled.

In patients diagnosed with MVA and stable angina without previous PCI, who did not have coronary angiogram or CCTA in the previous 24 months but within 5 years, a CCTA will be performed during screening period provided that:

- These patients meet all inclusion criteria including qualifying PET scan and $CFR < 2.0$ up to 4 weeks before Day 1 visit. If not, the patient will be screen failed and will not have CCTA.

The Investigator will call the patient to confirm the date for CCTA, to be performed in order to have the results before Day 1 visit to ascertain the absence of obstructive coronary arteries.

At the end of the screening visit, the patient should be informed and follow restriction rules for PET scan investigation: methylxanthines (eg, caffeine) will be forbidden 24 hours prior to the test otherwise PET scan should be re-scheduled one day after. All site visits whereby the PET assessment is not performed on the same day as the site visit will not require fasting or other dietary / medication restrictions.

Screening failure

If the patient is not eligible after this visit and after all reports are available, this information has to be entered into the IVRS/IWRS by a screening failure call.

In case the PET scan cannot be performed in the allowed time window for logistical reasons, the patient can be re-screened after consultation with the sponsor.

10.1.2 Visit 1: Baseline / Randomization / Day 1

The patient has to go on Day 1 morning to the investigational site for his / her visit.

Patients diagnosed with MVA and stable angina without PCI, who did not have a coronary angiogram or CCTA in the previous 24 months but between 24 months to 5 years, need to have

the PET assessment followed by the CCTA during the screening period. Other patients will have their PET scan up to 14 days before Day 1 visit or on Day 1 visit.

For the PET assessment, the patient should be in fasting state (at least 4 hours) and well hydrated and should avoid, in the following timely manner (whenever possible), the intake of:

- 24 hours before CFR assessment :
 - Anti-hypertensive drugs,
 - Beta blockers,
 - Calcium channel blockers,
 - Methylxanthines including caffeinated coffee, tea or other caffeinated beverages, caffeine-containing drug products.
- At least 4 hours before CFR assessment:
 - Nicotine,
 - Short acting nitrate.

If not, this visit should be re-scheduled one day after with the restrictions re-explained to the patient.

The following assessments are to be completed at Day 1 as follows:

- Quality of life questionnaires should be filled in prior any other assessment and without any help:
 - Seattle Angina Questionnaire,
 - Patients' perceptions of treatment and symptoms.
- Resources utilization.

Prior any IMP administration, the following assessments will be performed:

- Assessment of part of inclusion and exclusion criteria.
- Physical examination (including smoking habits).
- Patient diary evaluation: angina episodes with severity (intake of short-acting nitrate).
- Body weight.
- Body temperature.
- DNA blood sample (provided appropriate consent has been obtained).
- [REDACTED]
- Blood sampling for future use of samples (provided appropriate consent has been obtained).
- Blood sampling for renal function (blood creatinine and cystatin C).
- Blood sampling for hematology, biochemistry.

- Collection of urine for urinalysis.
- Vital signs including orthostatic BP measurements and resting 12 lead-ECG.
- Coronary Flow Reserve assessed by vasodilator stress PET scan with NIMPs administration (can be performed up to 14 days prior to Day 1).
- AEs collection.
- Concomitant treatments reporting.

One hour before dosing, a standard meal can be given to the patient.

Just before the study drug administration, 12 lead-ECG and vital signs assessments will be performed (only if PET scan is done at Day 1 or according to creatinine results availability if PET scan done prior to Day 1).

If the patient is still eligible after all assessments, the investigator or designee will call the IVRS/IWRS to randomize the patient and obtain a treatment number assigned by IVRS/IWRS.

If the patient is not eligible after these assessments, this information has to be entered into the IVRS/IWRS by a screening failure call.

Then the 1st IMP intake has to be given on Day 1.

After dosing the following assessments have to be performed according to the period flow chart (see at [Section 1.4](#)):

- Evaluation of AEs and concomitant medication.
- Vital signs at T1h and T3h post IMP intake.
- Resting 12 lead ECG.
- Collection of PK sample (T1h and T3h).

If no clinically relevant findings have been detected from all safety examinations until then, the patient can leave the unit in the evening or earlier depending on the investigator's judgment of Day 1.

Day 1 discharge time:

- Before the patient leave the unit, he/she will be given sufficient study drug (packaged in a Wallet) for 1 treatment week (± 2 days).
- At home, the patient will take the IMP twice a day (morning and bedtime) and will report on his patient diary IMP information and the angina episodes that will occur and short-acting nitrate intakes.
- In case a patient does not tolerate a dose, he/she should call the investigator to have an on-site visit. Based on the tolerability assessed at this visit, the investigator could decide to stop or modify study drug dose (the IVRS/IWRS will be called in that cases).

10.1.3 Visits 2, 3, and 4: Days 8, 15, and 22 (+/- 2 days)

During the titration phase, patient's visits are performed at the clinical site. The following assessments have to be performed before the administration:

- Physical examination may be symptoms driven at the investigator's discretion.
- Collection of information about concomitant medication/concomitant treatment reporting.
- AEs collection.
- Vital signs (BP & heart rate measurements including search of hypotension) and resting 12 lead-ECG before study drug administration.
- Collection for PK samples (pre-dose).
- Collection for renal function (blood creatinine and cystatin C).
- Collection for hematology (except at D15 and D22), biochemistry.
- Patient diary (one per week) review & dispensation.
- Call IVRS/IWRS to obtain the treatment kit code after specifying the chosen titration.
- After these assessments, the IMP morning administration could be done.
- In case a patient does not tolerate a dose, he/she should call the investigator to have an on-site visit. Based on the tolerability assessed at this visit, the investigator could decide to stop or modify study drug dose.
- Before the patient leave the unit, he/she will be given sufficient study drug (packaged in a Wallet) for 1 treatment week (± 2 days).
- At home, the patient will take the IMP twice a day (morning and bedtime) and will report on his patient diary IMP information and the angina episodes that will occur and short-acting nitroglycerin intakes.

10.1.4 Visit 5: End of treatment: Day 29 (or up to 2 days after at the latest) even in case of early IMP discontinuation

The patient arrives to the clinical site in the morning on Day 29 (or up to 2 days after at the latest) and should be in fasting state (at least 4 hours) and well hydrated and should avoid, in the following timely manner (whenever possible), the intake of as it relates to the PET assessment:

- 24 hours before CFR assessment :
 - Anti-hypertensive drugs,
 - Beta blockers,
 - Calcium channel blockers,
 - Methylxanthines including caffeinated coffee, tea or other caffeinated beverages, caffeine-containing drug products.
- At least 4 hours before CFR assessment :
 - Nicotine,

- Short acting nitrate.

IMP administration should be continued until the visit to the site.

The following assessments have to be performed:

- Quality of life questionnaires should be filled in prior any other assessment and without any help:
 - Seattle Angina Questionnaire,
 - Patients' perceptions of treatment and symptoms.
- Physical examination (including smoking habits).
- Patient diary collection.
- Body weight.
- Body temperature.
- Vital signs including search of orthostatic BP measurements and resting 12 lead-ECG.
- Blood sampling for renal function (blood creatinine and cystatin C).
- Blood sampling for hematology, biochemistry.
- Collection of urine for urinalysis.
- Collection of PK samples (pre-dose).
- AEs collection.
- Collection of information about any concomitant medications.

After IMP intake:

- Coronary flow reserve assessed by vasodilator stress PET scan with NIMPs administration, is performed approximately 1 to 2 hours after IMP intake.
- Collection of PK samples (1-3h post-dose).
- Call IVRS/IWRS to declare the end of treatment for this patient, except if patient has delay in end-of-treatment PET scan.

If no clinically relevant findings have been detected from all safety examinations until then, the patient can be discharged from the unit in the evening or earlier depending of the investigator's judgment.

Approximately seven days after the last study drug intake, the investigator will prescribe if needed anti-anginal drugs (ie, nitrates) and/or PDE 5 inhibitor.

Only if PET scan performed after Day 29 visit, at home, the patient will take the IMP twice a day (morning and bedtime) and will report on his patient diary IMP information and the angina episodes that will occur and short-acting nitroglycerin intakes.

In case of early IMP discontinuation:

- Within the first 2 weeks of study treatment patients are to be assessed as soon as possible after study drug stop, using the procedures (except PET scan) planned for the D29/end of treatment visit, including a pharmacokinetic sample (to be collected no later than 3 days after the last study drug intake).
- With at least 2 weeks of study treatment patients are to be assessed as soon as possible after study drug stop, using the procedures planned for the D29/end of treatment visit, including a pharmacokinetic sample (to be collected no later than 3 days after the last study drug intake). PET scan can be performed up to 3 days after study drug discontinuation.

10.1.5 Visit 6: End of study: Day 36 (+/- 2 days)

Visit at clinical site:

- Patient's diary review.
- Vital signs (BP & heart rate measurements including search of hypotension) and resting 12 lead ECG.
- Blood sampling for hematology, biochemistry.
- Blood sampling for renal function (blood creatinine and cystatin C).
- AEs collection.
- Collection of information about any concomitant medications.

Study restriction(s)

There is no restriction of meals with regard to contents or time schedule.

This visit is not mandatory in case of premature treatment discontinuation.

10.2 DEFINITION OF SOURCE DATA

All evaluations listed below that are reported in the CRF must be supported by appropriately signed identified source documentation related to:

- Patient identification.
- Medical/surgical history.
- Dates and times of visits and assessments.
- Physical examination, cardiological examination.
- Vital signs, body weight and height, body temperature.
- Resting 12-lead ECGs results.
- Laboratory result.
- Pharmacokinetic & Biomarker time points.

- Adverse events.
- IMP administration.
- Previous/concomitant medication, including start of medication and time of change in dosing regimen.
- SAQ.
- PET scan CFR reports of assessments performed during the patient's study participation.
- CCTA results if any.
- Coronary artery angiography results if any.
- Patient's diaries.
- Patient perceptions of treatment and symptoms.
- Resources utilization.

10.3 HANDLING OF PATIENT TEMPORARY OR PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

The IMP should be continued whenever possible. Permanent IMP discontinuation should be a last resort. Any IMP discontinuation should be fully documented in the CRF. In any case, the patient should remain in the study as long as possible.

- Pregnancy will lead to definitive treatment discontinuation in all cases.
- Additional stopping rules described in [Appendix A](#) and [Section 8.1](#) should be applied, if applicable.

10.3.1 Temporary treatment discontinuation with investigational medicinal product(s)

Not applicable.

10.3.2 Permanent treatment discontinuation with investigational medicinal product(s)

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator or the patient not to re-expose the patient to the IMP at any time. List of criteria for permanent treatment discontinuation

The patients may withdraw from treatment with the IMP if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision. All efforts should be made to document the reason(s) for treatment discontinuation and this should be documented in the e-CRF.

IMP may be permanently discontinued in case of the following events. The list is not intended to be exhaustive:

- Severe symptomatic orthostatic hypotension or postural dizziness (defined as requiring medical intervention or hospitalization) (see [Section 10.4.5](#)).

- Any serious or severe Grade 3 related adverse event will lead to permanent treatment discontinuation.
- Adverse events of lesser grade should be evaluated in the context of concomitant clinical and laboratory findings and, in the judgment of the Investigator, may be cause of permanent discontinuation of treatment for an individual subject.
- Symptoms of severe hypersensitivity or anaphylactic reactions.
- If [REDACTED] dose is not tolerated.
- Significant laboratory abnormalities (see [Section 10.4.6](#) and [Appendix A](#)):
 - Confirmed ALT >5 ULN or confirmed ALT >3 ULN and total bilirubin >2 ULN (unless the patient has Gilbert's disease documented by genetic testing),
 - Confirmed neutrophil count <1500/mm³ with or without signs of infection,
 - Suspected rhabdomyolysis with confirmed CPK >10 ULN,
 - Confirmed platelet count <100,000 cells/mm³ with or without spontaneous bleeding,
 - Confirmed decline in total white blood cell count of >50% compared to baseline and white blood cell count Grade 1 (<LLN -3000/mm³),
 - Confirmed decline in hemoglobin of >3 g/dL compared to baseline and hemoglobin level Grade 1 (< LLN -10g/dL) or higher of CTCAE terminology,
 - Confirmed QTc >500 ms.
- Pregnancy.
- Any adverse events, per Investigator's judgment, that may jeopardize the patient's safety.
- Any code breaking requested by the Investigator will lead to permanent treatment discontinuation.
- At the specific request of the Sponsor.

Any abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation before making a decision of permanent discontinuation of the IMP for the concerned patient. All efforts should be made to reassess in a clinically relevant timeframe, the clinical significance of lab abnormalities and corrective actions before making a decision of permanent discontinuation of the IMP for the concerned patient.

10.3.3 Handling of patients after permanent treatment discontinuation

Patients will be followed-up and every effort should be done to have the end of study treatment/Day 29 visit completed or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

All cases of permanent treatment discontinuation should be recorded by the Investigator in the appropriate pages of the e-CRF when considered as confirmed.

10.3.4 Procedure and consequence for patient withdrawal from study

The patients may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-patient contact follow-up, eg, medical records check. Patients requesting withdrawal should be informed that withdrawal of consent for follow-up may jeopardize the public health value of the study.

Every effort should be made to convince the patients to perform the end of study treatment/D29 with assessment of primary and secondary endpoints including blood samples and pharmacokinetic samples. The end of study visit (D36) one week later should be done. This visit is not mandatory in case of premature study drug discontinuation.

Patients who withdraw should be explicitly asked about the contribution of possible AEs to their decision to withdraw consent, and any AE information elicited should be documented. Preferably the patient should withdraw consent in writing and, if the patient or the patient's representative refuses or is physically unavailable, the site should document and sign the reason for the patient's failure to withdraw consent in writing.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the e-CRF and in the patient's medical records when considered as confirmed. In the medical record, at least the date of the withdrawal and the reason should be documented.

For patients who fail to return to the site, unless the patient withdraws consent for follow-up, the investigator should make the best effort to re-contact the patient (eg, contact patient's family or private physician, review available registries or health care databases), and to determine his/her health status, including at least his/her vital status. Attempts to contact such patients must be documented in the patient's records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter). The statistical analysis plan will specify how these patients inevaluable for their primary endpoints will be considered.

Patients who have withdrawn from the study cannot be re-randomized (treated) in the study. Their inclusion and treatment numbers must not be reused.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

An **adverse event** (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

Intensity of an AE is defined as:

- Mild: no modification of daily activities and does not require mandatory corrective/symptomatic treatment.
- Moderate: hinders normal daily activities and/or requires mandatory corrective/symptomatic treatment.
- Severe: prevents daily activities and requires mandatory corrective/symptomatic treatment.

10.4.1.2 Serious adverse event

A **serious adverse event** (SAE) is any untoward medical occurrence that at any dose:

- Results in death, or,
- Is life-threatening, or,
Note: The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization, or,
- Results in persistent or significant disability/incapacity, or,
- Is a congenital anomaly/birth defect.
- Is a medically important event.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered a medically important event. The list is not intended to be exhaustive:

- Intensive treatment in an emergency room or at home for:
 - Allergic bronchospasm,
 - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc),
 - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
- ALT >3 x ULN + total bilirubin >2 x ULN or asymptomatic ALT increase >5 x ULN.
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling).
- Bullous cutaneous eruptions.

10.4.1.3 Adverse event of special interest

An adverse event of special interest (AESI) is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified or removed during a study by protocol amendment.

- Pregnancy of a female subject entered in a study as well as pregnancy occurring in a female partner of a male subject entered in a study with IMP:
 - Pregnancy occurring in a female patient entered in the clinical trial or in a female partner of a male patient entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see [Section 10.4.1.2](#)),
 - In the event of pregnancy in a female participant, IMP should be discontinued,
 - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined.
- Symptomatic overdose (serious or nonserious) with IMP:
 - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic pills count) and defined as at least twice the intended dose within the intended therapeutic interval, adjusted according to the tested drug.

Of note, asymptomatic overdose has to be reported as a standard AE.

- Increase in alanine transaminase (ALT)>3xULN (see [Appendix A](#) of the protocol).
- QTc \geq 500ms.
- Hypotension/orthostatic hypotension symptomatic or not defined as:
 - Asymptomatic orthostatic hypotension with SBP decrease at Minute 3 or Minute 5 between seated and standing position \geq 30 mmHg,
 - SBP <90 mmHg,
 - Symptomatic orthostatic hypotension with SBP decrease at Minute 3 or Minute 5 between seated and standing position \geq 20 mmHg,
 - Symptoms of hypotension (either orthostatic or non-postural) include: presyncope, including any symptoms of dizziness, faintness or lightheadedness appearing while standing up and possibly caused by a drop in BP and/or appearing while standing up,
 - Whenever possible, concomitant medications, BP and heart rate measurements in seated and standing positions, plasma glucose level and ECG will be collected at or near the time of the event or per the investigator's clinical judgment,
 - For any such event, the appropriate AESI eCRF screen must be filled out.

Note: the following non-pharmacological measures will be encouraged by discussing with the patient: If a patient experiences faint-headedness or unusual dizziness, he or she will assume a seated position and, if still dizzy, either lie down or, while seated, place the head between the knees until dizziness has passed; the patient will be recommended to drink at least 12 ounces (375 mL) of fluid.

10.4.2 Serious adverse events waived from expedited regulatory reporting to regulatory authorities

Not applicable.

10.4.3 General guidelines for reporting adverse events

- All AEs, regardless of seriousness or relationship to IMP/NIMP, spanning from the signature of the informed consent form until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding page(s) or screen(s) of the eCRF:
 - Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP/NIMP or by the study procedure(s),
 - The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the Sponsor. Patients who experience an ongoing SAE or an AESI, at the prespecified study end-date, should be followed until resolution, stabilization, or death and related data will be collected,
 - When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient,
 - Laboratory, vital signs or ECG abnormalities are to be recorded as AEs only if:
 - Symptomatic and/or,
 - Requiring either corrective treatment or consultation, and/or,
 - Leading to IMP discontinuation or modification of dosing, and/or,
 - Fulfilling a seriousness criterion, and/or,
 - Defined as an AESI.

Instructions for AE reporting are summarized in [Table 5](#).

10.4.4 Instructions for reporting serious adverse events

In the case of occurrence of an SAE, the Investigator or any designees must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the e-CRF; the system will automatically send a notification to the monitoring team after approval of the Investigator within the e-CRF or after a standard delay.

- SEND (preferably by fax or e-mail) a photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the monitoring team whose name, fax number, and email address appear on the clinical trial protocol. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of a source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the e-CRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, patient status, etc) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge of the SAE. In addition, every effort should be made to further document any SAE that is fatal or life-threatening within a week (7 days) of the initial notification.
- A back-up plan (using a paper CRF process) is available and should be used when the e-CRF system does not work.

Any SAE brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by the IMP with a reasonable possibility, should be reported to the monitoring team.

10.4.5 Guidelines for reporting adverse events of special interest

For AESIs, the Sponsor must be informed immediately (ie, within 24 hours), as per SAE notification guidelines described in [Section 10.4.4](#), even if not fulfilling a seriousness criterion, using the corresponding pages of the CRF (to be sent) or screens in the e-CRF. Instructions for AE reporting are summarized in [Table 5](#).

10.4.6 Guidelines for management of specific laboratory abnormalities

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in [Appendix A](#).

The following laboratory abnormalities should be monitored, documented, and managed according to the related flow chart in protocol appendices.

- Neutropenia.
- Thrombocytopenia.
- ALT increase.
- Acute renal insufficiency.
- Suspicion of rhabdomyolysis.

Table 5 - Summary of adverse event reporting instructions

Event category	Reporting timeframe	Specific events in this category	Case Report Form completion		
			AE form	Safety Complementary Form	Other specific forms
Adverse Event (non-SAE, non-AESI)	Routine	Any AE that is not SAE or AESI	Yes	No	No
Serious Adverse Event (non-AESI or AESI)	Expedited (within 24 hours)	Any AE meeting seriousness criterion per Section 10.4.1.2	Yes	Yes	No
Adverse Event of Special Interest	Expedited (within 24 hours)	Pregnancy	Yes	Yes	Yes
		Symptomatic overdose with IMP	Yes	Yes	No
		ALT increase as defined in the protocol	Yes	Yes	Yes
		QTc \geq 500ms	Yes	Yes	No
		Hypotension/orthostatic hypotension (asymptomatic and symptomatic)	Yes	Yes	No

10.5 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor will report in an expedited manner:

- All SAEs that are both unexpected and at least reasonably related to the IMP (SUSAR), to the regulatory authorities, independent ethics committee (IECs)/institutional review boards (IRBs) as appropriate and to the Investigators.
- All SAEs that are expected and at least reasonably related to the IMPs to the regulatory authorities, according to local regulations.

Adverse events that are considered expected will be specified by the investigator's brochure.

Any other AE not listed as an expected event in the Investigator's Brochure or in this protocol will be considered unexpected.

For regulatory purposes, the treatment code will be unblinded at Sponsor Pharmacovigilance department level for reporting to the Health Authorities of any suspected unexpected adverse drug reaction (SUSAR) and reasonably associated with the use of the IMP according to either the judgment of the Investigator and/or the Sponsor. Apart from Sponsor Pharmacovigilance department, within the company and associated organizations, the results of this unblinding will remain undisclosed.

The Sponsor will report all safety observations made during the conduct of the trial in the clinical study report.

10.6 SAFETY INSTRUCTIONS

In case of signs or symptoms suggestive of hypotension or orthostatic hypotension occur, physical examinations will include respiratory, cardiovascular systems; clinical management of this hypotension should be undertaken by the investigator. If the event persisted, decision of IMP discontinuation should be discussed with the Sponsor.

10.7 ADVERSE EVENTS MONITORING

All events will be managed and reported in compliance with all applicable regulations, and included in the final clinical study report.

11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

The sample size calculations are based on the primary efficacy variable of uncorrected global CFR assessed by ¹³N-ammonia or ⁸²Rubidium PET scan change from baseline to Week 4.

Assumptions for sample size calculation:

- A large study of 2783 patients referred for rest/stress positron emission tomography suggested a SD 0.65 for CFR at baseline. With the hypothesis of correlation of 0.6 between baseline assessment and Week 4 assessment the SD for the change of baseline to week for could be estimated at 0.58
- A t-test at a 1-sided 5% significance level.

Based on the above assumptions, 35 evaluable patients per arm are needed for this study to detect a treatment effect of 0.35 with 80% of power. 10% more patients will be randomized in each group. Thus, approximately 78 patients will be randomized in this study, 39 per arm.

Calculations were made using East 6.3.

11.2 DISPOSITION OF PATIENTS

Screened patients are defined as any patient who originally met the inclusion criteria and signed the informed consent.

Randomized patients consist of all screened patients with a double-blind treatment kit number allocated and recorded in the IVRS/IWRS database, regardless of whether the treatment kit was used or not.

Patients treated without being randomized will not be considered as randomized and will not be included in any efficacy population. The safety experience of patients treated and not randomized will be reported separately, and these patients will not be in the safety population.

For any patient randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be assessed separately.

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy populations

11.3.1.1 Modified intent-to-treat population

The primary population for analysis will be the modified ITT (mITT) population: all randomized patients analyzed according to the treatment group allocated by randomization, who received at least a dose or part of a dose of the IMP and with an evaluable primary efficacy endpoint. The primary efficacy endpoint will be considered evaluable when the baseline CFR assessment is available.

11.3.2 Safety population

The safety population will be the as-treated population, defined as randomized population who did actually receive at least one dose or part of a dose of IMP and analyzed according to the treatment actually received.

In addition:

- Randomized patients for whom it is unclear whether they took the study medication will be included in the safety population as randomized.
- For patients receiving more than 1 study treatment during the trial, the treatment group allocation for as-treated analysis will be the active group if at least one active dose or part of a dose was taken.

11.3.3 Pharmacokinetic and biomarker analysis population

The population for all PK analyses will be all randomized and treated patients (safety population) having at least one sample.

The population for BM analysis will be randomized and treated patients from selected sites having at least a baseline and a post-baseline biomarker assessment.

11.4 STATISTICAL METHODS

11.4.1 Extent of study treatment exposure and compliance

11.4.1.1 Extent of investigational medicinal product exposure

Duration of IMP exposure is defined as: last dose date – first dose date +1 day, regardless of unplanned intermittent discontinuations.

11.4.1.2 Compliance

A given administration will be considered noncompliant if the patient did not take the planned dose of treatment as required by the protocol. No imputation will be made for patients with missing or incomplete data.

Treatment compliance, above-planned and under-planned dosing percentages will be summarized descriptively (N, mean, SD, median, min, and max). The percentage of patients with compliance <80% will be summarized. In addition, the number and percentage of patients with at least 1 above-planned dosing administration will be given, as well as the number and percentage of patients with 0, (0, 20%], and >20% under-planned dosing administrations.

11.4.2 Analyses of efficacy endpoints

11.4.2.1 Analysis of primary efficacy endpoint

Model assumptions for normality will be explored prior to the analysis testing.

Assuming that the change in CFR from baseline to Week 4 distribution is normal, an analysis of covariance (ANCOVA) model including the two following fixed categorical effect: treatment group (pooled SAR407899 doses versus placebo) and the presence of angiographically successful PCI (YES/NO) as well as a continuous fixed covariate of baseline CFR will be fitted. The interaction factors will be explored. The final model will provide adjusted least-squares means (LS means) estimates of the change from baseline to Week 4 in both treatment groups with their corresponding 95% confidence intervals (CIs). The difference of these estimates will be tested at the 1-sided 5% level using an appropriate contrast statement and the 95% confidence interval of the difference will be provided.

Let μ_0 and μ_1 be the population means of the change from baseline to Week 4 in CFR under placebo and SAR407899, respectively. The null hypothesis that will be tested is:

$H_0: \mu_0 = \mu_1$ versus $H_1: \mu_0 \neq \mu_1$.

Robustness of this statistical method will be assessed via sensitivity analyses detailed in the Statistical Analysis Plan (SAP), including different methodologies for missing data (multiple imputation and potentially pattern mixture modeling).

In this primary analysis, the mITT population is considered and the Week 4 assessments will be used regardless of whether the patient has previously discontinued the treatment.

11.4.2.2 Analyses of secondary efficacy endpoints

The score of the SAQ-Physical Limitation scale will be derived according to the SAQ scoring instructions.

Assuming that the change from baseline to Week 4 in SAQ-Physical Limitation score distribution is normal, a similar model as primary analysis will be fitted. The interaction factors will be explored. The final model will provide adjusted least-squares means (LS means) estimates of the change from baseline to Week 4 in both treatment groups with their corresponding 95% confidence intervals (CIs). The difference of these estimates will be tested at the 1-sided 10% level using an appropriate contrast statement and the 95% confidence interval of the difference will be provided.

In this analysis, the mITT population is considered and the Week 4 assessments will be used regardless of whether the patient has previously discontinued the treatment.

11.4.2.3 Multiplicity considerations

Results of secondary analysis are considered informative ONLY if the primary analysis is positive, therefore the study overall type I error does not need to be adjusted for multiplicity.

For secondary and exploratory efficacy endpoints, p-values will be provided for descriptive purpose only.

11.4.3 Analyses of safety data

The summary of safety results will be presented by treatment group on the basis of the safety population.

All safety analyses will be performed on the safety population using the following common rules:

- The baseline value is defined generally as the last available value before randomization.
- The analysis of the safety variables will be essentially descriptive and no hypothesis testing is planned.

The following definitions will be applied to laboratory parameters, vital signs and ECG.

- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, vital signs, and ECG.

PCSA criteria will determine which patients had at least 1 PCSA during the TEAE period, taking into account all evaluations performed during the TEAE period, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the PCSA percentage.

Observation period

- The TEAE observation period is defined as the time from the first dose of IMP up to 7 days after the last dose of IMP.
- The on-study period is defined as the time from randomization until the end of the study (see definition in [Section 6.2.1](#)).

11.4.3.1 Adverse events

Treatment-emergent AEs, treatment-emergent SAEs, TEAEs leading to treatment discontinuation and treatment-emergent AESIs will be summarized for each treatment group based on MedDRA coding of verbatim terms reported by investigators.

Analysis of TEAEs

Treatment emergent adverse event incidence tables will be presented by system organ class (SOC) (sorted by internationally agreed order), high-level group term (HLGT), high level term (HLT) and preferred term (PT), sorted in alphabetical order for each treatment group, the number (n) and percentage (%) of patients experiencing at least one TEAE. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group.

Analysis of all treatment-emergent SAEs

All treatment-emergent SAEs will be presented by primary SOC, HLGT, HLT, and PT, showing number (%) of patients with at least 1 serious TEAE, sorted by SOC internationally agreed order. The order levels (HLGT, HLT, PT) will be presented in alphabetical order. Listings will be provided for all SAEs by treatment group and patient with flags indicating on-treatment status.

Analysis of all TEAEs leading to permanent treatment discontinuation

TEAEs leading to treatment discontinuation will be presented by primary SOC, HLGT, HLT, and PT, showing number (%) of patients with at least 1 TEAE leading to permanent treatment discontinuation, sorted by SOC internationally agreed order. The order levels (HLGT, HLT, PT) will be presented in alphabetical order. Listings will be provided for all TEAE leading to permanent treatment discontinuation by treatment group and patient.

Analysis of treatment-emergent AESI:

Treatment-emergent AESI, by AESI category and PT, will show number (%) of patients overall, sorted by decreasing incidence of PT within each AESI category. The AESIs include, but are not limited to, the following categories and details of the MedDRA coding will be provided in the SAP: (see AESI list in [Section 10.4.1.3](#)): AESIs include hypotension/orthostatic hypotension symptomatic or not.

Analysis of Deaths

The following deaths summaries will be generated:

- Number (%) of patients who died by study period (TEAE, on-study) and reasons for death summarized on the safety population by treatment received.
- Death in nonrandomized patients or randomized and not treated patients.
- TEAE leading to death (death as an outcome on the AE CRF page as reported by the Investigator) by primary SOC , HLT, HLT and PT showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLT, HLT, and PT.

11.4.3.2 Laboratory data

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) of all laboratory variables will be calculated for each visit or study assessment (baseline, each post-baseline time point, endpoint) by treatment group. Listings will be provided with flags indicating the out of range values as well as the PCSA values.

The incidence of PCSA at any time will be summarized by treatment group for each laboratory parameter. Shift tables showing changes with respect to the baseline status will be provided.

11.4.3.3 Potential drug-induced liver injury

The liver function tests, namely ALT, AST, alkaline phosphatase, and total bilirubin, are used to assess possible drug-induced liver toxicity. The proportion of patients with PCSA values at any post-baseline visit by baseline status will be displayed by treatment group for each parameter. The proportion of patients with PCSA values at any post-baseline visit will also be displayed by duration of exposure for each treatment group.

A graph of distribution of peak values of ALT versus peak values of total bilirubin will also be presented. Note that the ALT and total bilirubin values are presented on a logarithmic scale. The graph will be divided into 4 quadrants with a vertical line corresponding to 3 x ULN for ALT and a horizontal line corresponding to 2 x ULN for total bilirubin.

The normalization (to ≤ 1 x ULN or return to baseline if baseline > 1 x ULN) of elevated liver function tests will be summarized by categories of elevation (3 x ULN, 5 x ULN, 10 x ULN, 20 x ULN for ALT and AST; 1.5 x ULN for alkaline phosphatase; and 1.5 x ULN and 2 x ULN for total bilirubin), with the following categories of normalization: never normalized, normalized after permanent discontinuation of study drug. Note that a patient will be counted only under the maximum elevation category.

The incidence of liver-related AEs will be summarized by treatment group. The selection of preferred terms will be based on standardized MedDRA query (SMQ) Hepatic disorder.

11.4.3.4 Vital signs data

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) of all vital signs variables with a focus on BP and orthostatic BP will be calculated for each visit or study assessment (baseline, each post-baseline time point, endpoint) by treatment group. Listings will be provided with flags indicating the out of range values as well as the PCSA values. The incidence of PCSA at any time will be summarized by treatment group for each vital signs variable. Shift tables showing changes with respect to the baseline status will be provided.

11.4.3.5 Electrocardiogram data

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) of all ECG variables will be calculated for each visit or study assessment (baseline, each post baseline time point, endpoint) by treatment group.

The incidence of PCSA at any during the TEAE period will be summarized by treatment group for each ECG variable. Shift tables showing changes with respect to the baseline status will be provided. Listings will be provided with flags indicating the PCSA values.

11.4.4 Analyses of pharmacokinetic and pharmacodynamic variables

PK data will summarized by treatment arm and timepoint using descriptive statistics (number of patients, arithmetic mean, standard deviation, geometric mean, coefficient of variation, minimum and maximum).

A population pharmacokinetic analysis may be conducted and will be reported in a separated report.

Correlation analysis may be conducted to explore the PK/PD relationship.

11.5 INTERIM ANALYSIS

Safety

A DMC will review the clinical safety data on a regular basis in an unblinded manner. The first analysis will occur once 19 patients (irrespective of treatment group) have completed the [REDACTED] dose level.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Investigator, and delegated Investigator staff and Subinvestigator, in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki, and the ICH guidelines for good clinical practice (GCP), all applicable laws, rules and regulations.

This clinical trial will be recorded in a free, publicly accessible, internet-based registry, no later than 21 days after the first patient enrollment, in compliance with applicable regulatory requirements and with Sanofi public disclosure commitments.

12.2 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the patient of all pertinent aspects of the clinical trial including the written information giving approval/favorable opinion by the ethics committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient's participation in the clinical trial, the written informed consent form should be signed, name filled in and personally dated by the patient and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form will be provided to the patient.

Prior to collection of blood for pharmacogenetics, the optional pharmacogenetic informed consent form (written) should be signed, name filled in, and personally dated by the patient and by the person who conducted the informed consent discussion. A copy of the signed and dated written optional informed consent form will be provided to the subject.

The informed consent form and the optional pharmacogenetic informed consent form used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate ethics committee (IRB/IEC) for approval/favorable opinion.

12.3 HEALTH AUTHORITIES AND INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

As required by local regulation, the Investigator or the Sponsor must submit this clinical trial protocol to the health authorities (competent regulatory authority) and the appropriate IRB/IEC, and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the chairman with IRB/IEC composition.

The clinical trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, informed consent form, Investigator's Brochure, Investigator's curriculum vitae [CV], etc) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

The IMP will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and the Sponsor.

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the health authorities (competent regulatory authority), as required by local regulation, in addition to the IRB/IEC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the health authorities (competent regulatory authority) and the IRB/IEC should be informed as soon as possible. They should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the Investigator's Brochure will be sent to the IRB/IEC and to health authorities (competent regulatory authority), as required by local regulation.

A progress report is sent to the IRB/IEC and in countries where applicable by local legislation and regulations to Health Authorities at least annually and a summary of the clinical trial's outcome at the end of the clinical trial.

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of the CRF, Discrepancy Resolution Form [DRF] or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

If any circuit includes transfer of data particular attention should be paid to the confidentiality of the patient's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as Subinvestigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All Subinvestigators shall be appointed and listed in a timely manner. The Subinvestigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical trial protocol and all necessary information.

13.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this clinical trial is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the CRFs. Thus, the main duty of the monitoring team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical trial.

At regular intervals during the clinical trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review study progress, Investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AESI documentation and reporting, AE documentation, IMP allocation, patient compliance with the IMP regimen, IMP accountability, concomitant therapy use and quality of data. Source document requirements

According to the ICH GCP, the monitoring team must check the CRF entries against the source documents, except for the pre-identified source data directly recorded in the CRF. The informed consent form will include a statement by which the patient allows the Sponsor's duly authorized personnel, the ethics committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the CRFs (eg, patient's medical file, appointment books, original laboratory records, etc). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

13.3 USE AND COMPLETION OF CASE REPORT FORMS (CRFS) AND ADDITIONAL REQUEST

It is the responsibility of the Investigator to maintain adequate and accurate CRFs (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the e-CRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the Sponsor as soon as they are entered in the e-CRF.

The computerized handling of the data by the Sponsor may generate additional requests (DRF) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the e-CRF.

13.4 USE OF COMPUTERIZED SYSTEMS

The complete list of computerized systems used for the study is provided in a separate document which is maintained in the Sponsor and Investigator study files.

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualification and training of each Investigator and Subinvestigator will be signed, dated and provided to the Sponsor prior to the beginning of the clinical trial.

14.2 RECORD RETENTION IN STUDY SITES

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The Investigator should retain the study documents at least 15 years after the completion or discontinuation of the clinical trial.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents following the clinical trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

14.3 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the clinical trial, including, but not limited to, the clinical trial protocol, personal data in relation to the patients, the CRFs, the Investigator's Brochure and the results obtained during the course of the clinical trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this clinical trial protocol and other necessary documentation to the ethics committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Subinvestigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Subinvestigators of the confidential nature of the clinical trial.

The Investigator and the Subinvestigators shall use the information solely for the purposes of the clinical trial, to the exclusion of any use for their own or for a third party's account.

14.4 PROPERTY RIGHTS

All information, documents and IMP provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Investigator shall not and shall cause the delegated Investigator staff /Subinvestigator not to mention any information or the Product in any application for a patent or for any other intellectual property rights.

All the results, data, documents and inventions, which arise directly or indirectly from the clinical trial in any form, shall be the immediate and exclusive property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the clinical trial.

As the case may be, the Investigator and/or the Subinvestigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

14.5 DATA PROTECTION

- The patient's personal data, which are included in the Sponsor database shall be treated in compliance with all applicable laws and regulations.
- When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- The Sponsor also collects specific data regarding Investigator as well as personal data from any person involved in the study which may be included in the Sponsor's databases, shall be treated by both the Sponsor and the Investigator in compliance with all applicable laws and regulations.

Subject's race or ethnicity (eg, Caucasian/white, Black, Asian/Oriental, others) will be collected in this study because these data are required by several regulatory authorities (eg, on afro American population for FDA).

14.6 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IECs/IRBs or regulatory authorities in countries requiring this document.

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the clinical trial protocol, good clinical practice, and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

14.8 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

14.8.1 By the Sponsor

The Sponsor has the right to terminate the participation of either an individual site or the study at any time, for any reason, including but not limited to the following:

- The information on the product leads to doubt as to the benefit/risk ratio.
- Patient enrollment is unsatisfactory.
- The Investigator has received from the Sponsor all IMP, means, and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon.
- Noncompliance of the Investigator or Subinvestigator, delegated staff with any provision of the clinical trial protocol, and breach of the applicable laws and regulations or breach of the ICH GCP.
- The total number of patients are included earlier than expected.

In any case the Sponsor will notify the Investigator of its decision by written notice.

14.8.2 By the Investigator

The Investigator may terminate his/her participation upon thirty (30) days' prior written notice if the study site or the Investigator for any reason becomes unable to perform or complete the clinical trial.

In the event of premature discontinuation of the study or premature close-out of a site, for any reason whatsoever, the appropriate IRB/IEC and regulatory authorities should be informed according to applicable regulatory requirements.

14.9 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a clinical study report and to provide a summary of study results to the Investigator.

14.10 PUBLICATIONS AND COMMUNICATIONS

The Investigator undertakes not to make any publication or release pertaining to the study and/or results of the study prior to the Sponsor's written consent, being understood that the Sponsor will not unreasonably withhold its approval.

As the study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, a primary presentation or publication of the study results based on global study outcomes shall be sought. However, if no multicenter publication is submitted, underway, or planned within twelve (12) months of the completion of this study at all sites, the Investigator shall have the right to publish or present independently the results of this study in agreement with other Investigators and stakeholders. The Investigator shall provide the Sponsor with a copy of any such presentation or publication for review and comment at least 30 days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other justified measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

The Investigator shall not use the name(s) of the Sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The Sponsor has the right at any time to publish the results of the study.

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this clinical trial protocol.

The Investigator should not implement any deviation from, or changes to the clinical trial protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC and/or notification/approval of health authorities (competent regulatory authority) of an amendment, as required by local regulation, except where necessary to eliminate an immediate hazard(s) to clinical trial patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this clinical trial protocol.

Any amendment to the clinical trial protocol requires written approval/favorable opinion by the IRB/IEC prior to its implementation, unless there are overriding safety reasons.

In case of substantial amendment to the clinical trial protocol, approval from the health authorities (competent regulatory authority) will be sought before implementation.

In some instances, an amendment may require a change to the informed consent form. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised informed consent form prior to implementation of the change and patient signature should be re-collected if necessary.

16 BIBLIOGRAPHIC REFERENCES

1. Murthy VL, Naya M, Foster CR, Hainer J, Gaber M, Di Carli G, Blankstein R, Dorbala S, Sitek A, Pencina MJ, Di Carli MF. Improved cardiac risk assessment with noninvasive measures of coronary flow reserve. *Circulation*. 2011;124:2215-24.
2. Marzilli M, Huqi A and Morrone D. Persistent Angina The Araba Phoenix of Cardiology. *Am J Cardiovasc Drugs*. 2010;10 Suppl.1:27-32.
3. Focardi M, Capati E, Affinito S, Urselli R and Marzilli M. Persistent angina after myocardial revascularization: a case report. *Heart Metab*. 2006; 31:27–9.
4. Patel M.R, Peterson E.D, Dai D, Brennan J.M, Redberg R.F, Anderson H.V et al. Low Diagnostic Yield of Elective Coronary Angiography. *N Engl J Med*. 2010;362:886-95.
5. Radico F, Cicchitti V, Zimarino M, De Catherina R. Angina pectoris and myocardial ischemia in the absence of obstructive coronary artery disease: practical considerations for diagnosis tests. *J Am Coll Cardiol Interv*. 2014;7:453-63.
6. Olson MB, Kelsey SF, Matthews K, Shaw LJ, Sharaf BL, Pohost GM, et al. Symptoms, myocardial ischaemia and quality of life in women: results from the NHLBI-sponsored WISE Study. *Eur Heart J*. 2003;24:1506-14.
7. Merz CN, Kelsey SF, Pepine CJ, Reichek N, Reis SE, Rogers WJ et al. The Women's Ischemia Syndrome Evaluation (WISE) study: protocol design, methodology and feasibility report. *J Am Coll Cardiol*. 1999;33:1453–61.
8. Bugiardini R, Pozzati A, Ottani F, Morgagni GL, Puddu P. Vasotonic angina: a spectrum of ischemic syndromes involving functional abnormalities of the epicardial and microvascular coronary circulation. *J Am Coll Cardiol*. 1993;22:417–25.
9. Shaw LJ, Bairey Merz CN, Pepine CJ, Reis SE, Bittner V, Kelsey SF et al. Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part I: gender differences in traditional and novel risk factors, symptom evaluation, and gender-optimized diagnostic strategies. *J Am Coll Cardiol*. 2006;47:S4–S20.
10. Suzuki H. Different definition of microvascular angina. *Eur J Clin Invest*. 2015;45(12):1360-6.
11. Izzo P, Macchi A, De Gennaro L, Gaglione A, Di Biase M and Brunetti N.D. Recurrent angina after coronary angioplasty: mechanisms, diagnostic and therapeutic options. *European Heart Journal: Acute Cardiovascular Care*. 2012;1(2):158–69.
12. Opherk D, Zebe H, Weihe E, Mall G, Dürr C, Gravert B et al. Reduced coronary dilatory capacity and ultrastructural changes of the myocardium in patients with angina pectoris but normal coronary arteriograms. *Circulation*. 1981;63(4):817–25.

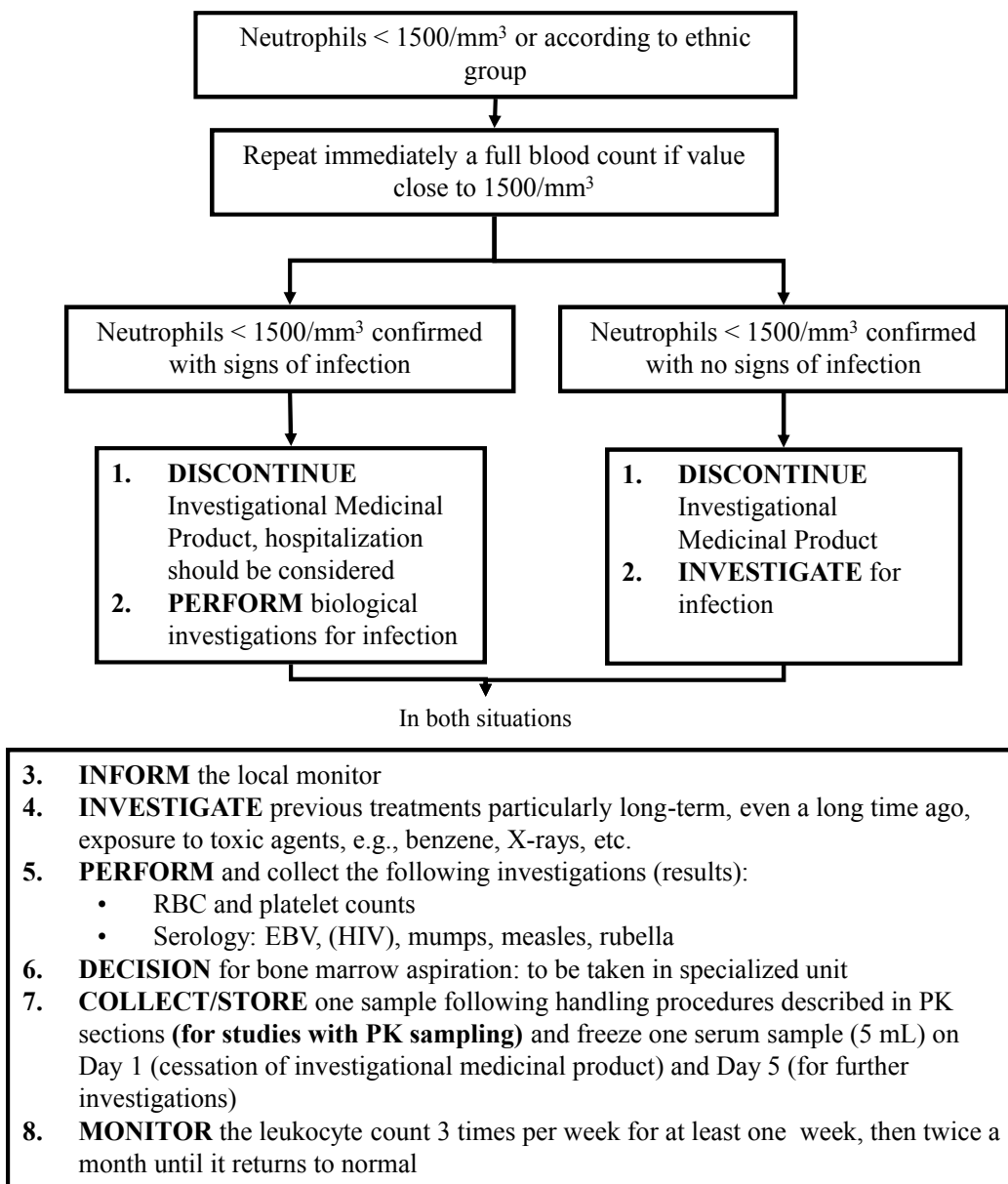
13. Chauhan A, Mullins PA, Taylor G, Petch MC, Schofield PM. Both endothelium-dependent and endothelium-independent function is impaired in patients with angina pectoris and normal coronary angiograms. *Eur Heart J.* 1997;18:60–8.
14. Sestito A, Lanza GA, Di Monaco A, Lamendola P, Carreri G, Tarzia P et al. Relation between cardiovascular risk factors and coronary microvascular dysfunction in cardiac syndrome X. *J Cardiovasc Med (Hagerstown).* 2011;12:322–7.
15. Egashira K, Inou T, Hirooka Y, Yamada A, Urabe Y, Takeshita A. Evidence of impaired endothelium-dependent coronary vasodilation in patients with angina pectoris and normal coronary angiograms. *N Engl J Med.* 1993;328:1659–64.
16. Shimokawa H, Satoh K. 2015 ATVB Plenary Lecture: translational research on rho-kinase in cardiovascular medicine *Arterioscler Thromb Vasc Biol.* 2015;35(8):1756-69.
17. Kanda T, Wakino S, Hayashi K, Homma K, Ozawa Y, Saruta T. Effect of fasudil on Rho-kinase and nephropathy in subtotaly nephrectomized spontaneously hypertensive rats. *Kidney Int.* 2003;64:2009-19.
18. Sawada N, Itoh H, Ueyama K, Yamashita J, Doi K, Chun TH, et al. Inhibition of rho-associated kinase results in suppression of neointimal formation of balloon-injured arteries. *Circulation.* 2000;101(17):2030-3.
19. Kataoka C, Egashira K, Inoue S, Takemoto M, Ni W, Koyanagi M, et al. Important role of Rho-kinase in the pathogenesis of cardiovascular inflammation and remodeling induced by long-term blockade of nitric oxide synthesis in rats. *Hypertension.* 2002;39:245-50.
20. Do e Z, Fukumoto Y, Takaki A, Tawara S, Ohashi J, Nakano M, et al. Evidence for Rho-Kinase activation in patients with pulmonary arterial hypertension. *Circ J.* 2009;73:1731-9.
21. Hata T, Goto C, Soga J, Hidaka T, Fujii Y, Idei N, et al. Measurement of Rho-associated kinase (ROCK) activity in humans: Validity of leukocyte p-MBS/t-MBS in comparison with vascular response to fasudil. *Atherosclerosis.* 2011;214:117-21.
22. Kikuchi Y, Yasuda S, Aizawa K, Tsuburaya R, Ito Y, Takeda M, et al. Enhanced Rho-Kinase activity in circulating neutrophils of patients with vasospastic angina. A Possible Biomarker for Diagnosis and Disease Activity Assessment. *J Am Coll Cardiol.* 2011;58:1231-7.
23. Löhn M, Plettenburg O, Ivashchenko Y, Kannt A, Hofmeister A, Kadereit D, Schaefer M, Linz W, Kohlmann M, Herbert JM, Janiak P, O'Connor SE, Ruetten H. Pharmacological characterization of SAR407899, a novel rho-kinase inhibitor. *Hypertension.* 2009;54(3):676-83.
24. Shimokawa H, Sunamura S, Satoh K. RhoA/Rho-Kinase in the Cardiovascular System. *Circ Res.* 2016;118(2):352-66.

25. Ming-Jui Hung, Wen-Jin Cherng. Clinical Applications of Transthoracic Doppler Echocardiographic Coronary Flow Reserve. Measurements in the Left Anterior Descending Coronary Artery. *Journal of Medical Ultrasound*. 2011;19:115-21.
26. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A et al. 2013 ESC guidelines on the management of stable coronary artery disease: The Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J*. 2013;34(38):2949-3003.
27. Berry C. Fractional flow reserve, coronary flow reserve and the index of microvascular resistance in clinical practice. *Radcliffe Cardiology*. 2014;1-6.
28. Spertus JA, Winder JA, Dewhurst T, Deyo R, Prodzinski J, McDonell M, et al. Development and evaluation of the Seattle Angina Questionnaire: a new functional status measure for coronary artery disease. *J Am Coll Cardiol*. 1995;25:333-41.
29. Chan PS, Jones PG, Arnold SA, Spertus JA. Development and validation of a short version of the Seattle angina questionnaire. *Circ Cardiovasc Qual Outcomes*. 2014;7:640-7.
30. El Fakhri G, Kardan A, Sitek A, Dorbala S, Abi-Hatem N, Lahoud Y et al. Reproducibility and accuracy of quantitative myocardial blood flow assessment with (82)Rb PET: comparison with (13)N-ammonia PET. *J Nucl Med*. 2009;50:1062-71.
31. El Fakhri G, Guerin G, Sitek A, Curillova Z, Agnostopoulos C, Dorbala S et al. Absolute myocardial blood flow quantification in Rb-82 cardiac PET using generalized factor and compartment analysis: a reproducibility study. *Eur J Nucl Med Molec Imaging*. 2006;33:S217.
32. Murthy VL, Lee BC, Sitek A, Naya M, Moody J, Polavarapu V, Ficaro EP and Di Carli MF. Comparison and prognostic validation of multiple methods of quantification of myocardial blood flow with 82Rb PET. *J Nucl Med*. 2014;55:1952-8.

17 APPENDICES

Appendix A General guidance for the follow-up of laboratory abnormalities by Sanofi

NEUTROPENIA

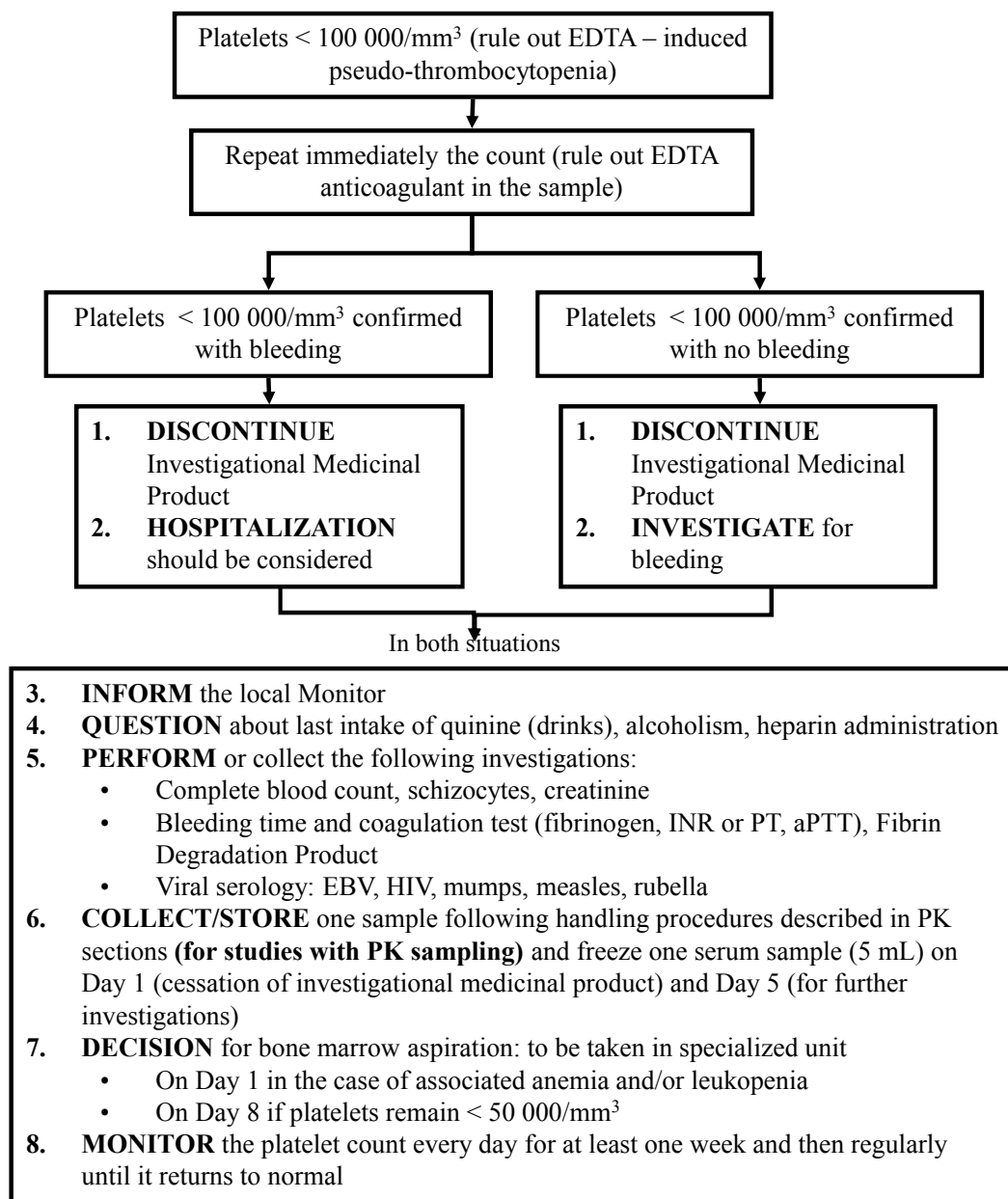


Note:

- The procedures described in the above flowchart are to be discussed with the patient only in case the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.
- For individuals of African descent, the relevant value of concern is <1000/mm³

Neutropenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting adverse events in [Section 10.4.3](#) is met.

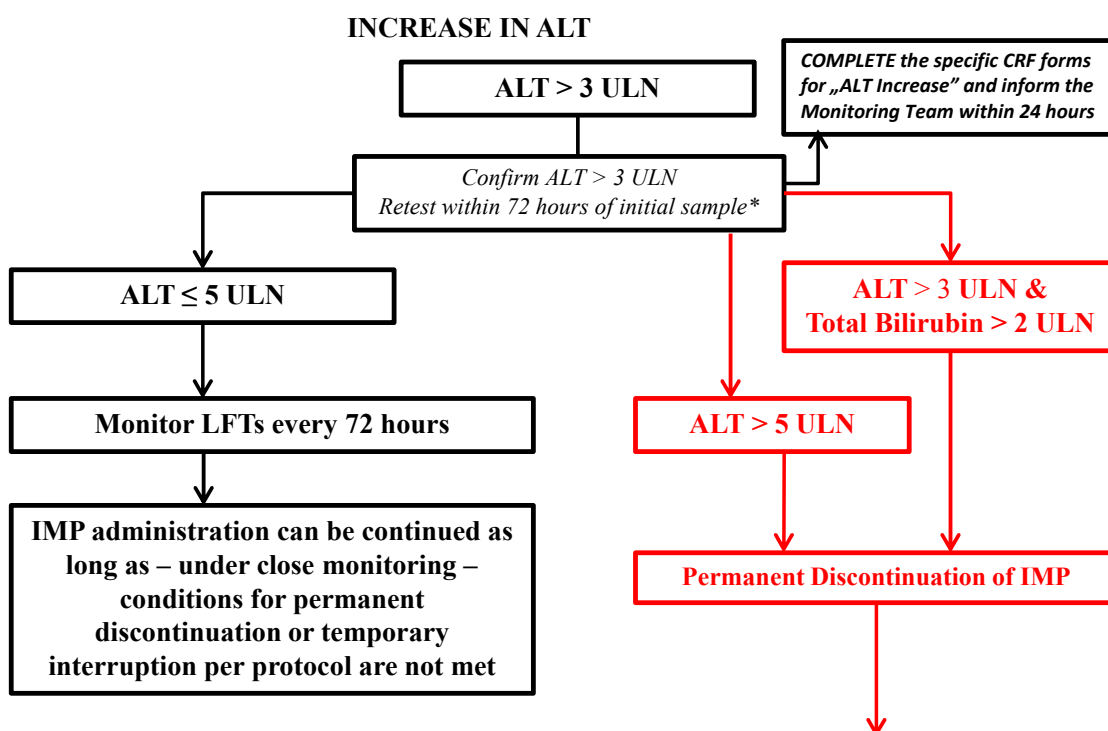
THROMBOCYTOPENIA



Note:

The procedures above flowchart are to be discussed with the patient only in case described in the the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.

Thrombocytopenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting adverse events in [Section 10.4.3](#) is met.



In ANY CASE, FOLLOW the instructions listed in the box below:

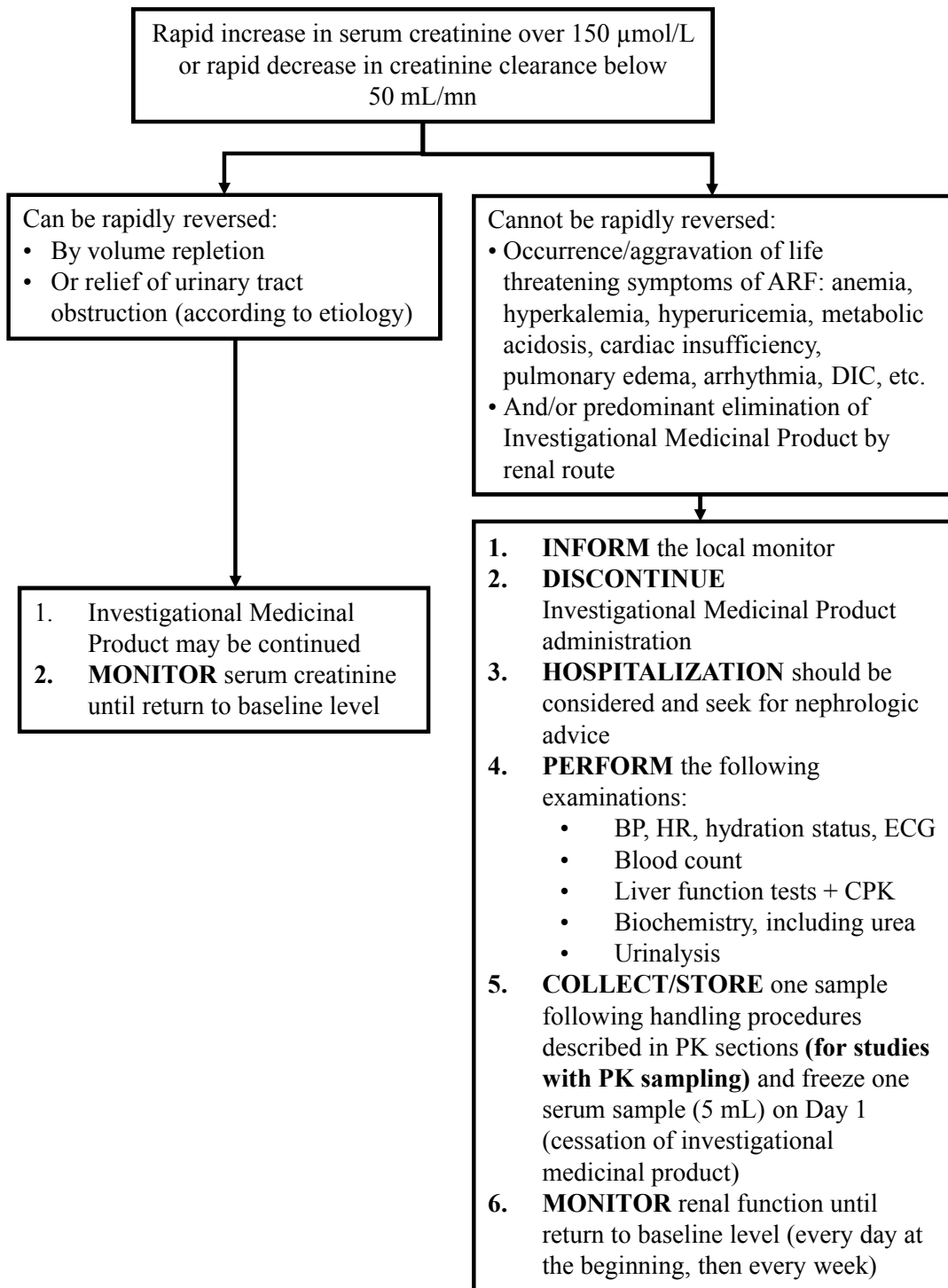
1. **INFORM** the Site Monitor who will forward the information to the Study Manager
2. **INVESTIGATE** specifically for malaise with or without loss of consciousness, dizziness, and/or hypotension and/or episode of arrhythmia in the previous 72 hours; rule out muscular injury
3. **PERFORM** the following tests:
 - LFTs: AST, ALT, alkaline phosphatase, total and conjugated bilirubin and prothrombin time / INR
 - CPK, serum creatinine, complete blood count
 - Anti-HAV IgM, anti-HBc IgM, (HBV-DNA if clinically indicated), anti-HCV and HCV RNA, anti-CMV IgM and anti-HEV IgM antibodies
 - Depending on the clinical context, check for recent infection with EBV, herpes viruses, and toxoplasma
 - Hepatobiliary ultrasonography (or other imaging investigations if needed)
4. **CONSIDER** Auto-antibodies: antinuclear, anti-DNA, anti-smooth muscle, anti-LKM
5. **CONSIDER** consulting with hepatologist
6. **CONSIDER** patient hospitalisation if INR>2 (or PT<50%) and/or central nervous system disturbances suggesting hepatic encephalopathy
7. **MONITOR LFTs after discontinuation of IMP:**
 - As closely as possible (or every 48 hours) until stabilization, then every 2 weeks until return to normal/baseline or clinical resolution.
8. **FREEZE** serum sample (5ml x 2)
9. **In case of SUSPICION of GILBERT Syndrome**, a DNA diagnostic test should be done

*If unable to retest in 72 hours, use original lab results to decide on further reporting/monitoring/discontinuation.

Note:

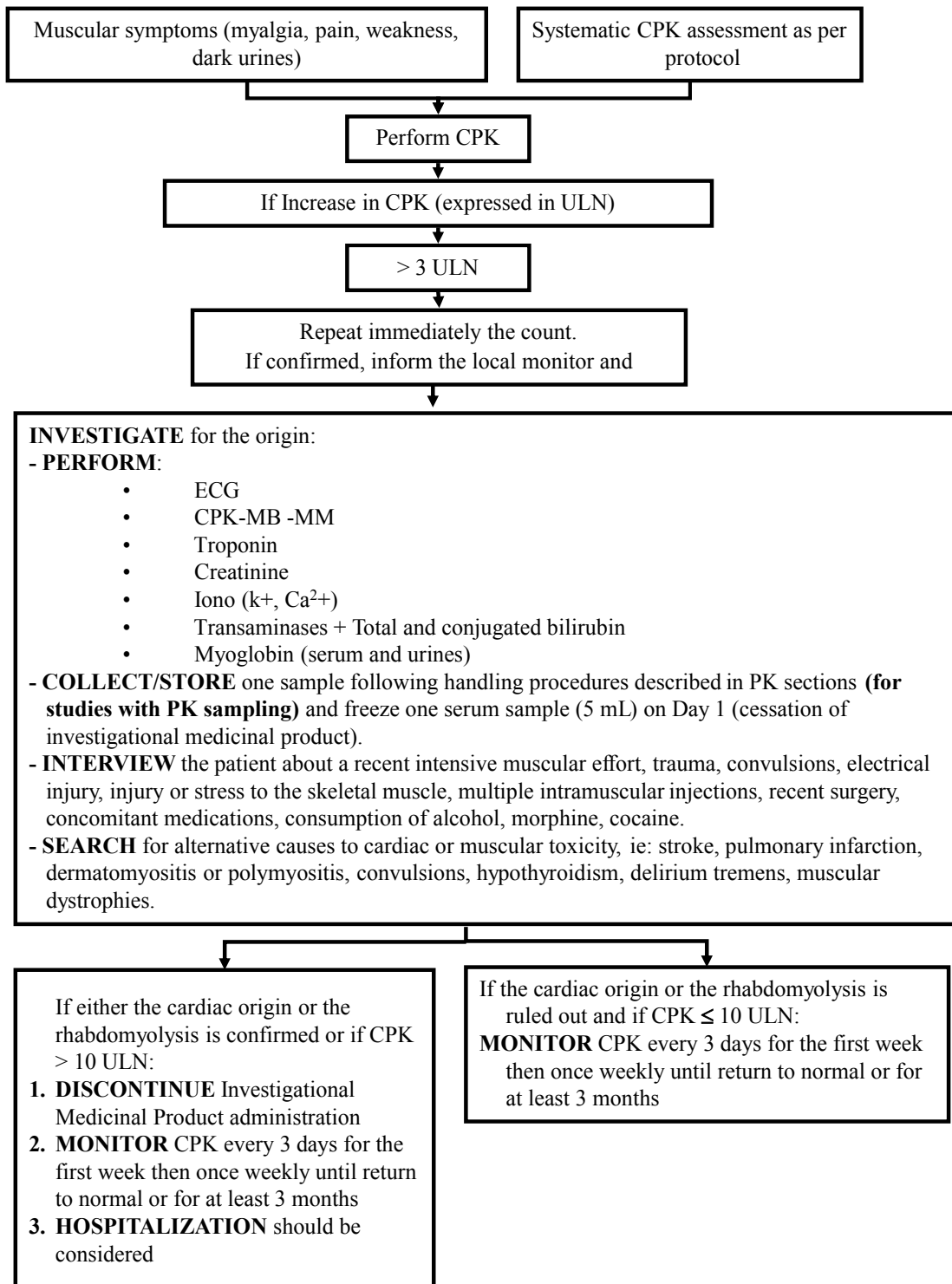
- “Baseline” refers to ALT sampled at baseline visit; or if baseline value unavailable, to the latest ALT sampled before the baseline visit. The algorithm does not apply to the instances of increase in ALT during screening.
- See [Section 10.4](#) for guidance on safety reporting.
- Normalization is defined as ≤ ULN or baseline value, if baseline value is >ULN.

ACUTE RENAL FAILURE



Acute renal failure is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting adverse events in [Section 10.4.3](#) is met.

SUSPICION OF RHABDOMYOLYSIS



Suspicion of rhabdomyolysis is to be recorded as an AE only if at least 1 of the criteria in the general guidelines for reporting adverse events in [Section 10.4.3](#) is met.

Appendix B Procedure for collection, handling, storage, and shipment of SAR407899 specimens for pharmacogenetic samples

1. SUMMARY OF HANDLING AND SUPPLIES FOR PHARMACOGENETIC SAMPLES

1.1 Sampling Supply Description

Pharmacogenetic specimens	Collection/Storage Tube: 2 vacutainer BECTON Dickinson 6 mL K2 EDTA with HEMOGARD closure,
---------------------------	--

1.2 Summary of handling procedures for pharmacogenetic samples

Sample type(s)	Pharmacogenetic
Blood sample volume	6 mL
Collection tube	a 6 mL Becton Dickinson K2 EDTA VACUTAINER™ Plus tubes with HEMOGARD™ closure (PN367863/4) sterile tubes
Anticoagulant	K ₂ EDTA
Blood handling procedures	Keep blood on ice and frozen within 30 minutes of sampling time. DO NOT CENTRIFUGE BLOOD
Storage conditions	-70°C or colder

2. COLLECTION/HANDLING/PROCESSING OF SAMPLES

The analytical methods used are extremely sensitive. All sampling procedures must be followed accurately.

2.1 Blood pharmacogenetic samples for DNA storage

- **Collection schedule:** Per protocol.
- **Procedure:**
 - Using a **waterproof pen**, write subject ID on label in space provided,
 - Collect 6 mL of blood, using the 6 mL Vacutainer Becton Dickinson K2 EDTA with HEMOGARD Closure provided, and gently invert tube 10-15 times permitting the specimen to mix with the anticoagulant,
 - **Under no circumstances should the tube be centrifuged,**
 - Ensure the sample tube is clearly and appropriately labeled as described above and in detail in Covance laboratory manual,
 - Immediately freeze and maintain the blood in an upright position at -70°C or colder. Samples must be stored on dry ice if a freezer is not immediately available,
 - Complete the laboratory requisition form (provided by Covance) for each sample.

- **Labeling of specimens:**

- Each sample tube should have attached to it the label provided by Covance,

DNA Subject ID:XXX-001-YYY ACT14656 / SAR407899 (preprinted) Bar code (preprinted) Accession number (preprinted)

- In the event of damage or loss of the provided labels, a new label should be immediately requested from Covance.

- **Storage**

- Samples must be kept at -70 °C or colder, organized in a rack in numeric order according to the subject ID, until ready for packaging and shipping.

3. PACKAGING AND SHIPMENT OF DNA PHARMACOGENETIC ANALYSIS

3.2 DNA for pharmacogenetic analysis sample

3.2.1 Packaging and shipment

- Samples and accompanying documents should be packaged according to the detailed instructions in Covance laboratory manual provided at the initiation of the study.
- Samples must be packaged according to IATA Dangerous Goods Regulations, Packing Instructions 650, using the packing materials provided by Covance.
- In the event that the packaging materials or instructions are lost, please contact the study Sponsor.
- Ship samples on dry ice to Covance as described in the Global Study Schedule, using the shipping materials provided.

Note: Additional detailed information can be found in Covance laboratory manual, provided at the beginning of the study. This includes additional details regarding:

- Sample collection kits.
- Sample collection procedures.
- Documentation procedures.
- Packing and shipping instructions.
- Sample kit resupply.
- How to get help.

4. SHIPMENT CONTACT NAMES AND ADDRESSES

Pharmacogenetic specimens for DNA storage:

Use for the Americas: USA and Canada, as well as Latin America and the Islands (Dominican Republic, etc):

Covance CLS Indianapolis

8211 SciCor Drive

Indianapolis, IN

46214-2985 USA

Tel: [REDACTED]

(local calls)

Tel: [REDACTED]

Fax: [REDACTED]

Use for Europe, the Middle East, and Africa:

Covance CLS Genève

Rue Moïse-Marcinhes 7

1217 Meyrin/Genève-CH

Tel: [REDACTED]

Fax: [REDACTED]



[REDACTED]						
[REDACTED]						
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

[Redacted]					
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]					
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]					
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]					
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]					
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]					
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]

ACT14656 Amended Protocol 03

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[REDACTED]	Clinical Approval	19-Apr-2018 19:24 GMT+0200
[REDACTED]	Clinical Approval	19-Apr-2018 20:41 GMT+0200