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Title Page

Protocol Title:

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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 **–** non-cardioembolic **STROKE s**tudy
Acronym:	**PACIFIC-STROKE**

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PPD PPD

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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 efficacy and safety of BAY 2433334 in patients following an acute non-cardioembolic ischemic stroke

Short Title: **PACIFIC-STROKE** - Phase 2 **P**rogram of **A**nti**C**oagulation via **I**nhibition of **F**X**I**a by the oral **C**ompound BAY 2433334 – non-cardioembolic **STROKE** study)

Rationale: This study will assess the dose response 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. Current guidelines recommend antiplatelet therapy for patients after a non-cardioembolic ischemic stroke / transient ischemic attack (TIA). The addition of a FXIa inhibitor on top of antiplatelet therapy is expected to lead to a benefit regarding secondary prevention of stroke combined with no or only minimal increase in bleeding and especially no increase in major bleeding.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• to assess the dose response of 3 different doses of BAY 2433334 compared to placebo in reducing the composite of symptomatic ischemic strokes and covert brain infarcts detected by magnetic resonance imaging (MRI) as well as other cerebro- and cardiovascular endpoints in participants with an acute non-cardioembolic ischemic stroke and who are treated with antiplatelet therapy.	**Primary Efficacy Endpoint** • composite of symptomatic ischemic stroke and covert brain infarcts detected by MRI **Secondary Efficacy Endpoint** • composite of symptomatic ischemic stroke and covert brain infarcts detected by MRI, CV death, myocardial infarction and systemic embolism • symptomatic ischemic stroke • covert brain infarcts detected by MRI • symptomatic ischemic stroke, CV death, myocardial infarction • symptomatic ischemic and hemorrhagic stroke • disabling stroke (mRS≥4) • all-cause mortality
• to evaluate whether the incidence of bleeding for BAY 2433334 is similar compared to placebo in participants with an acute non-cardioembolic ischemic stroke and who are treated with antiplatelet therapy.	**Primary Safety Endpoint** • composite of International Society on Thrombosis and Hemostasis (ISTH) major bleeding and clinically relevant non-major (CRNM) bleeding **Secondary Safety Endpoints** • all bleeding • ISTH major bleeding • ISTH CRNM bleeding • ISTH minor bleeding • Intracerebral hemorrhage (non-traumatic)

The primary efficacy **estimand** is the incidence of symptomatic ischemic stroke or covert brain infarcts detected by MRI in 6 months following a non-cardioembolic ischemic stroke in adult participants treated with antiplatelet therapy, while alive and regardless of treatment discontinuation, for each of the different doses of BAY 2433334 and placebo.

The primary safety **estimand** is the hazard ratio of the composite of International Society on Thrombosis and Hemostasis (ISTH) major bleeding and clinically relevant non-major (CRNM) bleeding comparing pooled BAY 2433334 with placebo following a non-cardioembolic ischemic stroke in adult participants treated with antiplatelet therapy and who have taken at least one dose of study medication of BAY 2433334 or placebo and while the participant is alive and exposed to study drug.

The secondary efficacy **estimand** for the following endpoints:

- composite of symptomatic ischemic stroke and covert brain infarcts detected by MRI, CV death, myocardial infarction and systemic embolism
- covert brain infarcts detected by MRI

is the incidence in 6 months of each of the individual endpoints following a non-cardioembolic ischemic stroke in adult participants treated with antiplatelet therapy, while alive and regardless of treatment discontinuation, for each of the different doses of BAY 2433334 and placebo.

The secondary efficacy **estimand** for the following endpoints:

- symptomatic ischemic stroke
- symptomatic ischemic stroke, CV death, myocardial infarction
- symptomatic ischemic and hemorrhagic stroke
- disabling stroke (mRS≥4)
- all-cause mortality

is the hazard ratio of each of the individual endpoints following a non-cardioembolic ischemic stroke in adult participants treated with antiplatelet therapy, while alive and regardless of treatment discontinuation, comparing each of the different doses of BAY 2433334 with placebo. Details are described in Section 9.4.3.

The secondary safety **estimand** is similar to the primary safety estimand for the following endpoints:

- all bleeding
- ISTH major bleeding
- ISTH CRNM bleeding
- ISTH minor bleeding
- Intracerebral hemorrhage (non-traumatic)

Details are described in Section 9.4.3.

Overall Design:

Study 19766 is a multicenter, randomized, placebo controlled, double-blind, parallel group, dose-finding study.

The study population includes participants to be randomized within 48 hours of onset of an acute non-cardioembolic ischemic stroke who are planned to be treated with antiplatelet therapy at the discretion of the investigator.

The study will consist of 2 parts, Part A (minor strokes) and Part B (minor and moderate strokes). The initiation of Part B will be based on an interim analysis.

Stratification will be based on whether participants will receive single or dual antiplatelet therapy after the index stroke and randomization.

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

Disclosure Statement: This is a parallel group treatment 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 1900 patients will be screened to achieve 1800 randomized participants for an estimated total of 450 evaluable participants per intervention group. More details are available in Section 9.2.

Intervention Groups and Duration:

BAY 2433334 is the sponsor's study drug under investigation. Placebo is used as comparator.

Study intervention duration and dose regimen are tabulated as follows:

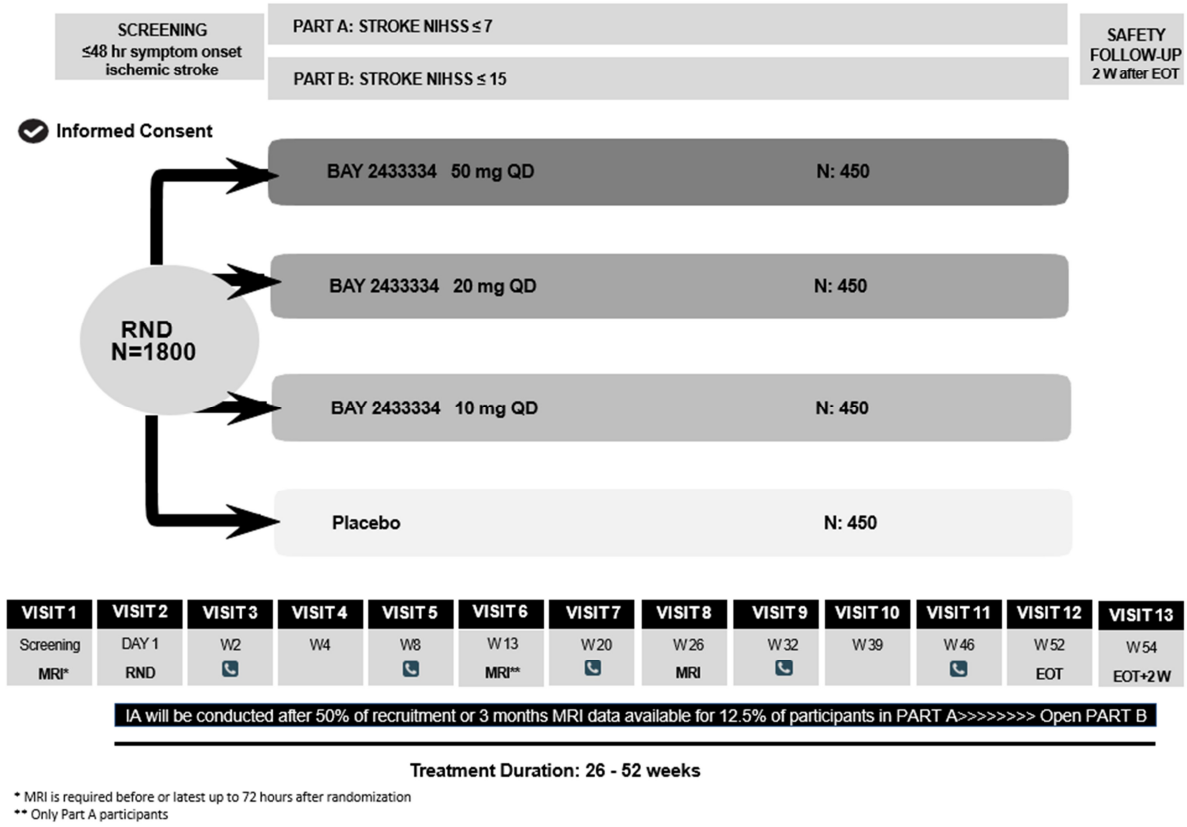
<table>
<tr><th>Study Period</th><th>Duration*</th><th>Dose and Frequency</th><th>Route of administration</th></tr>
<tr><td>Screening</td><td>Within 48 hours of the onset of symptoms of ischemic stroke</td><td rowspan="3">BAY 2433334 10 mg once daily
BAY 2433334 20 mg once daily
BAY 2433334 50 mg once daily
Placebo once daily</td><td rowspan="3">Oral</td></tr>
<tr><td>Intervention</td><td>26-52 weeks*</td></tr>
<tr><td>Safety Follow-up</td><td>2 weeks</td></tr>
<tr><td>Total planned number of participants</td><td colspan="3">Total planned study duration</td></tr>
<tr><td>1800</td><td colspan="3">Between 28 and 54 weeks</td></tr>
</table>

*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



Abbreviations:
EOT = End of Treatment; IA = Interim Analysis; MRI = Magnetic Resonance Imaging; OD = Once Daily; RND = Randomization, N = total number of participants, W = Week

1.3 Schedule of Activities (SoA)

Study periods (Duration)	**Screening (SCR)**[a]	**Intervention period** (from RND until End of Treatment visit [**EOT**], 26 to 52 weeks)											Early termination (ET)[b]	**Safety Follow-up (SFU)** (14 days after EOT or ET)
Visit number	**1**	**2**	**3**	**4**[g]	**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** -2 → 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[d]												
Demographics and biometrics	X													
Medical history	X													
Prior and Concomitant medication	X	X[d]	X[e]	X	X[e]	X	X[e]	X	X[e]	X	X[e]	X	X	X
Clinical procedures / assessments														
mRS[f], NIHSS assessment	X	X[d]				X[f]		X				X	X	
12-lead ECG[g]	X[c]	X[d]				X						X	X	
Vital signs (BP and HR)	X	X[d]		X		X		X		X		X	X	
Adverse events		←========== continuously==========→												
Outcome events[h]		←========== continuously==========→												
bMRI[i] [Part **A** and/or **B**] (study day and allowed time window)		**A,B** (-2→+3)				**A**[j] (±7)		**A,B** (±7)					**A,B** (+7)	
IxRS														
Randomization / Visit registration via IxRS	X	X				X		X		X		X	X	
Laboratory assessments														
Safety blood sample	X[k]	X[d,k]		X		X		X		X		X	X	

Study periods (Duration)	**Screening (SCR)***	**Intervention period** (from RND until End of Treatment visit [**EOT**], 26 to 52 weeks)											Early termination (ET)[b]	**Safety Follow-up (SFU)** (14 days after EOT or ET)
Visit number	**1**	**2**	**3**	**4**	**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** -2 → 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
Pharmacokinetic sample[l]				X				X					X	
Pharmacodynamic sampling[l]		X		X				X					X	
Pharmacogenetic sample		X												
Biomarker sampling[l]		X						X					X	
Study drug[m] administration														
Study drug[m] dispensation		X[n]				X[n]		X[n]		X[n]				
Study drug [m] intake at the site[l]		X		X				X				no intake		
Stud drug [m] collection and accountability						X		X		X		X	X	

Abbreviations: BP = blood pressure, CRF = case report form, ECG = electrocardiogram, eGFR = estimated glomerular filtration rate, EoT = end of treatment, ET = early termination, HR = heart rate, IxRS = Interactive Voice/Web Response System, MRI = magnetic resonance imaging, mRS = modified ranking score, NIHSS = National Institute of Health Stroke Scale, PD = pharmacodynamic(s), PK = pharmacokinetic(s), RND = randomization, SCR = screening, SFU = safety follow-up, SoA = Schedule of Activities, TIA = transient ischemic attack, W = week

[a] Screening, randomization and intake of first study drug must occur within 48 hours of symptom onset.
[b] The visit can be performed at a later time point if participant on inpatient rehabilitation facility and this visit cannot be arranged.
[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] In case screening and randomization are performed on the same day, this procedure does not need to be repeated.
[e] At Visit 3, 5, 7, 9 and 11: any new concomitant medication and AEs or outcome event will be captured during the calls.
[f] modified Ranking Score (mRS) (Section 10.10) and NIHSS (Section 10.11) should be assessed as follows:
Index event: at time of screening and time of randomization (NIHSS), day 7 after the event (or at hospital discharge, if this occurs before day 7; NIHSS and mRS), at 3, 6 and 12 months visits (mRS).
For recurrent stroke events: maximum score during hospitalization (NIHSS), day 7 after the event (or at hospital discharge, if this occurs before day 7: NIHSS and mRS); visit closest to 3 months after recurrent stroke (mRS).
[g] ECG machine that automatically calculates the heart rate and measures PR, QRS, QT and QTc intervals should be used.

[h] outcome events including all bleeding, death, MI, recurrent stroke and systemic embolism as well as events indicative of a potential outcome (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 study treatment.
[i] MRI is required before or latest within 72 after randomization.
[j] For part A only until Part B starts.
[k] Creatinine, eGFR results, AST and ALT values measured in the local laboratory for screening. Current local laboratory results available for the index hospitalization for the stroke can be used. Full safety laboratory assessments to be done at randomization in the central laboratory.
[l] Refer to Table 1–1 PK, PD and Biomarker sampling.
[m] "Study drug" refers to "study intervention' as defined in Section 6.1.
[n] At each contact, participants should be again instructed regarding study drug compliance.

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	2-4 h[b] Postdose	4-12 h[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 to remind the 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 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) 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 to remind the participants is recommended. However, in case Visit 8 is also the EOT visit as well as in case the sample is taken at ET visit, no study drug will be administered.

[e] If study drug is temporarily 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 study drug intake (i.e: on the PK / PD sampling day, as well as the day before that).

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 19766 will be a Phase 2 study with a 6 to 12 months treatment duration and will test BAY 2433334 against placebo in participants following an acute non-cardioembolic ischemic stroke who are planned to be treated with antiplatelet therapy at the discretion of the investigator.

The current clinical development of BAY 2433334 (FXIa inhibitor) includes two additional Phase 2 studies in participants with AF (study 19765) and in participants with AMI (study 20603). These two studies are planned to have a treatment duration of 3 months and 6 to 12 months, respectively, testing BAY 2433334 against apixaban (NOAC) and BAY 2433334 against placebo on top of dual antiplatelet therapy.

Each individual study will have its own objectives. However, in order to reach and draw conclusions concerning safety in general, and specially 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 assess the dose response of BAY 2433334 in order to determine the dose that is both efficacious and safe and that can be tested in a subsequent Phase 3 trial for the same indication.

Currently, patients with non-cardioembolic ischemic stroke are treated with antiplatelet therapy. No clinical studies have proven the benefit of anticoagulation therapy in patients with non-cardioembolic stroke. However, it has been shown that patients with a stroke have increased levels of FXI and patients with FXI deficiency have a lower risk for stroke.

In the planned Phase 2 study, BAY 2433334 will be tested against placebo, added on top of antiplatelet therapy. This approach is supported by data from the COMPASS study in patients with stable coronary and peripheral artery disease. Patients who received the combination of 2.5 mg bid rivaroxaban plus ASA had fewer ischemic/uncertain stroke when compared to those who received ASA alone (HR 0.58) (Sharma et al. 2019).

Inhibition of FXIa is expected to lead to a benefit versus placebo regarding secondary prevention of ischemic stroke as well as to not lead to a relevant increase in bleeding and especially major bleeding. This is based on the available preclinical data, data from patients with inherited FXI deficiency and first clinical data from 2 Phase 2 proof-of-concept studies in patients undergoing total knee replacement (please see Section 2.3).

The primary endpoint will be symptomatic ischemic stroke and covert brain infarcts. Covert brain infarcts are also called silent strokes and are identified by MRI. These are seen in 30% of the elderly and are 2-4 times more frequent compared with symptomatic strokes. Covert brain infarcts occur in regions of the brain that do not lead to typical stroke symptoms (i.e. hemiparesis) and hence clinical diagnosis, but they are linked to vascular cognitive impairment gait disorders, depression and dementia. In addition, available data indicate that covert brain infarcts are similarly reduced as symptomatic strokes by anticoagulation with rivaroxaban on top of single antiplatelet agent ASA in patients with a history of CAD or PAD based on COMPASS study (Sharma M et al. 2019)BAY 2433334 as an inhibitor of FXIa is therefore an attractive candidate to evaluate as a potential add-on to antiplatelet therapy in patients after an acute non cardioembolic stroke

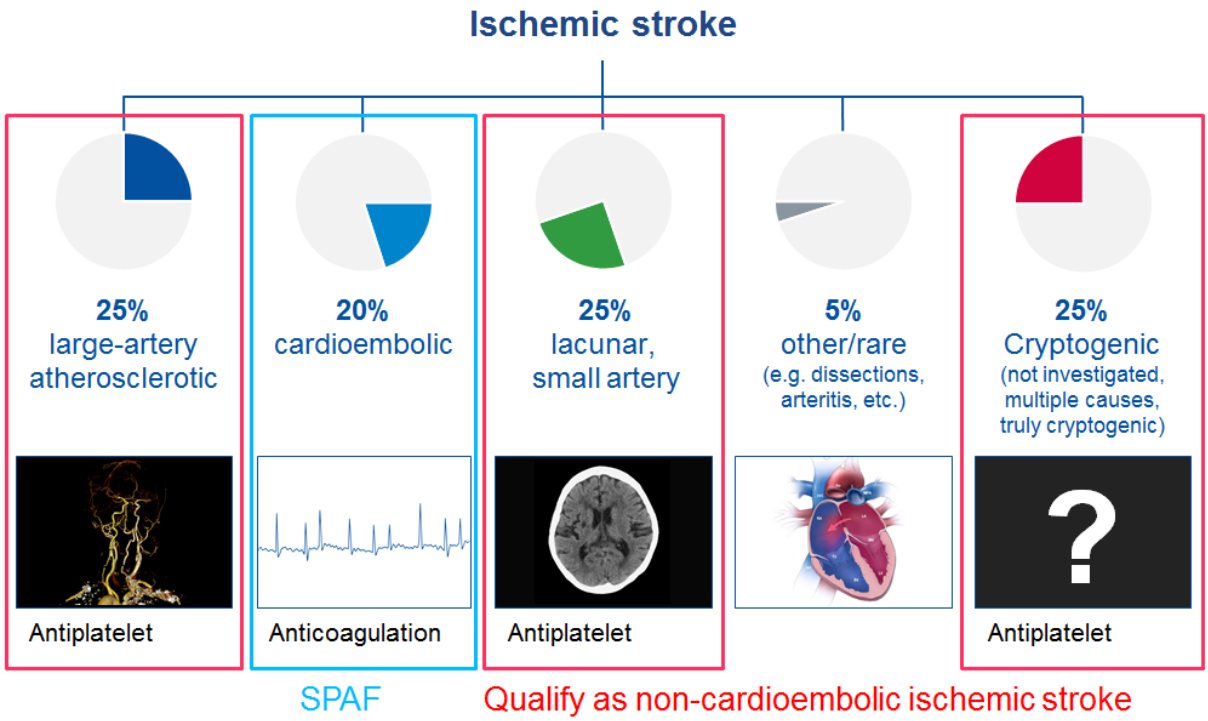
2.2 Background

2.2.1 Disease Background

Worldwide, 13.7 million people suffered a first ever stroke in 2016 and 5.5 million people died of a stroke (Johnson et al. 2019). About 25% of all ischemic strokes are recurrent strokes. The ischemic stroke recurrence rate is substantial and remains at 3 to 6% per year despite of guideline-recommended preventive therapies.

Non-cardioembolic stroke includes lacunar stroke, large artery arteriosclerotic stroke and cryptogenic stroke / ESUS, that together account for 75% of all ischemic strokes and are currently treated with antiplatelet therapy (e.g. ASA, clopidogrel, ASA + dipyridamole).

Figure 2–1 Ischemic stroke sub-type classification (TOAST criteria)



Source: adapted from (Adams et al. 1993, Hart et al. 2014);
TOAST = Trial of ORG 10172 in Acute Stroke Treatment.

2.2.2 Treatment Guidelines

For secondary prevention of stroke in patients with non-cardioembolic stroke, BAY 2433334 will be given on top of antiplatelet therapy, which represents standard of care according to current guidelines (2008 European Stroke Organization guideline (Ringleb et al. 2008), the 2014 American Heart Association revised guideline for the prevention of stroke (Kernan et al. 2014), 2018 guidelines for the early management of patients with acute ischemic stroke (Powers et al. 2018), the 2012 American College of Chest Physicians guideline (Lansberg et al. 2012), and the 2014 Canadian Best Practice Recommendations for Stroke Care (Coutts et al. 2015). Preferences for standard of care antiplatelet therapy varies by region and by country, stroke management guidelines recommend a range of single antiplatelet therapies that include acetylsalicylic acid (ASA), clopidogrel, the combination of ASA and dipyridamole or ASA and cilostazol. Recent studies (Johnston et al. 2018, Wang et al. 2013) support the use of dual antiplatelet therapy with ASA and clopidogrel for 21 days after an acute ischemic stroke, and although widely used in Europe and North America, this combination has not as yet been consistently advocated in stroke management guidelines (Johnston et al. 2016, Johnston et al. 2018, Wang et al. 2013).

The use of anticoagulation therapy in patients with non-cardioembolic ischemic stroke is currently not recommended. In contrast, in patients with atrial fibrillation (AF) suffering a stroke or TIA, anticoagulation is recommended, but initiation of NOACs is typically delayed

for 1-3-6-12 days after the stroke or TIA depending on the severity (TIA-minor-moderate-severe stroke).

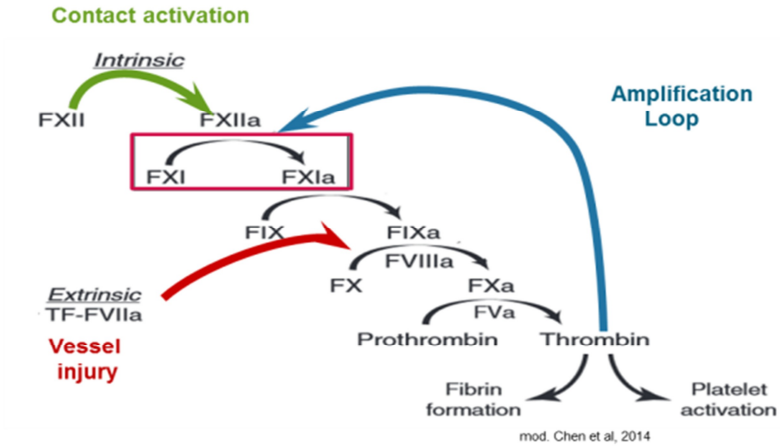
2.2.3 FXIa Inhibition: Mode of Action

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 (Figure 2–2). 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 2–2 Contact activation



Source: adapted from Chen et al. 2014 (Chen et al. 2014).

2.2.4 BAY2433334

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 BAY2433334 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 completed. 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 the evaluation is still ongoing. Therefore, the results are preliminary. It consisted of three parts: Part A, where 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 single dose (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 as 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 37%. This metabolite is not pharmacologically active.
- Terminal half-life is 14.5 to 16.0 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 AF, 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 non-cardioembolic ischemic stroke. Once daily doses of 10 mg, 20 mg and 50 mg will be tested in the study.

BAY 2433334 as a FXIa inhibitor in contrast 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 inhibition of FXI activity by a mean of > 95% and complete inhibition during 12 hours of the day. This was combined with a mean prolongation of aPTT of [redacted].

At this stage of development, the safety profile has not been established. The following information related to safety as well as potential risks for participants 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 BAY2433334 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 dosing in participants.
    - 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 no relevant bleeding events were reported so far.

A risk for bleeding cannot be excluded in patients after an acute non-cardioembolic ischemic stroke included in the Phase 2 study, as many patients with minor strokes will be treated on top of dual antiplatelet therapy during the initial phase. Therefore, bleeding will be closely monitored in the study and will be adjudicated by an independent clinical event committee. In addition, patients after an acute ischemic stroke have a risk for a hemorrhagic transformation of the stroke as well as for intracranial bleeding in general. Therefore, in patients with acute ischemic stroke, anticoagulants are initiated after a delay depending on stroke severity. Based on available data a lower risk for bleeding with FXIa inhibition is expected and therefore, early initiation is justified. However, in order to maximize the safety of participants Part A will be restricted to patients with a minor stroke. Eligibility will be expanded to include more severe strokes only after a thorough assessment of bleeding events during Part A.

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 liver. Based on this participants 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.

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 participants after an acute non-cardioembolic ischemic stroke will receive for the first time BAY 2433334. Study drug will be given on top of SoC therapy with antiplatelet therapy. The main objective of the study is to explore whether the addition of BAY 2433334 will lead to a dose response in reducing symptomatic strokes and covert brain infarcts and whether this is combined with no relevant increase in bleeding when

given on top of antiplatelet therapy. 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, secondary 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 assess the dose response of 3 different doses of BAY 2433334 compared to placebo in reducing the composite of symptomatic ischemic strokes and covert brain infarcts detected by MRI as well as other cerebro- and cardiovascular endpoints in participants with an acute non-cardioembolic ischemic stroke and who are treated with antiplatelet therapy.	**Primary Efficacy Endpoint** • composite of symptomatic ischemic stroke and covert brain infarcts detected by MRI **Secondary Efficacy Endpoint** • composite of symptomatic ischemic stroke and covert brain infarcts detected by MRI, CV death, myocardial infarction and systemic embolism • symptomatic ischemic stroke • covert brain infarcts detected by MRI • symptomatic ischemic stroke, CV death, myocardial infarction • symptomatic ischemic and hemorrhagic stroke • disabling stroke (mRS≥4) • all-cause mortality
• to evaluate whether the incidence of bleeding is similar for BAY 2433334 compared to placebo in participants with an acute non-cardioembolic ischemic stroke and who are treated with antiplatelet therapy.	**Primary Safety Endpoint** • composite of International Society on Thrombosis and Hemostasis (ISTH) major bleeding and clinically relevant non-major (CRNM) bleeding **Secondary Safety Endpoints** • all bleeding • ISTH major bleeding • ISTH CRNM bleeding • ISTH minor bleeding • Intracerebral hemorrhage (non-traumatic) **Exploratory Safety Endpoints** • TIMI clinically significant bleeding • TIMI major bleeding • TIMI minor bleeding • BARC bleeding definition Type 2, 3, 5 • BARC bleeding definition Type 3, 5 • BARC bleeding definition Type 1, 2, 3, 5

Exploratory	
• to explore additional pharmacokinetic and pharmacodynamic parameters, biomarkers and genetics • To further investigate the study intervention (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 Safety Endpoints** • FXIa inhibition, aPTT • Pharmacokinetics • Various biomarkers and genetics may be explored (e.g. diagnostic, safety, PD, monitoring, or potentially predictive biomarkers)

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

The primary efficacy estimand is the incidence of symptomatic ischemic stroke or covert brain infarcts detected by MRI in 6 months following a non-cardioembolic ischemic stroke in adult participants treated with antiplatelet therapy, while alive and regardless of treatment discontinuation, for each of the different doses of BAY 2433334 and placebo.

The primary safety estimand is the hazard ratio of the composite of International Society on Thrombosis and Hemostasis (ISTH) major bleeding and clinically relevant non-major (CRNM) bleeding comparing pooled BAY 2433334 with placebo following a non-cardioembolic ischemic stroke in adult participants treated with antiplatelet therapy and who have taken at least one dose of study medication of BAY 2433334 or placebo and while the participant is alive and exposed to study drug.

The secondary efficacy estimand for the following endpoints:

- composite of symptomatic ischemic stroke and covert brain infarcts detected by MRI, CV death, myocardial infarction and systemic embolism
- covert brain infarcts detected by MRI

is the incidence in six months of each of the individual endpoints following a non-cardioembolic ischemic stroke in adult participants treated with antiplatelet therapy, while alive and regardless of treatment discontinuation, for each of the different doses of BAY 2433334 and placebo.

The secondary efficacy estimand for the following endpoints:

- symptomatic ischemic stroke
- symptomatic ischemic stroke, CV death, myocardial infarction
- symptomatic ischemic and hemorrhagic stroke
- disabling stroke (mRS≥4)
- all-cause mortality

is the hazard ratio of each of the individual endpoints following a non-cardioembolic ischemic stroke in adult participants treated with antiplatelet therapy, while alive and regardless of treatment discontinuation, comparing each of the different doses of BAY 2433334 with placebo. Details are described in Section 9.4.3.

The secondary safety estimand is similar to the primary safety estimand for the following endpoints:

- all bleeding
- ISTH major bleeding
- ISTH CRNM bleeding
- ISTH minor bleeding
- Intracerebral hemorrhage (non-traumatic).

Details are described in Section 9.4.3.

4. Study Design

4.1 Overall Design

Study 19766 is a multicenter, randomized, placebo-controlled, double-blind, parallel group, dose-finding Phase 2 study. The overall study design is depicted in Figure 1–1.

The study population includes participants to be randomized within 48 hours of onset of an acute non-cardioembolic ischemic stroke who are planned to be treated with antiplatelet therapy at the discretion of the investigator. Approximately 1800 participants (450 per arm) will be randomized 1:1:1:1 to 1 of the 3 investigational drug arms (BAY 2433334) or the placebo arm, in addition to their standard of care antiplatelet background therapy.

The study will consist of 2 parts, Part A (minor strokes) and Part B (minor and moderate strokes) and the following periods:

- **Screening (Visit 1 until Visit 2)**: Within 48 hours of the onset of symptoms
    - Screening and randomization can take place on the same day if all information is available (Visits 1 and 2 are combined)
    - Imaging of brain (CT or MRI) must be available at screening to exclude hemorrhagic stroke or other causes of the symptoms.
    - All participants must have at least one MRI available meeting study MRI manual specifications either before randomization (as a clinically initiated MRI) or latest within 72 hours after randomization (as a study initiated MRI).
    - Participants must be screened, randomized and study treatment initiated within 48 hours after the onset of symptoms of the index event or after participants were last known to be without symptoms in case of wake-up stroke.
    - Stratification will be based on whether participants will receive single or dual antiplatelet therapy after the index stroke and randomization.
- **Treatment Period (Visit 2 through Visit 12):** At least 26 weeks up to 52 weeks

  Participants are required to receive concomitant antiplatelet therapy. For more details see Section 6.5.1.

  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.

  For details on Part A and B of the treatment phase see Section 4.1.1.
- **Safety Follow-up (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), at Week 13 (Visit 6), Week 26 (Visit 8), Week 39 (Visit 10) and at Week 52 / EOT (Visit 12).

Telephone calls will take place at Week 2 (Visit 3), Week 8 (Visit 5), Week 20 (Visit 7), Week 32 (Visit 9), Week 46 (Visit 11) as well as 2 weeks after the EOT visit for participants who will take study drug until the planned EOT (i.e. safety follow-up, Visit 13).

For participants who will prematurely discontinue from study drug, an early termination (ET) visit (Visit 12a) will take place as soon as possible at the study site. Participants are asked to continue the study schedule of visits until completing all the study visits or end of study is declared. Telephone calls will take place 2 weeks after the ET visit (i.e. safety follow-up, Visit 13). Further details are described in Section 7.1.

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

4.1.1 Study Design: Part A and Part B

Patients after an acute ischemic stroke have an increased risk for intracranial bleeding and hemorrhagic transformation of the ischemic stroke area. Patients may also receive thrombolysis as acute therapy. Therefore, in patients who had an ischemic stroke and who require anticoagulation therapy for example due to AF, anticoagulation is typically delayed with the decision for treatment initiation depending on stroke severity.

In order to address this safety concern (despite that none or only minimal increase in bleeding is expected for BAY 2433334) the study will consist of 2 parts with participants with less severe strokes to be enrolled in Part A and extended to more severe strokes in Part B if warranted by safety documented in Part A. In more detail:

Part A will enroll participants with minor stroke only, defined as NIHSS ≤7 at time of randomization, whereas in

Part B enrollment will be extended to:

- Participants with minor or moderate strokes: NIHSS≤ 15 at time of randomization
- Participants with thrombolysis or endovascular therapy (mechanical thrombectomy) can be randomized >24hr after the intervention; (i.e randomization can take place no earlier than 24 hours after having received these treatments).

The decision to initiate Part B will be taken as part of an interim analysis. This will take place after approximately 50% of participants have been enrolled in the study or MRI data (week 13) is available for approximately 12.5% of the participants. Besides data from this study, also data from the concurrently conducted Phase 2 studies in AF and acute myocardial infarction will be considered. For more details on the interim analysis process, see Section 9.5.

If the interim analysis indicates no concern (e.g. no clinically relevant increase in intracranial hemorrhage or hemorrhagic transformation of ischemic stroke), **Part B** will be initiated.

In the event that **Part B** is not initiated following the interim analysis, and there is no safety concern that warrants a stop of the study, enrolment will continue based on **Part A** eligibility criteria until the end of recruitment.

4.1.2 MRI Procedures

The required study MRI sequences to detect covert brain infarcts are based on brain MRIs done for routine clinical care of acute stroke patients. The focus is on the primary study

objective of detecting incident covert brain infarcts. MRI data will be transmitted to the central MRI Core Laboratory where MRI interpretation will be done blinded to treatment assignment to identify incident brain infarcts, comparing the initial study MRI to follow-up MRI. Details regarding the procedure, MRI requirements and logistics will be available in a MRI procedure manual.

The required study MRIs are to be performed:

- either before randomization (as a clinically initiated MRI) or within 72 hours after randomization (as a study initiated MRI) for all participants (Part A and B) and
- a final study MRI will be performed for all participants (Part A and B) at Week 26 (Visit 8) or ET
- a study MRI at Week 13 (Visit 6) will be performed for Part A participants only until Part B is open. Once Part B is open neither Part A or Part B participants will require the MRI imaging at Week 13.

In summary, all participants are required to undergo at least two MRIs that meet study requirements, and most participants enrolled during Part A will undergo a third MRI at week 13.

Clinical MRIs are acceptable for study purposes as long as they comply with the minimum requirements detailed in the MRI procedures manual. The MRI requirements were designed to make it feasible that at most stroke centers the clinical MRIs done for an acute stroke will qualify for use in the study and not requiring an additional study MRI.

If possible, the same MRI machine should be used for all study-related MRIs for an individual participant.

Further information is available in Section 10.9 and in a separate MRI procedures manual.

4.2 Scientific Rationale for Study Design

Study 19766 is a multicenter, randomized, placebo controlled, double-blind, parallel group, dose-finding Phase 2 study in 1800 patients (450 patients per arm) with an acute non-cardioembolic ischemic stroke. The study will apply the principles of randomization, stratification (by antiplatelet therapy; single vs. dual antiplatelet therapy) 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 BAY 2433334 there are no safety concerns related to the highest dose of 50 mg once daily tested in the study.

Treatment duration is planned for at least 26 and up to 52 weeks in this Phase 2 study in order to enable collection of sufficient number of bleeding events as well as efficacy events i.e. stroke events, over time. In addition, the longer treatment duration allows to identify signals on delayed adverse drug reaction.

Based on our assumptions, 7.5% of participants will experience a symptomatic stroke during the study conduct and in addition twice as many covert brain infarcts (15%) are expected leading to overall 22.5% at 6 months. During the whole study duration ~ 100 symptomatic strokes and ~ 200 covert brain infarcts (total ~ 300) are expected to be observed in the study

cohort. At the same time, ~ 70 major or CRNM bleeding are expected. This number of events is required to provide a signal of efficacy, reassurance about safety, and allow determination of the optimal dose to be selected for Phase 3.

The study is separated into 2 parts (Part A and Part B). In Part A, only patients with a minor stroke will be enrolled, whereas in Part B, the study will also be opened up to patients with moderate stroke and patients who have undergone thrombolysis or endovascular therapy. This approach has been chosen to address the increased risk of patients with ischemic stroke for hemorrhagic transformation of the ischemic stroke area, and a generally higher risk for intracranial bleeding. For more details, see section 4.1.1.

In this study, treatment initiation with BAY 2433334 is planned within 48 hours of onset of an acute ischemic stroke, as the risk for a recurrent stroke is highest during the early phase after a stroke with almost 7% risk at 48 hours and a 10% risk by 7 days, even for patients with initial mild clinical presentation (Johnston et al. 2016, Johnston et al. 2018, Wang et al. 2013). Early initiation is regarded as acceptable, because the oral FXIa inhibitor BAY 2433334 is expected to not increase the bleeding risk.

BAY 2433334 will be given on top of standard of care with background antiplatelet therapy. The decision on type of antiplatelet therapy will be left to the discretion of the treating physician, as there is variance in the current clinical practice. Mandating a single antiplatelet regimen might not be widely acceptable according to local practices or regional guidelines, but also not scientifically required, as the primary comparison will be BAY 2433334 versus placebo.

The current clinical development of BAY 2433334 is conducted with three Phase 2 studies in parallel. Apart from participants with non-cardioembolic ischemic stroke, other studies are being conducted in patients with AF as well as acute myocardial infarction (AMI). A common Independent Data Monitoring Committee (IDMC) will keep oversight of each one of the studies individually and as overall for Phase 2 studies of BAY 2433334.

The aim of these individual Phase 2 studies is to gain knowledge of the bleeding profile. It is not planned to perform hypotheses testing. However, this study (19766) is powered to detect a dose-response relationship for the primary efficacy outcome. Pooled data across the studies should will add precision concerning safety in terms of bleeding and general safety. For this purpose, data will be pooled within and across studies.

4.3 Justification for Dose

The study will test the once daily doses of 10 mg (low dose), 20mg (mid dose) and 50 mg (high dose) 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 for 9 days were tested in the Phase 1 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 dose linear 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: doses selection for Phase 2

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

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 within 48 hours of the onset of symptoms of an acute non-cardioembolic ischemic stroke (index event) documented to be not hemorrhagic by neuroimaging and with intention to be treated with antiplatelet therapy.

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. Participant must be 45 years of age and older at the time of signing the informed consent

Type of Participant and Disease Characteristics

2. Non-cardioembolic ischemic stroke with
   a. persistent signs and symptoms of stroke lasting for ≥ 24 hours OR
   b. acute brain infarction documented by computed tomography (CT) or MRI AND

c. with the intention to be treated with antiplatelet therapy during the study conduct[1]

3. Imaging of brain (CT or MRI) ruling out hemorrhagic stroke or another pathology that could explain symptoms (e.g. brain tumor, abscess, vascular malformation)
4. Severity of index event nearest the time of randomization:
   a. **Part A**: minor stroke (defined as NIHSS ≤ 7) can be enrolled
   b. **Part B**: participants with minor or moderate stroke and NIHSS ≤ 15 can be enrolled. Participants undergoing thrombolysis or endovascular therapy (mechanical thrombectomy) can be enrolled but at the earliest 24 hours after the intervention
5. Randomization within 48 hours after the onset of symptoms of the index event (or after patients were last known to be without symptoms in case of wake-up stroke)
6. Ability to conduct an MRI either before randomization or within 72 hours after randomization

Informed Consent

7. 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 procedure.

5.2 Exclusion Criteria

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

Medical Conditions

1. Prior ischemic stroke within last 30 days of index event
2. History of atrial fibrillation* or suspicion of cardioembolic source of stroke (*12-lead ECG or documented during cardiac rhythm monitoring)
3. Dysphagia with inability to safely swallow study medication at time of randomization
4. Contraindication to perform brain MRI (e.g. certain types of aneurysm clips, claustrophobia, patients that cannot lie supine for 30 minutes, patients whose body structure exceeds the restrictions of the local MRI instrument)
5. **Part A** only: thrombolysis or endovascular therapy (mechanical thrombectomy) performed for index event
6. Uncontrolled hypertension (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg) at randomization
7. Active bleeding; known bleeding disorder, history of major bleeding (intracranial, retroperitoneal, intraocular) or clinically significant gastrointestinal bleeding within last 6 months of randomization

[1] any antiplatelet therapy recommended by regional guidelines for secondary stroke prevention, single or dual, is permitted based on the choice of the treating physician see Section 6.5.1.

8. Known significant liver disease (e.g. acute hepatitis, chronic active hepatitis, cirrhosis) or hepatic insufficiency classified as Child-Pugh B or C (see Section 10.7), or ALT or AST > 2.5 x the upper limit, measured between enrollment and randomization
9. Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 calculated by Modification of Diet in Renal Disease (MDRD) (see Section 10.7), determined between enrollment and randomization.
10. Major surgery during last 30 days or planned major surgery or intervention within study period (e.g. Carotid endarterectomy, CABG)
11. Known allergy, intolerance or hypersensitivity to the study intervention (active substance or excipients).

Prior/Concomitant Therapy

12. Planned use or requirement of full dose and long term anticoagulation therapy during study conduct[2]
13. Anticipated need for chronic (more than 4 weeks) therapy with NSAIDs
14. 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

15. Known current alcohol and/or illicit drug abuse that may interfere with the participant's safety and/or compliance at the discretion of the investigator
16. 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
17. 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)
18. 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.
19. Any condition or therapy, which would make the participant unsuitable for the study (e.g. non-compliance) or otherwise vulnerable (e.g. participant in custody by order of an authority or a court) or life expectancy < 6 months.

[2] venous thromboembolism prophylaxis with LMWH or unfractionated heparin for short periods of time is allowed.

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 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) may 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 Interventions 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. BAY 2433334 is taken orally once a day in the morning, preferably around the same time each day. 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 interventions (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 immediately 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 low dose	BAY 2433334 medium dose	BAY 2433334 high 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	5 mg	5 mg and 15 mg	25 mg	NA
Dosage Level(s)	10mg	20mg	50mg	NA
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 all 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 (i.e. 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 intervention using an Interactive Web 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 whether participants will receive single or dual antiplatelet therapy after the index stroke and randomization.

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

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

Participants will be randomly assigned in a [1:1:1:1] ratio to receive study intervention. 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 2344443 and corresponding placebo are identical in appearance (size, color, shape). In order to maintain the blind, study interventions will be packaged in bottles labeled with a unique number which will be preprinted 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 participant'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 participant's treatment assignment unless this could delay emergency treatment of the participant. If a participant'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 dependent 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, inadvertent 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 (emergency) situations where aPTT may help to guide treatment decision. aPTT determinations obtained as part of the study protocol will not be reported to investigators 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 drug 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 drug and empty packages at study Visit 6, 8 10 and EOT (or ET) visit if applicable for accountability purposes. Any discrepancies between actual and expected amount of returned study medication must be discussed with the participant at the time of the visit, and any explanation must be documented in the source documents.

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
- Careful recording of medication received during the index event is required especially any thrombolysis and antithrombotic medication

The Medical Monitor (sponsor's Study Medical Expert) should be contacted if there are any questions regarding concomitant or prior therapy.

Special focus needs to be on antiplatelet, thrombolytics and anticoagulant medications. Any use of these medications in the week before the index stroke 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

The choice of antiplatelet therapy as standard of care background treatment during the study treatment period will be left to the discretion of the investigators and/or treating physician and should follow local standard of care guidelines. Antiplatelet therapy can include single and dual therapy with ASA, clopidogrel, dipyridamole or cilostazol. Dual antiplatelet therapy with ASA and clopidogrel may only be given for the first weeks after the index stroke.

Anticipated use of anticoagulants or/and other drugs that affect the coagulation system and specifically drugs that affect platelets other than the allowed background therapy exclude participation.

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 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 in the support of use of these agents.

6.5.3 Guidance for Management of Participants who Have Surgery or Percutaneous/Endoscopic Procedures

When possible, surgery and 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 surgery or 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 (BAY 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 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 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 Recurrent Ischemic Stroke

For participants who experience ischemic stroke during the study, a complete diagnostic work-up including brain and arterial imaging, at least 24-hour cardiac rhythm monitoring, and echocardiography is encouraged (but neither required by the study protocol nor reimbursed by the sponsor).

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 new Myocardial Infarction During the Study

For participants who experience a suspected new, acute cardiac ischemic event requiring unplanned hospitalization (unstable angina or acute MI), 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 drug should be temporarily discontinued upon hospital presentation for a suspected acute cardiac ischemic event to mitigate potential bleeding risks. Cardiac ischemic event (acute MI) 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 ischemic event, study drug should be restarted no earlier than 24 hours after the arterial sheath has been removed and / or no earlier than 24 hours after the last dose of intravenous / subcutaneous anticoagulant or intravenous antiplatelet agent has been administered. For participants who are treated with urgent or emergent CABG surgery for the new ischemic event after coronary angiography, 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.

6.6 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 (i.e, ET visit) and follow-up and for any further evaluations that need to be completed.

At the 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 only 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, systemic embolism, death, bleeding).

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 the event of a temporary interruption of study drug for any reason, study drug will be restarted as soon as medically justified in the opinion of the investigator. There is no predefined 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 the 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 family members, caretaker, legal representative, or treating 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 endpoint is the composite of symptomatic ischemic stroke and covert brain infarcts detected by MRI.

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 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:

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.

Ischemic stroke:

Either of the following is considered to be an ischemic stroke:

- Rapid onset (or present on awakening) of a new focal neurological deficit with clinical (>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)
- Acute worsening of an existing focal neurological deficit (e.g., the qualifying stroke) that is judged to be attributable to a new infarction or extension of the previous infarction in the same vascular territory, based on persisting symptoms/signs or imaging evidence of infarction and no evidence of a non-ischemic etiology. If imaging is inconclusive, persistent symptoms/signs must be significant (worsening of NIHSS score of 4 or more) and sustained (duration of ≥24 hours or until death).

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

8.1.1.1.1 Covert Brain Infarcts

Covert brain infarcts are defined as incident infarcts detected by serial MRI in the absence of an adjudicated stroke consistent with the location of the infarct. MRI criteria for brain infarction will be available in the MRI procedures manual.

8.1.2 Secondary efficacy endpoints

A definition of the secondary efficacy outcome events is provided as follows, and further specified in the charter of the clinical event committee (CEC).

Secondary efficacy endpoints are:

- composite of symptomatic ischemic stroke and covert brain infarcts detected by MRI, CV death, myocardial infarction and systemic embolism
- symptomatic ischemic stroke
- covert brain infarcts detected by MRI
- symptomatic ischemic stroke, CV death, myocardial infarction
- symptomatic ischemic and hemorrhagic stroke
- disabling stroke (mRS ≥4)
- all-cause mortality.

8.1.2.1 Systemic Embolism

Systemic embolism is defined as abrupt vascular insufficiency associated with clinical or radiological evidence of arterial occlusion in the absence of other likely mechanisms (this does not include thromboembolism of the pulmonary vasculature or venous thrombosis, e.g. pulmonary embolism or deep venous thrombosis).

8.1.2.2 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

8.1.2.3 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.

8.2 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 safety endpoint

The primary safety endpoint includes the analysis of the composite of ISTH major bleeding (Section 8.2.1.1) and clinically relevant non-major bleeding (Section 8.2.1.2).

8.2.1.1 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

8.2.1.2 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

8.2.2 Secondary safety endpoints

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

- all bleeding
- ISTH major bleeding (Section 8.2.1.1)
- ISTH CRNM bleeding (Section 8.2.1.2)
- ISTH minor bleeding (Section 8.2.2.1)
- Intracerebral hemorrhage (non-traumatic)

8.2.2.1 ISTH Minor bleeding

All other overt bleeding episodes not meeting the above criteria for ISTH major or clinically relevant non-major bleeding will be classified as minor bleeding (e.g. bleeding from a minor wound that does not prompt a face-to-face evaluation for a physical examination or laboratory testing).

8.2.3 Exploratory safety endpoint

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

- TIMI clinically significant bleeding
- TIMI major bleeding
- TIMI minor bleeding
- BARC bleeding definition Type 2, 3, 5
- BARC bleeding definition Type 3, 5
- BARC bleeding definition Type 1, 2, 3, 5

8.2.3.1 TIMI Bleeding Definitions

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).

8.2.3.2 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)

8.2.4 Physical Examinations

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

8.2.5 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 temperature, systolic and diastolic blood pressure, and pulse.

8.2.6 Electrocardiograms

- A single 12-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.

8.2.7 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 (e.g., 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 study procedures, 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 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 AEs will be collected from the start of the intervention until the 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 partners of male participants will be collected after the start of study intervention and until 4 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 related to the blinded treatment, the participant's treatment code will usually be unblinded before reporting to the

Health Authorities. Notifications of IECs / IRBs and investigators will be done according to all applicable regulations (see Section 8.3.4).

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

a. Bleeding
b. Death
c. Myocardial Infarction
d. Ischemic stroke
e. Systemic embolism

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 systemic embolism), 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 Event 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 the initial laboratory value elevation) 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 eCRF.

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 6.5.1 should be followed.

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

- Contact the Medical Monitor immediately.

- Closely monitor the participant for any AE/SAE and laboratory abnormalities until study drug can no longer be detected systemically (at least 5 days.).
- 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 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 the 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 intervention. At this visit, study intervention will be administered at the study center by study personnel and the exact time of study intervention 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 intervention as usual in the morning at home. At Visit 4 additional post-dose samples will be taken like 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 eCRF.
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 (CSR) 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
- Fibrinogen will be measured using a coagulation assay
- FXI concentration will be measured via ELISA using polyclonal antibodies
- 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 analyses.

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 participants are:

- NT-proBNP will be measured using an electrocheminulescence assay (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 laboratory 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 Assessments

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 primary efficacy objective is the assessment of the overall dose-response effect (evidence for effectiveness) based on the incidence proportions observed for the primary efficacy outcome at Day 180. To detect a dose-response signal, the null hypothesis: "The response (incidence proportion) at all four doses is equal" will be tested against the alternative "There is a dose-response relationship" for each of M=3 assumed potential dose-response shapes prespecified in a candidate set as described below. For each of the dose-response shapes a contrast test based on contrast coefficients optimized for the pre-specified dose-response shapes will be applied, taking the actual estimated treatment effect per treatment group into account. For each of the $K = 4$ treatment arms (i.e. the placebo group and the 3 active treatment arms of BAY 2433334) the response is denoted by $\mu_k, k = 1, \dots, K$.

For each model m, $m = 1, \dots, 3$, in the candidate set

the null hypothesis $H_{0m}: c_m \ \mu_m = 0$

will be tested against

the respective 1-sided alternative hypothesis $H_{1m}: c_m \ \mu_m \ > \ 0,$

where $c_m = (c_{m1}, \dots, c_{mk})'$ is an optimized contrast vector for the doses $\mu_m = (\mu_{m1}, \dots, \mu_{mK})' = (f_m \ (d_1, \theta_m), \dots, f_m \ (d_K, \theta_m))'$ and f is the dose-response model $\mu_m = f(d, \theta) + \epsilon$. A more detailed description of the MCP-Mod approach and the models used will be provided in Section 9.4.2.

9.2 Sample Size Determination

Sample size calculations were performed for establishing evidence of a drug effect across the doses, that is, detecting a statistically significant dose response signal for the primary efficacy outcome in this study using the MCP-Mod approach.

Assuming a true incidence for the primary efficacy outcome of 22.5% at Day 180 under placebo, a maximum relative risk reduction of 25% for BAY 2433334 relative to placebo, a set of plausible dose-response shapes including Emax and logistic models (chosen based on FXIa inhibition data, see Section 9.4.2), random allocation of participants to dose groups according to a 1:1:1:1 ratio and about 1% of participants without post-randomization data on the occurrence of the primary outcome, a sample size of 450 participants per dose groups will have at least 80% power to demonstrate a dose-response relationship, using a one-sided test at a type I error rate of α=0.10. Approximately 1900 patients will be screened to achieve 1800 randomized participants for an estimated total of 450 evaluable participants per intervention group.

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	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.
Pharmacokinetic Analysis Set	All BAY 2433334-treated patients 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)

9.4 Statistical Analyses

9.4.1 General Considerations

The statistical analysis plan (SAP) will be developed and finalized before the first interim analysis 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. 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. The cumulative incidence risk will be estimated for time to event variables. The hazard ratios and the corresponding confidence intervals will be estimated on separate Cox proportional hazards models for each comparison of a BAY 2433334 dose versus placebo. No comparison of the different doses of BAY 2433334 is planned.

All collected events will be analyzed summarized using methods like frequency tables and other descriptive statistics.

Analyses will be stratified will be stratified based on whether participants will receive single or dual antiplatelet therapy after the index stroke and randomization. The statistical analyses will be performed using SAS; the version used will be specified in the SAP.

9.4.2 Primary Endpoints

Efficacy analyses

The primary efficacy estimand is the incidence of symptomatic ischemic stroke or covert brain infarcts detected by MRI in 6 months following a non-cardioembolic ischemic stroke in adult participants with background antiplatelet therapy, while alive and regardless of treatment discontinuation, for each of the different doses of BAY 2433334 and placebo.

The primary efficacy analysis will be using the Full Analysis Set. All participants with a primary efficacy outcome up to Week 26 will be counted in the analysis. Of note the brain infarct component of the primary efficacy outcome can only be detected based on MRI.

Note that a study participant who dies before week 26 without having experienced a symptomatic ischemic stroke may not have had a post-randomization MRI performed to assess if s/he experienced a covert brain infarct before death. This data would be meaningful for the analysis but can no longer be collected due to death. The same holds true for participants who refuse to undergo a second MRI and/or that have a missing MRI at randomization.

For the main estimator corresponding to the primary efficacy estimand missing values for covert infarcts detected by MRI at week 26 will be handled as follows:
For participants in Part A who have a MRI at week 13, the result of that MRI will be used if a covert infarct was detected.
For participants without a symptomatic stroke and missing MRI evaluation (up to or) at week 26 it will be assumed that the proportion of participants with a covert infarct is the same as in participants without a symptomatic stroke with a MRI evaluation at week 26 (Quan et al. 2007).

The MCP-Mod method combining MCP (multiple comparison procedures) principles with modeling techniques will be used for the primary statistical analysis. This method allows the flexibility of modeling for dose estimation, while preserving the robustness to model misspecification associated with MCP procedures.

3 active doses of BAY 2433334 will be used in this study: 10 mg, 20 mg, and 50 mg, with an additional placebo arm, corresponding to a 0 mg dose. The incidence proportion at dose x will be transformed to a normal distributed variable μ_x, the estimated logit of the incidence proportion at dose x. For the dose-response relationship the functional relationship is

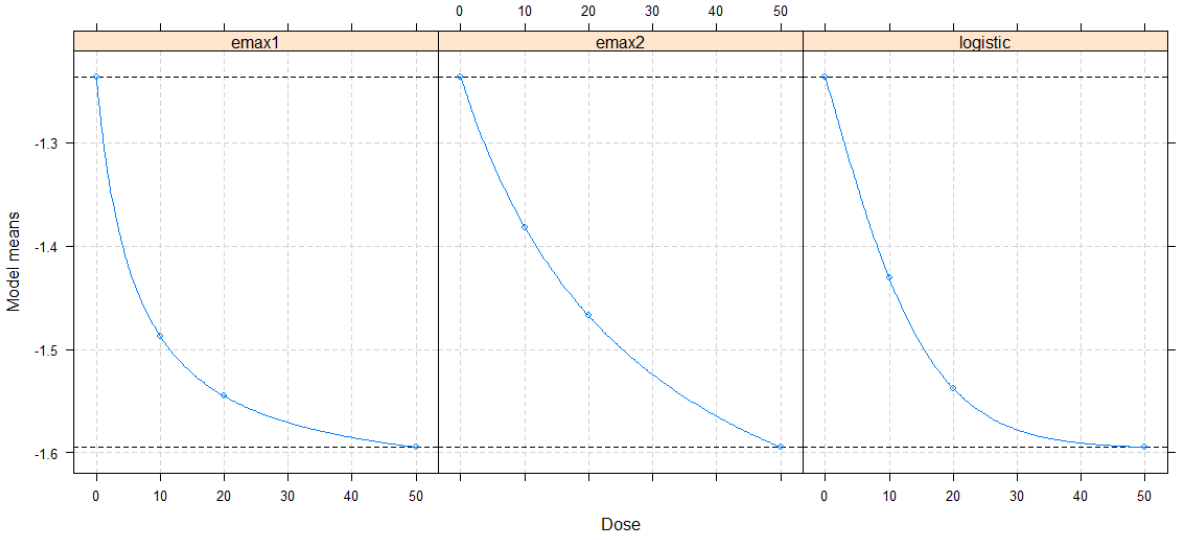
$$\mu_x = f(x, \theta) + \epsilon.$$

It is assumed that the relative incidence risk is 22.5% at Day 180 under placebo and there is a relative risk reduction of 25% under the highest dose.

The candidate set of models for $f(x, \theta)$ consists of three models, two (standardized) Emax models with parameter ED_{50}= 6 and ED_{50}= 29 and a (standardized) logistic model with the parameter $ED_{50} = 0.05$ and $\delta = 8.25$. All three candidate models assume a monotonically decreasing dose-response. The parameter of the models are based on pharmacokinetic data. The dose-response candidate models are shown in the Table below.

Model	Response as function of dose d
Emax1	–1.24 – 0.40d / (6 + d)
Emax2	–1.24 – 0. 57d / (29 + d)
Logistic	–0.88 – 0.72d / (1 + exp((0.05 - d) / 8.25))

The corresponding dose-response relationships of the candidate models are shown in the Figure below.



Based on these models and the observed data optimal contrasts c_m and the corresponding critical value will be calculated. (For a detailed description see the SAP).

Based on the optimal contrast and the critical values a one-sided test with $\alpha = 0.1$ based on the maximum value of the test statistics for the models in the candidate set will be performed. The MCP-Mod method takes multiplicity into account. Thus no further multiplicity adjustments has to be performed.

If for at least one contrast the test is statistically significant, a dose-response signal is established. Out of the statistically significant models in the candidate set a best model can be selected for the next step: modeling and estimation. The selection of the dose-estimation model will be based on an assessment of the p value. If no candidate model is statistically significant, the procedure stops indicating that a dose-response relationship cannot be established from the observed data. The modelling of the dose-response relationship will be done using least-squares parameter estimation.

For the primary efficacy estimand sensitivity analyses are planned to investigate the impaction of potentially missing values due to missing MRI scans. Assumptions made for participants with a missing MRI are described in the following:

1. Assume these participants had no covert infarct.
2. Assume these participants had a covert infarct.
3. Assume only those participants in the BAY 2433334 treatment arms had a covert infarct while the participants in placebo arm did not have a covert infarct (worst case analysis).

As supplementary analysis only the participants who have a MRI at randomization and at week 26 will be analyzed, i.e. the population in the primary efficacy estimand is changed.

This also excludes participants in Part A, who have an MRI at randomization and week 13, but not at week 26.

There will be no formal comparison of the different doses of BAY 2433334.

Safety analyses

The primary safety estimand is the hazard ratio of the composite of International Society on Thrombosis and Hemostasis (ISTH) major bleeding and clinically relevant non-major (CRNM) bleeding comparing pooled BAY 2433334 with placebo following a non-cardioembolic ischemic stroke in adult participants treated with antiplatelet therapy and who have taken at least one dose of study medication of BAY 2433334 or placebo and while the participant is alive and exposed to study drug.

The primary safety estimator will be hazard ratio for the composite in a Cox proportional hazards model comparing the pooled BAY 2433334 treatment arms with placebo. All events from first intake of study drug up until 2 days after permanent study drug discontinuation will be counted. As supplementary analyses the analyses will be done on the ITT data set and counting all events from randomization until final follow-up.
These analyses will be replicated for the comparison of each dose of BAY 2433334 and placebo.

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

9.4.3 Secondary Endpoints

Efficacy analyses

The secondary efficacy analyses for the endpoints that include the evaluation of the MRI will be different from those that will be performed for the endpoints that do not include it.

The secondary efficacy estimand for the following endpoints:

- composite of symptomatic ischemic stroke and covert brain infarcts detected by MRI, CV death, myocardial infarction and systemic embolism
- covert brain infarcts detected by MRI

is the incidence in 6 months of each of the individual endpoints following a non-cardioembolic ischemic stroke in adult participants treated with antiplatelet therapy while alive and regardless of treatment discontinuation, for each of the different doses of BAY 2433334 and placebo.

The secondary efficacy estimand for the following endpoints:

- symptomatic ischemic stroke
- symptomatic ischemic stroke, CV death, myocardial infarction
- symptomatic ischemic and hemorrhagic stroke
- disabling stroke (mRS≥4)
- all-cause mortality

is the hazard ratio of each of the individual endpoints following a non-cardioembolic ischemic stroke in adult participants treated with antiplatelet therapy, while alive and regardless of treatment discontinuation, comparing each of the different doses of BAY 2433334 with placebo. The endpoints will be analyzed with point estimators and confidence intervals for the proportion of participants with an event.

Time to event endpoints will be analyzed as described in 9.4.1.

Sensitivity analyses will be done similar as for the primary efficacy outcome and described in the SAP.

Safety endpoints

The secondary safety estimand is the hazard ratio of each of the individual endpoints comparing pooled BAY 2433334 with placebo in adult participants after non-cardioembolic ischemic stroke and who have taken at least one dose of study medication of BAY 2433334 or placebo and while the participant is alive and exposed to study drug for the endpoints:

- all bleeding
- ISTH major bleeding
- ISTH CRNM bleeding
- ISTH minor bleeding
- Intracerebral hemorrhage (non-traumatic).

The analyzes will follow those of the primary safety estimand.

9.4.4 Tertiary/exploratory Analyses

Exploratory safety endpoints are: TIMI clinically significant bleeding, TIMI major bleeding, TIMI minor bleeding, BARC bleeding definition Type 2, 3, 5, BARC bleeding definition Type 3, 5 and BARC bleeding definition Type 1, 2, 3, 5.

Exploratory other endpoints are FXIa inhibition, aPTT and various biomarkers.

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, as well as the mandatory pharmacodynamic markers will be described in the statistical analysis plan finalized before database lock. Optional pharmacodynamic markers as well as exploratory biomarkers may be described in the statistical analysis plan finalized before database lock, if they are available in time. Otherwise they may be reported under separate cover. The population PK analysis and exploratory or optional biomarkers may 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 2 other ongoing Phase 2 studies will be reviewed together when the pre-defined criteria for the 2 interim analyses have been reached. The overall approach of the 2 interim analysis 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 may 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 3 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 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 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 the interim analysis is specific for the decision for this study only, data and especially bleeding data from the other 2 studies will be taken into consideration.

The second interim analysis will occur when sufficient data are available from all 3 Phase 2 studies. This interim analysis may occur, when approximately 80% of all planned participants, taken all 3 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 2 interim analysis may be close together, the decision could be taken to just conduct one interim analysis.

As part of the 2 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 efficacy and safety data for study 19766, and of the overall safety data across all 3 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 (e.g., 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 modification 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 who will be required to give consent for their data to be used as described in the informed consent.
- 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 3 Phase 2 studies with BAY 2433334, as well as 2 sponsor representatives, will ensure the overarching integrity of the 3 studies. 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 is to support protocol development, to facilitate the conduct of the study, to advise the sponsor on clinical, medical, and scientific questions and to initiate publications. The Steering Committee will consist of the National Leaders from the participating countries, three physicians from the clinical coordinating center (Population Health Research Institute, Canada), the director of the MRI Core Lab, and two Bayer representatives. Additional details of the committee will be specified in the Steering Committee charter.

10.1.5.3 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)
- Systemic embolism

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 01 JAN 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 trials 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 (e.g., 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 (e.g., 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 15 years 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 TrialMaster. Participant data necessary for analysis and reporting will be entered/transmitted into a validated database or data system (SPECTRUM).

Data required according to this protocol will be recorded by study site personnel via data entry into the internet based EDC software system TrialMaster, which the ARO (Academic Research Organization) has licensed from OmniComm. TrialMaster has been validated by OmniComm and the ARO for use in its clinical studies. TrialMaster 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/ARO 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 PHRI and transferred on a periodic basis to Bayer's internal computer system via a secure Virtual Private Network.

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

All personnel with access to the TrialMaster 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 TrialMaster 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 ARO/Bayer. Data entries made in the TrialMaster 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, GCP, and sponsor'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, 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 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 GCP and regulatory requirements, a member of the sponsor'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 Section 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)

Investigators 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 (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- 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 <u>NOT</u> 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 (e.g., 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 (e.g., 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

- SAE reporting via email transmission of the scanned paper CRF is the preferred method to transmit this information to the Sponsor via PPD.
- In rare circumstances and in the absence of email transmission tools or 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 Event Reporting Process Overview

If an AE or SAE is a potential outcome event (all bleeding, death, MI, stroke, TIA and systemic embolism [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 SFU 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 Section 10.9).

All bleeding events including fatal bleeding will be captured in the eCRF. SAE which are bleeding terms will also be reported to the sponsor's PV Department in an expedited manner. Symptomatic intracerebral / intraparenchymal hemorrhages as well as symptomatic subarachnoid hemorrhages will be captured as bleeding and as stroke. All subdural / epidural hematoma and asymptomatic intracranial bleeding are only reported as bleeding.

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 (e.g., 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, (e.g. 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. The initial 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 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 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 gestational 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, 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 laboratory 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), ferritin levels, iron, iron binding capacity, antinuclear antibody, and smooth muscle antibodies. Participant 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 participant's baseline. If close liver monitoring is not possible, then the participant 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 participant 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 the regular last scheduled study visit (ie, Safety Follow-up Visit; in case of permanent discontinuation of study intervention, the planned 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 AEs 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: Study MRI procedure

The minimum requirements for the study MRIs are outlined in the table below. In addition, it is encouraged to also collect T1- and T2 weighted sequences and have a slice gap ≤ 1mm in order to detect smaller infarcts. However, this is optional and not required.

	Minimum Requirements	**Preferred / Optional**
Sequences	FLAIR DWI ADC SWI, SWAN, GRE or equivalent per local MRI routine protocol	T1-weighted T2-weighted
Field strengths	≥ 1 Tesla	
Slice thickness	1 - 5 mm	
Slice gap	≤ 2 mm	≤ 1 mm

Study sites will be required to demonstrate that study-sponsored MRIs that meet the minimum study criteria outlined above can be obtained in advance of enrolling participants. Detailed instructions will be provided to sites, followed by submission to the central MRI Core Lab of an MRI of an inanimate phantom object.

The study MRIs will be transmitted to the central MRI Core Lab that will be responsible for analyzing all MRIs blinded to treatment assignment.

More detailed information regarding image acquisition and processing will be found in a separate MRI procedures manual.

10.10 Appendix 10: Modified Ranking Score

Modified ranking score (mRS)

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; despite symptoms, able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Death

TOTAL (0–6): _____

Source: adapted from (Banks and Marotta 2007, van Swieten et al. 1988).

10.11 Appendix 11: NIH Stroke Scale

NIH stroke scale (NIHSS)

Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e., repeated requests to patient to make a special effort).
At the end the scores of all items need to be summed up.

Instructions	Scale Definition	Score
1a. Level of Consciousness: The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 **= Alert;** keenly responsive. 1 **= Not alert**; but arousable by minor stimulation to obey, answer, or respond. 2 **= Not alert**; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic.	_____
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.	0 **= Answers** both questions correctly. 1 **= Answers** one question correctly. 2 **= Answers** neither question correctly.	_____
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 **= Performs** both tasks correctly. 1 **= Performs** one task correctly. 2 = **Performs** neither task correctly.	_____

Instructions	Scale Definition	Score
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	0 **= Normal.** 1 **= Partial gaze palsy;** gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 **= Forced deviation,** or total gaze paresis not overcome by the oculocephalic maneuver.	_____
3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.	0 = **No visual loss.** 1 = **Partial hemianopia.** 2 = **Complete hemianopia.** 3 = **Bilateral hemianopia** (blind including cortical blindness).	_____
4. Facial Palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.	0 = **Normal** symmetrical movements. 1 = **Minor paralysis** (flattened nasolabial fold, asymmetry on smiling). 2 = **Partial paralysis** (total or near-total paralysis of lower face). 3 = **Complete paralysis** of one or both sides (absence of facial movement in the upper and lower face).	_____

Instructions	Scale Definition	Score
5. Motor Arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** limb holds 90 (or 45) degrees for full 10 seconds. 1 = **Drift;** limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = **Some effort against gravity;** limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = **No effort against gravity;** limb falls. 4 = **No movement.** UN = **Amputation** or joint fusion, explain: _____ **5a. Left Arm** **5b. Right Arm**	 _____ _____
6. Motor Leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** leg holds 30-degree position for full 5 seconds. 1 = **Drift;** leg falls by the end of the 5-second period but does not hit bed. 2 = **Some effort against gravity;** leg falls to bed by 5 seconds, but has some effort against gravity. 3 = **No effort against gravity;** leg falls to bed immediately. 4 = **No movement.** UN = **Amputation** or joint fusion, explain: _____ **6a. Left Leg** **6b. Right Leg**	 _____ _____
7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.	0 = **Absent.** 1 = **Present in one limb.** 2 = **Present in two limbs.** UN = **Amputation** or joint fusion, explain: _____	 _____

Instructions	Scale Definition	Score
8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.	0 = **Normal;** no sensory loss. 1 = **Mild-to-moderate sensory loss;** patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = **Severe to total sensory loss;** patient is not aware of being touched in the face, arm, and leg.	_____
9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	0 = **No aphasia;** normal. 1 = **Mild-to-moderate aphasia;** some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = **Severe aphasia;** all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = **Mute, global aphasia;** no usable speech or auditory comprehension.	_____
10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	0 = **Normal.** 1 = **Mild-to-moderate dysarthria;** patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = **Severe dysarthria;** patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = **Intubated** or other physical barrier, explain:_____	_____

Instructions	Scale Definition	Score
11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	0 = **No abnormality.** 1 = **Visual, tactile, auditory, spatial, or personal inattention** or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = **Profound hemi-inattention or extinction to more than one modality;** does not recognize own hand or orients to only one side of space.	———

Source: adapted from (Brott et al. 1989, Lyden et al. 1994, Pugh et al. 1973)

10.12 Appendix 12: Abbreviations

AE	Adverse Event
AESI	Adverse event of special interest
ACC	American College of Cardiology
AF	Atrial fibrillation
AG	Joint stock company, *Aktiengesellschaft*
AHA	American Heart Association
ALT	Alanine aminotransferase
AMI	Acute myocardial infarction
AP	Alkaline phosphatase
APCC	Activated prothrombin complex concentrate
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
BMS	Bristol-Myers Squibb
BP	Blood pressure
BUN	Blood urea nitrogen
CABG	Coronary artery bypass graft
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CHEST	American College of Chest Physicians
CIOMS	Council for International Organizations of Medical Sciences

CHMP	Committee for Medicinal Products for Human Use
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
CT	Computed tomography
CTFG	Clinical Trial Facilitation Group
CV	Cardiovascular
CYP3A4	Cytochrome P450, family 3, subfamily A, polypeptide 4
e.g.	For example, *exempli gratia*
ECG	Electrocardiogram
ECLIA	Electrochemiluminescence Immunoassay
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
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
FEIBA	Factor eight inhibitor bypass activity
FiM	first in man
FFP	Fresh frozen plasma
4F-PCC	4-factor Prothrombin complex concentrate
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
HR	Heart rate
HRS	Heart Rhythm Society
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 committee
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
ISTH	International Society on Thrombosis and Hemostasis
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
LSH	Life Science Data Hub
LV	Left ventricular
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MD	Medical doctor
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 a day
$P2Y_{12}$	G_i-coupled platelet receptor for adenosine diphosphate
PCI	Percutaneous coronary intervention
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PT	Prothrombin time
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 (count)

RND	Randomization
ROTEM	Rotational thromboelastometry
SAC	Statistical 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
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 thromboembolism
vWF	Von Willebrand Factor
W	Week
WBC	White blood cell (count)
WOCBP	Woman of Childbearing Potential

11. References

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