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Title page

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

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

Bayer study drug BAY 2433334 / INN

Clinical study phase:	Phase 2b	**Date:**	26 JAN 2022
Study No.:	20603	**Version:**	1.0
Author:	PPD		

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

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Abbreviations

AE	Adverse event
AESI	Adverse event of special interest
AF	Atrial fibrillation
ALT	Alanine aminotransferase
AMI	Acute myocardial infarction
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
CV	Cardiovascular
CYP4A4	Cytochrome P450, family 3, subfamily A, polypeptide 4
DAPT	Dual antiplatelet therapy
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
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
mRS	Modified Rankin Score
NIHSS	National Institutes of Health Stroke Scale
NT-proBNP	N-terminal pro B-type Natriuretic Peptide
$P2Y_{12}$	Chemoreceptor for adenosine diphosphate
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
STEMI	ST-elevation myocardial infarction
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 with a 6 to 12 months treatment duration tests BAY 2433334 against placebo in patients following an AMI who are treated with dual antiplatelet therapy (DAPT).

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

Each individual study has its own objectives, and study results will be analyzed and reported individually in the respective Clinical Study Reports (CSRs). However, in order to reach and draw conclusions concerning safety in general, and especially bleeding, the program is designed to pool the data across the three Phase 2 studies to help further characterize safety and efficacy.

The SAP is based on the protocol version 1.0, approved on 22 OCT 2019.

2. Study Objectives

The primary efficacy objective of the study is to to evaluate whether the oral FXIa inhibitor BAY 2433334 compared to placebo leads to a lower incidence of CV death, MI, stroke and stent thrombosis in participants with an AMI and who are treated with dual antiplatelet therapy.

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

The primary and secondary safety objective of the study is to evaluate whether the incidence of bleeding is similar for BAY 2433334 (10, 20 and 50 mg pooled) compared to placebo in participants with an AMI and who are treated with dual antiplatelet therapy.

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

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

Table 2–1 Objectives and Endpoints

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

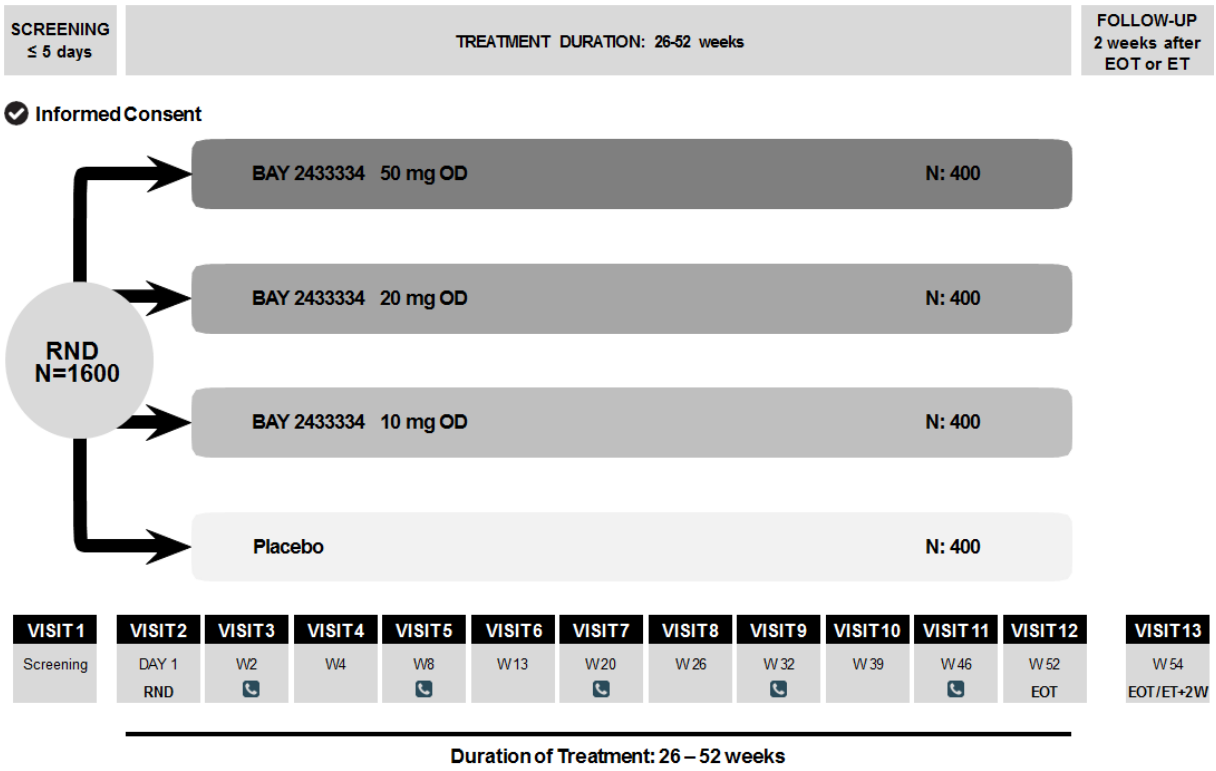
Abbreviations: aPTT = activated partial thromboplastin time, BARC = Bleeding Academic Research Consortium, CV = cardiovascular, ISTH = International Society on Thrombosis and Hemostasis, AMI = acute myocardial infarction, DAPT = dual antiplatelet therapy, MI = myocardial infarction, TIMI = thrombolysis in myocardial infarction

3. Study Design

Study 20603 is a multicenter, randomized, placebo controlled, double-blind, parallel group, dose-finding Phase 2 study. Figure 3–1 displays the overall study design.

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

Figure 3–1 Study design overview



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

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

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

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

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

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

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

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

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

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

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

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

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

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

4. General Statistical Considerations

4.1 General Principles

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, as applicable.

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 efficacy events will be performed by the CEC group who will review events in a blinded fashion and will algorithmically and manually adjudicate 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)
- MI
- Stroke (ischemic, hemorrhagic, undetermined)
- Stent thrombosis

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

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

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 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. Generally 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 treatment, 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 outcome**
  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.
- **Incomplete time of outcome**
  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.

4.4 Interim Analyses and Data Monitoring

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

The first of the two interim analyses was conducted once about 50% of the participants of the PACIFIC Stroke study 19766 had been randomized to assess the safety of BAY 2433334 to include participants with more severe cases of stroke in that study. The second interim analysis was planned when approximately 80% of all planned participants, taken all three studies together, would have been randomized. This interim analysis was not performed.

A separate interim SAP was prepared by the SAC.

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

4.5 Data Rules

4.5.1 Baseline values

Baseline values for vital sign measures and laboratory values 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 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.

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.

Events at the day of randomization will be counted if the time of occurrence is later than the time of first study intervention intake.

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 ITT data scope all events from randomization up until scheduled end of treatment visit 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.

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 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. It may include episodes leading to self-discontinuation of medical therapy by the patient without consulting 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, 4 or 5 and
3. does meet one of the following criteria (1) requires non-surgical, medical intervention by healthcare professional and/or (2) leads to hospitalization or increased level of care and/or (3) prompts evaluation[a].

[a] 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[b] 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[b] 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, does include intraspinal), and/or
2. subcategories confirmed by autopsy or imaging or lumbar puncture and/or
3. intraocular bleeding compromising vision

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

A bleeding will be counted as BARC bleeding **Type 4 (CABG-related)** if it is

1. perioperative intracranial bleeding with 48 h and/or requires
2. reoperation after closure of sternotomy for the purpose of controlling bleeding and/or
3. Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period and/or
4. Chest tube output ≥2L within a 24-h period

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.

4.5.5.2 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 hemocrit 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. has any overt sign of hemorrhage that requires medical or surgical treatment, laboratory or imaging evaluation, or prolonged hospitalization and
3. does not meet criteria for major or minor bleeding event.

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

1. it is not related to a CABG procedure and
2. is an overt bleeding event that does not meet the criteria above

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 during study.

4.5.5.3 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.

4.5.6 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.

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.

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

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 permanent discontinuation of study intervention
- Flow of participant 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 CRF 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 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 important 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 or african American, Asian, other)
- Region (North America; Western Europe; Eastern Europe; Asia)
- Age (< 65, 65 – 75, > 75 years)
- Age over 65 years (yes/no)
- 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 (yes/no)
- Prior MI (yes/no)
- Prior CABG (yes/no)
- Chronic Kidney Disease (yes/no)
- Coronary Artery Disease (yes/no)
- Peripheral Artery Disease (yes/no)
- Hypertension (yes/no)
- Diabetes Mellitus (yes/no)
- Intended $P2Y_{12}$ inhibitor use (ticagrelor/prasugrel versus clopidogrel) after hospital discharge
- Type of index MI (STEMI/NSTEMI)
- PCI for index event (yes/no)
- CABG for index event (yes/no)

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, and
- concomitant medication, i.e. medications taken within the treatment period.

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

Separate tables will be provided for anticoagulants, antiplatelet therapy used and for strong CYP4A4 inhibitors and inducers. In addition, information of duration of DAPT use (at randomization, 1, 3, 6 months, EOT) will be provided.

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 subgroup(s):

- intended $P2Y_{12}$ inhibitor use (ticagrelor/prasugrel versus clopidogrel) after hospital discharge

6.1.7 Region Classification

Countries will be grouped into regions in the following way:

Region	Country
Western Europe	AUSTRIA
	BELGIUM
	GERMANY
	ITALY
	NETHERLANDS
	SPAIN
	SWEDEN
	SWITZERLAND
	UNITED KINGDOM
Eastern Europe	CZECH REPUBLIC
	HUNGARY
	POLAND
Asia	JAPAN
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 hazard ratio of the composite of CV death, MI, stroke and stent thrombosis comparing BAY 2433334 (20 and 50 mg pooled) with placebo in adult participants with an AMI treated with DAPT while alive and regardless of treatment discontinuation.

6.2.1.2 Primary Efficacy Analyses

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

For time-to-event variables number and percentages of participants with an efficacy endpoint will be shown by intervention arm and for pooled BAY 2433334 20 and 50 mg arms.

Incidence rate will be calculated for each intervention arm and the pooled arms 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 (Unkel, et al. 2019) 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 (Nelson 1982).

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 (Allignol, Beyersmann and Schmoor 2016).

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 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 csHRs, 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 (Gray 1988) test for equivalence of the cumulative incidence functions, stratified by intended $P2Y_{12}$ inhibitor use, 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.

6.2.1.3 Sensitivity analyses for the primary efficacy analysis

The primary efficacy analyses will be repeated for

- the model described above, but without stratification factor
- each level of the stratification factor
- the estimation on the safety set and the treatment emergent data scope (as described for the safety estimand).

6.3 Secondary efficacy

6.3.1 Secondary efficacy estimands

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

For each of the individual enpoints:

- All cause mortality
- CV death
- MI
- Stroke (ischemic and hemorrhagic)
- Stent thrombosis

6.3.2 Secondary efficacy analyses

The analyses of the secondary efficacy endpoints will be the same as described for the primary efficacy analysis.

6.3.3 Subgroup analyses

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

- Intended $P2Y_{12}$ inhibitor use (ticagrelor/prasugrel versus clopidogrel) after hospital discharge (stratification factor)
- 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, ≥ 30kg/m^2)
- eGFR (< 60; 60-90; >90 mL/min)
- History of stroke / TIA (yes/no)
- Prior MI (yes/no)
- Prior CABG (yes/no)
- Chronic Kidney Disease (yes/no)
- Coronary Artery Disease (yes/no)
- Peripheral Artery Disease (yes/no)
- Hypertension (yes/no)
- Diabetes Mellitus (yes/no)
- Type of MI (STEMI/NSTEMI)
- PCI for index event (yes/no)
- CABG for index event (yes/no)

For these subgroups number and percentages of participants with an efficacy endpoint will be presented.

CsHRs 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. Forest plots will be generated.

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 will 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 and visit, 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 #20603, will be excluded from statistics accordingly (see also Section 4.5.6).

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. Samples which are collected outside of the predefined windows will nevertheless be valid for PK analysis.

6.4.2 Pharmacodynamics

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 drug 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.

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)
- D-Dimer versus inhibition of FXIa (AXIA)
- D-Dimer versus aPTT

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.
- D-Dimer 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

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

6.5.1.2 Primary Safety Analyses

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

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.

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. (Nelson 1982)

The cause specific and subdistribution hazard ratios and the 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 <*individual endpoint*> comparing pooled BAY 2433334 with placebo in adult participants with an AMI treated with DAPT and who have taken at least one dose of study medication of BAY 2433334 or placebo and while the patient is alive and exposed to study drug

For each of the individual endpoints:

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

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

6.5.1.4 Tertiary/exploratory Safety Analyses

Exploratory safety endpoints are:

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

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 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 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.

6.5.4 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.

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.

6.5.5 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 displayed by means of descriptive statistics and change from baseline.

6.5.6 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).

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. Any AEs starting after 2 days of the last intake of study intervention until the safety follow up visit will be considered post-treatment AEs. 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.

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 (TE)AEs, (TE)SAEs and (TE)AESIs will be given, and will include the following information:

- maximum intensity for any (TE)AE,
- (TE)AE related deaths,
- (TE)AE resulting in permanent discontinuation of study intervention,

Post-treatment AEs will be summarized by frequency tables.

6.6 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 AE and therefore listed in the respective AE tables.

If the number of participants with a diagnosed 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.

7. Document history and changes in the planned statistical analysis

Not applicable

8. References

Allignol, Beyersmann, and Schmoor. "Statistical issues in the analysis of adverse events in time-to-event-data." *Pharmaceutical Statistics*, no. 15 (2016): 297-305.

Gray. "A class of k-sample tests for comparing the cumulative incidence risk of a competing risk." *The Annals of Statistics* 16, no. 3 (1988): 1141-1154.

Nelson. *Applied Life Data Analysis.* New York: Wiley, 1982.

Unkel, et al. "On estimands and the analysis of adverse events in the presence of varying follow-up times within the benefit assesment of therapies." *Pharmaceutical Statistics*, no. 18 (2019): 166-183.