1.2 POTENTIAL TITRATION SCHEDULES & DECISION RULES STUDY

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 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 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	Titration Phase				Maintenance Phase	End-of-study
	D-28 to D-1	**D1** (see separate flow chart for this visit)	**D8 (+/-2days)**	**D15 (+/-2days)**	**D22 (+/-2days)**	**D29 (+2days)** EOT/early discontinuation	**D36 (+/-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
	D-28 to D-1	D1 (see separate flow chart for this visit)	D8 (+/-2days)	D15 (+/-2days)	D22 (+/-2days)	D29 (+2days) EOT/early discontinuation	D36 (+/-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[j]		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.

Phase	Screening	Titration Phase				Maintenance Phase	End-of-study
	Up to 6 weeks D-42 to D-1	**D1** (see separate flow chart for this visit)	**D8 (+/-2days)**	**D15 (+/-2days)**	**D22 (+/-2days)**	**D29 (+2days)** EOT/early discontinuation	**D36 (+/-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[j]		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.

Day	**D1**						
Time (hour/minute)[a]	**-4H**	**-3H**	**-2H30**	**-0H30**	**0H**	**1H**	**3H**
Vital signs[g], 12 lead-ECG[f]		X		X		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, 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.

Day	**PET scan up to 28 days or up to 14 days**	**D1**			
Time (hour/minute)[a]		**Prior dosing**	**0H**	**1H**	**3H**
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.

Day	D29					
Time (hour/minute)[a]	**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			X[j]		

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.

TIA: transient ischemic attack
TPD: total perfusion deficit

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 ≥20mmHg, 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

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.

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}Rubidium 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

- 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".

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.

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

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.

Patients who do not met 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

- 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:

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 ≥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 ≥30 mmHg,
  - SBP <90 mmHg,
  - Symptomatic orthostatic hypotension with SBP decrease at Minute 3 or Minute 5 between seated and standing position ≥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 ≥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 remained 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 ^{13}N-ammonia or ^{82}Rubidium 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.

11.4.2.2 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 , HLGT, HLT and PT showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, 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.

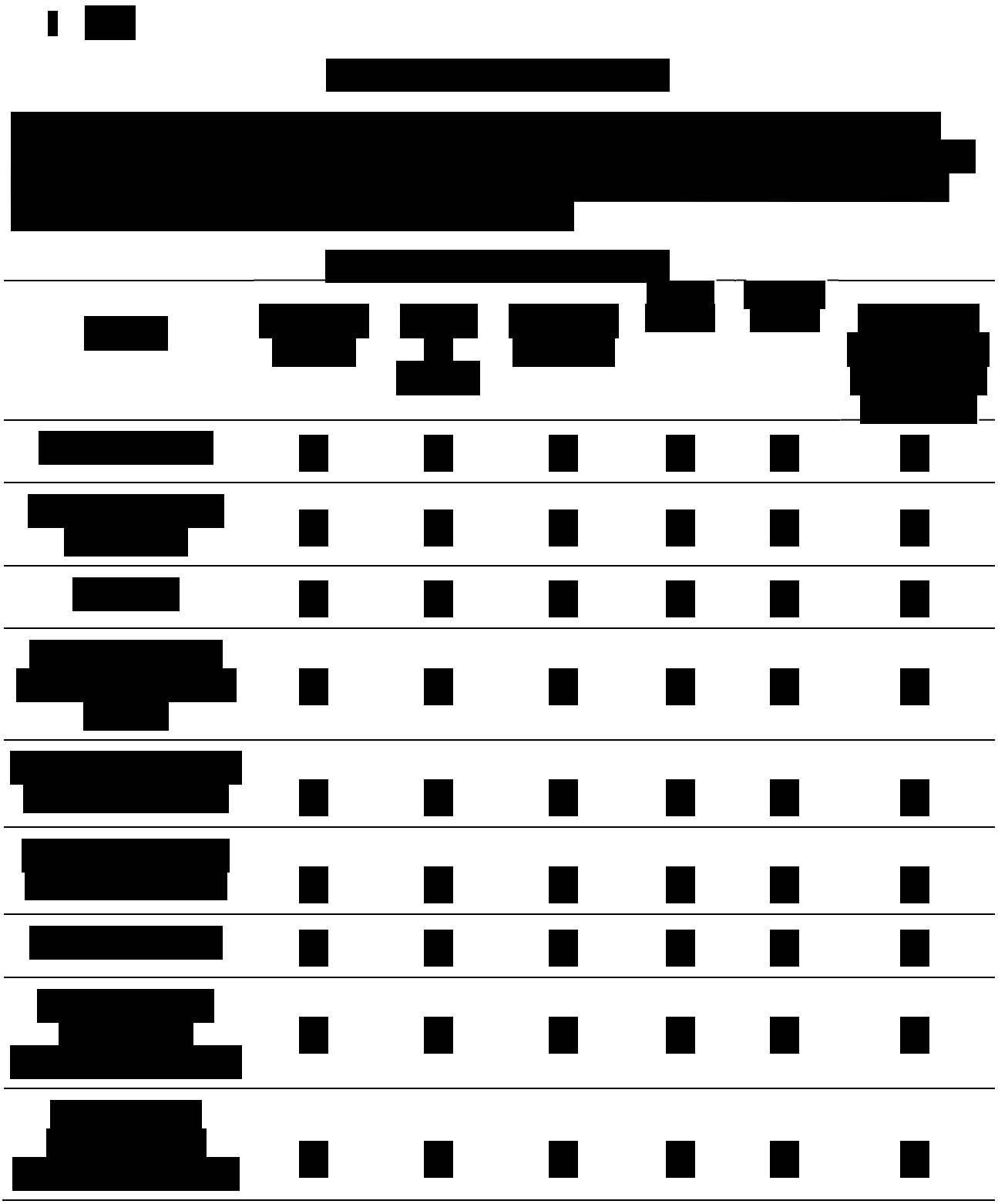
11.4.3.3 Potential drug-induced liver injury

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 >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.



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**
	Up to 6 weeks D-42 to D-1	**D1** (see separate flow chart for this visit)	**D8 (+/-2days)**	**D15 (+/-2days)**	**D22 (+/-2days)**	**D29 (+2days)** EOT/early discontinuation	**D36 (+/-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

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.

1.4.2 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**			
Time (hour/minute)[a]		**Prior dosing**	**0H**	**1H**	**3H**
Visit start	X	X			
End of visit	X				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,f]	X[d]				
NIMP administration	X[h]				
IVRS/IWRS			X		
Randomization			X		
IMP administration			X		

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**					
Time (hour/minute)[a]	**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[i]	
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					

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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).

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

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}Rubidium PET scan <2.0.

I 02. Signed written informed consent.

I 03. Not under any administrative or legal supervision.

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 ^{13}N-ammonia or ^{82}Rubidium 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.

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.

9.2.4.2 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.

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
[redacted]	10 mL	1	10 mL
[redacted]	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 ^{13}N-ammonia or ^{82}Rubidium 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.

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 inform 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.

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.

- 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.

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.

11.4.3.4 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.