Document Type:	Statistical Analysis Plan
Official 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
NCT Number:	NCT04304508
Document Date:	26-Jan-2022

Title page

Study 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: 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 (**PACIFIC-STROKE**)

Bayer study drug BAY 2433334 / Asundexian

Clinical study phase:	Phase 2b	**Date:**	26JAN 2022
Study No.:	19766	**Version:**	2.0
Author:	PPD		

This Statistical Analysis Plan is produced on a word-processing system and bears no signatures.

The approval of the Statistical Analysis Plan is documented in a separate Signature Document.

Table of Contents

Abbreviations

AE	Adverse event
AESI	Adverse event of special interest
AF	Atrial fibrillation
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
ASA	Acetylsalicylic acid
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AXIA	Activated Factor XIa activity
BARC	Bleeding Academic Research Consortium
CABG	Coronary artery bypass graft
CEC	Clinical Events Committee
CRF	Case report form
CRNM	Clinically relevant non-major
csHR	Cause-specific hazard ratio
CSR	Clinical study report
CT	Computed tomography
CV	Cardiovascular
CYP3A4	Cytochrome P450, family 3, subfamily A, polypeptide 4
DWI	Diffusion-weighted imaging
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EOT	End of treatment
ET	Early Termination
F1.2	F1.2 fragment of prothrombin
FAS	Full Analysis Set
FXIa	Activated Factor XI
hsCRP	High-sensitivity C-reactive protein
IDMC	Independent data monitoring committee
ISTH	International Society on Thrombosis and Hemostasis
ITT	Intention-to-treat
LOQ	Limit of quantification
LPFV	Last participant first visit
MCP	Multiple comparison procedures
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Score
NIHSS	National Institutes of Health Stroke Scale
NT-proBNP	N-terminal pro B-type Natriuretic Peptide
PD	Pharmacodynamic(s)
PDS	PD analysis set
PK	Pharmacokinetic(s)
PT	Preferred term
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SOC	System organ class
SSSRI	Selective Serotonine Reuptake Inhibitor
TAFI	Thrombin-activatable fibrinolysis inhibitor
TAT	Thrombin antithrombin complex
TIA	Transient ischemic attack
TIMI	Thrombolysis in myocardial infarction
ULN	Upper limit of normal

1. Introduction

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.

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.

The SAP is based on the protocol version 1.0, approved on 24 OCT 2019.

2. Study Objectives

The primary efficacy objective of the study is 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 in participants with an acute non-cardioembolic ischemic stroke and who are treated with antiplatelet therapy.

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 patients treated with antiplatelet therapy, while alive and regardless of intervention discontinuation, for each of the different doses of BAY 2433334 and placebo.

Note, that covert brain infarcts can only be assessed in participants without a recurrent symptomatic ischemic stroke in the time of the baseline MRI and the MRI used for analyses.

The primary and secondary safety objective of the study is 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.

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 patients treated with antiplatelet therapy and who have taken at least one dose of study intervention of BAY 2433334 or placebo and while the participant is alive and exposed to study intervention.

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).

The secondary efficacy objective is to assess the dose response of 3 different doses of BAY 2433334 compared to placebo in reducing other cerebro- and cardiovascular endpoints in

participants with an acute non-cardioembolic ischemic stroke and who are treated with antiplatelet therapy.

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.

Exploratory efficacy and safety objectives are:

- to explore additional pharmacokinetic and pharmacodynamic parameters, biomarkers and genetics, and
- 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.

An overview of the objectives and corresponding endpoints is given in Table 2–1.

Table 2–1 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 Efficacy Endpoints** • Composite of all stroke, myocardial infarction and CV death **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: 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

3. Study Design

3.1 Overall Design

Study 19766 is a multicenter, randomized, placebo-controlled, double-blind, parallel group, dose-finding Phase 2 study.

The study population includes patients 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.

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

The study will consist of 2 parts, Part A (minor strokes) and Part B (minor and moderate strokes and participants undergoing thrombolysis or endovascular therapy for the qualifying stroke) 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 intervention 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.

  The planned double-blind treatment phase starts at randomization and ends at week 52 or the study intervention end date (i.e. 26 weeks after the last participant of the study has been randomized).

  For details on Part A and B of the treatment phase see Section 3.1.1.
- **Safety Follow-up (Visit 13):** 14 days (+ 7 days) after EOT or ET.

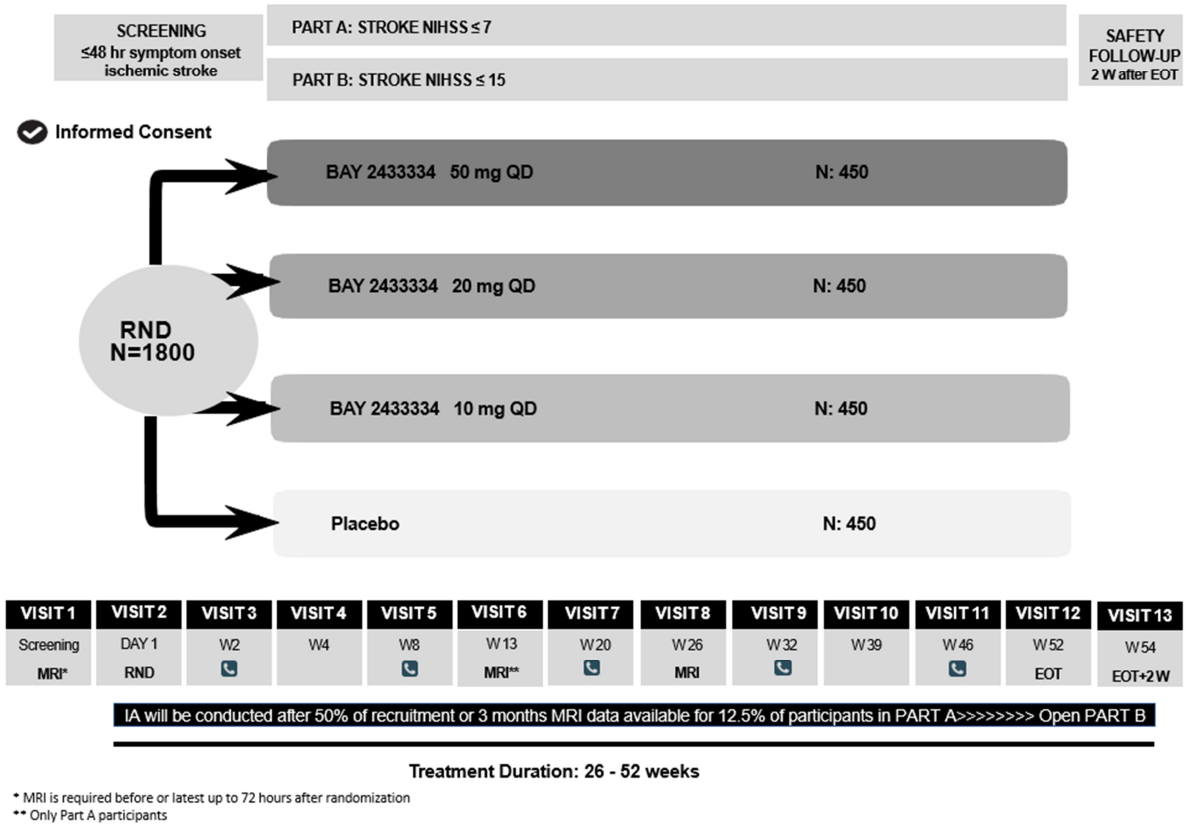
Study visits will take place as visits at the study sites and telephone calls. Visits at the study sites take place at screening and randomization (Visit 1 and Visit 2), at Week 4 (Visit 4), at Week 13 (Visit 6), Week 26 (Visit 8), Week 39 (Visit 10) and at Week 52 / EOT (Visit 12).

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 intervention until the planned EOT (i.e. safety follow-up, Visit 13).

For participants who will prematurely discontinue the study intervention, 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. An ET MRI will be obtained as soon after discontinuation as possible; a 26-week MRI will not be obtained in ET participants Telephone calls will take place 2 weeks after the ET visit (i.e. safety follow-up, Visit 13).

The study design is presented in Figure 3–1.

Figure 3–1: 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

3.1.1 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.

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.

If Part B is not initiated following the interim analysis, enrolment will continue based on Part A eligibility criteria until the end of recruitment.

3.1.2 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 the 26-week follow-up MRI or ET MRI. Details regarding the procedure, MRI requirements and logistics will be available in an 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, whichever occurs first
- 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.

4. General Statistical Considerations

4.1 General Principles

The statistical evaluation will be performed by using the software package SAS release 9.4 (SAS Institute Inc., Cary, NC, USA).

All variables will be analyzed by descriptive statistical methods. The number of data available and missing data, mean, standard deviation, minimum, quartiles, median, and maximum will be calculated for metric data. Frequency tables will be generated for categorical data.

Data will be displayed by randomized intervention arm and overall.

Potential pre-specified clinical outcome events will be submitted for adjudication to an independent clinical event committee (CEC). Adjudication of all bleeding events as well as potential exploratory efficacy events will be performed by the CEC group who will review events in a blinded fashion and will algorithmically and standard adjudicated and classify the following events in a consistent and unbiased manner according to definitions contained in the CEC charter:

- 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)
- Myocardial infarction
- 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 and 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.

4.2 Handling of Dropouts

In rare instances, it may be necessary for a participant to permanently discontinue 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. In this study, all efforts must be taken to engage participants to comply with all study procedures and to continue to be followed until the end of the study.

A participant who prematurely discontinues the study for any reason is defined as a “dropout” if the participant is randomized to study intervention. A participant is regarded a “screening failure” if he or she consented to participate in the study but is not subsequently assigned to study intervention.

In all cases, the reason for withdrawal must be recorded in the electronic case report form (eCRF) and in the participant's medical records.

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

A participant may withdraw of consent at any time. This 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. All data collected before withdrawal of consent will be used for analysis.

The number of participants who prematurely discontinue the study during the treatment period or during the post-treatment observation phase for any reason, as well as the reasons for premature discontinuation of study, will be displayed by treatment arm. Baseline characteristics will be displayed by premature discontinuation (yes/no) from study. The number of participants who are considered lost to follow-up or withdrew consent during the treatment period or during the post-treatment observation phase will be displayed by treatment arm.

4.3 Handling of 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 safety follow-up visit and all required data will be collected.

Data from participants who prematurely discontinue the study will be used to the maximum extent possible. Participants that discontinued from study intervention will remain in the study to be evaluated for bleeding and efficacy outcome events until their planned regular end of treatment visit. 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.

Additional descriptive analyses in the presence of missing data

All dropouts will be carefully evaluated with respect to

- baseline characteristics,
- potential differences between the treatment groups in the proportion of participants withdrawals or in the timing of withdrawals, and
- the reasons for premature discontinuation of study and/or study intervention, and potential dropout patterns will be described.

General rules

When appropriate, the following rules will be implemented so as not to exclude participant from statistical analyses due to missing or incomplete data:

- **Incomplete date of outcomes and start and end dates for study intervention**
  When only partial dates are available, the following rule will be used for the derivation of dates for efficacy and safety events as well as for the date of adverse events (AEs): any event will be assumed to happen as early as possible, i.e. the earliest of the timeframe known but not earlier than the last date where the participant is known event free.This means that missing days will be replaced by the 1st day, missing months by January. If the whole date is missing use randomization date respestively last contact date for fatal events. If randomization or the last contact date (applies for fatal events) is after the imputed date, impute with that respective date.
- **Incomplete time of outcomes and start and end dates for study intervention**
  For events happening at the day of first study intervention intake with no timepoint it will be assumed that they happen after the first intake of study intervention, i.e. the time of study intervention intake will be used for the time of the outcome.
- **Missing MRI**
  Covert brain infarcts will only be detected by MRI. In cases MRIs are missing, imputation rules as described in Section 6.2.1.4 apply.

4.4 Interim Analyses and Data Monitoring

An independent Data Monitoring Committee (IDMC) will review safety data according to the IDMC charter. No alpha adjustment is required. No formal interim analysis is planned. Two non-formal interim analyses were planned, and the statistical analysis will be done by an independent statistical analysis center. The first of the two interim analyses 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). A second interim analysis was planned for when approximately 80% of all planned participants were randomized in the study. A decision was taken during the study to not conduct this interim analysis.

A separate SAP was prepared for this.

4.5 Data Rules

4.5.1 Baseline values

Baseline values for vital sign measures, laboratory values and ECG data are planned to be taken at visit 2 before administration of study intervention. If these values are not available, values taken before first administration of study intervention will be considered (e.g., values taken on visit 1 or up to 14 days before randomization). In case of more than one available value before first administration of study intervention, the value closest to visit 2 will be taken.
Participants for whom an MRI meeting study requirement is performed before randomization (as clinically initiated MRI) do not need to perform a study-initiated MRI. However, in case both MRI exist, and both were evaluable by the Core Lab the study initiated one will be used as baseline MRI, if taken within 72 hours after randomization.

4.5.2 Data Scopes

Treatment emergent data scope

For the treatment emergent data scope all events from first intake of study intervention until 2 days after the last intake of study intervention will be counted. The time to event for participants with no event until 2 days after the last intake of study intervention (end of data scope) will be censored at that day.

This data scope will be used to handle intercurrent events according to the “while on treatment” strategy.

Intention-to-treat (ITT) data scope

For the intention-to-treat (ITT) data scope all events from randomization up until scheduled end of treatment visit (end of data scope) will be counted. The time to event for participants with no event up until the end of treatment visit will be censored at that day.

This data scope will be used to handle intercurrent events according to the “treatment policy” strategy.

4.5.3 Time-to-Event variables

For the treatment emergent data scope, the time from first intake of study intervention to an event is of interest. The time to an event (in days) will be derived the following:

$$\text{Date of Event} - \text{Date of first study intervention intake} + 1.$$

For time to event variables in the intention-to-treat (ITT) data scope the time from randomization to an event is of interest. The time to an event (in days) will be derived the following:

$$\text{Date of Event} - \text{Date of randomization} + 1.$$

Survival functions, incidence rates and cumulative hazard calculations will be done only for endpoints with at least 3 events in at least one intervention arm. (Cause specific) hazard ratios (csHR) will be calculated only if in one arm at least 3 events and in addition at least 1 event in each of the compared treatment arm occur.

If intervention arms are pooled the number of events needed applies on the pooled arm not on each intervention arm. Composite events that include incident covert brain infarcts cannot be analyzed as time-to-event because the time of onset of covert brain infarcts is not known.

4.5.4 Special cases of censoring

In special cases, the censoring differs from the section before.

If no event is observed, the censoring date will be determined by the following:

- In case of death of the participant before the scheduled end of treatment visit:
  - the date of the death.
- In case the participant dies after the scheduled end of treatment visit but before the safety follow-up (Visit 13)
  - the censoring date according to the “treatment policy” strategy is the date of the end of treatment visit
  - the censoring date according to the “while on treatment” strategy is the earliest of 2 days after last study intervention intake and the date of death.
- In case the participant is lost to follow up before end of data scope
  - the last study contact date, defined as the latest date of any visit date and dates of any (outcome) events
  - if the vital status is known alive at any date after the last study contact date: for the event death (including CV and non-CV death): the date of this information.
- In case the participant withdraws consent before end of data scope
  - the date of withdrawal of informed consent
  - if the vital status is known alive at any date after the last study contact date: for the event death (including CV and non-CVdeath): the date of this information.

4.5.5 Classification of investigator reported bleeding

Bleedings will be adjudicated by an independent CEC. To compare the investigator reported bleeding with the adjudicated bleeding an investigator reported bleeding classification is needed.

4.5.5.1 ISTH Major Bleeding, ISTH Clinically Relevant Non-Major and ISTH Minor Bleeding

A bleeding will be counted as investigator reported ISTH major bleeding if:

1. The outcome of the bleeding is fatal and/or
2. The bleeding is symptomatic and site is in a critical area or organ, i.e. bleeding site is: intracranial, intraocular, intraspinal, pericardial, retroperitoneal, intraarticular, or intramuscular with compartment syndrome and/or
3. The bleeding is clinically overt
    a. with a recent decrease in the hemoglobin level of ≥2 g/dl within 48 hours of bleeding event, that was related to the bleeding event and/or
    b. leading to transfusion of 2 or more unites of packed red blood cells or whole blood.

A bleeding will be counted as investigator reported ISTH Clinically Relevant non-major (ISTH CRNM) bleeding if it is considered any sign or symptom of hemorrhage, does not fit the ISTH definition of major bleeding but does meet at least one of the following criteria:

1. requiring any healthcare professional guided treatment to control the bleeding
2. leading to hospitalization or increased level of care
3. prompting a face to face (i.e. not just a telephone or electronic communication) evaluation

A bleeding is considered any sign or symptom of hemorrhage, if the bleeding is overt, i.e. visible or documented by imaging.

An increased level of care is similar to the requirement 3., i.e. prompting a face to face (i.e. not just a telephone or electronic communication) evaluation.

An overt bleeding that does not met the criteria for either ISTH major or clinically relevant non-major bleeding will be classified as ISTH minor bleeding.

4.5.5.2 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, TIMI minor bleeding and TIMI Bleeding event requiring medical attention.

A bleeding will be counted as non-CABG related TIMI Major bleeding if

1. it is not related to a CABG procedure and
2. is any symptomatic intracranial hemorrhage and/or
3. has clinically overt signs of hemorrhage (including imaging) associated with a drop in hemoglobin of ≥ 5 g/dl (or when hemoglobin concentration is not available, an absolute drop in hemocrit of ≥ 15%) and/or
4. is fatal (bleeding leading to death within 7 days).

A bleeding will be counted as non-CABG related TIMI Minor bleeding if

1. it is not related to a CABG procedure and

2. has clinically overt signs of hemorrhage (including imaging) associated with a fall in hemoglobin of 3 to < 5 g/dl (or when hemoglobin concentration is not available, a fall in hematocrit of 10 to < 15%.

A bleeding will be counted as non-CABG related TIMI Bleeding event requiring medical attention if

1. it is not related to a CABG procedure and
2. requires medical treatment, surgical treatment, or laboratory evaluation and
3. does not meet criteria for major or minor bleeding event.

A bleeding will be counted as non-CABG minimal TIMI Bleeding event if

1. it is an overt bleeding and
2. does not meet criteria for major or minor TIMI Bleeding event or a TIMI Bleeding event requiring medical attention

A bleeding is related to a CABG procedure if the site of bleeding is Cardiovascular system – CABG related. No specific analysis on CAGB related TIMI bleeding is planned due to the expected low number of CABG in a stroke population.

4.5.5.3 BARC Bleeding Definition

In this study the BARC bleeding definitions will be used. For that, different types are defined.

A bleeding will be counted as BARC bleeding Type 1 if it

1. is not actionable and does not cause the participant to seek any unscheduled performance of studies, hospitalization, or treatment by a healthcare professional.

A bleeding will be counted as BARC bleeding Type 2 if it

1. has any overt, actionable sign of hemorrhage (e.g. more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) and
2. does not fit the criteria for type 3 or 5 and
3. requires non-surgical, medical intervention by healthcare professional and/or
4. leads to hospitalization or increased level of care and/or
5. prompts evaluation*.

*A bleeding "prompts evaluation" if it leads to diagnostic testing (laboratory or imaging).

BARC bleeding Type 3 subdivides in types 3a, 3b and 3c.

A bleeding will be counted as BARC bleeding Type 3a if

1. it is an overt bleeding with a hemoglobin drop# of 3 to <5 g/dL and/or
2. any transfusion with overt bleeding is related to the bleeding.

A bleeding will be counted as BARC bleeding Type 3b if it

1. is an overt bleeding with a hemoglobin drop# of ≥5 g/dL and/or
2. is cardiac tamponade and/or

3. requires surgical intervention for control (excluding dental/nasal/skin/hemorrhoid) and/or
4. requires intravenous vasoactive agents.

A bleeding will be counted as BARC bleeding Type 3c if

1. it is intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, includes intraspinal), subcategories confirmed by autopsy or imaging or lumbar puncture and/or
2. intraocular bleeding compromising vision

#The hemoglobin drop can be corrected for transfusion. 1 U of packed red blood cells or whole blood equals 1g/dL hemoglobin.

BARC bleeding Type 5 are fatal bleedings. They are subdivided into Type 5a and Type 5b.

A bleeding will be counted as BARC bleeding Type 5a if it

1. is probable fatal, i.e. no autopsy or imaging confirmation is done but it is clinically suspicious.

A bleeding will be counted as BARC bleeding Type 5b if it

1. is definite fatal, i.e. it is overt or autopsy or imaging confirmation has been done.

4.5.6 Intracranial hemorrhage

The secondary safety endpoint non traumatic intracerebral hemorrhage is defined as a hemorrhagic stroke on the recurrent stroke CRF page that is in addition classified as a bleeding with bleeding site Intracranial – Subarachnoid, Intracranial – Intraparenchymal (excluding microbleeds), or Intracranial – Intraventricular and Spontaneous causality of bleeding, excluding all symptomatic and hemorrhagic transformation, defined by the PT "Hemorrhagic transformation".

In addition three further bleeding definitions for intracranial hemorrhage will be defined.

The endpoint "other symptomatic non traumatic intracerebral hemorrhage" is defined as a sympotomatic bleeding with either bleeding site: Intracranial - Epidural / extradural or Intracranial – Subdural and spontaneous or traumatic causality of bleeding or bleeding site Intracranial – Subarachnoid and instrumented/medical procedure causality of bleeding or a hemorrhagic transformation with PT "Hemorrhagic transformation".

The exploratory endpoint: "Any asymptomatic bleeds detected by clinical neuroimaging" is defined as a bleeding that is neither "non traumatic intracerebral hemorrhage" primary hemorrhagic stroke, nor "non traumatic intracerebral hemorrhage", that is asympotomatic, if recorded a bleeding with bleeding site "Intracranial - Epidural / extradural", "Intracranial – Subdural", "Intracranial – Subarachnoid", "Intracranial - Intraparenchymal (excluding microbleeds)", "Intracranial – Intraventricular", "Intracranial – Indetermined", or "Intracranial – Other", an reported AE with category "Other", SOC being "Central nervous disorders" and PT including the term "hemorrhage".

"Symptomatic and asymptomatic intracranial hemorrhages seen by MRI" are hemorrhagic transformations identified on Week 13 or Week 26 MRI with an evidence other than "No", a new or a extension of extraparenchymal intracranial hemorrhage compared with the baseline scan, specified as new or extension of cortical superficial siderosis or subarachnoid

hemorrhage or a new intracranial hemorrhage detected by study MRI. This endpoint will be analyzed before and after treatment start.

4.5.7 Blind Review of important deviations and validity findings

The results of the final data assessment will be documented in the final list of important deviations, validity findings and assignment to analysis set(s). Any changes to the statistical analysis prompted by the results of the review of study data will be documented in an amendment and, if applicable, in a supplement to this SAP.

Pharmacokinetic values to be excluded from the statistical analysis will be documented and respective flags will be incorporated in the clinical database.

5. Analysis Sets

5.1 Assignment of analysis sets

Final decisions regarding the assignment of participants to analysis sets will be made during the review of study data before data base closure and documented in the final list of important deviations, validity findings and assignment to analysis set(s).

- **Full analysis set (FAS)**
  A participant will be included in the FAS if he/she is randomized to study intervention.
- **Safety analysis set (SAF)**
  A participant will be included in the SAF if he/she is randomized to study intervention and has taken at least one dose of the study intervention.
- **Pharmacokinetic Analysis Set**
  A participant will be included in the pharmacokinetic analysis set, if he/she has received active intervention, has at least 1 valid plasma concentration of BAY 2433334 without protocol deviation, which would interfere with the evaluation of the PK data.
- **Pharmacodynamic Analysis Set**
  A participant will be included in the pharmacodynamic analysis set, if he/she has received active intervention, has at least 1 valid plasma concentration of BAY 2433334 without protocol deviation, which would interfere with the evaluation of the PK data, has at least 1 valid pharmacodynamic value and is without protocol deviation, which would interfere with the evaluation of the pharmacodynamic data. All PD analyses will be performed on the PD analysis set (PDS).

6. Statistical Methodology

The primary analysis population for efficacy analyses will be the FAS while for safety analyses the SAF will be used.

Confidence intervals will be two-sided 90% confidence intervals. Tests will be performed at a one-sided type I error rate of α=0.10. In the MCP step in the primary efficacy analysis adjustment for multiplicity will be performed.

6.1 Population characteristics

6.1.1 Disposition

The following will be tabulated by intervention group and overall:

- Study sample sizes by region and country
- Study sample sizes by country and site
- Participants disposition
- Number of participants and primary reasons for screening failures
- Number of participants and primary reasons for premature discontinuation of study intervention
- Flow of subject through study epochs with number of participants and primary reasons for premature permanent discontinuation for each study phase

Incidences for permanent discontinuation of the double-blinded study intervention and of the follow-up period will be provided by randomized study intervention groups, based on the case report form data.

Kaplan-Meier estimates will be used to present

- time to the date of last double-blind dose of study intervention,
- time to the date of last follow-up contact,

all calculated as days from randomization, by study intervention group.

Other details regarding visit adherence (e.g., visit completed in person, by telephone, through third party) and completion as well as study intervention adherence collected via CRFs will be summarized using frequency tables by visit and study intervention group.

6.1.2 Protocol Deviations

No per protocol analysis set will be defined in this study. The number of participants with major protocol deviations and validity findings according to the CRF will be summarized together with the relevant reasons, by study intervention group.

6.1.3 Demography and baseline characteristics

Demographic and baseline data as collected in the CRF will be evaluated descriptively for the FAS as well for the SAF, by intervention groups and overall. No statistical tests will be performed to compare these characteristics across intervention groups.

Descriptive statistics (such as mean, standard deviation, median, quartiles, minimum and maximum) will be provided for continuous variables.

Counts and (appropriate) percentages will be provided for categorical variables.

Besides others, the following variables will be displayed:

- Sex
- Race (White, Black, Asian, other)
- Region (North America; Western Europe and Australia; Eastern Europe; Asia)
- Age (<65, 65 – 75, >75 years)
- BMI (<25, ≥25 to <30, ≥30kg/m^2)

- Weight (<60, 60-90, >90 kg)
- eGFR (<60, 60-90, >90 mL/min)
- Blood pressure
- History of stroke or TIA prior to index event (yes/no)
- Chronic Kidney Disease (yes/no)
- Coronary Artery Disease (yes/no)
- Hypertension (yes/no)
- Diabetes (yes/no)
- History of GI bleeding (yes/no)
- Tobacco use (Never, Former, Current)
- Thrombolysis and/or endovascular therapy (yes/no)
- NIHSS score of index event at randomization (≤3, 4-7, ≥8)
- mRS score of index stroke at Day 7 (0-1, ≥2)
- Stroke subtype of index event (large artery atherosclerosis, small vessel occlusion, other etiology, undetermined etiology)
- Selective serotonine reuptake inhibitor (SSRI) use

Baseline characteristics of the index stroke will be displayed in a separate table.

6.1.4 Medical history

Medical history data will be evaluated by frequency tables, showing the number and percentage of participants with medical history findings (i.e., previous diagnoses, diseases or surgeries) that started before the first intake of study intervention and that are considered relevant for the participant's study eligibility using MedDRA Primary System Organ Class / Preferred Term.

6.1.5 Prior and concomitant medication

Prior and concomitant medication will be evaluated by frequency tables, showing the number and percentage of participants with

- prior medication, i.e. medications taken before start of study intervention, regardless of when they ended,
- concomitant medication, i.e. medications taken within the treatment period
- ongoing concomitant medication at start of study intervention,
- medication started during the treatment period, and
- medication started after stop of study intervention.

Prior and concomitant medication will be shown by ATC classes and subclasses.

Separate tables will be provided for anticoagulants, thrombolytics (rTPA), antiplatelet therapy used and for CYP3A4 inhibitors and inducers.

A separate table for concomitant prohibited medication will be shown.

6.1.6 Subgroup analyses

Selected demography and baseline characteristics, medical history and prior and concomitant medication tables will be repeated for the following subgroups:

- Antiplatelet therapy after index event (Single antiplatelet therapy, dual antiplatelet therapy)
- Study part (Part A, Part B)
- Time from index event onset to randomization (≤24, >24 hrs)
- Time from index event onset to baseline MRI (≤48, >48 hrs)
- NIHSS of index stroke at randomization (≤3, 4-7, >7)
- Thrombolysis and/or thrombectomy (EVT) (any yes/both no)

6.1.7 Region Classification

Countries will be grouped into regions in the following way:

Region	Country
Western Europe and Australia	AUSTRALIA
	AUSTRIA
	BELGIUM
	DENMARK
	FINLAND
	FRANCE
	GERMANY
	ITALY
	NETHERLANDS
	PORTUGAL
	SPAIN
	SWEDEN
	SWITZERLAND
	UNITED KINGDOM
Eastern Europe	BULGARIA
	CZECH REPUBLIC
	HUNGARY
	POLAND
	RUSSIAN FEDERATION
	SLOVAKIA
Asia	JAPAN
	CHINA
North America	UNITED STATES

6.2 Efficacy

6.2.1 Primary Efficacy

6.2.1.1 Primary Efficacy Estimand

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 intervention discontinuation, for each of the different doses of BAY 2433334 and placebo.

6.2.1.2 Primary Efficacy Analyses

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 at Week 26. 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 $\mu_m = f(d, \theta) + \epsilon$.

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 Week 26 under placebo and there is a relative risk reduction of 25% under the highest dose.

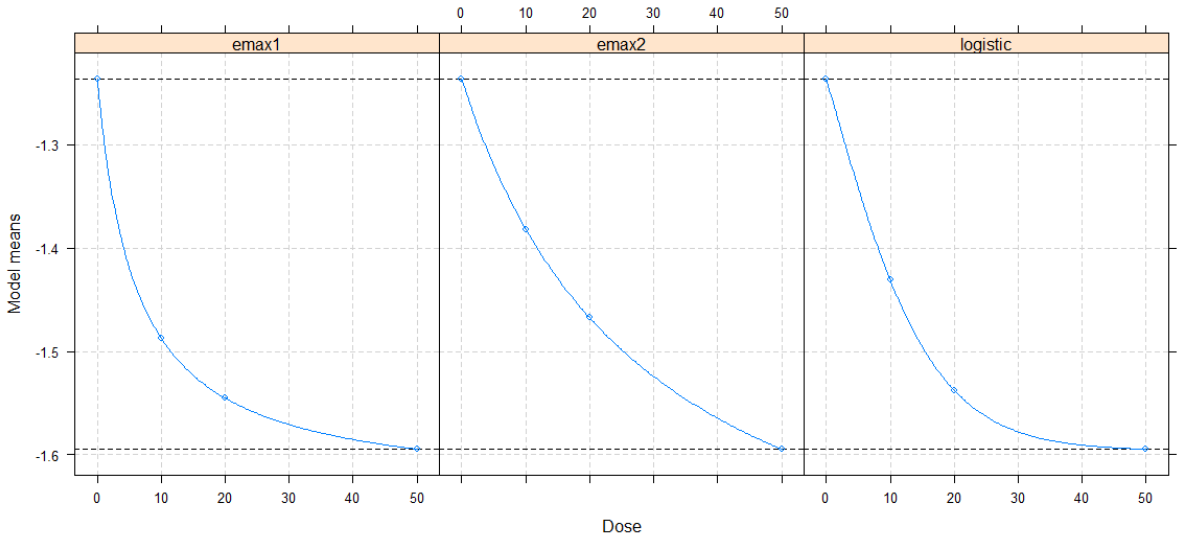
The candidate set of models for $f(x, \theta)$ consists of three models, two (standardized) Emax models with parameter ED_{50}= 6 and ED_{50}= 29 and a (standardized) logistic model with the parameter $ED_{50} = 0.05$ and $\delta = 8.25$. All three candidate models assume a monotonically decreasing dose-response. The parameter of the models are based on pharmacokinetic data. The dose-response candidate models are shown in Table 6–1.

Table 6–1 Dose-response models used in the candidate set

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

The corresponding dose-response relationships of the candidate models are shown in Figure 6–1.

Figure 6–1: Dose-response models used in the candidate set



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.

The primary efficacy variable is the composite of:

- Symptomatic ischemic stroke from randomization until study Day 183, and
- Covert brain infarct detected by MRI up to Week 26 (Visit 8).

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.

Based on these models and the observed data optimal contrasts c_m and the corresponding critical value will be calculated. This will be done using the estimated covariance matrix of a logistic regression model.

Based on the optimal contrast and the critical values a one-sided test with $\alpha = 0.10$ 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 will 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.

This approach follows the general extension of the original MCP-Mod approach (1) by Pinheiro et al. (2).

The estimators for the responses and the corresponding covariance matrix will be calculated using the SAS procedure GLIMMIX:

```
PROC GLIMMIX data = dataset;
CLASS treatment;
MODEL status(event='1') = trtgrpn / solution noint dist=binary covb;
RUN;
/*
where
dataset  = name of sub-dataset including all FAS participants
trtgrpn  = variable coding randomized antithrombotic treatment group
status   = status of the participant at event time (0 = right-censored,
           1 = event)
*/
```

The further implementation of the MCP-Mod approach using SAS follows Bornkamp, Bezlyak and Bretz (3), especially using the `%optcont` macro for the calculation of optimal contrasts.

Events will be counted in the intention-to-treat data scope for the FAS.

The number of participants with a primary efficacy endpoint and the percentage will be shown by intervention arm.

In addition calculations on the crude incidence ratio of the primary efficacy outcome will be done:

The (crude) incidence proportion of the primary efficacy endpoint is defined as the number participants with an event in 26 weeks divided by the number of participants randomized in the treatment arm i.e.

$$\widehat{CI}_A = \frac{\#Participants\ with\ an\ event}{\#Participants\ randomized\ to\ treatment\ A}.$$

These incidences proportions will be estimated for each dose of BAY 2433334 and the placebo arm. The ratio of the (crude) incidence proportions is defined as

$$\widehat{CIR} = \frac{\widehat{CI}_{BAY\ 2433334}}{\widehat{CI}_{Placebo}}.$$

The corresponding 90% two-sided confidence intervals will be calculated using the Farrington-Manning score for an exact confidence interval. The calculation of the ratio of crude incidences and the confidence intervals will be done for each dose of BAY 2433334 compared with placebo by using SAS code corresponding to the following:

```
proc freq data=<dataset>;
     tables trtgroup * status / alpha=0.1;
     exact relrisk (method=FMSCORE);
run;

/*
where
dataset  = name of sub-dataset including all SAF participants randomized to
           respective BAY2433334 treatment group and control group
trtgrpn  = variable coding randomized antithrombotic treatment group
           (0 = Placebo control group, 1 = BAY2433334 treatment
status   = status of the participant at event time (0 = right-censored,
           1 = event of interest)
*/
```

6.2.1.3 Derivation of covert brain infarcts seen by MRI events

For the endpoint "covert brain infarct seen by MRI" the following rule applies:

In a first step each MRI (Visit 8 (Week 26) and Visit 6 (week 13)) will be classified by reviewer. In case a consensus review exists, the consensus reviewer evaluation will be used for analysis, for all other cases first reviewer evaluation will be used.
MRI at Visit 8 (week 26): if more than one or more new brain infarcts are detected the participant is considered having a covert brain infarct detected by MRI. If no new brain infarcts are detected and MRI is evaluable the participant is considered not a covert brain infarct detected by MRI.

For participants in Part A with an evaluable MRI at Visit 6 (Week 13) or participants with an MRI at ET Visit that is labeled as Week 13 MRI, an additional rule applies for participancts without evaluable MRI at Visit 8 (Week 26): If one or more than one new brain infarcts are detected, the participant is considered having a covert brain infarct detected by MRI. If no new brain infarct is detected at week 13 there will be no conclusion on covert brain infarcts detected by MRI. These subjects will have a missing value and the endpoints covert brain infarct detected by MRI will be imputed.

In addition in some analyses the covert brain infarcts detected at Week 13 will not be counted.

6.2.1.4 Missing 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 and/or for whom no evaluable (by Core Lab) MRI is available for baseline and/or Week 26. In addition, it might be possible that a participant in Part A does not have an MRI at randomization but at Week 13 and Week 26.

For the main estimation of the primary efficacy estimand the following imputation rules for missing values for covert brain infarcts detected by MRI at Week 26 apply:

- For participants in Part A who have an MRI at Week 13 and at randomization, the result of that MRI will be used if a covert infarct was detected. In all analyses these participants will be counted as having an MRI evaluation at Week 26.

- The same holds true for participants in Part A who have an evaluable MRI at Week 13 and at Week 26, but not at randomization and for whom a new covert brain infarct (compared to the MRI in Week 13) is detected at the MRI at the Week 26. In all following analyses these participants will be counted as having an MRI evaluation at Week 26. In case no new covert brain infarct was detected at Week 26, the participant will be handled as not having an evaluable MRI at Week 26.
  The number of imputed covert brain infarcts detected by MRI will be shown by study intervention arm and overall. The total number of imputed covert brain infarcts detected by MRI will be derived as the sum of the number of imputed covert brain infarcts detected by MRI per study intervention arm.
- For participants without a symptomatic stroke and missing MRI evaluation at Week 26 the number of unobserved covert brain infarct will be estimated. For that the method of Quan et al. (4) will be used. 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.
  The number of estimated unobserved covert infarcts will be calculated for each dose group by $n_{oe} = \mathrm{n}_{\mathrm{miss,i}} * r_i$, with $\mathrm{n}_{\mathrm{miss,i}}$ the number of participants without a symptomatic stroke and missing MRI evaluation at Week 26 in dose group i and r_i the proportion of participants in dose group i without a symptomatic stroke and a MRI evaluation at Week 26 that have a covert brain infarct. The estimated number of missing covert infarcts will be rounded to the next integer.

The number of imputed covert brain infarcts detected by MRI will be shown by study intervention arm and overall, divided into new covert brain infarcts seen in subjects with incomplete MRI follow-up and covert brain infarcts imputed by the method of Quan et al. (4).

6.2.1.5 Sensitivity analyses for the primary efficacy analysis

The primary efficacy analyses will be repeated for the levels of the stratification factor. Dose-response curves will be modeled independent of a significant signal in the MCP step.

The impact of the potentially missing values due to MRI will be analyzed. The following assumption for participants without an evaluable MRI scan at Week 26 will be done:

- Assume that these participants have no covert brain infarct.
- Assume that these participants have a covert brain infarct.
- Assume that only the participants in the BAY 2433334 intervention arms have a covert brain infarct while the participants in the placebo do not have a covert brain infarct (worst case scenario).

Additionally, the imputation described in Section 6.2.1.4 will be done separately for participants in Part A and Part B.

Sensitivity analyses that restrict the CBI seen by MRI to following following subgroups will be provided:

- CBI that include the cortex
- Covert brain infarct that are DWI positive.

In another sensitivity analysis only the participants with more than one evaluable MRI at Week 26 will be analyzed, i.e. the population of the primary estimand will be restricted. This also excludes participants in Part A, who have an MRI at randomization and Week 13, but not

at Week 26. In addition, a sensitivity analysis restricted to patients on treatment at the Visit at Week 26 will be done.

6.3 Secondary efficacy

6.3.1 Secondary efficacy estimands

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 patients treated with antiplatelet therapy while alive and regardless of intervention 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 patients treated with antiplatelet therapy, while alive and regardless of intervention discontinuation, comparing each of the different doses of BAY 2433334 with placebo.

6.3.2 Secondary efficacy analyses

Events will be counted in the intention-to-treat data scope for the FAS.

The number of participants with a secondary efficacy endpoint and the percentage will be shown by treatment arm. Missing evaluated MRIs will be imputed only for participants in Part A for whom a new covert brain infarct was seen at any MRI (e.g. at Week 13 compared to randomization or at Week 26 compared to Week 13, if no MRI at randomization took place.

The number and the percentage of participants with a covert brain infarct detected by MRI will be shown by treatment arm for all participants in the FAS. To overcome double counting of symptomatic ischemic strokes and newly detected covert brain infarcts, the number and percentage of participants with a covert brain infarct detected MRI will be shown for participants that do not have a symptomatic ischemic stroke up until Visit 8.

The number and percentage of participants with an efficacy event composite of symptomatic ischemic stroke and covert brain infarcts detected by MRI, CV death, myocardial infarction and systemic embolism will be shown by treatment arm. For the time-to-event variables of that composite only events up until study Day 183 will be counted.

For time to event variables number and percentages of participants with an efficacy endpoint will be shown by intervention arm and overall.

Incidence rate will be calculated for each intervention arm and overall with an 90% confidence interval.

The incidence rate (IR) will be expressed as "participants with an event per 100 participant years". For that the following formula (5) is used:

$$IR = \frac{\#\ Participants\ with\ an\ event}{\sum time\ to\ event\ (or\ censoring)(in\ days)/(100 * 365.25)}.$$

The 90% confidence interval for the IR will be computed as

$$\left[\frac{IR * \chi^2(0.05; 2e)}{2e}; \frac{IR * \chi^2(0.95; 2e)}{2e}\right],$$

with $\chi^2(q; 2e)$ the q quantile of a chi square distribution with 2e degrees of freedoms and e the number of participants with an event. (6)

In addition, time-to-first-event analyses taking competing events into account will be performed. For that Aalen-Johansen estimates for the cause specific cumulative risk will be presented.

The competing event for the efficacy events is death or non-CV death for endpoints that include CV death. There will be no competing event for all-cause mortality.

The cumulative incidence, i.e. the probability of having a specific event E at or before a timepoint t, $P(T \leq t, E = 1)$, will be estimated for time to event endpoints by Aalen-Johansen estimators with the competing event as defined before. For the Aalen-Johansen estimator the cumulative hazard calculated by the cause-specific Nelson-Aalen estimator is needed. The calculation of the estimators follows Allignol, Beyersmann and Schmoor (7).

The cause-specific Nelson-Aalen estimator for an event E at timepoint t is calculated as:

$$\hat{\Lambda}_E(t) = \sum_{t_j \leq t} \frac{\#Participants\ with\ an\ event\ E\ at\ t_j}{\#Participants\ under\ risk\ at\ t_j}.$$

The Aalen-Johansen estimator takes the difference of the cause-specific Nelson-Aalen estimator into account, weighted with the Kaplan-Meier survival function, i.e. the Aalen-Johansen estimator for time t is defined as:

$$\widehat{AJ_E}(t) = \sum_{t_j \leq t} \hat{S}(t_{j-1})(\hat{\Lambda}_E(t_j) - \hat{\Lambda}_E(t_{j-1}))\ .$$

To derive the Aalen-Johansen estimators and the corresponding confidence intervals, SAS program code corresponding to the following will be used:

```
PROC LIFETEST DATA = <dataset> ALPHA=0.1 ERROR=AALEN;
      STRATA TRTGRPN;
      TIME TTEVLAUE * STATUS(1)/failcode=0;
RUN;

/*
where
dataset  = name of sub-dataset including all FAS participants randomized to
           respective BAY2433334 treatment group and control group
trtgrpn  = variable coding randomized antithrombotic treatment group
ttevalue = time to first occurrence of outcome event or competing event
status   = status of the participant at event time (0 = event of interest,
           1 = right-censored,, 2,3… = competing event(s))
stratumn = variable for stratification factor (two levels)
*/
```

To estimate the relative change in the instantaneous rate of the occurrence of the primary safety outcome in participants taking BAY 2433334 versus placebo according to the defined estimand, csHRs and their associated confidence intervals will be derived from a stratified cause-specific Cox proportional hazards regression model. The results will be presented together with estimates of the csHRs for the associated competing risks. Corresponding to a (non-formal) superiority testing, a stratified log-rank test will be used.

To derive the cause specific hazard ratios, the p-value for the stratified log-rank test and the corresponding confidence intervals, SAS program code corresponding to the following will be used:

```
PROC PHREG DATA = <dataset>;
  MODEL ttevalue*status(1,2,3)=trtgrpn / RL ALPHA=0.1 TIES=EFRON;
  STRATA stratumn;
RUN;

/*
where
dataset  = name of sub-dataset including all FAS participants randomized to
           respective BAY2433334 treatment group and control group
trtgrpn  = variable coding randomized antithrombotic treatment group
ttevalue = time to first occurrence of outcome event or competing event
status   = status of the participant at event time (0 = event of interest,
           1 = right-censored, 2,3,… = competing event(s))
stratumn = variable for stratification factor
*/
```

In a supplementary analysis the objective will be explored from a different angle, comparing the probability for the primary safety outcome as compared to the hazard rates based on a Fine-Gray model and Gray's (8) test for equivalence of the cumulative incidence functions, stratified by antiplatelet therapy, will be performed.

To derive the cause subdistribution hazard ratios for the Fine-Gray model, the corresponding confidence intervals program code corresponding to the following will be used:

```
PROC PHREG DATA = <dataset>;
STRATA STRATUMN;
MODEL TTEVALUE*STATUS(1) = TRTGRPN / RL ALPHA = 0.1 eventcode(FG)=0;
RUN;

/*
where
dataset  = name of sub-dataset including all FAS participants randomized to
           respective BAY2433334 treatment group and control group
trtgrpn  = variable coding randomized antithrombotic treatment group
ttevalue = time to first occurrence of outcome event or competing event
status   = status of the participant at event time (0 = event of interest,
           1 = right-censored, 2,3,… = competing event)
stratumn = variable for stratification factor
*/
```

For Gray's test SAS program code corresponding to the following will be used:

```
PROC LIFETEST DATA = DATASET ERROR=AALEN ;
STRATA STRATUMN / GROUP=TRTGRPN;
TIME TTEVALUE * STATUS(1)/failcode=0;
RUN;

/*
where
dataset  = name of sub-dataset including all FAS participants randomized to
           respective BAY2433334 treatment group and control group
trtgrpn  = variable coding randomized antithrombotic treatment group
ttevalue = time to first occurrence of outcome event or competing event
status   = status of the participant at event time (0 = event of interest,
           1 = right-censored, 2,3,… = competing event)
stratumn = variable for stratification factor (two levels)
*/
```

Cause-specific and subdistribution HRs will be calculated for the respective event and the competing event(s). These hazard ratios and corresponding confidence intervals will be estimated on separate cause-specific hazard models for the comparison of the each of the doses of BAY 2433334 versus placebo. No comparison of the different doses of BAY 2433334 is planned.

6.3.3 Subgroup analyses

For the primary and for selected secondary efficacy endpoints subgroups analyses will be done for the following subgroups:

- Antiplatelet therapy after index event (single antiplatelet therapy, dual antiplatelet therapy)
- Sex
- Race (White, Black, Asian, other)
- Region (North America, Western Europe and Australia, Eastern Europe, Asia)
- Weight (<60; 60-90; >90 kg)
- Age Group (<65 years, 65 – 75 years, >75 years)

- BMI (<25, ≥25 to <30, ≥30 kg/m^2)
- eGFR (< 60; 60-90; >90 mL/min)
- History of stroke / TIA prior to index stroke (yes/no)
- Extra- or intracranial atherosclerosis proximal to the qualifying stroke (yes/no)
- Carotid artery atherosclerosis identified by vascular imaging (yes/no)
- Chronic Kidney Disease (yes/no)
- Coronary Artery Disease (yes/no)
- Hypertension (yes/no)
- Diabetes (yes/no)
- Old brain infarct detected by baseline MRI (yes/no)
- Hemorrhagic transformation of index stroke by baseline MRI (yes/no)
- DWI (+) lesion on index stroke confirmed by MRI (yes/no)Thrombolysis and/or endovascular therapy (yes/no)
- Tobacco use (Never, Former, Current)
- NIHSS score of index event at randomization (≤3, 4-7, ≥8)
- mRS score of index stroke at Day 7 (0-1, ≥2)
- Time from onset of qualifying stroke to randomization (<= 24 hrs; >24 hrs)
- Stroke subtype of index event (large artery atherosclerosis, small vessel occlusion (lacune), other determined etiology, undetermined etiology)

An old brain infarct detected by MRI is defined as a brain infarct on the baseline MRI with DWI negative.

A hemorrhagic transformation of the index stroke is defined as a brain infarct with DWI positive on the MRI and a response on the evidence of hemorrhagic transformation other than "No" as reported by the MRI core lab.

Extra- or intracranial atherosclerosis proximal to the qualifying stroke is defined as evidence of atherosclerosis involving the extra- or intracranial arteries and a maximum degree of stenosis/plaque proximal to the index stroke ticked either >0-50% or >50%.

Carotid artery atherosclerosis identified by vascular imaging is defined as evidence of atherosclerosis involving the extra- or intracranial arteries and the carotid artery is involved.

For these subgroups descriptive tables of crude incidence will be presented. In treatment arms with 3 or more events exposure-adjusted incidence rates will be presented for time to event endpoints. Cause-specific hazard ratios will be calculated for each of the subgroups, if enough events in that subpopulation exist. Homogeneity of study intervention effect in these subgroups will be assessed by adding a covariate for the subgroup variable and the corresponding intervention – subgroup interaction to the respective cause specific hazards model.
Note that, the probability of observing at least one statistically significant but spurious interaction is high despite the lack of a biological or pharmacological basis for expecting an interaction as the number of subgroup analyses may be large. Thus, any significant interactions will be interpreted as "flags" to prompt further investigation.

6.4 Pharmacokinetics/pharmacodynamics

The population PK analysis and pharmacodynamic analyses may be presented separately from the CSR and will be described in a separate analysis plan.

6.4.1 Pharmacokinetics

BAY 2433334 concentrations will be summarized per sampling interval, separated according to actual dose.

All valid results will be included in the listings and graphical displays of the individual data, which are displayed using actual times. Measurements taken outside the predefined time window will be flagged by the pharmacokinetic expert to be excluded from the calculation of the summary statistics (with respect to planned times) in order to avoid biased results. Samples flagged for other reasons, as defined in the respective guidance document for PK validity for study #19766, will be excluded from statistics accordingly (see also Section 4.5.7).

The analyses will be focused on descriptive statistics. The following statistics will be calculated for each of the sampling intervals: arithmetic mean, standard deviation and coefficient of variation, geometric mean, geometric standard deviation (re-transformed standard deviation of the logarithms), and coefficient of variation, minimum, median, maximum value and the number of measurements.

Means at any time will only be calculated if at least 2/3 of the individual data will be measured and will be above the limit of quantification (LOQ). For the calculation of the mean value a data point below LOQ will be substituted by one half of the limit.

Plots will be prepared by naïve pooling all individual plasma concentrations versus actual relative study times (time of sample collection after time of study intervention administration, time after most recent dose) using both a linear and semi-logarithmic scale, and presented by treatment. Samples which are collected outside of the predefined windows will nevertheless be valid for PK analysis.

6.4.2 Pharmacodynamics

BAY 2433334 pharmacodynamics will be summarized per sampling interval, separated according to actual dose.

All valid results will be included in the listings and graphical displays of the individual data, which are displayed using actual times.

Samples flagged for other reasons, as defined in the respective guidance document for PK validity for study #19766, will be excluded from statistics accordingly (see also Section 4.5.7) This will pertain to main PD parameters aPTT and AXIA only.

The analyses will be focused on descriptive statistics. The following statistics will be calculated for each of the sampling intervals: arithmetic mean, standard deviation and coefficient of variation, geometric mean, geometric standard deviation (re-transformed standard deviation of the logarithms), and coefficient of variation, minimum, median, maximum value and the number of measurements.

Means at any time will only be calculated if at least 2/3 of the individual data will be measured and will be above the limit of quantification (LOQ). For the calculation of the mean value a data point below LOQ will be substituted by one half of the limit.

Plots will be prepared by pooling all individual PD data (naïve pooling) versus actual relative study times (time of sample collection after time of study intervention administration, time after most recent dose) using both a linear and semi-logarithmic scale, and presented by visit and treatment, for absolute values, change from baseline and ratio to baseline. Samples which are collected outside of the predefined windows will nevertheless be valid for PD analysis.PD analyses will be done for aPTT, activated Factor XIa activitiy, Factor XII activity and Factor XII concentration.The following PD/PD correlations will be provided as scatterplots (with observed values, changes from baseline and ratios to baseline):

- aPTT versus inhibition of FXIa (AXIA)

The following PK/PD correlations will be provided as scatterplots (with observed values, changes from baseline and ratios to baseline):

- aPTT versus plasma concentrations of BAY 2433334.
- inhibition of FXIa (AXIA) versus plasma concentrations of BAY 2433334.

The following data rules apply:

- Changes from baseline = Actual value - Baseline value
- Ratio to Baseline = Actual value / Baseline value

Baseline is defined as last value prior to first intake of BAY 2433334.

Further data-driven exploratory analyses may be applied.

For the calculation of the mean value a data point below LOQ will be substituted by one half of the limit.

6.5 Safety

6.5.1 Primary Safety

6.5.1.1 Primary Safety Estimand

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 intervention of BAY 2433334 or placebo and while the participant is alive and exposed to study intervention.

6.5.1.2 Primary Safety Analyses

The primary safety estimator is the hazard ratio for the composite of ISTH major bleeding and clinical relevant non-major bleeding in a Cox proportional hazards model comparing the pooled BAY 2433334 intervention arms with placebo. All events from first intake of study intervention up until 2 days after permanent study intervention discontinuation will be counted.

These analyses will be replicated for the comparison of each dose of BAY 2433334 and placebo.

The time to event analyses will follow the analyses for efficacy outcomes. In addition, the competing event “permanent discontinuation of study intervention will be analysed.

Taking the time under risk into account, the exposure-adjusted incidence rate will be calculated for each treatment arm with an 90% confidence interval.

The exposure-adjusted incidence rate will be expressed a "subjects with an event – per 100 participant years". For that the following formula is used:

$$IR_{adj} = \frac{\#Participants\ with\ an\ event}{\sum time\ under\ treatment\ (in\ days)/(100 * 365.25)}$$

The 90% confidence interval for the exposure-adjusted IR will be computed as

$$\left[\frac{IR_{adj} * \chi^2(0.05; 2e)}{2e}; \frac{IR_{adj} * \chi^2(0.95; 2e)}{2e}\right],$$

with $\chi^2(q; 2e)$ the q quantile of a chi square distribution with 2e degrees of freedoms and e the number of participants with an event.(6)

The cause specific and subdistribution hazard ratios and corresponding confidence intervals will be estimated on separate models for the comparison of the pooled doses of BAY 2433334 and placebo and the comparison of each dose of BAY 2433334 and placebo (if applicable). No comparison of the different doses of BAY 2433334 is planned.

6.5.1.3 Secondary Safety Analyses

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 intervention for the endpoints:

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

The main analyses will follow the main estimation for the primary safety endpoint.

6.5.1.4 Exploratory Safety 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.

For these endpoints, descriptive tables of crude incidence will be presented. In treatment arms with 3 or more events exposure-adjusted incidence rates will be presented. No comparison between the different treatment arms is planned.

Descriptive tables of crude incidences of investigator-reported bleeding will be shown for all bleeding scales (ISTH, TIMI, BARC). A table will compare adjudicated and investigator-reported bleeding outcomes.

6.5.2 Subgroup analyses

Subgroup analyses for primary and selected secondary safety events will be done in the same subgroups as for efficacy variables. In addition SSRI use will be a subgroup for bleeding events.

6.5.3 Analyses related to COVID-19

Analysis due to COVID-19 pandemic will be described in this section but might affect all sections of the analyses.

A description of the number of study participants whose assessments and follow up in the study was impacted by the COVID-19 pandemic will be shown. In addition, a listing of all study participants affected by the COVID-19 pandemic by unique subject number identifier and by investigational site, and a description of how the individual's participation was altered will be created.

For the primary safety estimand the intercurrent event "Treatment discontinuation due to COVID-19 related events" will be handled similar to any other premature discontinuation, i.e. all events from first intake of study intervention up until 2 days after the last intake of study intervention will be counted.

Events that occur in timely relationship to a COVID-19 diagnosis (7 days before diagnosis and 30 days after diagnosis) will be shown separately for efficacy (in the full analysis set) and safety (for the safety set).

Protocol deviations due to COVID-19 will be shown in the protocol deviations section as a separate category.

COVID-19 disease itself will be counted as an adverse event and therefore listed in the respective adverse event tables.

If the number of participants with a dignosed COVID-19 disease is sufficiently high (i.e. 10 participants or more), the following sensitivity analyses will be done for the efficacy and safety outcomes:

The primary estimand will handle the COVID-19 disease with an "while not having COVID-19 disease" approach and censor any participants data 14 days before the (first) start of a COVID-19 disease.

In addition the number of subjects with an event occurring after COVID-19 disease will be shown for efficacy and safety events.

6.5.4 Vital Signs

Vital signs (systolic and diastolic blood pressure, heart rate) obtained at Visit 1 (Screening), Visit 2 (Randomization [if not on the same day as Visit 1]), Visit 4, Visit 6, Visit 8, Visit 10, as well as Visit 12 (end of treatment visit [EOT]) or Visit 12a (early termination [ET]) will be displayed by means of descriptive statistics and change from baseline. Data from unscheduled visits will not be analyzed but only shown in listings.

6.5.5 Laboratory parameter

Only centrally analyzed blood samples will be considered for analysis.

Central laboratory parameters (e.g. AST, ALT, eGFR), Visit 2 (Randomization), Visit 4, Visit 6, Visit 8, Visit 10, as well as Visit 12 (EOT) or Visit 12a (ET) will be displayed by

means of descriptive statistics and change from baseline. Data from unscheduled visits will not be analyzed but only shown in listings.

Number of participants with treatment emergent high abnormalities will be shown overall and by visit for the following laboratory parameter:

- AST or ALT > 3xULN
- AST and/or ALT >3xULN and bilirubin > 2xULN
- AST or ALT >5xULN
- AST or ALT >8x ULN
- eGFR < 30 mL/min.

6.5.6 Biomarker

Exploratory biomarker analyses, that might be performed optionally and/or only in a subset of participants are:

- NT-proBNP
- hsCRP
- Thrombin-activatable fibrinolysis inhibitor (TAFI)
- C1 inhibitor activity
- TAT, and
- F1.2

The analyses will be performed at Visit 1 before the first dose and Visit 8 (Week 26) or Early Termination visit.

The biomarkers will be by means of descriptive statistics and change from baseline.

6.5.7 Electrocardiograms

A single 12-lead ECG will be performed at Visit 1 (Screening), Visit 2 (Randomization, if not on the same day as Visit 1), Visit 6 as well as Visit 12 (EOT), or Visit 12a (ET). QRS, QT and QTc intervals will be displayed by means of descriptive statistics and change from baseline. Data from unscheduled visits will not be analyzed but only shown in listings.

The number of participants with abnormal electrocardiograms findings will be displayed by visit.

6.5.8 Adverse events

The investigator has to record on the respective CRF pages all adverse events occurring in the period from start of intervention (first day of study intervention) until the safety follow-up visit. The original terms used by investigators to report AEs via the CRFs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

For each AE, the number and percentage of participants who experienced at least 1 occurrence of the given event will be tabulated according to the affected primary System Organ Class (SOC) and preferred term (PT) by randomized intervention arm. A total column will be included in all safety summaries.

Frequency tables, showing an overall summary of number of participants with AEs, study intervention-related AEs, SAEs and AESIs will be given, and will include the following information:

- maximum intensity for any AE,
- AE related deaths,
- AE resulting in permanent discontinuation of study intervention,
- Treatment-emergent AE.

Any AEs starting from the first intake of study intervention until 2 days of the last intake of study intervention will be considered treatment-emergent. Determination of whether an event is treatment-emergent will be derived after the missing or incomplete AE start date is imputed. Imputation rules for missing and incomplete AE start data are described in Section 4.3.

The severity or intensity of an (S)AE should be graded by the investigator with the following guidance:

- 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 criteria as described in the definition of an SAE, not when it is rated as severe.

7. Document history and changes in the planned statistical analysis

- SAP Version 1.0 approved on 17 MAR 2020
- Version 2, approved 26 JAN 2022, adds definition of derivation of covert brain infarcts detected by MRI, age ranges, clarifies some subgroups and adds analyses related to COVID-19; added bleeding definition including intracranial hemorrhage, added regions grouping, changes in competing event analyses, added crude incidence ratios for primary efficacy endpoint.

8. References

1. Bretz F, Pinheiro JC, Branson M. Combining multiple comparisons and modeling techniques in dose response studies. Biometrics. 2005 Sep;61(3):738-48.
2. Pinheiro J, Bornkamp B, Glimm E, Bretz F. Model-based dose finding under model uncertainty using general parametric models. Statistics in medicine. 2014 May 10;33(10):1646-61.
3. Bornkamp B, Bezlyak V, Bretz F. Implementing the MCP-Mod procedure for dose-response testing and estimation. Modern Approaches to Clinical Trials Using SAS: Classical, Adaptive, and Bayesian Methods. 2015:193-224.
4. Quan H, Zhang D, Zhang J, Devlamynck L. Analysis of a binary composite endpoint with missing data in components. Statistics in medicine. 2007 Nov 20;26(26):4703-18.
5. Unkel S, Amiri M, Benda N, Beyersmann J, Knoerzer D, Kupas K, Langer F, Leverkus F, Loos A, Ose C, Proctor T. On estimands and the analysis of adverse events in the presence of varying follow-up times within the benefit assessment of therapies. Pharmaceutical statistics. 2019 Mar;18(2):166-83.

6. Nelson WB. Applied life data analysis. New York: Wiley; 1982.
7. Allignol A, Beyersmann J, Schmoor C. Statistical issues in the analysis of adverse events in time-to-event data. Pharmaceutical statistics. 2016 Jul;15(4):297-305.
8. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. The Annals of statistics. 1988 Sep 1:1141-54.