Document Type:	Study protocol
Official Title:	Multicenter, randomized, placebo controlled, double-blind, parallel group, dose-finding Phase 2 study to evaluate the efficacy and safety of BAY 2433334 in patients following an acute myocardial infarction
NCT Number:	NCT04304534
Document Date:	22-Oct-2019

Title Page

Protocol Title:

Multicenter, randomized, placebo controlled, double-blind, parallel group, dose-finding Phase 2 study to evaluate the efficacy and safety of BAY 2433334 in patients following an acute myocardial infarction

Protocol Number:	20603
Amendment Number:	not applicable
Compound Number:	BAY 2433334
Study Phase:	Phase 2b
Short Title:	Phase 2 **P**rogram of **A**nti**C**oagulation via **I**nhibition of **F**X**I**a by the oral **C**ompound BAY 2433334 – **A**cute **M**yocardial **I**nfarction study
Acronym:	**PACIFIC-AMI**

Sponsor Name and Legal Registered Address:

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Regulatory Agency Identifier Number(s):

IND: 145673

EudraCT: 2019-003244-79

Approval Date: **22 OCT 2019**

Sponsor Signatory

PPD

22 OCT 2019

PPD PPD

PPD

Date

Medical Monitor (Study Medical Expert) name and contact information can be found in the Trial Master File (TMF).

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1. Protocol Summary

1.1 Synopsis

Protocol Title: Multicenter, randomized, placebo controlled, double-blind, parallel group, dose-finding Phase 2 study to evaluate the efficacy and safety of BAY 2433334 in patients following an acute myocardial infarction.

Short Title: **PACIFIC-AMI -** Phase 2 **P**rogram of **A**nti**C**oagulation via **I**nhibition of **F**X**I**a by the oral **C**ompound BAY 2433334 **– A**cute **M**yocardial **I**nfarction study

Rationale: This study will explore a dose range of BAY 2433334 in order to determine the dose that is efficacious and safe and that can be used in a Phase 3 study in the same indication. Rivaroxaban in addition to single or dual antiplatelet therapy (acetylsalicylic acid +/- clopidogrel) is the only non-Vitamin K oral anticoagulants (NOAC) approved for secondary prevention of acute coronary syndrome (ACS) in Europe. In addition, the COMPASS study has also shown the benefit of this combination (rivaroxaban in addition to acetylsalicylic acid) in patients with stable coronary artery disease (CAD)/peripheral artery disease (PAD). The clinical use of antiplatelet therapies together with an anticoagulant in acute coronary syndrome is limited due to concerns about bleeding risk. The inhibition of FXIa on top of antiplatelet therapy is expected to not lead to a relevant increase in bleeding and especially major bleeding, while maintaining the efficacy benefit shown for the combination of antiplatelet therapies and rivaroxaban.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• to evaluate whether the oral FXIa inhibitor BAY 2433334 compared to placebo leads to a lower incidence of cardiovascular (CV) death, MI, stroke and stent thrombosis in participants with an acute myocardial infarction and who are treated with dual antiplatelet therapy	**Primary Efficacy Endpoint** • the composite of CV death, MI, stroke and stent thrombosis **Secondary Efficacy Endpoints** • all cause mortality • CV death • MI • stroke • stent thrombosis
• to evaluate whether the incidence of bleeding is similar for BAY 2433334 compared to placebo in participants with an acute myocardial infarction and who are treated with dual antiplatelet therapy	**Primary Safety Endpoint** • Bleeding Academic Research Consortium (BARC) definition type 2, 3 and 5 **Secondary Safety Endpoints** • all bleeding • BARC bleeding definition type 3, 5 • BARC bleeding definition type 1, 2, 3, 5

The primary efficacy estimand is the hazard ratio of the composite of CV death, MI, stroke and stent thrombosis comparing BAY 2433334 (20 and 50 mg pooled) with placebo in adult participants with an AMI treated with DAPT while alive and regardless of treatment discontinuation.

The secondary efficacy estimands are defined following the same approach for the individual secondary endpoints as done for the primary efficacy estimand.

The primary safety estimand is the hazard ratio of BARC type 2, 3 and 5 bleeding comparing pooled BAY 2433334 with placebo in adult participants with an AMI treated with DAPT and who have taken at least one dose of study medication of BAY 2433334 or placebo and while the patient is alive and exposed to study drug

The secondary safety estimands are defined following the same approach for the individual secondary endpoints as done for the primary safety estimand.

Overall Design:

Study 20603 is a multicenter, randomized, placebo controlled, double-blind, parallel group, dose-finding study.

The study population includes participants following an AMI with a plan for treatment with DAPT (acetylsalicylic acid + $P2Y_{12}$ inhibitor) after discharge from hospital.

Participants will be screened and have to be randomized within 5 days of hospitalization for the index AMI event.

Stratification will be based on the intended $P2Y_{12}$ inhibitor use (ticagrelor/prasugrel versus clopidogrel) after hospital discharge.

Participants should have the initial coronary angiography and revascularization procedures, either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), as treatment for the index AMI event performed before randomization. However, a planned, staged PCI procedure can be performed after randomization.

If all information is available, participants can be randomized on the day of screening.

Disclosure Statement: This is a parallel-group study with 4 arms that is participant and investigator blinded

Intervention Model: Parallel

Primary Purpose: Treatment

Number of Arms: 4 arms (3 investigational drug arms and 1 placebo arm)

Number of Participants:

Approximately 1650 participants will be screened to achieve 1600 randomly assigned to study intervention for an estimated total of 400 evaluable participants per intervention group. More details are available in Section 9.2 Sample Size Determination.

Intervention Groups and Duration:

BAY 2433334 is the sponsor's study intervention under investigation. Placebo is used as comparator. Study intervention duration and dose regimen are tabulated as follows:

Study Period	Duration*	Dose and Frequency	Route of administration
Screening	≤ 5 days		Oral
Intervention	26-52 weeks*	BAY 2433334 10 mg once daily BAY 2433334 20 mg once daily BAY 2433334 50 mg once daily Placebo once daily	
Safety follow-up	2 weeks		

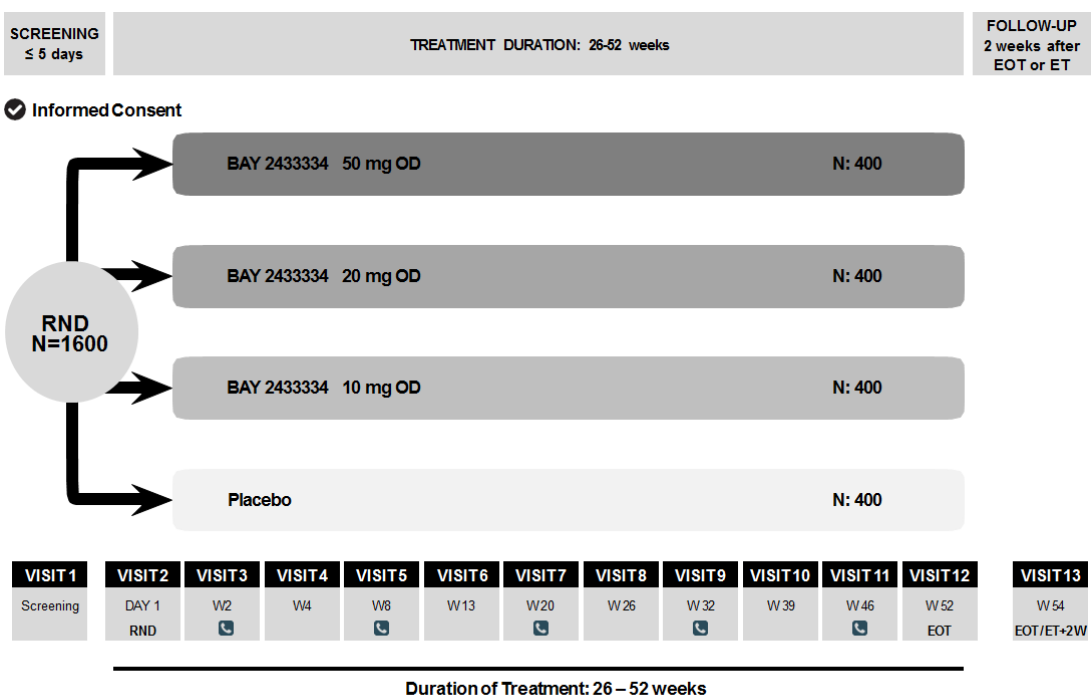
Total planned number of patients	Total planned study duration
1600	Between 28 and 54 weeks

*The Study Treatment End Date will be 26 weeks after randomization of the last enrolled participant in the study. Participants active on treatment at the time the last participant is randomized in the study, the maximum treatment duration beyond this date will be no longer than an additional 26 weeks. Thus, participants will have a total treatment duration of a minimum 26 weeks to a maximum of 52 weeks.

Data Monitoring Committee: Yes

1.2 Schema

Figure 1–1 Study design overview



Background therapy: plan for dual antiplatelet therapy at hospital discharge for AMI

EOT= End of Treatment, OD=Once Daily, RND=Randomization, N = total number of participants, W = week

1.3 Schedule of Activities (SoA)

Study periods / (Duration)	**Screening (SCR)***	**Intervention period (26-52 weeks, from RND until End of Treatment visit [EOT])**											**Early termination (ET)**	**Safety Follow-up (SFU) (14 days after EOT or ET)**
Visit number	**1**	**2**	**3**	**4[f]**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**12a**	**13**
Visit type	site	Site	☎	site	☎	site	☎	site	☎	site	☎	site	site	☎ (site)
Week [W] Study day and allowed deviations	**SCR** -5 → 1	**RND / W0** 1	**W2** 15±4	**W4** 29±4	**W8** 57±4	**W13** 92±4	**W20** 141±4	**W26** 183±4	**W32** 225±4	**W39** 274±4	**W46** 323±4	**W52/EOT** 365±4	**Any time** ET+7	**EOT or ET[c]+2 weeks** 379+7
Administrative procedures														
Signed informed consent	X													
Pharmacogenetic consent	X													
Dispense study contact card	X													
Inclusion and exclusion criteria	X	X[a]												
Demographics and biometrics	X													
Medical history	X													
Prior and Concomitant medication	X	X[a]	X[i]	X	X[i]	X	X[i]	X	X[i]	X	X	X	X	X
Clinical procedures / assessments														
12-lead ECG[d]	X	X[a]				X						X	X	
Vital signs (BP and HR)	X	X[a]		X		X		X		X		X	X	
Adverse events		←========== Continuously ==========→												
Outcome events[h]		←========== Continuously ==========→												
IxRS														
Randomization / Visit registration via IxRS	X	X				X		X		X		X	X	
Laboratory assessments														
Safety blood sample	X[e]	X[a,e]		X		X		X		X		X	X	
Pharmacokinetic sample[g]				X				X					X	
Pharmacodynamic sampling[g]		X		X				X					X	

Study periods / (Duration)	Screening (SCR)*	Intervention period (26-52 weeks, from RND until End of Treatment visit [EOT])											Early termination (ET)	Safety Follow-up (SFU) (14 days after EOT or ET)
Visit number	**1**	**2**	**3**	**4[h]**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**12a**	**13**
Visit type	site	Site	☎	site	☎	site	☎	site	☎	site	☎	site	site	☎ (site)
Week [W] Study day and allowed deviations	**SCR** -5 → 1	**RND / W0** 1	**W2** 15±4	**W4** 29±4	**W8** 57±4	**W13** 92±4	**W20** 141±4	**W26** 183±4	**W32** 225±4	**W39** 274±4	**W46** 323±4	**W52/EoT[c]** 365±4	**Any time** ET+7	**EoT or ET[c]+2 weeks** 379+7
Pharmacogenetic sample[g]		X												
Biomarker sampling[g]		X						X					X	
Study drug[j] administration														
Study drug[j] dispensation		X[b]				X		X		X				
Study drug[j] intake at the site[g]		X		X				X				no intake		
Study drug[j] collection and accountability						X		X		X		X	X	

Abbreviations: BP = blood pressure, CRF = case report form, ECG = electrocardiogram, EoT = end of treatment, ET = early termination, HR = heart rate, IxRS = Interactive Voice/Web Response System, MI = myocardial infarction PD = pharmacodynamic(s), PK = pharmacokinetic(s), RND= randomization, SCR = screening, SFU = safety follow -up, SoA = Schedule of Activities, TIA = transient ischemic attack

[*] Screening and randomization must occur during hospitalization and latest within 5 days of hospital admission. Intake of the first dose of study drug will start as soon as possible and on the same day as randomization (day 1).

[a] if screening and randomization are performed on the same day, this procedure does not need to be repeated.

[b] at each contact, participants should be reminded regarding study drug compliance.

[c] Participants will perform their safety follow-up phone call 2 weeks after the EoT visit or the ET visit whichever occurs earlier. (i.e. in case of Early Termination 2 weeks after last study drug intake).

[d] ECG machine that automatically calculates the heart rate and measures PR, QRS, QT and QTc intervals should be used.

[e] Creatinine and eGFR results as well as AST and ALT values measured in the local laboratory for screening. Current laboratory results available for the index hospitalization for the myocardial infarction can be used. Full safety labs done at randomization (Central Lab).

[f] The visit can be performed at a later time point if participant on inpatient rehabilitation facility and this visit cannot be arranged.

[g] Refer to Table 1–1: PK, PD and Biomarker sampling

[h] Outcome events including all bleeding, death, MI, stroke and stent thrombosis as well as events indicative of a potential outcome (see Section 10.1.5.4) need to be reported on dedicated forms in the eCRF on an ongoing basis, even if the participant is permanently discontinued from the study treatment.

[i] at visits 3, 5, 7, 9 and 11: any new concomitant medication and AEs or outcome events will be captured during the telephone calls.

[j] "Study drug" refers to "study intervention' as defined in Section 6.1.

PK, PD and Biomarkers sampling

An overview of the PK, PD and Biomarkers sampling is shown in Table 1–1

Table 1–1 PK, PD and Biomarker Sampling

	Day 1 (Visit 2)	Week 4 (Visit 4[a])			Week 4 or later (Visit 4 or subsequent visit)	Week 26 (Visit 8)/ET[d]
	Predose Day 1	Predose	0.5-1.5h postdose	2-4h[b] postdose	4-12h[b,c] postdose	Predose
PK[e]		x	x	x	x	x
PD[e]	x	x	x	x	x	x
Biomarkers Plasma	x					x
Biomarkers Serum	x					x
Genetics	x					

Abbreviations: ET = Early termination, PD = pharmacodynamic(s), PK = Pharmacokinetic(s)

[a] At Visit 4: in order to collect pre-dose samples for PK and PD, participants should take their study drug at the site only after blood sampling. The investigator must record the time when the study drug is taken at the site. A phone call before V4 to remind participants is recommended.

[b] The minimum time between the 2-4 h post-dose and the 4-12 h post-dose samples, if collected the same day, should be at least 1 hour.

[c] The late sample 4-12 hr post-dose sample can be taken at week 4 (visit 4) or at a later-on visit (e.g. Visit 6). The exact time of when the study drug was administered must be recorded as well as PK and PD post-dose sample collection time.

[d] At Visit 8 (week 26) participants should take their study drug at the site, in order to collect pre-dose samples for PK/PD and biomarkers. However, in case Visit 8 is also the EOT visit as well as in case of ET visit, no study drug will be administered.

[e] If study drug is temporily stopped, PK/PD blood samples should only be obtained if study drug has been restarted and sustained for at least 4 days, see Section 7.1.1

The exact times of PK, PD and biomarker sampling need to be recorded as well as the time of the most recent / associated study drug intake (i.e. on the PK/PD sampling day, as well as the previous day).

2. Introduction

BAY 2433334 is a direct, potent inhibitor of activated coagulation factor XI (FXIa) being developed for three main indications:

1. Prevention of stroke and systemic embolism in patients with AF (cardioembolic stroke prevention)
2. Secondary stroke prevention in patients after an ischemic stroke (large artery, lacunar stroke, or embolic stroke of undetermined source [ESUS]) (non-cardioembolic stroke prevention)
3. Prevention of major adverse cardiac events (CV death, MI, stroke) in patients after an acute myocardial infarction (AMI).

Study 20603 will be a Phase 2 study with a 6 to 12 months treatment duration and will test BAY 2433334 against placebo in patients following an AMI who are treated with dual antiplatelet therapy.

The current clinical development of BAY 2433334 includes two additional Phase 2 studies in patients with AF (study 19765, 3 months treatment duration, apixaban as comparator) and in patients with non-cardioembolic ischemic stroke (study 19766, 6-12 months treatment duration, on top of primarily single antiplatelet therapy, placebo as comparator).

Each individual study will have its own objectives. However, in order to reach and draw conclusions concerning safety in general, and especially bleeding, the program is designed to pool the data across the three Phase 2 studies to help further characterize safety and efficacy.

2.1 Study Rationale

This Phase 2 study will explore a dose range of BAY 2433334 in order to determine the dose that is efficacious and safe and that can be used in a Phase 3 trial in the same indication.

The benefit of the concept of adding anticoagulation to antiplatelet treatments has been proven by rivaroxaban for ACS in the ATLAS TIMI 51 trial (rivaroxaban in addition to single or dual antiplatelet therapy consisting of acetylsalicylic acid [ASA] +/- clopidogrel), and for patients with stable CAD/PAD in the COMPASS trial (rivaroxaban in addition to ASA). However, its clinical use in ACS is limited, as patients and healthcare providers are concerned about the bleeding risk for triple therapy including 2 antiplatelet therapies (ASA + $P2Y_{12}$ inhibitors) and an anticoagulant.

The use of BAY 2433334, as an oral FXIa inhibitor, could address this concern, as it is expected not to lead to a relevant increase in bleeding and especially major bleeding, while maintaining the efficacy benefit of a combination of antiplatelet therapies and an anticoagulant. This is based on the available preclinical data, data from patients with inherited FXI deficiency and first clinical data from two Phase 2 proof-of-concept studies in patients undergoing total knee replacement (please see Section 2.3).

BAY 2433334 as an inhibitor of FXIa is therefore an attractive candidate to evaluate as a potential add-on to dual antiplatelet therapy in patients after an acute myocardial infarction.

2.2 Background

2.2.1 Disease Background

CV disease is the most common cause of mortality worldwide, and the majority of CV mortality is attributable to coronary heart disease (CHD). The incidence and prevalence rates of CHD remain high throughout the developed world. In the United States (US), the American Heart Association (AHA) reported that the prevalence of CHD in adults ≥20 years of age is 7.0%. Acute myocardial infarction is a subcategory of CHD and typically leads to an acute onset of chest pain or discomfort. The majority of myocardial infarctions arise from an acute rupture of an atherosclerotic plaque that leads to a complete blockage of the blood flow in a coronary artery and consequently damage of the heart.

According to a current report of the American Heart Association, the prevalence of MI is 3.1% of US adults (7.9 Million US Americans), and the annual incidence rate of MI in the US is 935,000. Within one year after MI, 19% of men and 26% of women aged 45 years and older will die.

2.2.2 Treatment Guidelines

Following an acute myocardial infarction, patients remain in a persistent hypercoagulable state and are at risk for adverse thromboembolic events. European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS) guidelines (Valgimigli et al. 2018) recommend that in patients with ACS, regardless of initial treatment strategy, DAPT with a $P2Y_{12}$ inhibitor combined with ASA is recommended for 12 months unless there are contraindications such as excessive risk for bleeding.

Similar guidelines are available from the ACC/AHA. The AHA guidelines (AHA/ACC 2014) also recommend 12 months of DAPT for patients without significant bleeding risks. Both guidelines suggest that the duration of DAPT be adjusted to the individual patient's risk of recurrent ACS vs. risk of bleeding.

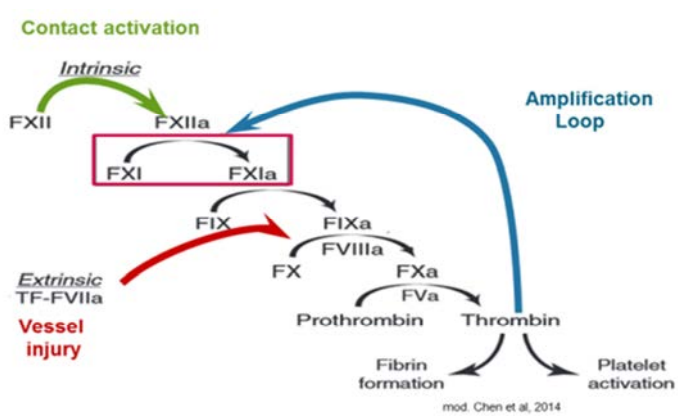
2.2.3 FXIa Inhibitor: Mode of Action

BAY 2433334 is a direct, potent inhibitor of activated coagulation factor XI (FXIa).

The plasma serine protease zymogen factor XI (FXI) is activated after initiation of the contact activation pathway via factor XIIa (FXIIa) and during the amplification phase as part of a positive feedback loop through activation by thrombin. FXIa is thought to contribute strongly to clot progression, which may potentially lead to vessel occlusion and pathological manifestations of thrombosis, but has minor impact on hemostasis due to its limited role in the initiation phase of the extrinsic pathway.

FXIa inhibition by BAY 2433334 may offer the opportunity to prevent thrombosis without interference with primary hemostasis and to thereby set a paradigm shift compared to Vitamin K antagonists and Non-Vitamin K oral anticoagulants (NOACs).

Figure 2–1 Contact activation



Source: adapted from (Chen et al. 2014)

2.2.4 BAY 2433334

2.2.4.1 Preclinical / Toxicology Data

Preclinical data using FXI-deficient mice or studies using pharmacological inhibition of FXIa in different animal models, for example a FeCl-induced thrombosis model, showed a benefit in reduced thrombus formation. The data indicate that higher efficacy might be possible to achieve when compared to the therapeutic doses of NOACs.

The benefit in these animal models was combined without an associated increase in bleeding time as is seen for NOACs in these models. Importantly, no further increase in bleeding time was seen even when BAY 2433334 was given on top of dual antiplatelet therapy.

Data regarding toxicology studies as well as more preclinical data can be found in the Investigator`s Brochure but are also partly described in the benefit/risk section (see Section 2.3).

2.2.4.2 Clinical Data

So far, 156 healthy male subjects have received treatment with BAY 2433334 in doses ranging from 5 mg to 150 mg after single dosing and up to 100 mg once daily in multiple dose settings.

Safety

The single dose escalation study (study 19372) with BAY 2433334 is clinically complete. Single doses of 5 mg to 150 mg have been investigated, as well as a food effect study part with 25 mg. No clinically relevant signs or symptoms of bleeding were observed.

The multiple dose escalation study (study 19665) has also been clinically completed and evaluation is still ongoing. Therefore, the results are preliminary. It consisted of three parts: Part A, wherein 25 mg, 50 mg and 100 mg BAY 2433334 were given once daily over 9 consecutive days, part B, where 25 mg were given twice daily, and part C, where a midazolam interaction was investigated with 25 mg and 75 mg BAY 2433334.

Overall, BAY 2433334 was safe and well tolerated. More details on safety can be found in the Investigator`s Brochure.

Pharmacodynamics

The following pharmacodynamic parameters were investigated in both the FiM study (study 19372) and MDE study (study 19665): aPTT, FXI activity (AXIA assay), and FXI concentration. Bleeding time was investigated after single dose administration only (study 19372)

A dose dependent prolongation of aPTT was observed after single dosing with a close direct correlation between aPTT and plasma concentration:

- In the 25 mg OD dose step of the multiple dose (MD) study 19665 a prolongation of aPTT of CCI (mean, compared to baseline) after single dosing and CCI (mean) at steady state was seen.

- In the 50 mg OD dose step of the MD study 19665 a prolongation of aPTT of CCI (mean, compared to baseline) after single dosing and CCI (mean) at steady state was seen.
- In the 100 mg OD dose step of the MD study 19665 a prolongation of aPTT of CCI (mean, compared to baseline) after single dosing and CCI (mean) at steady state was seen.

FXI activity (AXIA assay) is inhibited by a mean of ~85% after 25 mg SD and a mean of ~95% (25 mg OD) at steady state. After 50 mg and 100 mg SD and MD, activated FXI activity is inhibited by a mean of >95% both after first dose and at steady state. The duration of the inhibition of FXI activity (AXIA assay) is dose dependent. Complete inhibition was reported for 12 hours for 50 mg at steady state and this is prolonged up to 24 hours for 100 mg at steady state.

Pharmacodynamic parameters aPTT and FXI activity correlated well with observed plasma concentrations of BAY 2433334.

No relevant changes of FXI concentration or PT were observed in either study.

No clinically relevant changes in bleeding time were observed after single dose application.

Pharmacokinetics

The key pharmacokinetics features of BAY 2433334 based on current available data and when administered as IR tablets can be summarized as follows.

- BAY 2433334 is absorbed with a median time to reach maximum plasma concentration (t_{max}) of 2 to 4 hours (fasted state).
- There is no hint for any deviation from dose-proportionality found for doses between 5 mg and 150 mg.
- Relative bioavailability of BAY 2433334 administered as IR tablet amounted to approximately 89.5% with regard to AUC and of 86.0% with regard to C_{max} compared to administration as an oral solution.
- A high-fat, high-calorie meal has minor effect on the AUC of 25 mg BAY 2433334 (decrease of 12.4%) and results in a reduced absorption rate (31.4% decrease in maximum plasma concentration [C_{max}] and 2.5 h prolongation in t_{max}).
- The variability was low to moderate for AUC and C_{max} (%geoCV approx. 15 to 30%).
- The degree of accumulation of BAY 2433334 is low regarding $C_{max,md}$ or $AUC_{\tau,md}$ after once daily multiple dosing with R_AC_{max} between 1.4 and 1.6 and R_AAUC between 1.5 and 1.7.
- Pharmacokinetics were linear over time.
- The metabolite M-10 (BAY 2826102, formed by amide hydrolysis of the central amide and subsequent *N*-acetylation) is expected to be a main compound in human plasma with a metabolic ratio to parent drug of approx. 24 to 30%. This metabolite is not pharmacologically active.

- Terminal half-life is 14.0 to 17.4 hours supporting once daily dosing.
- Low apparent oral plasma clearance (CL/F) of about 3.19–4.27 L/h was observed in geometric mean (corresponding to a blood clearance/F of 4.54-6.07 L/h).
- Based on preliminary evaluation of the 50 mg dose step in the multiple dose escalation study (study 19665) renal elimination was low (15%).
- Based on the preliminary ethnic evaluation up to the 50 mg dose step of single and multiple dose in Caucasians (study 19665) and Japanese (study 19667), there is no large difference in PK between races though geometric mean of AUC and C_{max} in Japanese were slightly higher than in Caucasians.
- Based on preliminary evaluation the strong CYP3A4 inhibitor itraconazole increased BAY 2433334 exposure by 100% (2-fold) while maximum plasma concentrations were not changed (study 19664). Terminal half-life was prolonged from 16 to 29 hours.

More details can be found in the Investigator's Brochure.

2.3 Benefit/Risk Assessment

The FXIa inhibitor BAY 2433334 is an oral anticoagulant, that is planned to be developed for patients with atrial fibrillation, acute myocardial infarction as well as non-cardioembolic ischemic stroke. This Phase 2 study will be the first study investigating BAY 2433334 in patients after an acute myocardial infarction. Once daily doses of 10 mg, 20 mg and 50 mg will be tested in the study.

BAY 2433334 as a FXIa inhibitor is expected to have a lower risk for clinically significant bleeding when compared to other oral anticoagulants (VKAs and NOACs) is not expected to increase the risk for clinically significant bleeding, while leading to an efficacy benefit.

The expected clinical profile of BAY 2433334 is based on preclinical data as well as clinical data from FXI-deficient individuals and other FXI-targeting compounds. The separation of bleeding and efficacy might be explained by the fact that inhibition of FXIa affects the intrinsic and propagation pathways but keeps the extrinsic pathway unaffected, that is activated in case of vessel injury.

At this stage of development there is no clinical evidence available yet to confirm the efficacy benefit of BAY 2433334. However, the data supporting that this compound is expected to lead to prevention of thrombosis events in the intended indications are the following:

- FXI-deficient knockout mice are protected from thrombosis. In addition, in various thrombosis models in rabbits, BAY 2433334 demonstrated reduced thrombus weight, and this was seen when given with or without antiplatelets. While therapeutic doses of NOACs lead to a 20-30% reduction in thrombus formation in the same animal models, BAY 2433334 was able to reduce the thrombus formation by up to ~ 90%.
- In people with inherited Factor XI deficiency, a rare coagulation deficiency caused by either reduced production of factor XI or by production of a loss-of-function factor XI molecule, a lower risk for venous thromboembolic events as well as cardiovascular events and especially stroke has been reported.

- Increased levels of FXI are reported as a risk factor for venous thromboembolism and myocardial ischemia or stroke. Whether there is a causal relationship is unclear.
- A first proof of concept targeting FXI as anticoagulant has been shown by a FXI Antisense Oligonucleotide. Reducing FXI levels in patients undergoing total knee arthroplasty (TKA) led to an improved prevention of postoperative venous thromboembolism (VTE), when compared to enoxaparin. Based on modeling approaches, the inhibition levels of FXIa activity in the study can be achieved with the 20 mg and 50 mg doses of BAY 2433334 (see also the Investigator's Brochure).
- Phase 1 studies in healthy volunteers are not able to assess efficacy. However, after multiple dosing the highest planned dose of 50 mg to be tested in Phase 2 lead to complete of inhibition during 12 hours of the day. This was combined with a mean prolongation of aPTT of CCI .

At this stage of development, the safety profile has not been established. The following information related to safety as well as potential risks for patients is available:

1. Bleeding is the main safety concern related to antithrombotic therapies. For an inhibitor of FXIa a lower bleeding risk is expected. Data supporting this are listed below:
    - FXI-deficient knockout mice do not show as bleeding phenotype. In addition, in the thrombosis animal models no increase in bleeding time (gum and ear) was reported. Importantly, no further increase in bleeding time was seen when BAY 2433334 was given on top of dual antiplatelet. In addition, in the toxicology studies no relevant bleeding was reported for up to 37-fold the expected human exposure of the planned 50 mg multiple dose in patients.
    - Patients with inherited FXI deficiency are typically identified when presenting with a prolonged activated partial thromboplastin time (aPTT) in routine clinical testing. There is no direct association between FXI activity levels and bleeding risk, though historically and predominantly in the Ashkenazi Jewish population, FXI deficiency has been categorized as having a mild bleeding phenotype that generally only manifests following injury or trauma in tissues with high fibrinolytic activity.
    - In the completed and ongoing Phase 1 studies conducted with BAY 2433334, no relevant bleeding events were reported so far.

    A risk for bleeding cannot be excluded in patients after an acute myocardial infarction included in the Phase 2 study especially as patients will be treated on top of dual antiplatelet therapy. Therefore, bleeding will be closely monitored in the study and will be adjudicated by an independent clinical event committee.
2. In toxicology studies, the liver was identified as a target organ in the rat but not in the dog. This included dose-dependent spontaneous, mostly transient increases in liver enzymes in single animals without clear correlation to histopathological findings in the livers. Based on this, patients with a >2.5 ALT or AST increase will be excluded from the study and liver findings during the study are defined as AE of special interest in the study.

3. Single doses of BAY 2433334 up to 150 mg and multiple doses up to 100 mg once daily for 9 days have been safe and well tolerated. This included general safety, laboratory, vital signs and ECGs. The doses were 2 and 3-fold higher than planned in this Phase 2 study.
4. Based on preliminary evaluation the strong CYP3A4 inhibitor itraconazole increased BAY 2433334 exposure by 100% (2-fold) while maximum plasma concentrations were not changed (study 19664). Terminal half-life was prolonged from 16 to 29 hours. Therefore, strong CYP3A4 inhibitors and inducers should not be taken concomitantly with BAY 2433334 in this study until further information is available.

In order to ensure the safety of the participants during the study conduct an independent data monitoring committee (IDMC) will monitor the safety of all participants enrolled in all 3 Phase 2 studies with a focus on bleeding and general safety. In addition, a focus of the IDMC review will be on any stroke occurring during the study.

Several Factor XI (FXI) and activated Factor XI (FXIa) inhibitor assets are currently in development as antithrombotics, including antisense oligonucleotides (ASOs), antibodies and small molecules (SMOLs).

In summary, in this Phase 2 study patients after an acute myocardial infarction will receive for the first time BAY 2433334. Study drug will be given on top of their usual therapy with dual antiplatelet therapy. The main objective of the study is to evaluate whether the addition of BAY 2433334 will lead to no relevant increase in bleeding when given on top of dual antiplatelet therapy and that this is combined with a treatment benefit in terms of reduction of CV death, MI, stroke and stent thrombosis. An additional objective is to guide dose selection for Phase 3. Currently, available preclinical and clinical data from the ongoing study regarding the key risks do not indicate an unfavorable risk profile for BAY 2433334. The overall risk is anticipated to be acceptable in the context of the drug benefit.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of BAY 2433334 may be found in the Investigator's Brochure.

3. Objectives and Endpoints

Objectives and endpoints (primary and exploratory) of the study are reported below, in Table 3–1. Please refer to Section 9.4 for further details.

Table 3–1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• to evaluate whether the oral FXIa inhibitor BAY 2433334 compared to placebo leads to a lower incidence of CV death, MI, stroke and stent thrombosis in participants with an acute myocardial infarction and who are treated with dual antiplatelet therapy	**Primary Efficacy Endpoint** • the composite of CV death, MI, stroke and stent thrombosis **Secondary Efficacy Endpoints** • all cause mortality • CV death • MI • stroke • stent thrombosis
• to evaluate whether the incidence of bleeding is similar for BAY 2433334 compared to placebo in participants with an acute myocardial infarction and who are treated with dual antiplatelet therapy	**Primary Safety Endpoint:** • Bleeding Academic Research Consortium (BARC) classification definition type 2, 3 and 5 **Secondary Safety Endpoints** • all bleeding • BARC bleeding definition type 3, 5 • BARC bleeding definition type 1,2,3,5 **Exploratory Safety Endpoints** • TIMI clinically significant bleeding events • TIMI major bleeding events • TIMI minor bleeding events • ISTH major and clinical relevant non-major bleeding • ISTH major bleeding
Exploratory	
• to explore additional pharmacokinetic and pharmacodynamic parameters, biomarkers and genetics • to further investigate the study intervention and similar drugs (i.e. mode-of-action-related effects and / or safety) and to further investigate pathomechanisms deemed relevant to cardiovascular diseases and associated health problems	**Other Exploratory Endpoints** • FXIa inhibition, aPTT • Pharmacokinetics • Various biomarkers and genetics may be explored (e.g. diagnostic, safety, pharmcodynamic, monitoring, or potentially predictive biomarkers)

Abbreviations: aPTT = activated partial thromboplastin time, BARC = Bleeding Academic Research Consortium, CV = cardiovascular, ISTH = International Society on Thrombosis and Hemostasis, MI = myocardial infarction, PD= pharmacodynamic,TIMI = Thrombolysis in myocardial infarction

The primary efficacy estimand is the hazard ratio of the composite of CV death, MI, stroke (ischemic and hemorrhagic) and stent thrombosis comparing BAY 2433334 (20 and 50 mg pooled) with placebo in adult participants with an AMI treated with DAPT while alive and regardless of treatment discontinuation.

The secondary efficacy estimands are defined following the same approach for the individual secondary endpoints as done for the primary efficacy estimand.

The primary safety estimand is the hazard ratio of BARC type 2, 3 and 5 bleeding comparing pooled BAY 2433334 with placebo in adult participants with an AMI treated with DAPT and who have taken at least one dose of study intervention of BAY 2433334 or placebo and while the patient is alive and exposed to study drug.

The secondary safety estimands are defined following the same approach for the individual secondary endpoints as done for the primary safety estimand.

4. Study Design

4.1 Overall Design

Study 20603 is a multicenter, randomized, placebo controlled, double-blind, parallel group, dose-finding phase 2 study. Figure 1–1 displays the overall study design.

Approximately 1600 participants (400 per arm) from approximately 150 study centers worldwide will be randomized 1:1:1:1 to one of the three investigational drug arms (BAY 2433334) or to the placebo arm, in addition to their SoC dual antiplatelet background therapy (for details see Section 6.5).

Stratification will be based on the intended $P2Y_{12}$ inhibitor use (ticagrelor/prasugrel versus clopidogrel) after hospital discharge.

The number of participants with STEMI enrolled in the study will be limited to no more than 50% of all participants.

The maximum duration of study participation is planned to be approximately 55 weeks, consisting of:

- **Screening Period (Visit 1 until Visit 2)** : ≤ 5 days

  Participants will be screened and have to be randomized during hospitalization for the index AMI event and latest within 5 days of hospital admission. Participants should have the initial coronary angiography and revascularization procedures, either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), as treatment for the index AMI event performed before randomization. However, a planned, staged PCI procedure can be performed after randomization.

  If all information is available, participants can be randomized on the day of screening.

- **Treatment Period (from Visit 2 through Visit 12)**: Minimum 26 weeks and 52 weeks maximum

  The duration of the planned double-blind interventional treatment for each participant will be 26 to 52 weeks.

The planned double-blind treatment phase starts at randomization and ends at week 52 or the study treatment end date. Participants active on treatment at the time the last participant is randomized in the study, the maximum treatment duration beyond this date will be no longer than an additional 26 weeks. Thus, participants will have a total treatment duration of a minimum 26 weeks to a maximum of 52 weeks.

- **Safety Follow-up Period (Visit 13)**: 14 days (+ 7 days) after EoT or ET

Study visits will take place as visits at the study sites and telephone calls. Visits at the study sites take place at screening and randomization (Visit 1 and Visit 2), at Week 4 (Visit 4), Week 13 (Visit 6), Week 26 (Visit 8), Week 39 (Visit 10) and at Week 52 / EoT (Visit 12).

Telephone calls take place at Week 2 (Visit 3), Week 8 (Visit 5), Week 20 (Visit 7), Week 32 (Visit 9) and at Week 46 (Visit 11), as well as 2 weeks after the end of treatment visit (i.e. safety follow-up, Visit 13).

For participants who prematurely discontinue from the study drug, an ET visit (Visit 12a) should take place as soon as possible as on-site visit. Participants are asked to continue the study schedule of visits until completing all the study visits or end of study is declared. Telephone calls take place 14 days after ET visit (i.e. Safety follow-up, Visit 13). Further details are reported in Section 7.1.

Details of study procedures and their timing are summarized in the SoA (Section 1.3).

4.2 Scientific Rationale for Study Design

This Phase 2 dose finding study in patients after an AMI will test three doses of BAY 2433334 against placebo. This will allow to test different degrees of FXIa inhibition and determine the dose to be tested in Phase 3.

Study 20603 is a multicenter,randomized, placebo controlled, double-blind, parallel group, dose-finding Phase 2 study in patients after an AMI. The study will apply the principles of randomization, stratification (by intended $P2Y_{12}$ inhibitor use [ticagrelor/prasugrel versus clopidogrel] after hospital discharge) and double-blinding in order to prevent bias in the inclusion of patients or reporting of safety or efficacy events.

In addition, the study will follow a parallel group design in order to prevent bias in the data due to e.g. different sites in different countries enrolling at different timepoints into the study or in case of any seasonally related differences. There does not appear to be a requirement for a dose escalation approach, because based on the available preclinical and clinical data for BAY2433334 there are no safety concerns related to the highest dose of 50 mg once daily tested in the study.

The study is placebo controlled and will allow to test whether the addition of BAY 2433334 on top of the standard therapy with dual antiplatelet therapy leads to a lower incidence of major CV events (CV death, stroke, MI and stent thrombosis) and without increasing the incidence of bleeding.

CV death, MI, stroke and stent thrombosis are used to assess efficacy in this study and have been used as endpoints in earlier studies in patients with an acute coronary syndrome or acute

myocardial infarction. Bleeding will be primarily assessed using the BARC bleeding definition.

Participants will be treated on top of dual or later single antiplatelet therapy as prescribed by their treating physician. The choice of $P2Y_{12}$ inhibitor therapy (ticagrelor, clopidogrel or prasugrel) and duration of treatment with DAPT after hospital discharge for the index AMI, will be left to the discretion of the treating physician and should follow local standard of care guidelines. Thus, the study background therapy will reflect how patients are normally treated and also allows to assess the combination of the study drug with different $P2Y_{12}$ inhibitors (clopidogrel, ticagrelor, prasugrel) rather than requiring the same for all participants.

4.3 Justification for Dose

The study will test the once daily dose of 10 mg (low dose), 20 mg (mid dose) and 50 mg (high dose) dose of BAY 2433334.

The selection of the high dose in this study was not limited by the safety and tolerability data from toxicology studies, nor from the results of the human Phase 1 studies conducted in healthy volunteers. Single doses up to 150 mg or multiple doses up to 100 mg once daily for 9 days were tested in the Phase I studies. Due to these favorable results , the dose selection for the Phase 2 studies was primarily based on pharmacodynamic assays (preclinical and Phase 1 studies) including aPTT and FXIa activity.

Modeling approaches of the available Phase 1 data were used to predict the doses for Phase 2 studies with the goal to select doses that cover a broad range of inhibition of FXIa and lead to different degrees of increases in aPTT (Table 4–1).

- The high dose of 50 mg was chosen to reach significant inhibition of FXIa and to achieve maximum efficacy. However this dose should not lead to a complete inhibition of FXIa during the majority of the day. The selected 50 mg dose is expected to lead to a mean FXIa activity of 7 % with FXIa activity <10% during 14 hours of the day. aPTT is predicted to increase to CCI at trough and CCI at peak.

- The mid dose of 20 mg was selected as the second dose to reflect a linear dose response related to FXIa inhibition. This dose leads to a mean FXIa activity of 23%

- 10 mg was selected as the low dose, as lower doses lead to no or only minimal increases in aPTT. For the 10 mg dose, the expected mean FXIa activity is 45% and aPTT is increased to CCI at trough and CCI at peak.

Table 4–1 BAY 2433334: dose selection

Humans, multiple dose, modelled OD dosing	Predicted FXIa activity			Predicted aPTT increase	
	Trough %	Peak %	Mean %	Trough %	Peak %
50 mg	13	3	7	CC	CC
20 mg	40	11	23	CC	CC
10 mg	67	27	45	CC	CC

Abbreviations: aPTT = activated partial thromboplastin time, OD = once a day

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled study visit.

The end of the study is defined as the date of the last visit of the last participant in the study globally.

5. Study Population

The study will enroll adult participants during hospitalization for the index AMI event and latest within 5 days of hospital admission with the plan to receive DAPT after hospital discharge for the index AMI. The number of participants with STEMI enrolled in the study will be limited to no more than 50% of all participants.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Male and female participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participants must be 45 years of age or older, at the time of signing the informed consent

Type of Participant and Disease Characteristics

2. Acute myocardial infarction[1] (excluding MI associated with PCI or CABG revascularization procedures) with:
   a. clinical symptoms of acute myocardial infarction AND
   b. elevated biomarkers of myocardial necrosis (creatine kinase-muscle and brain isoenzyme [CK-MB] or cardiac troponins) AND
   c. at least one of the following risk factors need to be fulfilled:
      i. Age ≥ 65 years
      ii. Prior MI (before the index AMI event)
      iii. Prior peripheral arterial disease
      iv. Diabetes Mellitus
      v. Prior coronary artery bypass grafting (CABG)

   AND

[1] Differentiation will be made between ST elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI). For diagnosis of STEMI the following criteria will need to be fulfilled: Elevation of ST-segment more than 0.1 millivolt (mV) in 2 or more contiguous ECG leads, or new bundle branch block, or ST-segment depression 0.1 mV or greater in 2 of the precordial leads V1-V4 with evidence suggestive of true posterior infarction

d. initial angiography and revascularization procedures, either PCI or CABG, as treatment for the index event performed before randomization. (Note: a planned, staged PCI procedure can be performed after randomization)

3. Plan for dual antiplatelet therapy (ASA + $P2Y_{12}$ inhibitor) after hospital discharge for the index AMI

4. Randomization during hospitalization for the index AMI event and latest within 5 days of hospital admission

Informed Consent

5. Capable of giving signed informed consent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. Written informed consent has to be signed before any study-specific procedure.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Hemodynamically significant ventricular arrhythmias or cardiogenic shock at time of randomization
2. Uncontrolled hypertension (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg) at randomization
3. Active bleeding; known bleeding disorder, history of major bleeding (intracranial, retroperitoneal, intraocular) or clinically significant gastrointestinal bleeding within last 6 months of randomization
4. Prior ischemic stroke within last 30 days of index event
5. Known significant liver disease (e.g. acute hepatitis, chronic active hepatitis, cirrhosis) or hepatic insufficiency classified as Child-Pugh B or C (see Section 10.6), or ALT or AST > 2.5 x the upper limit of normal, measured as part of the hospitalization for the index event and before randomization
6. Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 calculated by Modification of Diet in Renal Disease (MDRD) formula (see Section 10.7), determined as part of the hospitalization for the index event and measured before randomization
7. Major surgery during last 30 days or planned major surgery or intervention within study period
8. Known allergy, intolerance or hypersensitivity to either of the study interventions (active substance or excipients)

Prior/Concomitant Therapy

9. Planned use or requirement of full dose and long term anticoagulation therapy during study conduct[2]
10. Anticipated need for chronic (more than 4 weeks) therapy with NSAIDs
11. Concomitant use of any of the following therapies within 14 days (or at least five half-lives of the active substance whatever is longer) before randomization and first study intervention administration (see Section 6.5):
    - Strong inhibitors of cytochrome P450 isoenzyme 3A4 (CYP3A4) e.g. human immunodeficiency virus protease inhibitors, systemically used azole-antimycotic agents, clarithromycin or telithromycin
    - Strong inducers of CYP3A4, e.g. phenytoin, carbamazepine, phenobarbital, rifampicin or St. John's wort

Other

12. Known current alcohol and/or illicit drug abuse that may interfere with the participants safety and/or compliance at the discretion of the investigator
13. Women of childbearing potential (women are considered of childbearing potential if they are not surgically sterile or postmenopausal, defined as amenorrhea for > 12 months). Male participants not willing to use condoms when sexually active with a woman of childbearing potential
14. Close affiliation with the investigational site or sponsor; e.g. a close relative of the investigator, or a dependent person (e.g. employee or student of the investigational site or the sponsor)
15. Previous (within 30 days or 5 half-lives of the investigational drug, whichever is longer) or concomitant participation in another clinical study with investigational medicinal product(s) or device(s). Registries and observational studies are allowed.
16. Any condition or therapy, which would make the participant unsuitable for the study (e.g. non-compliance, dysphagia with inability to swallow study intervention) or otherwise vulnerable (e.g. participant in custody by order of an authority or a court), or a life-expectancy < 6 months

5.3 Lifestyle Considerations

No restrictions during any of the study periods pertaining to lifestyle (except for the above mentioned substance abuse) and / or diet apply.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet

[2] Not applicable to DVT prophylaxis with LMWH or unfractionated heparin for short periods of time.

the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and eligibility criteria.

Individuals who do not meet the criteria for participation in this study (screen failure) must not be rescreened.

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Study Intervention(s) Administered

The following study interventions will be administered in the study:

- BAY 2433334: sponsor's study drug under investigation
- Placebo to BAY 2433334

BAY 2433334 is supplied in various strengths as film-coated, immediate-release tablets with identical appearance. The immediate release tablets will be provided as pink, oval, film-coated tablets containing either 5 mg, 15 mg or 25 mg of BAY 2433334 (Table 6–1).

The study intervenions (tablets) are not to be broken, halved or crushed, and should be swallowed whole with a glass of water in the morning. Participants will have to take two tablets from two different bottles (one tablet from each bottle) for one dose. Study drug (tablets) can be taken irrespective of food intake.

Matching placebos for BAY 2433334 are supplied in the same way.

Missed study intervention dose

The planned double-blind treatment phase starts at randomization and ends at week 52 or the study treatment end date (i.e. 26 weeks after the last participant of the study has been randomized), whichever is earlier, or when study drug is permanently discontinued. Study drug will start as soon as possible after randomization (day 1), and is expected to continue through the end of the planned treatment period as described above.

If a dose of study intervention is missed, the participant should take a dose immediately on the same day. The dose should not be doubled to make up for a missed dose.

Table 6–1 Study interventions

Arm name	BAY 2433334 high dose	BAY 2433334 medium dose	BAY 2433334 low dose	Placebo
Intervention Name	BAY 2433334	BAY 2433334	BAY 2433334	Placebo
Type	Drug	Drug	Drug	Placebo
Dose formulation	tablet	tablet	tablet	Tablet
Unit dose strengths	25 mg	5 mg and 15 mg	5 mg	N/A
Dosage Level(s)	50 mg	20 mg	10 mg	N/A
Frequency	Once a day in the morning	Once a day in the morning	Once a day in the morning	Once a day in the morning
Route of Administration	oral	Oral	oral	Oral
Use	experimental	experimental	experimental	Placebo
IMP/AxMP	IMP	IMP	IMP	IMP
Packaging and Labeling	HDPE bottles with desiccant capsule	HDPE bottles with desiccant capsule	HDPE bottles with desiccant capsule	HDPE bottles with desiccant capsule

Abbreviation: AxMP = auxiliary medicinal product; IMP= investigational medical product; NA= not applicable

All study interventions will be labelled according to the requirements of local regulations.

For administered study interventions, a system of numbering in accordance with all requirements of Good Manufacturing Practice (GMP) will be used, ensuring that each dose can be traced back to the respective bulk batch of the ingredients.

A complete record of batch numbers and expiry dates of all investigational interventions and placebo as well as the labels will be maintained in the sponsor's study file.

In all cases BAY 2433334 or placebo is administered on top of standard of care, consisting of antiplatelet therapy. The choice of antiplatelet therapy will be left to the discretion of the treating physician and can include single or dual antiplatelet therapy (see Section 6.5.1).

The choice of background antiplatelet therapy will be documented in the patient records and captured in the eCRF.

6.2 Preparation/Handling/Storage/Accountability

All study interventions will be stored at the investigational site in accordance with Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP) requirements and the instructions given by the clinical supplies department of the sponsor or its affiliates.

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored

(manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the Investigator Site File.

6.3 Measures to Minimize Bias: Randomization and Blinding

All participants will be centrally assigned to randomized study drug using an InteractiveWeb Response System (IWRS). To accomplish random assignments, computer-generated randomization lists specified by the sponsor's responsible statistician will be prepared by Randomization Management at the study sponsor. The randomization lists are provided to an IWRS vendor. Before the study is initiated, the log in information & directions for the IWRS will be provided to each site.

The randomization will be stratified based on the intended $P2Y_{12}$ inhibitor use (ticagrelor/prasugrel versus clopidogrel) after hospital discharge.

Study drug will be dispensed at the study visits summarized in SoA (Section 1.3).

Returned study intervention should not be re-dispensed to the participants.

Patients will be randomly assigned in a [1:1:1:1] ratio to receive study drug. Investigators will remain blinded to each participant’s assigned study intervention throughout the course of the study.

Tablets containing 5 mg, 15 mg or 25 mg of BAY 2433334 and corresponding placebo are identical in appearance (size, color, shape). In order to maintain the blind study drugs will be packed in bottles labeled with a unique number which will be pre-printed on each bottle. In addition, participants will be provided with 2 bottles either with active drug or placebo depending on the randomization outcome.

6.3.1 Unblinding

The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the responsibility for determining if unblinding of a patient’s treatment assignment is warranted. If the investigator is unavailable, and a treating physician not associated with the study requests emergency unblinding, the emergency unblinding requests are forwarded to the study specific emergency medical advice 24 hours/7 day service. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a patient’s treatment assignment unless this could delay emergency treatment of the patient. If a patient’s treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

BAY 2433334 is known to prolong the activated partial thromboplastin time (aPTT) in a dose depended manner. aPTT is a commonly used functional coagulation test widely used in clinical practice in patients using anticoagulants and is as well commonly used during acute hospitalizations, and as a pre-procedural screening test. Thus, inadverted unblinding of the participant or investigator might take place in cases where aPTT test results are known. Therefore, the measurement of aPTT during the study conduct is strongly discouraged and should only be done in case of an (emergency) situation, where aPTT may help to guide treatment decision. aPTT determinations as part of the study will not be reported to investigator during the study in order to maintain the blinding.

6.4 Study Intervention Compliance

Participant compliance with study intervention will be assessed at each visit by direct questioning. At each dispensing visit (V6, V8 and V10) and at EoT (V12) or ET (V12a) visit, compliance will be assessed by counting returned tablets/capsules. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

To monitor compliance, the investigator will be required to document drug dispensing and return for each participant. Overall compliance with study intervention intake should be between 80% and 120% of the scheduled dose at the end of study treatment. The date of dispensing the study intervention to the participant will be documented. Study intervention will be dispensed according to the schedule provided in the SoA (Section 1.3).

Participants should be instructed to bring all unused study intervention and empty packages at Visit 6 , 8, 10 and EoT (or ET) visit for accountability purposes. Any discrepancies between actual and expected amount of returned study medication must be discussed with the participant the time of the visit, and any explanation must be documented in the source records.

6.5 Prior and Concomitant Therapy

Any relevant medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Special focus needs to be given to antiplatelet and anticoagulant medications. Any use in the week before the index AMI event, prior to screening, as well as concomitant use from study entry until the last scheduled study visit of the participant, needs to be captured on the specified concomitant medication page.

The concomitant use of NSAID therapy during the study is strongly discouraged since this has been shown to increase the risk of gastrointestinal (GI) bleeding. However, if a NSAID drug must be temporarily used, it is recommended that the lowest possible dosage for the shortest duration possible be selected, not to exceed 4 weeks. Should analgesics be needed, use of paracetamol/acetaminophen is recommended.

Concomitant therapy with any of the following drugs is prohibited from 14 days (or at least five half-lives of the active substance, whatever is longer) before first study intervention administration, until at least 48 hours after last study intervention administration:

- Strong inhibitors of cytochrome P450 isoenzyme 3A4 (CYP3A4) e.g. human immunodeficiency virus protease inhibitors (ritonavir, indinavir, nelfinavir, atazanavir, or saquinavir), systemically used azole antimycotic agents (ketoconazole, itraconazole, voriconazole, or posaconazole), clarithromycin, telithromycin
- Strong inducers of CYP3A4, e.g. phenytoin, carbamazepine, phenobarbital, rifampicin, or St. John's wort

A separate complete list with prohibited medications will be provided to the investigator.

6.5.1 Concomitant Antiplatelet Therapy

In all cases, the investigational BAY 2433334 or placebo is administered on top of standard of care treatments for post-MI patients, consisting of dual antiplatelet therapy and later single antiplatelet therapy. The choice of $P2Y_{12}$ inhibitor therapy (ticagrelor, clopidogrel or prasugrel) and duration of treatment with DAPT after hospital discharge for the index AMI , will be left to the discretion of the treating physician and should follow local standard of care guidelines. The use of the antiplatelet background therapy (ASA and $P2Y_{12}$ inhibitors) will be documented on the eCRF .

6.5.2 Guidance for Management of Participants who have Bleeding During the Study

If a participant has serious bleeding during the study treatment period that requires hospitalization, the following routine measures should be considered:

- Temporarily or permanently discontinue the randomized study medication. The decision to discontinue study drug, temporarily or permanently, will be at the discretion of the treating physician and must be documented.
- Temporarily discontinue antiplatelet therapies (aspirin and/or the chosen $P2Y_{12}$ inhibitor) until the bleeding event is sufficiently controlled, based upon the discretion of the treating physician.
- Investigate other causes of serious bleeding such as coagulopathies, thrombocytopenia, kidney/liver dysfunction, or other concomitant medications.
- Consider usual supportive treatments for bleeding, including local control of bleeding through standard procedures based upon the bleeding location, fluid replacement, blood transfusion, and fresh frozen plasma (FFP) transfusion. Consideration may also be given to the use of an antifibrinolytic agent, such as tranexamic acid or ε-amino caproic acid (Tomaselli et al. 2017) .

If bleeding cannot be controlled by the above measures, consider urgent surgical or non-surgical procedures to stop the bleeding (emergency surgery, arterial embolization, endoscopic cauterization, etc) and unblinding of the randomized treatment assignment.

For those participants treated with BAY 2433334, administration of the procoagulants can also be considered, but there are no definite data to support the use of these agents.

6.5.3 Guidance for management of participants who have non-cardiac surgery or non-cardiac percutaneous/endoscopic procedures

When possible, non-cardiac surgery and non-cardiac percutaneous/endoscopic procedures should be planned and delayed for at least 24 hours to allow for a 24-hour washout period after temporary discontinuation of randomized study drug to mitigate risks of bleeding.

For urgent or emergent non-cardiac surgery or non-cardiac percutaneous/endoscopic procedures, when waiting for 24 hours is not an option to allow for study drug wash out after temporary discontinuation, the increased risks of procedural bleeding should be assessed against the urgency of the procedure based upon the clinical situation. Peri-procedure management may in part, depend on the randomized treatment assignment (BÀY 2433334 or placebo) and unblinding of treatment assignment may be necessary. In general, the treatment recommendations should follow the Guidelines for Severe Perioperative Bleeding Management (Kozek-Langenecker SA et al. 2013). The procedure should be conducted in such a way to minimize the risk of bleeding.

Treatment of participants receiving BAY 2433334 during urgent or emergency non-cardiac procedures may be guided by published data regarding patients with an inherited FXI deficiency. Apart from giving FXI concentrate (FXI) as replacement therapy to cover a surgical bleeding event (Ling et al. 2016), there have been reports in the literature about the successful use of tranexamic acid or ε-amino caproic acid for the management of these patients with a FXI deficiency when undergoing surgery (Duga and Salomon 2013). More detailed information may be found in the Investigator's Brochure.

6.5.4 Guidance for management of participants who experience a suspected ischemic stroke during the study

The treatment assignment may have to be emergently unblinded if necessary, to facilitate management decisions (e.g. intravenous thrombolysis or intra-arterial thrombolysis in case of mechanical clot removal).

For participants with acute ischemic stroke who are receiving BAY 2433334, the risk of bleeding with use of intravenous thrombolysis is unknown and has not been studied; hence a clear recommendation in this situation cannot be given. However, it is not recommended that a thrombolytic agent be given unless it is known that the study intervention (BAY 2433334) has not been taken in the previous 48 hours, and the aPTT is normal. In this case, the risk of bleeding associated with thrombolysis is not expected to be increased (and unblinding may not be necessary).

For participants who undergo thrombolysis; study medication should be withheld until at least 24 hours after thrombolysis.

Mechanical clot removal (thrombectomy) without thrombolysis may be performed in any case.

6.5.5 Guidance for management of participants who experience a suspected new, acute recurrent cardiac ischemic event during the study

For participants who experience a suspected new, acute recurrent cardiac ischemic event requiring unplanned hospitalization (unstable angina or AMI), standard of care medications should be administered according to local practice guidelines and based upon the chosen invasive procedure (dual antiplatelet therapy, if not already being used, intravenous/subcutaneous anticoagulants, or intravenous antiplatelet therapies such as glycoprotein IIb/IIIa inhibitors or cangrelor). Study intervention does not need to be discontinued upon hospital presentation for a suspected acute recurrent cardiac ischemic event. Recurrent cardiac ischemic event (AMI) endpoint reporting guidelines and processes should be followed for these situations.

For participants who undergo urgent or emergent coronary angiography (with or without PCI) as treatment for the new recurrent ischemic event, continuation of blinded study intervention and concomitant peri-procedural use of standard parenteral or subcutaneous anticoagulants (unfractionated heparin, bivalirudin, low molecular weight heparin) during PCI is recommended.

For participants who are treated with urgent or emergent CABG surgery, study drug should be stopped (if possible) 24 hours before the surgery and restarted no earlier than 24 hours after the post-surgical drains (chest tubes) have been removed.

The treatment assignment may have to be emergently unblinded to facilitate decisions regarding treatment with intravenous fibrinolytics for acute ST-elevation MI. For participants who are receiving BAY 2433334, the risk of bleeding related to the concomitant use of an intravenous fibrinolytic is unknown and has not been studied. For participants treated with intravenous fibrinolytics, study drug should be restarted no earlier than 24 hours after receiving fibrinolytics.

6.5.6 Guidance for management of participants who undergo elective coronary angiography, PCI, or CABG during the study

For participants who undergo elective (scheduled) coronary angiography, with or without elective PCI after randomization or in case of a staged PCI procedure for the index AMI event continuation of blinded study intervention and concomitant peri-procedural use of standard parenteral or subcutaneous anticoagulants (unfractionated heparin, bivalirudin, low molecular weight heparin) during PCI is recommended. For participants who undergo elective CABG surgery , study intervention should be temporarily discontinued for at least 24 hours before elective CABG is performed. Study intervention should be restarted no earlier than 24 hours after the post-surgical drains (chest tubes) have been removed.

6.6 Dose Modification

This protocol does not allow any alteration from the outlined dosing schedule (Section 4.3).

6.7 Intervention after the End of the Study

No further study intervention is planned following the End of the Study. For the definition of "End of Study" please refer to Section 4.4.

Any further therapy at the end of the study is at the discretion of investigator/treating physician.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for bleeding and efficacy outcome events until the planned regular end of treatment. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

An ET visit is only applicable to participants who prematurely discontinue intake of study intervention; such participants should undergo the ET visit as soon as possible, after permanent discontinuation of study intervention. A safety follow up visit (telephone call) will occur 14 days after the day of the premature discontinuation of study intervention (+ 7 days window). If the ET visit falls into the time window for the safety follow up visit (≥ 2 weeks after permanent discontinuation of study intervention), a safety follow up visit will not be performed.

In this study, outcome events and vital status data are crucial to the primary analysis and must be collected until the end of the study, as participants will still be part of the study even if they are no longer taking study medication. Therefore, all efforts will be taken to motivate participants to comply with all study procedures and to continue to be followed until the end of the study for each participant (i.e. 26 to 52 weeks).

Study intervention will not be routinely discontinued in participants reaching a potential outcome event or in case of unblinding unless there is a safety concern or a clear indication for an alternative antithrombotic therapy as determined by the local investigator.

Specifically, a permanent discontinuation of study intervention will be required, if concomitant treatment with any of the following medications has to be taken for the remaining duration of the study conduct:

- requirement of full dose and long term anticoagulation therapy during study conduct (e.g de novo atrial fibrillation, pulmonary embolism)
- strong CYP3A4 inhibitors as well as strong CYP3A4 inducers.

Discontinuation of study intervention for abnormal liver function should be considered by the investigator when a participant meets one of the conditions outlined below or if the investigator believes that it is in best interest of the participant (please also refer to Section 10.5 for the requirements for liver function monitoring)

- ALT or AST > 8 x ULN
- ALT or AST > 5 x ULN for more than 2 weeks
- ALT or AST > 3 x ULN and (total bilirubin > 2 x ULN or INR > 1.5)
- ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and / or eosinophilia (> 5%)

See the SoA for data to be collected at the time of premature intervention discontinuation (ie, ET visit) and follow-up and for any further evaluations that need to be completed.

At time of permanent discontinuation of the study intervention, the participant is expected to continue regular study clinic visits at the investigator's site as outlined in the protocol.

If this is not possible for any reason, the investigator and participant must discuss and determine further follow-up options, as listed below, in descending order of preference:

1. Participant will be contacted by phone at the regular follow-up intervals
2. Participant allows his / her treating physician, e.g. general practitioner or a family member, to be contacted or his medical file checked at the regular follow-up interval, or at least once at study end (if allowed in respective country)
3. Participant will be contacted once at the planned End of Treatment period (Planned regular EoT visit for the participant)

After permanent discontinuation of the study intervention, the following will need to be collected at the regular study visits and up to the regular end of treatment visit, preferentially directly from the participant and as agreed to by the participant during the initial informed consent process:

- Vital Status
- Antiplatelet and anticoagulant medications
- Outcome events (MI, stroke, death, bleeding, stent thrombosis).

If a participant is unwilling or unable to return for follow-up visits in person or have follow-up contacts, sites should collect as much follow-up visit information as possible, including contacting the participant or the participant's representative, family member or treating physician by telephone or by mail. If applicable, vital status may be obtained by reviewing the participant's medical or public sources (e.g. social media, health insurance, public [death] registry), unless this process is not allowed by local regulations.

Withdrawal of Consent

Note: None of the above options is considered a withdrawal of consent.

A withdrawal of consent should only occur in exceptional cases and means that the participant does not agree to any kind of follow-up and specifically refuses any further contact with the investigator (see Section 7.2)

7.1.1 Temporary Discontinuation

In case of a temporary study medication interruption for any reason, study medication will be restarted as soon as medically justified in the opinion of the investigator. There is no defined maximum limit for temporary treatment interruption.

If study interventions were temporarily stopped, PK/PD blood samples should only be obtained if study interventions have been restarted and sustained for at least 4 days.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral compliance, or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- At the time of informed consent, participants will be explained all the options to continue in the study after permanent discontinuation of study intervention (see Section 7.1). This will be re-discussed at the time of permanent discontinuation of study intervention and the participant's specific agreement will be documented. Participants will agree to be contacted to obtain follow-up information should they decide to stop the intervention.
- When a participant withdraws consent from study participation before completing the study, meaning that the participant does not agree to any kind of follow-up and specifically refuses any further contact with the investigator, the reason for consent withdrawal is to be documented in the source document. Public information can be used to obtain vital status for these participants where allowed by local regulations.

7.3 Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly (twice) fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered lost to follow up.
- In order to reduce risk for lost to follow-up the site should collect 2 alternative means of contact for each participant e.g. contact information of the participant's children, caretaker, legal representative, or primary physician. The correctness of these contact details should be checked regularly at the study visits.
- A patient locator service may be used to re-establish contact with a participant in case the site has exhausted all means of regaining contact, if the participant will agree to this in the ICF.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1 Efficacy Assessments

The efficacy assessments include primary and secondary endpoints of the study (see Section 3).

8.1.1 Primary Efficacy Endpoint

The primary efficacy endpoints of the study include the analysis of a composite of:

- CV death
- MI
- Stroke (ischemic and hemorrhagic)

- Stent thrombosis

A definition of the primary efficacy outcome events is provided as follows and further specified in the charter of the clinical event committee (CEC). Details on the time periods for collecting Outcome Events information are reported in Section 10.8.

8.1.1.1 Cardiovascular Death

Cardiovascular death includes death due to stroke, myocardial infarction, heart failure or cardiogenic shock, sudden death or any other death due to other cardiovascular causes. In addition, death due to non-traumatic hemorrhage will be included.

8.1.1.2 Myocardial Infarction

The term acute myocardial infarction (MI) is used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. According to the MI Universal Definition from 2018 (Thygesen et al. 2018) the diagnosis of MI requires the combination of:

- Presence of acute myocardial injury (changes in cardiac biomarkers) **and**
- Evidence of acute myocardial ischemia derived from the clinical presentation, electrocardiographic changes, or the results of myocardial or coronary artery imaging, or in case of post-mortem pathological findings irrespective of biomarker values.

Five types of myocardial infarction can be differentiated:

- Type 1 Spontaneous myocardial infarction
- Type 2 MI secondary to an ischemic imbalance
- Type 3 MI resulting in death when biomarker values are unavailable
- Type 4a MI related to percutaneous coronary intervention (PCI)
- Type 4b MI related to stent thrombosis
- Type 4c MI related to re-stenosis associated with PCI
- Type 5 MI related to coronary artery bypass grafting (CABG)

8.1.1.3 Stroke

Stroke is defined as an acute episode of focal or global neurological dysfunction caused by an injury of the brain, spinal cord, or retina as a result of hemorrhage or infarction.

Differentiation is made regarding ischemic stroke and hemorrhagic stroke.

Hemorrhagic stroke is defined as an acute, atraumatic extravasation of blood into the brain parenchyma, intraventricular, or subarachnoid space with associated neurological symptoms. This does not include microbleeds nor hemorrhagic transformation of an ischemic stroke.

An ischemic stroke is defined as rapid onset (or presence on awakening) of a new focal neurological deficit with clinical ($\geq$ 24 hours symptoms / signs) or imaging evidence of infarction that is not attributable to a non-ischemic cause (i.e. not associated with infection, tumor, seizure, severe metabolic disease).

The term undetermined stroke will apply when sudden focal neurological deficits persist for 24 hours (or death if occuring before 24 hours) but without neuroimaging or autopsy.

8.1.1.4 Stent Thrombosis

Uniform definitions have been developed and were updated by the Academic Research Consortium-2 (ARC-2), incorporating diagnostic certainty as well as timing

Definition Based on Diagnostic Certainty of Stent Thrombosis (ST) (Garcia-Garcia et al. 2018):

- "Definite" ST: The highest level of certainty. Either angiographic or pathological confirmation of stent thrombosis.
- "Probable" ST: Regardless of the time after the index procedure, any myocardial infarction that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause

In this trial the categories of "probable" ST are excluded and only "definite" ST is selected as endpoint.

Definition Based on *Timing* of Stent Thrombosis (ST):

- Acute ST*: 0 to 24 hrs after stent implantation
- Subacute ST*: >24 hours to 30 days after stent implantation
- Late ST: >30 days to 1 year after stent implantation
- Very late ST: >1 year after stent implantation

  *Acute or subacute can also be summarized under the term early stent thrombosis (0 to 30 days).

8.1.2 Secondary Efficacy Endpoint

The secondary efficacy endpoints of the study include the individual components of the CV death, MI, stroke, stent thrombosis and all cause mortality.

A definition of the efficacy outcome events is provided in Section 8.1.1 and further specified in the Clinical Event Committee Charter.

8.2 Safety Assessments

The safety assessments include primary, secondary and exploratory endpoints of the study. At each visit during the study as specified in the SoA, the investigator will evaluate the participant for the occurrence of bleeding events. All necessary information to classify bleeding events according to the ISTH, the Thrombolysis In Myocardial Infarction (TIMI) and the Bleeding Academic Research Consortium (BARC) criteria will be collected in the CRF.

8.2.1 Primary and Secondary Safety Endpoints

Primary Safety Endpoints

- Bleeding Academic Research Consortium (BARC) definition type 2, 3 and 5 as defined by the (Section 8.2.1.1)

Secondary Safety Endpoints

- all bleeding
- BARC bleeding definition type 3, 5
- BARC bleeding definition type 1, 2, 3, 5

8.2.1.1 BARC Bleeding Definition

The BARC bleeding definition encompasses the following bleeding types (type 4: CABG-related bleeding is not applicable to this study):

- **Type 0:** no bleeding
- **Type 1:** bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional
- **Type 2:** any overt, actionable sign of hemorrhage (e.g. more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation
- **Type 3:**

  Type 3a

  - Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL* (provided hemoglobin drop is related to bleed)
  - Any transfusion with overt bleeding

  Type 3b

  - Overt bleeding plus hemoglobin drop ≥ 5 g/dL* (provided hemoglobin drop is related to bleed)
  - Cardiac tamponade
  - Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
  - Bleeding requiring intravenous vasoactive agents

  Type 3c

  - Intracranial hemorrhage (does not include microbleeds or hemorrhagic
  - transformation, does include intraspinal); subcategories confirmed by autopsy or imaging or lumbar puncture
  - Intraocular bleed compromising vision

- **Type 5:** fatal bleeding

  Type 5a

  - Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious

  Type 5b

  - Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

*Corrected for transfusion (1 U packed red blood cells or 1 U whole blood=1g/dL hemoglobin)

8.2.2 Exploratory Safety Endpoints

The exploratory safety endpoints include the analysis of the following outcome events:

- TIMI clinically significant bleeding
- TIMI major bleeding
- TIMI minor bleeding
- ISTH major and clinical relevant non-major bleeding
- ISTH major bleeding

8.2.2.1 TIMI Bleeding Definition

The non-CABG related TIMI clinically significant bleeding definition encompasses the following bleeding types excluding events that are related to a CABG procedure:

- **TIMI Major Bleeding**
  - Any symptomatic intracranial hemorrhage
  - Clinically overt signs of hemorrhage (including imaging) associated with a drop in hemoglobin of ≥ 5 g/dL (or when the hemoglobin concentration was not available, an absolute drop in hematocrit of ≥ 15%).
  - Fatal bleeding (bleeding that directly results in death within 7 days)
- **TIMI Minor Bleeding**
  - Any clinically overt sign of hemorrhage (including imaging) that was associated with a fall in hemoglobin concentration of 3 to < 5 g/dL (or, when hemoglobin concentration was not available, a fall in hematocrit of 10 to < 15%).
- **TIMI Bleeding Events Requiring Medical Attention**
  - Any bleeding event that required medical treatment, surgical treatment, or laboratory evaluation and did not meet criteria for a major or minor bleeding event, as defined above.

In addition to TIMI significant bleeding also TIMI major bleeding and TIMI minor bleeding will be analyzed (Chesebro et al. 1987).

8.2.2.2 ISTH Major Bleeding

An event that meets at least one of the below criteria for a major bleeding event according to the definition given by the ISTH:

- Fatal bleeding, and/or
- Symptomatic bleeding in a critical area or organ (intracranial, intraocular, intraspinal, pericardial, retroperitoneal, intraarticular, or intramuscular with compartment syndrome), and/or
- Clinically overt* bleeding associated with a recent decrease in the hemoglobin level of ≥ 2 g/dL (20 g/L; 1.24 mmol/L) compared to the most recent hemoglobin value available before the event, and/or
- Clinically overt* bleeding leading to transfusion of 2 or more units of packed red blood cells or whole blood

*overt bleeding requires the identification of the bleeding location and the hemoglobin drop and/ or transfusion needs to be related to the bleeding

8.2.2.3 ISTH Clinically Relevant Non-Major Bleeding

Clinically relevant non-major bleeding is considered any sign or symptom of hemorrhage that does not fit the criteria for the ISTH definition of major bleeding, but does meet at least one of the following criteria (Kaatz et al. 2015):

- requiring medical intervention by a healthcare professional
- leading to hospitalization or increased level of care
- prompting a face to face (i.e. not just a telephone or electronic communication) evaluation

8.2.3 Physical Examinations

- Height and weight (also referred to as biometrics in the SoA) will be measured and recorded at screening (see Section 1.3).

8.2.4 Vital Signs

- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include systolic and diastolic blood pressure, and pulse

8.2.5 Electrocardiograms

- A single12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

8.2.6 Clinical Safety Laboratory Assessments

- See Section 10.2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 14 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or the medical monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA.
    - If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.3 Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Section 10.3.

Events identified as Adverse Events of Special Interest (AESI) for the study are specified in Section 8.3.7

AEs that are outcome events according to the study protocol are further described in Section 8.3.6 and Section 10.3.5.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. They remain responsible for following up SAEs or AEs considered related to the study intervention or those that caused the participant to discontinue the study intervention and/or study. AESIs have to be followed up regardless of causality or relationship to the study intervention.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the start of intervention (first day of study intervention intake) until the safety follow-up visit at the time points specified in the SoA (Section 1.3).

All AE will be collected from the start of intervention until the safety follow-up visit at the time points specified in the SoA (Section 1.3).

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstances should this exceed 24 hours after the investigator becomes aware of this event, as indicated in Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2 Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and serious and non-serious AEs of special interest (as defined in Section 8.3.7), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.

8.3.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

- For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 94 days after the last dose intake.
- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6 Disease-Related Events

During the study there will be incidences where AEs are also potential efficacy or safety endpoints.

In compliance with applicable regulations, in the event of a SUSAR (see Section 8.3.4) related to the blinded treatment, the participant's treatment code will usually be unblinded before reporting to the health authorities. Notifications of ethic committees and investigators will be done according to all applicable regulations (see Section 10.3.4).

The following disease- and treatment-related events are common in participants with acute myocardial infarction who are being treated with an anticoagulant:

a. Bleeding
b. Death
c. Myocardial Infarction
d. Ischemic stroke
e. Stent thrombosis

These events will be recorded on the corresponding CRF page in the participant's CRF.

These events will also be monitored and adjudicated by a Central Event Committee (CEC) on an ongoing basis.

In addition, these events require reporting to the sponsor according to the standard process of expedited reporting of SAEs within 24 hours of the investigator's awareness of the event, along the timelines set for reporting of SAEs and AESIs.

However, due to their expectedness, efficacy endpoints listed above (b-e: death, myocardial infarction, ischemic stroke, and stent thrombosis), including events indicative of those outcome events (e.g. TIA, cardiac, chest pain) will not be subject to systematic unblinding and expedited SUSAR reporting to health authorities.

8.3.7 Adverse events of special interest

Adverse events of special interest (AESIs) will be all AEs related to hepato-biliary dysfunction , i.e. relevant increases in the respective liver lab values (ALT > 3 x ULN or AST > 3 x ULN with confirmatory re-testing within 5 days of initial lab value elevation), see Section 10.5, with or without symptoms such as e.g. nausea, vomiting, right upper quadrant abdominal pain, fatigue, weakness, weight loss and jaundice. Re-testing of lab values can be performed at the local lab and needs to be documented in the CRF.

AESIs have to be reported to the sponsor within 24 hours of the investigator's awareness, i.e. along the timelines set for SAEs (even though they may not be classified as serious), as described in Section 8.3.1.

8.4 Treatment of Overdose

For this study, any dose of BAY 2433334 greater than 3 assigned daily doses (i.e. more than 6 tablets) within a 24-hour time period will be considered an overdose.

The sponsor does not recommend specific treatment for an overdose of BAY 2433334, as a specific antidote for the study drug is not available. The use of activated charcoal to reduce absorption may be considered.

Due to the mechanism of action, an overdose of the study drug could potentially result in hemorrhage. In case of bleeding linked to overdose the guidance on bleeding management as found in Section 6.5.2 should be followed.

In the event of an overdose, the investigator/treating physician should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until study drug can no longer be detected systemically (at least 5 days.).
4. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5 Pharmacokinetics

For the investigation of systemic exposure to BAY 2433334 and its relationship with treatment effects, the plasma concentrations of BAY 2433334 and optionally of its metabolite M-10 (BAY 2826102) will be determined at different time points using a sparse sampling approach in all participating participants. Details about the collection, processing, storage and shipment of samples will be provided separately (e.g. in the Laboratory Manual). Study personnel responsible for bioanalytics will be unblinded and will have access to the

randomization list. Analysis of samples from participants not treated with BAY 2433334 is optional.

Blood samples will be collected at the time points indicated in the SoA (Section 1.3). PK samples obtained at additional time points based on the investigator's discretion will not qualify as a protocol deviation and will be used for PK analysis as well. Deviations from the specified sampling intervals will be documented and taken into account for the PK analysis. Date and time of the PK sample collection and date and time of most recent study intervention intake (ie, both of the PK/PD sampling day, and of the day before that) must be documented.

At Visit 4 and 8, a trough sample for the determination of BAY 2433334 plasma concentrations will be drawn before intake of study drug. At this visit, study intervention will be administered at the study center by study personnel and the exact time of study drug intake on the day before the visit and on the day of the visit and the exact sampling time will be recorded in the eCRF. Ideally, the study personnel should contact the participant prior to the respective Visit to remind them not to take the study drug as usual in the morning at home. At Visit 4 additional post-dose samples will be taken as indicated in the SoA (Section 1.3)

The PK data and the relationship of the BAY 2433334 exposure parameters (e.g. C_{max}, AUC) with treatment effects might be evaluated using population approaches (e.g. non-linear mixed effect modeling) including potential influence of relevant participant co-variables. Analysis and report will be done under a separate cover. This evaluation might be started prior to database lock: if this is applicable, appropriate measures will be taken to maintain blinding of the study team.

PK samples will be analyzed, using validated analytical methods. Quality control (QC) and calibration samples will be analyzed concurrently with study samples. The results of calibration samples and QC samples will be reported in the Bioanalytical Report which will be included in the CSR for this study.

8.6 Pharmacodynamics

Blood sampling for PD parameters is scheduled for the time points as given in Section 1.3.
The actual date and time of blood sampling will be documented in the CRF.
All PD parameters will be measured using validated methods.

Quality control and calibration samples will be analyzed concurrently with study samples. For selected PD parameters, the results of QC samples will be reported together with analyte concentrations in the Clinical Study Report of this study.

Concentrations of the analyte are calculated according to the method description. Detailed method descriptions of all PD methods will be filed with the study report.

The following parameters will be used to assess the PD effects after administration of the investigational drug, but will be performed optionally and/or only in a subset of participants:

- aPTT will be measured using a coagulation assay via kaolin-trigger
- Activated Factor XIa activity (AXIA) will be analyzed using a kaolin-trigger and a fluorogenic substrate readout

- D-Dimer will be measured using an immunoturbidometric method
- FXI concentration will be measured via ELISA using polyclonal antibodies
- Fibrinogen will be measured using a coagulation assay
- Factor XII activity will be assessed with an aPTT-based coagulation test using FXII-deficient plasma. Factor XII concentration will be analyzed using an enzyme-linked immunosorbent assay (ELISA).
- vWF antigen level and vWF ristocetin cofactor (i.e. vWF functional activity) will be analyzed using turbidometric assays.

The study sponsors reserve the right not to conduct all or part of the above mentioned analysis.

In addition, blood samples will be taken for exploratory biomarker work (see Section 8.8).

Detailed information about the collection, processing, storage and shipment of the samples will be provided separately (e.g. sample handling sheets and / or laboratory manual).

8.7 Genetics

Genetic as well as non-genetic analyses will be part of the biomarker investigations in this study. See Section 8.8 for details.

8.8 Biomarkers

Exploratory biomarker analyses (scheduled for the time points as given in Section 1.3), that might be performed optionally and/or only in a subset of patients are:

- NT-proBNP will be measured using an electrochemiluminescence immunoassay (ECLIA)
- hsCRP will be measured using an immunoturbidometric method
- Thrombin-activatable fibrinolysis inhibitor (TAFI) and C1 inhibitor activity will be measured using chromogenic substrate assays
- TAT and F1.2 will be analyzed using immunoassays

In addition to the biomarkers described above, further biomarkers related to the mode of action or the safety of BAY 2433334 and similar drugs may be examined. The same applies to further biomarkers deemed relevant to cardiovascular diseases and associated health problems. These investigations may include e.g. diagnostic, safety, PD, monitoring, or potentially predictive biomarkers.

Those additional analyses may include genetic as well as non-genetic biomarkers. Genetic investigations may be of any kind, except for whole genome sequencing. Results will be reported under separate cover, if the evaluations are performed.

Details on the collection, processing, storage, and shipment of biomarker samples will be provided in separate documents (e.g., sample handling sheets or lab manual). Samples may be stored for a maximum of 15 years (or according to local regulations) following the end of the study at a facility selected by the sponsor to enable further analyses.

8.9 Immunogenicity Assessment

Not applicable.

8.10 Health Economics/Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. Statistical Considerations

9.1 Statistical Hypotheses

The aim of the study is to estimate the incidence of MACE and bleeding events of BAY 2433334 and compare it with the incidence of placebo.

No formal hypothesis testing is planned in this study.

9.2 Sample Size Determination

Approximately 1650 participants will be screened to achieve 1600 randomly assigned to study intervention for an estimated total of 400 evaluable participants per intervention group.

With a sample size of 400 participants per treatment arm, an incidence risk for a primary safety event of 4.5% at Day 180 for all treatment arms, and a proportion of about 5% of the randomized participants not contributing post-randomization information about the occurrence of primary bleeding events, it is expected that about 70 participants will have experienced a primary safety outcome until Day 180.

With 70 participants with a primary bleeding event and an observed HR of 1.0 for the comparison of BAY 2433334 (all doses pooled) to placebo, the upper bound of the 2-sided 90% CI for the HR will be approximately 1.44. If the true HR is 1.0 the power to observe a 2-sided 90% CI for the HR below 1.82 is 80%.

9.3 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF
Full Analysis Set	All participants randomized to study drug.
Safety Set	All participants randomly assigned to study drug and who take at least 1 dose of study drug. Participants will be analyzed according to the intervention they actually received.
Pharmacokinetic Analysis Set	All BAY 2433334-treated participants with at least 1 valid plasma concentration and without protocol deviation, which would interfere with the evaluation of the PK data.

Abbreviations: ICF = Informed consent form, PK = pharmacokinetic(s)

The primary and secondary safety endpoints will be analyzed using the Safety Set. The analysis of the full analysis set will be used as a supportive analysis. Pharmacokinetic and pharmacodynamic data will be analyzed using the Pharmacokinetic analyses set.

9.4 Statistical Analyses

9.4.1 Gerenal considerations

The statistical analysis plan (SAP) will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints and estimands.

The aim of this study is to gain knowledge of the safety profile and the efficacy of BAY 2433334.

For the intercurrent event “discontinuation of study treatment” the “treatment policy” strategy is chosen for efficacy estimands and the “while on treatment” strategy is chosen for safety estimands.

The intercurrent event Death will be handled with the while alive strategy.

Confidence intervals will be two sided 90% - confidence intervals.

Time to event variables will be analyzed using Kaplan-Meier estimates of cumulative risk and cumulative hazard functions. The hazard ratios and the corresponding confidence intervals will be estimated on separate Cox proportional hazard models for each comparison. No comparison of the different doses of BAY 2433334 is planned.

Efficacy and bleeding outcomes will be analyzed based on time to their first occurrence. The incidence risk for outcome events will be estimated separately for the doses of BAY 2433334 and/or for the pooled doses and/or the 20 and 50 mg doses combined and compared to placebo.

The bleeding risk of BAY 2433334 (all doses pooled) as compared to placebo will be estimated using the Cox proportional hazards model.

Main Data scope for safety of the trial is the treatment emergent data scope, counting all events from first intake of study drug until 2 days after last study drug intake.

The efficacy of BAY 2433334 (20 and 50 mg pooled) as compared to placebo will be estimated using the Cox proportional hazards model.

Main Data scope for efficacy of the trial is the ITT data scope, counting all events from randomization until end of study

All time-to-event analyses will be stratified by intended $P2Y_{12}$ inhibitor use (ticagrelor/prasugrel versus clopidogrel) if not mentioned different.

All collected events will be analyzed descriptively, using methods like frequency tables and others.

The statistical analyses will be performed using SAS; the version used will be specified in the statistical analysis plan (SAP).

9.4.2 Primary endpoints

Efficacy analysis

The primary efficacy estimand is: The hazard ratio of the composite of CV death, MI, stroke and stent thrombosis comparing BAY 2433334 (20 and 50 mg pooled) with placebo in adult participants with an AMI treated with DAPT while alive and regardless of treatment discontinuation.

The primary efficacy estimator will be the hazard ratio from a Cox proportional hazards model comparing BAY 2433334 (20 and 50 mg pooled) with placebo. The estimation will be performed on the full analysis set and the ITT data scope.

As sensitivity analyses the estimation on the Safety set and the treatment emergent data scope will be performed.

In addition, incidence proportions for the primary efficacy endpoint will be reported.

Safety Analyses

The primary safety estimand is: The hazard ratio of BARC type 2, 3 and 5 bleeding comparing pooled BAY 2433334 with placebo in adult participants with an AMI treated with DAPT and who have taken at least one dose of study intervention of BAY 2433334 or placebo and while the participant is alive and exposed to study drug.

The primary safety estimator will be the hazard ratio from a Cox proportional hazards model comparing BAY 2433334 (all doses pooled) with placebo. The estimation will be performed on the safety set and the treatment emergent data scope.

As sensitivity analyses the estimation on the full analysis set and the ITT data scope will be performed.

In addition, incidence proportions for the primary safety endpoint will be reported.

9.4.3 Secondary endpoints

Efficacy analysis

The secondary efficacy estimands are: The hazard ratio of <*individual endpoint*> of comparing BAY 2433334 (20 and 50 mg pooled) with placebo in adult participants with an AMI treated with DAPT while alive and regardless of treatment discontinuation

For each of the individual enpoints:

- All cause mortality
- CV death
- MI
- stroke (ischemic and hemorrhagic)
- stent thrombosis

Safety analysis

The secondary safety estimands are: The hazard ratio of <*individual endpoint*> comparing pooled BAY 2433334 with placebo in adult participants with an AMI treated with DAPT and

who have taken at least one dose of study medication of BAY 2433334 or placebo and while the patient is alive and exposed to study drug

For each of the individual enpoints:

- all bleeding
- BARC bleeding definition Type 3, 5
- BARC bleeding definition Type 1, 2, 3, 5

9.4.4 Tertiary/exploratory endpoints

Exploratory safety endpoints are:

- TIMI clinically significant bleeding
- TIMI major bleeding
- TIMI minor bleeding
- ISTH major and clinical relevant non-major bleeding
- ISTH major bleeding

The analyses of these endpoints will be specified in the SAP.

9.4.5 Other Safety Analyses

Adverse Events (AE) will be analyzed by descriptive statistics, such as frequency tables. All AEs will be tabulated according to the affected system organ class and preferred term, as coded by the medical dictionary for regulatory affairs (MedDRA).

9.4.6 Other Analyses

PK, pharmacodynamic, and biomarker exploratory analyses will be described in the statistical analysis plan finalized before database lock. The population PK analysis will be presented separately from the main clinical study report (CSR).

9.5 Interim Analyses

Two non-formal interim analyses are planned to be performed in the Phase 2 program to assess the efficacy and safety profile of BAY 2433334 during the Phase 2 study conduct. Data from this study as well as the two other ongoing Phase 2 studies will be reviewed together when the pre-defined criteria for the two interim analyses have been reached. The overall approach of the 2 interim analyses is regarded as acceptable, as these are exploratory Phase 2 studies and not pivotal studies.

Analyses of the unblinded safety and efficacy data will be performed by a third party, i.e. the statistical analysis center (SAC) that supports the IDMC and thus, is independent of the study team and the sponsor. A small group of academic leaders (Executive Committee) including the heads of the three Steering Committees that have been established for the individual studies and sponsor representatives will participate in the review of these data. IDMC members will also be included in this review. The data will be kept strictly confidential by this group and will not be shared with the study team and the SC. Thus, the study integrity

will not be impacted and the study conduct will otherwise not be altered by the results of this interim analysis.

The interim analysis will include selected and predefined study data primarily as aggregated data for this individual study but may also include pooling of some data across all three ongoing Phase 2 studies.

The first interim analysis will be conducted once about 50% of the participants (800 participants) with a minor non-cardioembolic ischemic stroke (NIHSS ≤ 7) are enrolled in the study 19766 or 3 months MRI data are available for at least 12.5% of participants (200 participants). If the review confirms the safety profile of BAY 2433334 and raises no concern regarding (intracranial) hemorrhage or hemorrhagic transformation of the ischemic stroke, Part B of the study 19766 will be initiated, during which from then on participants with more severe cases of stroke (NIHSS ≥ 8 and ≤ 15) can also be included as well as participants after thrombolysis or endovascular therapy (mechanical thrombectomy). Even though the primary focus for this interim analysis is specific for the decision for the stroke study 19766 only, data and especially bleeding data from this study and study19765 will be taken into consideration.

The second interim analysis will occur when sufficient data are available from all three Phase 2 studies. This interim analysis may occur, when approximately 80% of all planned participants, taken all three studies together, are randomized. This meeting will aim to assess whether the interim data support decision making on dose and design for a potential Phase 3 clinical development program while the Phase 2 studies are still ongoing and may allow interaction with Health Authorities before final data from the studies are available.

The timepoints when these two interim analyses occur are difficult to predict and will depend e.g. on study start time, number of sites and countries, on the enrollment rate and other factors in all three studies. In case the timepoints for the two interim analysis may be close together, the decision could be taken to just conduct one interim analysis.

As part of the two interim analyses the additional objective to potentially change the dose during the ongoing Phase 2 studies will be assessed. This will allow flexibility in case of unexpected findings during the review of the data, e.g. stop of the highest dose (in case of an unexpected higher bleeding rate in the highest dose or in the combination with antiplatelet therapy) or addition of a lower or higher dose or replacement of one dose (in case of a difference in pharmacokinetics or PD parameters such as inhibition of FXIa in the patient populations compared to healthy volunteers).

9.6 Independent Data Monitoring Committee (IDMC)

An independent data monitoring committee (IDMC) will be involved in the review of the safety data for study 20603, and of the overall safety data across all three Phase 2 studies with BAY 2433334 (Section 10.1.5.3). Detailed information on the roles and responsibilities of the IDMC will be described in the IDMC Charter.

10. Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants. Any substantial modifications of the protocol will be submitted to the competent authorities as substantial amendments for approval, in accordance with ICH Good Clinical Practice and national and international regulations.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- Pharmacogenetic samples will be taken during the study. Study participants will be asked to sign a separate informed consent for pharmacogenetic research.

10.1.4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5 Committees Structure

10.1.5.1 Executive Committee

The Executive Committee, which consists of external experts in the area of neurology and cardiology and will include the Steering Committee heads of the three Phase 2 studies with BAY 2433334, as well as two sponsor representatives, will ensure the overarching integrity of the three Phase 2 studies with BAY 2433334. Details of the committee will be specified in the Executive Committee Charter.

10.1.5.2 Steering Committee (SC)

The main task of the Steering Committee, which is composed of a panel of experts in the field of cardiology, is to support the protocol development and the conduct of the study, to advise

the sponsor on clinical, medical, and scientific questions, and to support publications. Details of the committee will be specified in the Steering Committee charter.

10.1.5.3 Independent Data Monitoring Committee (IDMC)

Ongoing safety monitoring during the conduct of the study will be performed by an external and unblinded IDMC. An independent statistical analysis center (SAC) will be involved in processing unblinded safety data for the IDMC. Analysis periods and procedures will be defined in an operational charter (IDMC Charter) filed in the study file. Following data review, the IDMC will provide written recommendations that will be transferred to Bayer. All other definitions will be provided in the IDMC charter.

10.1.5.4 Clinical Events Committee (CEC)

Potential pre-specified clinical outcome events will be submitted for adjudication to an independent CEC. Adjudication of all bleeding events as well as efficacy events will be performed by members of the CEC who will review events in a blinded fashion and will adjudicate and classify the following events in a consistent and unbiased manner according to definitions contained in the CEC charter. The adjudication will also include algorithm approaches:

- Bleeding events according to the following classifications:
    - ISTH (major, clinically relevant non-major and minor)
    - TIMI (major, minor, requiring medical attention, minimal)
    - BARC (type 1,2,3,5)
- Death (CV death [including death with unknown cause] or non-CV death)
- MI
- Stroke (ischemic, hemorrhagic, undetermined)
- Stent thrombosis

In addition, events that might be indicative of a potential outcome event will be reported as outcome events to ensure that no outcome event is missed. This includes for example TIA and hospitalization for cardiac chest pain with increased cardiac enzymes reported.

Data entry procedures and documentation necessary for case adjudication will also be described in the CEC charter. Adjudication results will be the basis for the final analysis.

10.1.6 Dissemination of Clinical Study Data

Result summaries of Bayer's sponsored clinical studies in drug development Phases 2, 3 and 4 and Phase 1 studies in patients are provided in the Bayer Trial Finder application after marketing authorization approval in line with the position of the global pharmaceutical industry associations laid down in the "Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases". In addition, results of clinical drug trials will be provided on the publicly funded website www.ClinicalTrials.gov and EU Clinical Trials Register in line with the applicable regulations.

Bayer commits to sharing upon request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials

in patients for medicines and indications approved in the United States (US) and European Union (EU) on or after January 01, 2014 as necessary for conducting legitimate research.

All Bayer-sponsored clinical trials are considered for publication in the scientific literature irrespective of whether the results of the clinical studies are positive or negative.

10.1.7 Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- If the participant withdraw consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

10.1.7.1 Data Recording

The data collection tool for this study will be a validated electronic data capture system called RAVE. Participant data necessary for analysis and reporting will be entered/transmitted into a validated database or data system (LSH).

Data required according to this protocol will be recorded by study site personnel via data entry into the internet based EDC software system RAVE, which Bayer has licensed from Medidata Solutions Worldwide. RAVE has been validated by Medidata Solutions Worldwide and Bayer for use in its clinical studies. RAVE allows for the application of software logic to set-up data entry screens and data checks to ensure the completeness and accuracy of the data entered by the site personnel. Bayer extensively applies the logic to ensure data are complete and reflect the clinical data requirements of the study. Data queries resulting from the application of the software logic are resolved by the site personnel. The data are stored at a secure host facility maintained by Medidata Solutions Worldwide and transferred on a periodic basis to Bayer's internal computer system via a secure Virtual Private Network.

All access to the RAVE system is through a password-protected security system that is part of the RAVE software. All internal Bayer and external investigator site personnel seeking access must go through a thorough RAVE training process before they are granted access to RAVE for use in Bayer's clinical studies. Training records are maintained.

All personnel with access to the RAVE system are supported by a Service Desk staffed with trained personnel to answer questions and ensure access is maintained such that data entry can proceed in a timely manner.

The RAVE System contains a system-generated audit trail that captures any changes made to a data field, including who made the change, why the change was made and the date and time it was made. This information is available both at the investigator’s site and at Bayer. Data entries made in the RAVE EDC screens are supported by source documents maintained for all participants enrolled in this study.

Data recorded from screening failures

At minimum, the following data should be recorded in the CRF:

- Demographic information (participant number; year of birth / age; sex; if applicable race / ethnicity)
- Date of informed consent
- Relevant inclusion/exclusion criteria
- Reason for premature discontinuation
- Date of last visit.

These data will be transferred to the respective database.

10.1.7.2 Monitoring

In accordance with applicable regulations, ICH-GCP, and sponsor’s/CRO’s procedures, monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and sponsor’s requirements. When reviewing data collection procedures, the discussion will also include identification and documentation of source data items.

The sponsor/designee will monitor the site activity to verify that the:

- Data are authentic, accurate and complete.
  Supporting data may be requested (example: blood glucose readings to support a diagnosis of diabetes).
- Safety and rights of participants are being protected
- Study is conducted in accordance with the currently approved protocol (including study treatment being used in accordance with the protocol)
- Any other study agreements, ICH-GCP, and all applicable regulatory requirements are met.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

10.1.7.3 Data processing

Data will be collected as described in Section 10.1.7.1. Clinical data management will be performed in accordance with applicable sponsor's/CRO's standards and data cleaning procedures. This is applicable for data recorded on eCRF as well as for data from other sources (e.g. IxRS, laboratory, adjudication committees).

For data coding (e.g. AEs, medication), internationally recognized and accepted dictionaries will be used.

After its initial release for biometrical analysis, additional data release for analysis is possible, to include, for example, the following data: pharmacokinetic data, pharmacodynamic data, anti-drug antibody data etc.

10.1.7.4 Missing data

All efforts will be made to collect complete data for all participants randomized in this study. Participants will be followed up to the study end and all required data will be collected, regardless of participants' compliance with study drug use or the visit schedule.

Data from participants who prematurely terminate the study will be used to the maximum extent possible. All missing or partial data will be presented in the participant data listing as they are recorded in the eCRF. Data are collected primarily through an EDC system, which allows ongoing data entry and monitoring.

10.1.7.5 Audit and inspection

To ensure compliance with ICH-GCP and regulatory requirements, a member of the sponsor's (or a designated CRO's) quality assurance unit may arrange to conduct an audit to assess the performance of the study at the study site and of the study documents originating there. The investigator/institution will be informed of the audit outcome.

In addition, inspections by regulatory health authority representatives and IEC(s)/IRB(s) are possible. The investigator should notify the sponsor immediately of any such inspection.

The investigator/institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to

discuss findings and any issues. Audits and inspections may occur at any time during or after completion of the study.

10.1.7.6 Archiving

Essential documents shall be archived safely and securely in such a way that ensures that they are readily available upon authorities' request.

Participant (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution or private practice. Where the archiving procedures do not meet the minimum timelines required by the sponsor, alternative arrangements must be made to ensure the availability of the source documents for the required period.

The investigator/institution notifies the sponsor if the archival arrangements change (e.g. relocation or transfer of ownership).

The investigator site file is not to be destroyed without the sponsor's approval.

The contract with the investigator/institution will contain all regulations relevant for the study site.

10.1.8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the source data identification checklist
- The site must implement processes to ensure availability of all required source documentation (e.g. participant file, local laboratory report, etc.). A source document checklist (not part of this protocol) will be used at the site to identify the source data for key data points collected and the monitor will work with the site to complete this.
- Race and ethnic group may be entered directly into the CRF, without availability of corresponding source documentation. Thus, these CRF data will be the source and no additional source documentation will be available. For all other data, source documentation must be available at the site.

10.1.9 Study and Site Start and Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 10–1 will be performed by the central laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 10–1: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Platelet count Red blood cell (RBC) count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	White blood cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry[1]	Aspartate Aminotransferase (AST) Alanine Aminotransferase (ALT) Alkaline phosphatase (AP) Gamma glutamyl transpeptidase (γGT) Bilirubin, total and direct		
	Lactate dehydrogenase (LDH) Creatinine kinase (CK)		
	Blood Urea Nitrogen (BUN) Creatinine eGFR		
	Lipase Amylase		
	Sodium Potassium Calcium		
	Uric acid Glucose Cholesterol (total, HDL, LDL) Triglycerides Albumin Total protein Thyroid-stimulating hormone (TSH)		

NOTES:
[1] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Appendix 10.5.

Abbreviations: ALT = alanine aminotransferase, AP = alkaline phosphatase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, CK = creatinine kinase, eGFR = estimated glomerular filtration rate, γGT = gamma glutamyl transpeptidase, HDL = high-density lipoprotein, LDH = lactate dehydrogenase, LDL = low-density lipoprotein, MCH = mean corpuscular hemoglobin, MCV = mean corpuscular volume, RBC = red blood cell (count), TSH = thyroid-stimulating hormone, WBC = white blood cell (count)

Investigator must document their review of each laboratory safety report.

The name and address for the central laboratory service provider can be found in the documentation supplied by the vendor. In the event of implausible results, the laboratory may measure additional parameters to assess the quality of the sample (e.g. clotted or hemolyzed) and to verify the results. The results from such additional analyses may neither be included in the clinical database of this study nor evaluated further. If the results are relevant, the investigator will be informed to determine follow-up activities outside of this protocol.

All exploratory biomarkers are not used routinely in practice and will be analyzed in batches. Therefore, timely reporting of the results will not be possible during the study and review of the results will not assist participant care.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, “lack of efficacy” or “failure of expected pharmacological action” also constitutes an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

- The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant 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.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct

normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE 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 participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the sponsor in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

- The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:
  - Mild: An event that is easily tolerated by the participant, causing minimal

discomfort and not interfering with everyday activities.

- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission** of the SAE data to [the sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations,

histopathological examinations, or consultation with other health care professionals.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide PPD with a copy of any post mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the [sponsor] within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE Reporting to the sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form and transmit to PPD
- Contacts for SAE reporting can be found in the Investigator Site File.

SAE Reporting to the sponsor via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Sponsor via PPD
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the Investigator Site File.

10.3.5 Outcome Event Reporting Process Overview

If an AE or SAE is a potential outcome event (all bleeding, death, MI, stroke, TIA and stent thrombosis [Section 8.3.6]), it must be collected and reported on the dedicated forms on an ongoing basis, until the participant has completed the study. Thus, even if a participant is no longer taking study medication this would be until the end of the regular, planned end of treatment for this participant (i.e. until the participant's last visit. After completion of safety follow-up visit, for participants that prematurely discontinued study intervention, there is no further requirement for reporting AEs. Only potential outcome events are to be reported (refer to section 8.3.1 and 10.8).

10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Müllerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

Postmenopausal Female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
- A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement (>40 IU/L) is required.

- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

- Female participants must be of non-child bearing potential as per Clinical Trial Facilitation Group (CTFG) guidelines.
- Male participants must agree to use condoms when sexually active with a woman of childbearing potential from the time of the first dose to 7 days after the last dose of study intervention. This is in line with the CTFG guideline, as BAY 2433334 is non genotoxic but data related to teratogenicity/fetotoxicity in early pregnancy (Segment 2 studies) are not available at this stage of development. In addition, all men must not donate sperm during the study.

Male Participants with Partners Who Become Pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants Who Become Pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, after obtaining the signed informed consent from both parents, unless local law or specific circumstances of the respective case allow otherwise, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported for medical reasons will be reported as an AE or SAE.

- A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at >22 weeks gestional age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.

10.5 Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Any participant with an ALT or AST > 3 x ULN must be re-tested as soon as possible but at the latest within 48-72 hours of the investigator becoming aware of the result. This re-testing and any subsequent testing based on elevated levels should include measurement of ALT, AST, total and direct bilirubin, AP and INR, and will be assessed by local laboratory. There also should be inquiry made about symptoms.

Every effort should be made to clarify the etiology of elevated levels and lab testing may include, but not be limited to, testing for viral hepatitis, cytomegalovirus, Epstein-Barr virus, human immunodeficiency virus (once the participant has provided written consent), testing of ferritin levels, iron, iron binding capacity, antinuclear antibody, and smooth muscle antibodies. Patient management is at the discretion of the treating physician but the investigator may continue the study drug during retesting.

Liver function test monitoring should be performed as above for all participants with elevated ALT or AST >3 ULN even if the study drug is interrupted until tested values have normalized or returned to patient's baseline. If close liver monitoring is not possible then the patient should discontinue study medication.

For ALT or AST > 3 x ULN concurrent with a total bilirubin > 2 x ULN, every effort should be made to promptly clarify any possible underlying disease(s).

The frequency of liver function tests based on re-test values is shown in **Table 10**–2.

Table 10–2 Liver function monitoring

ALT, AST level at re-test	Frequency	Further notice
ALT or AST > 3 x ULN	2-3 times a week	Obtain details on liver related symptoms and exclude other causes of liver enzyme elevations
ALT or AST ≤ 3 x ULN	Once a week	Until return to normal or patient baseline levels

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal

Discontinuation of treatment should be considered if:

- ALT or AST > 8 x ULN
- ALT or AST > 5 x ULN for more than 2 weeks
- ALT or AST > 3 x ULN **and** (total bilirubin > 2 x ULN or INR > 1.5)

- ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and / or eosinophilia (> 5%)

10.6 Appendix 6: Calculating the Child-Pugh score

The severity of liver disease (**Table 10**–3) will determine the Child-Pugh score (**Table 10**–4).

Table 10–3 Grading of severity of liver disease

Factor	+1	+2	+3
Bilirubin (mg/dL)	< 2	2 – 3	> 3
Albumin (g/dL)	> 3.5	2.8 – 3.5	< 2.8
International Normalized Ratio	< 1.7	1.7 – 2.3	> 2.3
Ascites	None	Mild	Moderate / Severe
Encephalopathy	None	Grade I - II	Grade III – IV

Source: adapted from (Pugh et al. 1973)

Table 10–4 Child-Pugh score

Child-Pugh Class	A	B	C
Points	5 – 6	7 – 9	10 – 15

Source: adapted from (Pugh et al. 1973)

10.7 Appendix 7: Calculating glomerular filtration rate

In accordance with established nephrology practice and guidelines, renal function at baseline and throughout the study will be assessed by means of the estimated glomerular filtration rate (eGFR), calculated using the Modification of Diet in Renal Disease (MDRD) study abbreviated formula.

Isotope dilution mass spectroscopy (IDMS)-traceable MDRD Study Equation:

Conventional units (serum creatinine level is measured in mg/dL)

GFR (mL/min/1.73 m^2) = 175 x (serum creatinine)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.212 if African American)

GFR can be estimated using the calculator provided in the following link:

http://www.kidney.org/professionals/kdoqi/gfr_calculator.

For further information on assessing renal function using GFR estimates (Levey et al. 2006)

10.8 Appendix 8: Outcome Events: Data Collection

All outcome events (efficacy and safety) are to be captured and reported from randomization until participant´s regular last scheduled study visits (ie, Safety Follow-up Visit; in case of permanent discontinuation of study intervention, the planned regular EoT visit). The eCRF will contain specific Outcome Event pages, as well as AEs subpages to capture the outcome events occurring throughout the study. The following points need to be considered when reporting outcome events.

- Outcomes events occurring **after randomization** and **before the first intake of the study intervention**: the outcome event will be considered part of the medical history and should be reported in the outcome event eCRF page
- Outcomes events occurring **after randomization and after first intake of study intervention and up to the SFU visit**: the outcome event will be considered both AE and outcome event and should be reported in both in the AE page and in the AE's subpage for outcome events.
- Outcome events occurring **after SFU visit through the end of the study (for participant who discontinue study intervention):** the outcome events should be collected until completion of participant´s regular scheduled study visits and should be reported in the outcome event eCRF page.

10.9 Appendix 9: Abbreviations

ACC	American College of Cardiology
ACS	Acute coronary syndrome
AE	Adverse Event
AESI	Adverse event of special interest
AF	Atrial fibrillation
AG	Joint stock company, Aktiengesellschaft
AHA	American Heart Association
ALT	Alanine aminotransferase
AMI	Acute myocardial infarction
AP	Alkaline phosphatase
aPTT	Activated partial thromboplastin time
ARC	Academic Research Consortium
ASA	Acetylsalicylic acid
ASO	Antisense oligonucleotide
AST	Aspartate Aminotransferase
AUC	Area under the curve
AXIA	Activated Factor XIa activity
AxMP	Auxiliary medicinal product
BARC	Bleeding Academic Research Consortium
BID	Twice a day, *Bis in die*
BL	Baseline
BP	Blood pressure
BUN	Blood urea nitrogen
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CEC	Clinical event committee
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CHD	Coronary heart disease
CK	Creatinine kinase
CL/F	Apparent oral plasma clearance
C_{max}	maximum observed concentration reached after administration
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report form
CSR	Clinical study report
CTFG	Clinical Trial Facilitation Group
CRNM	Clinical relevant non-major
CRO	Contract Research Organization
CV	Cardiovascular
CYP3A4	Cytochrome P450, family 3, subfamily A, polypeptide 4
DAPT	Dual antiplatelet therapy
e.g.	For example, *exempli gratia*

eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ECG	Electrocardiogram
ECLIA	Electrochemiluminescence Immunoassay
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOT	End of Treatment
ESC	European Society of Cardiology
ESUS	Embolic stroke of undetermined source
ET	Early termination
EU	European Union
EudraCT	European Clinical Trials Database
F1.2	F1.2 fragment of prothrombin
FAS	Full Analysis Set
FeCl	Ferric chloride
FiM	first in man
FFP	Fresh frozen plasma
FSH	Follicle stimulating hormone
γGT	Gamma glutamyl transpeptidase
GCP	Good Clinical Practice
geoCV	Geometric coefficient of variation
GFR	Glomerular filtration rate
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HDL	High-density lipoprotein
HDPE	High-density polyethylene
HIPAA	Health Insurance Portability and Accountability Act
Hb	Hemoglobin
HR	Hazard ratio
HRT	Hormonal replacement therapy
hsCRP	High-sensitivity C-reactive protein
i.e.	That is, *id est*
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonization
IDMC	Independent data monitoring commitee
IDMS	Isotope dilution mass spectroscopy
IEC	Independent Ethics Committee
IMP	Investigational medical product
IND	Investigational New Drug
INN	International non-proprietary name
INR	International normalized ratio
IR	Immediate release

IRB	Institutional Review Board
ISTH	International Society on Thrombosis and Hemostasis
ITT	Intent-to-treat
IV	Intravenous(ly)
IVRS/IWRS,IxRS	Interactive Voice/Web Response System
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LSF	Liquid service formulation
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MD / MDE	Multiple dose / multiple dose escalation
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MRI	Magnetic resonance imaging
N	Total number of participants
NA	Not applicable
NIHSS	National Institutes of Health Stroke Scale
NJ	New Jersey
NOAC	Non-Vitamin K oral anticoagulant
NSAID	Nonsteroidal anti-inflammatory drug
NT-proBNP	N-terminal pro B-type Natriuretic Peptide
OD	Once daily
$P2Y_{12}$	Purinergic receptor P2Y, G-protein coupled, 12
PAD	Peripheral artery disease
PCI	Percutaneous coronary intervention
PD	Pharmacodynamic
PK	Pharmacokinetic(s)
QC	Quality control
R_AAUC	Accumulation ratio for AUC
R_AC_{max}	Accumulation ratio for C_{max}
RAVE	Data collection tool
RBC	Red blood cell
RND	Randomization
SAC	Statictical analysis center
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SAS	Statistical analysis software
SC	Steering Committee
SCR	Screening
SD	Single dose
SFU	Safety follow-up
SMOL	Small molecule
SoA	Schedule of activities

SOC	System Organ Class
SUSAR	Suspected unexpected serious adverse reaction
TAFI	Thrombin-activatable fibrinolysis inhibitor
TAT	Thrombin-antithrombin complex
TIA	Transient ischemic attack
TIMI	Thrombolysis in myocardial infarction
TKA	Total knee arthroplasty
TM	Trademark
t_{max}	Time to reach maximum drug concentration in plasma
TMF	Trial Master File
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US/USA	United States/United States of America
VKA	Vitamin K antagonist
VTE	Venous thromoembolism
vWF	Von Willebrand Factor
W	Week
WBC	White blood cell
WOCBP	Woman of childrenbearing potential

11. References

AHA/ACC. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: Executive Summary. 2014.

Chen Z, Seiffert D, Hawes B. Inhibition of Factor XI activity as a promising antithrombotic strategy. Drug Discov Today. 2014 Sep;19(9):1435-9.

Chesebro JH, Knatterud G, Roberts R, Borer J, Cohen LS, Dalen J, et al. Thrombolysis in Myocardial Infarction (TIMI) Trial, Phase I: A comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. Circulation. 1987 Jul;76(1):142-54.

Duga S, Salomon O. Congenital factor XI deficiency: an update. Semin Thromb Hemost. 2013 Sep;39(6):621-31.

Garcia-Garcia HM, McFadden EP, Farb A, Mehran R, Stone GW, Spertus J, et al. Standardized End Point Definitions for Coronary Intervention Trials: The Academic Research Consortium-2 Consensus Document. Eur Heart J. 2018 Jun 14;39(23):2192-207.

Kaatz S, Ahmad D, Spyropoulos AC, Schulman S, Subcommittee on Control of A. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. J Thromb Haemost. 2015 Nov;13(11):2119-26.

Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med. 2006 Aug 15;145(4):247-54.

Ling G, Kagdi H, Subel B, Chowdary P, Gomez K. Safety and efficacy of factor XI (FXI) concentrate use in patients with FXI deficiency: a single-centre experience of 19 years. Haemophilia. 2016 May;22(3):411-8.

Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973 Aug;60(8):646-9.

Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth Universal Definition of Myocardial Infarction (2018). J Am Coll Cardiol. 2018 Oct 30;72(18):2231-64.

Tomaselli GF, Mahaffey KW, Cuker A, Dobesh PP, Doherty JU, Eikelboom JW, et al. 2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol. 2017 Dec 19;70(24):3042-67.

Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2018 Jan 14;39(3):213-60.