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Title page

Study Title: Randomized, active comparator-controlled, double-blind, double-dummy, parallel group, dose-finding Phase 2 study to compare the safety of the oral FXIa inhibitor BAY 2433334 to apixaban, a NOAC, in patients with atrial fibrillation

Short Title: Phase 2 **P**rogram of **A**nti**C**oagulation via **I**nhibition of **FXI**a by the oral **C**ompound BAY 2433334 – **A**trial **F**ibrillation study (**PACIFIC-AF**)

Bayer study drug BAY 2433334 / INN

Clinical study phase:	Phase 2b	**Date:**	14 OCT 2021
Study No.:	19765	**Version:**	2.0
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Abbreviations

AE	Adverse event
AF	Atrial fibrillation
ALT	Alanine aminotransferase
ASA	Acetylsalicylic acid
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BARC	Bleeding Academic Research Consortium
CABG	Coronary artery bypass graft
CEC	Clinical Events Committee
CI	Confidence interval
CRF	Case report form
csHR	Cause-specific hazard ratio
CV	Cardiovascular
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
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
NOAC	Non-Vitamin K oral anticoagulant
NT-proBNP	N-terminal pro B-type Natriuretic Peptide
PK	Pharmacokinetic(s)
PT	Preferred term
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SFU	Safety follow up
SOC	System organ class
TAFI	Thrombin-activatable fibrinolysis inhibitor
TAT	Thrombin antithrombin complex
TIA	Transient ischemic attack
TIMI	Thrombolysis in myocardial infarction
VKA	Vitamin K antagonist

1. Introduction

This Phase 2 study will explore two doses of BAY 2433334 in order to determine a lower risk for bleeding when compared to apixaban (a NOAC) as well as the dose that is safe and can be used in a Phase 3 study in the same indication.

Current treatment guidelines recommend the use of long-term oral anticoagulant therapy such as VKAs, or NOACs.

Despite a better benefit-risk profile for NOACs when compared to VKAs, patients receiving NOACs continue to have a significant risk for developing strokes, systemic embolism and CV

death. In addition, even though NOACs lead to less intracranial hemorrhage compared to VKAs, there is still a significant risk for major and clinically relevant non-major bleeding.

BAY 2433334, as an oral FXIa inhibitor, is expected to show a benefit in reducing the risk for stroke in patients with AF in Phase 3. At the same time BAY 2433334 is expected to have a low bleeding risk. This is based on the available preclinical data, data from patients with inherited FXI deficiency and first clinical data from 2 Phase 2 proof-of-concept studies in participants undergoing total knee replacement.

BAY 2433334 is therefore an attractive candidate to evaluate as a potential replacement for NOAC therapy in patients with AF.

The SAP is based on the protocol version 1.0 (approved: 25 SEP 2019).

2. Study Objectives

The primary safety objective of the study is to evaluate if the oral FXIa inhibitor BAY 2433334 when compared to apixaban leads to a lower incidence of bleeding in participants with AF.
The primary safety estimand is the ratio of the proportions of the composite of ISTH major and clinically relevant non-major bleeding within 3 months comparing pooled doses of BAY 2433334 and comparator drug apixaban in adult participants with AF who have taken at least one dose of study medication of BAY 2433334 or comparator drug apixaban, while the participant is alive and exposed to study intervention.

There are no primary efficacy objectives for this trial.

Exploratory efficacy and safety objectives are:

- to explore the efficacy of BAY 2433334 compared to apixaban in reducing the risk for cardiovascular events (CV death, MI, stroke, systemic embolism) in participants with atrial fibrillation,
- 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 evaluate that the oral FXIa inhibitor BAY 2433334 when compared to apixaban leads to a lower incidence of bleeding in participants with AF	**Primary Safety Endpoints** • composite of ISTH major and clinically relevant non-major bleeding **Secondary Safety Endpoints** • all bleeding • ISTH major bleeding • ISTH clinically relevant non-major bleeding • ISTH minor bleeding **Exploratory Safety Endpoints** • TIMI clinically significant bleeding • TIMI major bleeding • TIMI minor bleeding • BARC bleeding definition type 1, 2, 3, 5 • BARC bleeding definition type 3, 5 • BARC bleeding definition type 2, 3, 5 • BARC bleeding definition type 1
Exploratory	
• to explore the efficacy of BAY 2433334 compared to apixaban in reducing the risk for cardiovascular events (CV death, MI, stroke, systemic embolism) in participants with atrial fibrillation • 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	**Exploratory Efficacy Endpoint** • composite as well as individual components of CV death, MI, ischemic stroke, systemic embolism • all-cause mortality **Other Exploratory Endpoints** • FXIa inhibition, aPTT, D-Dimer • Pharmacokinetics • Various biomarkers (e.g. diagnostic, safety, pharmacodynamic, monitoring, or potentially predictive biomarkers)

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

3. Study Design

Study 19765 is a multicenter, randomized, active-comparator controlled, double-blind, double-dummy, parallel group, dose-finding Phase 2 study.

The study population includes participants of 45 years of age or older with AF documented by ECG evidence with:

- CHA_2DS_2-VASc score ≥ 2 if male or
- CHA_2DS_2-VASc score ≥ 3 if female.
- Indication for treatment with an oral anticoagulant in:

- any participant currently not treated with an oral anticoagulant (e.g. treatment naïve) or alternatively,
- participant on a NOAC in case of at least one bleeding risk feature (history of a prior bleed within the last 12 months requiring medical attention and / or moderate renal dysfunction with eGFR 30-50 ml/min and / or current clinically indicated antiplatelet therapy with acetylsalicylic acid [ASA] ≤ 100 mg).

Stratification will be based on whether participants received a NOAC before study start or were not treated with any oral anticoagulant.

The planned study duration will be 14-16 weeks, consisting of:

- **Screening period (visit 1 until visit 2)**: 2 weeks (participants will be screened and have to be randomized within 2 weeks of screening. If all information is available, a participant can be randomized on the day of screening (visits 1 and 2 are combined).
- **Treatment period (from visit 2 through visit 6 [EOT] or visit 6a [ET])**: 12 weeks
- **Safety follow-up (visit 7 [SFU])**: 14 days (+ 7 days) after EOT or ET.

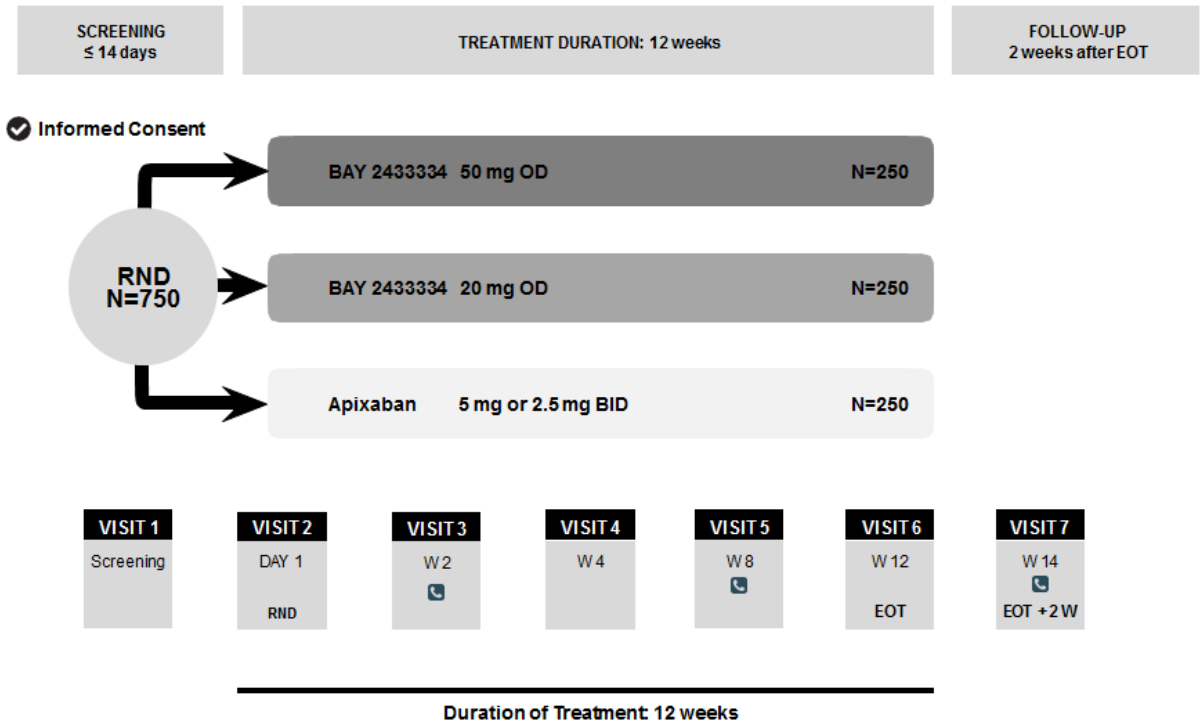
Study visits will take place as visits at the study sites and telephone calls. Visits at the study sites take place at screening and randomization (visit 1 and visit 2), at week 4 (visit 4) and week 12 (i.e. EOT, visit 6).

Telephone calls will take place at week 2 (visit 3), week 8 (visit 5), as well as 2 weeks after the EOT visit for participants who will take study intervention until the planned EOT (i.e. SFU, visit 7).

For participants who prematurely discontinue from study intervention, an early termination (ET) visit (visit 6a) will take place as soon as possible as visit at the study sites. Telephone calls take place 14 days after the ET visit (i.e. SFU, visit 7).

The study design is presented in Figure 3-1: Study design overview.

Figure 3-1: Study design overview



Note: Participants receiving BAY 2433334 will also receive the apixaban matching placebo.
Participants receiving apixaban will also receive the BAY 2433334 matching placebo.
During the safety follow-up, further therapy (e.g. NOAC) is at discretion of the investigator.

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 treatment arm.

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 members of the CEC who will review events in a blinded fashion and will adjudicate and classify the following events in a consistent and unbiased manner according to definitions contained in the CEC charter:

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

- Stroke (ischemic, hemorrhagic, undetermined)
- Systemic embolism

In addition, events that might be indicative of a potential outcome event will be reported as outcome events to ensure that no outcome event is missed. This includes for example TIA and hospitalization for cardiac chest pain 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 some 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 patients to comply with all study procedures and to continue to be followed until the end of the study.

A subject who discontinues study participation prematurely for any reason is defined as a "dropout" if the subject is randomized to study treatment. A subject 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 subject'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 is unable to be contacted by the study site. A participant may withdrawal 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 subjects who prematurely discontinue the study during the treatment phase 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 subjects who are considered lost to follow-up during the treatment phase 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 drug 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: 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 drug intake with no timepoint it will be assumed that they happen after the first intake of study drug, i.e. the time of study drug intake will be used for the time of the outcome.

4.4 Interim Analyses and Data Monitoring

An independent Data Monitoring Committee 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 are planned, and the statistical analysis will be done by an independent statistical analysis center. A separate SAP will be prepared for this.

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 drug. If these values are not available, values taken before first administration of study drug will be considered (e.g., values taken on Visit 1). In case of more than one available value before first administration of study drug, the non-missing 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 drug up until 2 days after the last intake of study treatment will be counted. The time to event for participants with no event until 2 days after the last intake of study drug (end of data scope) will be censored at that day.
For events at the day of randomization will be counted if the time of occurrence is later than the time of first study drug 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 intention-to-treat (ITT) data scope all events from randomization up until end of treatment visit (Visit 6) (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 drug to an event is of interest. The time to an event (in days) will be derived the following:

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

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 treatment arm. (Cause specific) hazard ratios (csHR) will be calculated only if in addition at least 1 event in each of the compared treatment arm occur.

If treatment arms are pooled the number of events needed applies on the pooled arm not on each treatment 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 visit 6:
  - the date of the death.
- In case the participant dies after the end of treatment visit (visit 6) but before the safety follow-up (visit 7)
  - the censoring date according to the "treatment policy" strategy is the date of visit 6
  - the censoring date according to the "while on treatment" strategy is the earliest of 2 days after last study drug 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 CV-death): 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 $\geq$ 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 bleeding if it is considered any sign or symptom of hemorrhage, but 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 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. 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 mininal TIMI Bleeding event if

1. it is an overt bleeding and
2. does not meet criteria for major or minor TIMI Bleedign 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.

In addition to TIMI significant bleeding also TIMI major bleeding and TIMI minor bleeding will be analyzed, i.e. adding bleeding events that fulfill all criteria of the respective bleeding but that are related to a CABG procedure.

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 be counted as BARC bleeding Type 2 if it

1. has any overt, actionable sign of hemorrhage 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 it

1. 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 it

1. 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 subdivide 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 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.

5. Analysis Sets

5.1 Assignment of analysis sets

Final decisions regarding the assignment of subjects 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 subject will be included in the FAS if he/she is randomized to a treatment group.

Safety analysis set (SAF)

A subject will be included in the SAF if he/she is randomized to a treatment group and has taken at least one unit of the study medication.

Pharmacokinetic Analysis Set

A subject will be included in the pharmacokinetic analysis set, if it has received active treatment, has at least 1 valid plasma concentration of BAY 2433334 and is without protocol deviation, which would interfere with the evaluation of the PK data.

Pharmacodynamic Analysis Set

A subject will be included in the pharmacodynamic analysis set, 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 all analyses will be the SAF. Tables will be shown by treatment arm and overall. No adjustment for multiplicity will be performed.

6.1 Population characteristics

6.1.1 Disposition

The following will be tabulated by treatment 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 medication
- Number of participants and primary reasons for premature discontinuation of study follow up.

Incidences for permanent discontinuation of the double-blinded study drug and of the follow-up period will be provided by randomized study treatment 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 treatment,
- time to the date of last follow-up contact,

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

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

6.1.3 Demography and baseline characteristics

Demographic and baseline data as collected in the CRF will be evaluated descriptively for the SAF as well for the FAS, by treatment groups and overall. No statistical tests will be performed to compare these characteristics across treatment 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 years, 65 – 75 years, > 75 years)
- BMI: < 25; ≥ 25 to < 30; ≥ 30kg/m^2
- Weight: <60; 60-90; >90 kg
- eGFR: <50; 50-80; >80 mL/min
- AF pattern: Paroxysmal, Persistent, Long-standing persistent, Permanent
- For patients currently treated with a NOAC the following subgroups will be defined
    - History of a prior bleed within the last 12 months requiring medical attention (yes/no)
    - Moderate renal dysfunction with eGFR 30-50 ml/min (yes/no)
    - Current clinically indicated antiplatelet therapy with ASA ≤ 100 mg (yes/no)
- Stroke or TIA prior to enrollment (yes/no)
- Time from AF diagnosis to randomization: ≤30 days; 30 days to 3 months; > 3months
- Chronic Kidney Disease (yes/no)
- Coronary Artery Disease (yes/no)
- Hypertension (yes/no)
- Diabetes (yes/no)
- Tobacco use: Never; Former; Current

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 signing of the informed consent and that are considered relevant for the participant's study eligibility using MedDRA Primary System Organ Class / Preferred Term. Number and percentages of subjects with AF pattern will be shown separately.

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 drug, regardless of when they ended,

- concomitant medication, i.e. medications taken within the treatment period
- ongoing concomitant medication at start of study drug,
- medication started during the treatment period, and
- medication started after stop of study medication.

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

Separate tables will be provided for anticoagulants, 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:

- Prior use of NOAC (yes/no)
- Risk factors for apixaban dosage (0-1, 2-3)

6.2 Efficacy

Efficacy analyses in this study will be exploratory only.

Exploratory endpoints for this study are:

- the composite as well as individual components of CV death, MI, ischemic stroke, and systemic embolism,
- all-cause mortality.

Events will be counted in the intention-to-treat data scope for the full analysis set.

The number of participants with an efficacy endpoint and percentages will be shown by treatment arm.

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 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 (KM) survival function, i.e. the Aalen-Johansen estimator for time t is defined as:

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

Gray's (Gray 1988) test for equivalence of the cumulative incidence functions, stratified by prior usage of NOAC, will be performed. To derive the Aalen-Johansen estimators and the test statistics with the corresponding confidence intervals, SAS program code corresponding to the following will be used:

```
PROC LIFETEST DATA = <dataset> ALPHA=0.1 ERROR=AALEN;
  STRATA stratumn / GROUP=trtgrpn;
  TIME ttevalue * status(0)/eventcode=1;
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
           (0 = apixaban control group, 1 = BAY2433334 treatment
ttevalue = time to first occurrence of outcome event or competing event
status   = status of the participant at event time (0 = right-censored,
           1 = event of interest, 2 = competing event)
stratumn = variable for NOAC stratification factor (two levels)
*/
```

Cause-specific HRs will be calculated for the respective event and the competing event. The cause-specific hazard ratios and the corresponding confidence intervals will be estimated on separate cause-specific hazard models for the comparison of the pooled doses of BAY 2433334 versus apixaban and for each treatment dose of BAY 2433334 versus apixaban (if applicable). No comparison of the different doses of BAY 2433334 is planned.

To derive the cause specific hazard ratios and the corresponding confidence intervals, SAS program code corresponding to the following will be used:

```
PROC PHREG DATA = <dataset>;
  MODEL ttevalue*status(0)=trtgrpn / RL ALPHA=0.1 EVENTCODE=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 = right-censored,
           1 = event of interest, 2 = competing event)
stratumn = variable for stratification factor (two levels)
*/
```

6.3 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.

6.3.1 Pharmacokinetics

BAY 2433334 and BAY 2826102 concentrations will be summarized per sampling interval and visit, separated according to actual dose.

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 (CV), geometric mean, geometric standard deviation (re-transformed standard deviation of the logarithms), and CV, 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 were measured and were above the lower limit of quantification (LLOQ). For the calculation of the mean value a data point below LLOQ will be substituted by ½ LLOQ.

Plots will be prepared by naïve pooling all individual plasma concentrations (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. Samples which are collected outside of the predefined windows will nevertheless be valid for PK analysis.

6.3.2 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.

6.4 Safety

6.4.1 Primary Safety

6.4.1.1 Primary Safety Estimand

The primary safety estimand is the ratio of the proportions of the composite of ISTH major and clinically relevant non-major bleeding within 3 months comparing pooled doses of BAY 2433334 and comparator drug apixaban in adult participants with AF who have taken at least one dose of study medication of BAY 2433334 or comparator drug apixaban, while the participant is alive and exposed to study intervention.

6.4.1.2 Primary Safety Analyses

The primary estimator is the ratio of incidence proportions of the primary safety endpoint observed in participants who are under treatment with BAY 2433334 (all doses pooled) and the active comparator for up to 12 weeks with corresponding 90% confidence interval.

The (crude) incidence proportion of the primary safety endpoint is defined as the number participants with an event in 12 weeks while the participant is under exposure of study drug (counting treatment according to the treatment emergent data scope) divided by the number of participants in the treatment arm who took at least one dose of study drug, (the SAF population) i.e.

$$\widehat{CI}_A = \frac{\#Participants\ with\ an\ event}{\#Participants\ that\ took\ at\ least\ one\ dose\ of\ study\ drug\ A}.$$

These incidences proportions will be estimated for BAY 2433334 arm (all doses pooled) and the apixaban arm. The main estimator for this study is the ratio of the (crude) incidence proportions

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

The corresponding 90% two-sided confidence interval 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 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 = apixaban control group, 1 = BAY2433334 treatment
status   = status of the participant at event time (0 = right-censored,
           1 = event of interest)
*/
```

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)

In addition to the main analysis, 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 events for the primary safety endpoint are Death (all causes) and premature discontinuation.

The cumulative incidence risk, 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 in section 6.2.

The difference of the Aalen-Johansen estimators at day 85 (week 12) between BAY 2433334 treatment and Apixaban will be presented with a 90% confidence interval.

As the Aalen-Johansen estimator is approximately normal distributed (Aalen, Borgan and Gjessing 2008), the difference of Aalen-Johansen estimators is approximately normal distributed. Thus, the two-sided 90% confidence interval is obtained via:

$$\left[\left(\widehat{AJ}^{BAY}(85) - \widehat{AJ}^{Apixaban}(85)\right) \pm z_{0.95}\sqrt{\sigma^2\left(\widehat{AJ}^{BAY}(85)\right) + \sigma^2\left(\widehat{AJ}^{BAY}(85)\right)}\right],$$

with $\widehat{AJ}^{TRT}(85)$ the Aalen-Johansen estimator for treatment TRT at day 85, $z_{0.95}$ the 95% quantile of the standard normal distribution and $\sigma^2(\widehat{AJ}^{TRT}(85))$ the estimated variance of the Aalen-Johansen estimator at day 85, estimated with the Aalen method.

All analyses will be done for the pooled doses of BAY 2433334 and for each of the two doses.

csHRs will be calculated for the respective event and the competing event. Gray's test of equivalence of the cumulative incidence functions, stratified by prior usage of NOAC, will be performed. The cause specific hazard ratios and the corresponding confidence intervals will be estimated on separate models for the pooled doses of BAY 2433334 and each comparison (if applicable). No comparison of the different doses of BAY 2433334 is planned.

6.4.1.3 Secondary Safety Analyses

The secondary safety estimands are the ratios of the proportions of participants experiencing the individual endpoints within 3 months, comparing pooled doses of BAY 2433334 and comparator drug apixaban in adult participants with AF who have taken at least one dose of study intervention (BAY 2433334 or apixaban, the comparator drug), while the participant is alive and exposed to study intervention for each of the endpoints:

- all bleeding
- ISTH major bleeding
- ISTH clinically relevant non-major bleeding
- ISTH minor bleeding.

The main analyses will follow the main estimation for the primary safety endpoint. In treatment arms with 3 or more events, in addition exposure-adjusted incidence rates and Aalen-Johansen estimators will be presented.

6.4.1.4 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
- BARC bleeding definition type 1, 2, 3, 5, and.
- BARC bleeding definition type 1.

For these endpoints the analyses follow the the estimations for the other bleeding. 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.

6.4.2 Subgroup analyses

For the primary endpoint and the endpoint all bleeding, subgroups analyses will be done for the following subgroups:

- Treated with NOAC at randomization (yes/no)
- Atrial fibrillation paroxysmal, persistent/permanent
- Weight (<60; 60-90; >90 kg)
- Age Group (< 65 years, 65 – 75 years, > 75 years)
- eGFR: <50; 50-80; >80 mL/min
- Risk factors for apixaban dosage (0-1, 2-3)
- Sex
- Race: White, Black, Asian, other
- Region: North America; Western Europe; Eastern Europe; Asia (Japan)
- Stroke or TIA prior to enrollment (yes/no)
- Treated with mild and moderate CYP3A4 inhibitors + inducers at randomization (yes/no)
- CHA2DS2VASc-Score (2&3 vs. > 3 for male participants, 3&4 vs. >4 for female participants)

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.

Comparison between treatment arms is only planned for the following subgroups:

- Treated with NOAC at randomization (yes/no)
- Stroke or TIA prior to enrollment (yes/no)
- Atrial fibrillation paroxysmal, persistent/permanent
- Risk factors for apixaban dosage (0-1, 2-3)

6.4.3 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 drug up until 2 days after the last intake of study treatment will be counted.

Subgroup analyses for incidence tables will include the subgroup "Participants that are effected to any site closing due to COVID-19" will include all subjects that are randomized at sites that are closed due to COVID-19 before their individual end of treatment visit, resp. last study contact date, whatever is earlier. If there are more than one phase of closing in a site no distinction between the phases will be done.

Demographics, Medical history as well of the tables showing the number of participants with an efficacy or safety event will be additionally shown for this subgroup.

Protocotol 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 repective adverse event tables

If the number of patients 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 patients 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.

6.4.4 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 as well as during Final visit (Visit 6) and Early termination visit (Visit 6a) will be displayed by means of descriptive statistics and change from baseline.

6.4.5 Laboratory parameter

Only centrally analyzed blood samples will be considered for analysis.

Central laboratory parameters (e.g. AST, ALT, eGFR) obtained at Visit 1 (Screening), Visit 2 (Randomization (if not on the same day as Visit 1)), Visit 4 as well as during Final visit (Visit 6) and Early termination visit (Visit 6a) 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.

6.4.6 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 at the final Visit or Early Termination visit prior to the dose of open-label anticoagulant.

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

6.4.7 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)) as well as during Final visit (Visit 6) and Early termination visit (Visit 6a). QRS, QT and QTc intervals will be displayed by means of descriptive statistics and change from baseline.

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

6.4.8 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 treatment arm. A total column will be included in all safety summaries.

Frequency tables, showing an overall summary of number of participants with AEs, study drug 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 drug,
- treatment emergent AE.

AEs will be considered treatment-emergent if they begin after the first administration of study drug and they do not start after more than 2 days after the last administration. Determination of whether or not 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.

6.4.9 Pregnancies

Any reported pregnancy occurring in female participants will be displayed. In addition, any reported pregnancy occurring in female partners of male participants after start of study intervention up until 4 days of the last intake of study drug will be displayed.

7. Document history and changes in the planned statistical analysis

- SAP Version 1.0 completed 10 DEC 2019
- SAP Version 2.0: Changes in categorization of age added SAS code and statement on multiplicity adjustment, clarification of exploratory efficacy variable; add section for COVID-19 related (sensitivity) analyses; update Pharmacokinetics analysis part; changes in subgroups; add TIMI minimal bleeding definition, completed on 14 OCT 2021

8. References

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