Official Title of Study:

An Open-label, 2 x 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban vs. Vitamin K Antagonist and Aspirin vs. Aspirin Placebo in Patients with Atrial Fibrillation and Acute Coronary Syndrome and/or Percutaneous Coronary Intervention

NCT Number: NCT02415400

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STATISTICAL ANALYSIS PLAN

An Open-label, 2 x 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban vs. VKA and Aspirin vs. Aspirin Placebo in Patients with Atrial Fibrillation and Acute Coronary Syndrome and/or Percutaneous Coronary Intervention

PROTOCOL(S) CV185316

VERSION # 2.0

NEW or MODIFIED **STATISTICAL ANALYSIS PLAN** APPROVAL PAGE

Study Specific SAP

An Open-label, 2 x 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban vs. VKA and Aspirin vs. Aspirin Placebo in Patients with Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention

CV185316

Prepared by [redacted]

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[redacted]

2 STUDY DESCRIPTION

Patient who meets inclusion / exclusion criteria will be randomized via IVRS using a 2 x 2 factorial design to either apixaban or VKA and to either aspirin or aspirin placebo. Randomization will be stratified by indication at enrollment (ACS vs. PCI). The factorial design will compare open label apixaban to open label VKA and compare blinded low-dose aspirin to aspirin placebo, with background P2Y12 inhibitor.

2.1 Study Design

Patients with a recent ACS and/or undergoing PCI with either active or a history of NVAF and planned treatment with P2Y12 agent and oral anticoagulation will be evaluated for eligibility during their ACS or post-PCI hospitalization. Randomization can be performed up to 14 days after the ACS or PCI and should take place as early as possible after cessation of parenteral anticoagulant and when clinically stable. Both patients with and without prior VKA treatment can be included in this trial. Patients who are on a VKA prior to randomization will have VKA discontinued and will not be dosed with apixaban for 4 days or until the INR is less than 2.0. At the time of enrollment, each patient who meets inclusion / exclusion criteria will be randomized via IVRS using a 2 x 2 factorial design to either apixaban or VKA and to either aspirin or placebo. Randomization will be stratified by indication at enrollment (ACS vs. PCI). Overall, the trial will is planned to enroll at least 1/3 of patients with a recent ACS.

Approximately 500 sites will participate in this study, which will be conducted globally including participation of countries located in North America, Europe, Asia and Latin America.

The treatment period for all agents, including P2Y12 inhibitor, will be 6 months. Study visits will be at 1, 3 and 6 months (end of treatment) and 30 days post treatment. Phone visits will occur at

months 2, 4 and 5. INR monitoring will take place in accordance with routine care at the respective center but the level of INR control will be collected and centrally monitored. To assure study drug compliance and maintain INR in target range, at least monthly contact will be scheduled in both the apixaban and VKA arms.

2.2 Treatment Assignment

At the time of enrollment, each subject will be assigned a unique sequential subject number by IVRS. The IVRS will be available 24 hours per day, seven days a week. The subject number will consist of a unique 5 digit number which is assigned sequentially within a study (starting with 00001) by the IVRS. This number will be used for identification throughout the study and will not be used for any other subject.

Each subject who meets the inclusion/exclusion criteria will be randomly assigned to one of the two open label treatment groups: apixaban or VKA, with each treatment arm having an allocation probability of a half (0.50). At the same time, subjects will be randomly assigned in a blinded fashion to aspirin or matching placebo.

The randomization will be stratified by indication at enrollment (PCI/ACS).

2.3 Blinding and Unblinding

Apixaban or VKA will be open-label.

Aspirin (or matching placebo) will be blinded. Requests for emergency unblinding for patient, only, should be made by the investigator(s) to the designated regional medical monitor or, if that person cannot be contacted, to the global medical monitor.

2.4 Protocol Amendments

Document	Date of Issue	Summary of Change
Revised Protocol 04	21-Aug-2018	Incorporates Amendment 07 and Administrative Letters 03 and 04.
Amendment 07	21-Aug-2018	Amendment 07 - (1) Describes the use of hierarchical statistical testing to analyze the data for apixaban vs VKA and aspirin vs aspirin placebo; (2) Notes the change in the Medical Monitor and his contact information.
Administrative Letter 04	26-Mar-2018	Change in Medical Monitor Contact information
Administrative Letter 03	21-Nov-2017	Date corrected on title page of protocol
Revised Protocol 03	11-Oct-2017	Incorporates Amendment 05 and Administrative Letter 02
Amendment 05	11-Oct-2017	The purpose of Amendment 05 is to reword inconsistent language in the current protocol to clarify the patient eligibility criteria, add an efficacy composite endpoint of all-cause death/all-cause re-hospitalization and to correct typographical errors. In addition, Amendment 05 lists some of the data not specified in the protocol but included in the electronic case report form; this data is planned for potential secondary publications.
Administrative Letter 02	04-May-2017	Medical Monitor Address Change
Revised Protocol 02	28-Apr-2016	Incorporates Amendment 02

Document	Date of Issue	Summary of Change
Amendment 02	28-Apr-2016	The purpose of amendment 02 is to clarify the hypothesis, objectives and patient population in regard to patients who have non-valvular atrial fibrillation and acute coronary syndrome and/or PCI by adding the word "and" in front of "PCI" throughout the protocol, editing the study schematic, as well as to add clarifying language to the targeted SAE reporting section. Table 4-1 was updated to include BMS study medication that will be supplied in some countries where local sourcing is not an option. In addition sections 4.3, 4.8, 4.9, and 9.2.2 were updated based on the mandatory language in the revised protocol model document.
Revised Protocol 01	05-Apr-2016	Incorporates Amendment 01 and Administrative Letter 01
Amendment 01	05-Apr-2016	The purpose of this amendment is to clarify language for the targeted SAE reporting, add language referencing stopping guidance in the DMC charter, and correct omissions from the original protocol. In the inclusion section, wording was changed to accommodate countries where age of adulthood is not 18 years of age. [redacted] Study was originally meant to allow patients who had balloon angioplasty, either with or without a stent being placed. Removing the word "with a stent" allows balloon angioplasty without stent. Additional language on unstable angina entry also added for clarification of the population. In addition, other revisions and/or clarifications are listed below within the synopsis and the protocol body. 1. Addition of word "and" after ACS in multiple places to clarify the population. 2. Replaced word antiplatelet with anticoagulant in hypothesis 3. In study figure 3.1.1 clarified exclusion box for CABG 4. Corrected exclusion criteria typo for serum creatinine from 133 micromol/L to 221 micromol/L 5. Deleted duplicate text for WOCBP who are breastfeeding. 6. Deleted Aspirin Placebo from Adverse drug reactions. 7. Added additional subcriteria under "other criteria". 8. Clarified Prohibited/restricted treatments paragraph 9. Corrected greater than and less than signs 10. Asterisk added for Visits 1-3 in Short Term Procedure Outline 11. Clarified SAE reporting 12. Added paragraph to DMC 13. Clarified wording for Drug Study Records. 14. Added 2 abbreviation to terms table 15. Corrected any typographical errors.

2.5 Data Monitoring Committee

This study will be conducted under the monitoring of an independent Data Monitoring Committee (DMC), whose activities will be described in a DMC charter.

3 OBJECTIVES

3.1 Primary

Dual Primary Objectives:

- To determine if apixaban is noninferior to VKA (INR target range 2.0 - 3.0) on the combined endpoint of ISTH major bleeding and clinically relevant non-major bleeding in patients with NVAF who develop ACS or undergo PCI with concomitant P2Y12 inhibitor therapy
- To determine if anticoagulant plus single antiplatelet therapy with a P2Y12 inhibitor is superior to anticoagulant plus dual antiplatelet therapy with a P2Y12 inhibitor and aspirin on the combined outcome of ISTH major bleeding or clinically relevant non-major bleeding in patients with NVAF who develop ACS or undergo PCI with planned concomitant P2Y12 inhibitor therapy.

3.2 Secondary

To compare apixaban and VKA (with concomitant P2Y12 inhibitor therapy), in patients with NVAF who develop ACS and/or undergo PCI, with respect to:

- Superiority on ISTH major or CRNM bleeding
- Superiority for the composite of all-cause death and all-cause re-hospitalization
- Death, stroke, myocardial infarction, stent thrombosis, urgent coronary revascularization

To compare aspirin and aspirin placebo (with concomitant P2Y12 inhibitor therapy), in patients with NVAF who develop ACS and/or undergo PCI, with respect to:

- The composite of all-cause death and all-cause re-hospitalization
- Death, stroke, myocardial infarction, stent thrombosis, urgent coronary revascularization

[redacted]

To compare aspirin and aspirin placebo (with concomitant P2Y12 inhibitor therapy), in patients with NVAF who develop ACS or undergo PCI, with respect to:

[redacted]

4 ENDPOINTS

4.1 Primary Endpoints

The dual primary endpoints are:
The primary endpoint for apixaban versus VKA is time from the first dose to first occurrence of confirmed ISTH major and CRNM bleeding (NI analysis)

The primary endpoint for aspirin versus placebo is the time from first dose to first occurrence of confirmed ISTH major and CRNM bleeding

4.2 Secondary Endpoint(s)

The secondary endpoint for apixaban versus VKA includes

- the time from first dose to first occurrence of confirmed ISTH major or CRNM bleeding (Superiority analysis)
- the time from first dose to first occurrence of the composite of all-cause death and all-case re-hospitalization
- the time from randomization to first occurrence of confirmed composite endpoints of death and ischemic events (stroke, myocardial infarction, stent thrombosis, urgent revascularization)

The secondary endpoint for aspirin versus placebo includes

- the time from first dose to first occurrence of the composite of all-cause death and all-case re-hospitalization
- the time from randomization to first occurrence of confirmed composite endpoints of death and ischemic events (stroke, myocardial infarction, stent thrombosis, urgent revascularization)

[redacted]

5 SAMPLE SIZE AND POWER

A total of 357 primary endpoint events and 4600 subjects will provide 77% power for test of NI using a stratified log rank test of apixaban versus VKA, assuming a NI margin of 1.2, with major or CRNM bleeding event rates in apixaban and VKA groups of 8.1% per half year and 9% per half year, respectively, one-sided significance level of 0.025, six month follow up, and a 1% per year of loss to follow up. The NI margin was selected because an absolute risk difference of greater than 1.8% (20% of VKA event rate of 9%) in bleeding is considered to be a clinically meaningful difference.

This sample size will also provide at least 77.5% power for superiority test of apixaban versus VKA assuming a risk reduction of 25% and a two-sided significant level of 0.05.

A blinded assessment of primary endpoint event rate will be performed after 50% of subjects have completed the study. The analyses will focus on the aggregate event rate and the sample size may

be increased if the aggregate event rate is lower than anticipated. The blinded event rates will be estimated by an independent statistician not associated with BMS and not otherwise associated with apixaban, and will be provided to the Executive Committee. Sample size may be adjusted (depending on availability of resources) to provide sufficient power for both non-inferiority and superiority test on the primary endpoint and secondary endpoint. Up to a maximum of 8842 subjects may be randomized to maintain appropriate power for both non-inferiority and superiority test on the primary endpoint and secondary endpoint using the pre- specified rule below. Table 8.1-1 give a guideline for sample size adjustment.

Table 8.1-1: Sample Size Adjustment for Non-inferiority and Superiority Test on the Primary

Observed blinded Event Rate When 50% Patients Complete Tx/half year	Assumed Apixaban Event Rate/half year	Assumed Control Event Rate/half year	# of events	Total Sample Size 80% Power for both NI and superiority
7.6%	0.072	0.08	379	5514
6.65%	0.063	0.07	379	6308
5.7%	0.054	0.06	379	7360
4.75%	0.045	0.05	379	8842

Assume time to event follow exponential distribution, 6 months fix follow up, 25% risk reduction for superiority test, and 10 % risk reduction for NI test. Nquery 2.0 and EAST 5.4 are used for the sample size calculation and power calculation of NI and superiority.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

In all listings, summaries and statistical analyses, the term "**Intended Treatment Period**" will refer to the period from the day of randomization through the day of end of 6-month treatment visit for the subjects who complete 6-month treatment. For subjects who discontinue treatment early:

1. if they complete the 6-month visit, the "**Intended Treatment Period**" will be from day of randomization to the day of the 6-month visit
2. if the subjects do not have the 6-month visit, the "**Intended Treatment Period**" will be from the day of randomization to the earlier of the end date of follow up or intended 6-month treatment for subjects.

This period will be the basis for the summaries of efficacy.

In all listings, summaries and statistical analyses, the term "**Treatment Period**" will refer to the period from the first day of study medication through:

- 2 days after the last dose of study drug when summarizing

– bleeding endpoints

- 30 days after the last dose of study drug when summarizing
  - deaths (as an outcome of an SAE)
  - SAEs
- 2 days (for non-serious AEs) or 30 days (for SAEs) after the last dose of study drug when summarizing
  - overall AEs
  - AEs leading to study drug discontinuation

First dose and last dose of study medication will be defined based on oral anticoagulant and antiplatelet separately. This period will be the basis for the summaries of safety.

In all listings and summaries, the term "**Follow-up Period**" will refer to the period starting the day of the end of treatment visit to the Follow-up visit or phone call which is 30 ± 7 days.

6.2 Treatment Regimens

The Randomized Subjects Data Set will consist of all randomized subjects. In this data set, subjects are categorized to the group to which they were assigned by the IVRS (oral anticoagulant or antiplatelet separately), regardless of the treatment actually received. Efficacy endpoints will be summarized according to the **As Randomized** group.

The Treated Subjects Data Set will consist of all subjects who receive at least one dose of study drug and are categorized to the group to which they are assigned by the IVRS (oral anticoagulant or antiplatelet separately) unless the same incorrect treatment is received throughout the study, in which case the treatment group will be equal to the treatment received. Safety endpoints will be summarized according to the **As Treated** group.

6.3 Populations for Analyses

The following population will be used for the analyses.

Enrolled Population

The Enrolled Subjects population consists of all subjects who signed informed consent.

Randomized Population for analysis can be defined as:

Randomized Population for oral anticoagulant: consists of all randomized subjects who are randomized to oral anticoagulant study drug.

Randomized Population for antiplatelet: consists of all randomized subjects who are randomized to antiplatelet study drug.

In these populations, subjects are categorized according to the **As Randomized** group. The intention-to-treat population of all randomized subjects will be used to analyze all efficacy endpoints.

Treated Population for analysis can be defined as:

Treated Population for oral anticoagulant: is a subset of the Enrolled Population consisting of all subjects who were randomized and received at least one dose of oral anticoagulant study drug.

Treated Population for antiplatelet: is a subset of the Enrolled Population consisting of all subjects who were randomized and received at least one dose of antiplatelet study drug.

When summarizing data using these populations, subjects are categorized to the **As Treated** group.

Evaluable Populations:

is a subset of the *Treated Population for oral anticoagulant* excluding subjects with protocol deviations expected to affect the primary safety endpoint (see Section 7.2). In the case of treatment assignment error, the data collected up to the start of incorrect treatment will be included.

7 STATISTICAL ANALYSES

7.1 General Methods

All analyses will be performed in SAS® using version 9.2 or higher. Unless otherwise stated, all hypothesis tests will be performed using two-sided tests at the 5% significance level.

Continuous variables will be summarized using descriptive statistics including means, standard deviations, minima, maxima and quartiles, and qualitative or discrete variables will be summarized using absolute and relative frequencies.

Time to Event Analyses

Unless specified, calculation of p-values and construction of point estimates and CIs for HR will be based on Cox proportional hazard models. Stratification variables will be included in the model as stratification factors. Additional covariates may be included as described in Sections 7.5 and 7.6. Ties will be handled using Breslow's methodology.

Event rates will be estimated and plotted over time using Kaplan-Meier methodology.

Testing Strategy

A hierarchical testing strategy described below will be used to compare the effects of apixaban and VKA between treatment groups.

- Non-inferiority (NI) for the primary endpoint, a composite of ISTH major and CRNM bleeding, will be tested first.
- If NI is not demonstrated, then nominal p-values will be presented for subsequent comparisons between apixaban and VKA
- If NI is demonstrated, then superiority for the composite of ISTH major and CRNM bleeding will be tested. If superiority is not demonstrated, then nominal P-values will be presented for subsequent comparisons between apixaban and VKA.
- If superiority for the composite of ISTH major and CRNM bleeding is demonstrated, then superiority for the composite of all-cause death and all-cause re-hospitalization will be tested. If superiority is not demonstrated, then nominal p-values will be presented for subsequent comparisons between apixaban and VKA.

- If superiority for the composite of all-cause death and all-cause re-hospitalization is demonstrated, then the composite of all-cause death and ischemic events will be tested.

All tests will be performed at the two-sided $\alpha = 0.05$ significance level.

7.2 Study Conduct

Relevant protocol deviations will be identified for all subjects who are randomized. Relevant Protocol Deviation Criteria expected to affect the primary safety endpoint are as follows:

- Subject randomized but not dosed
- Error in treatment assignment resulting in a subject being dosed with an incorrect treatment. This deviation will include only subjects who received apixaban (any dose) but were assigned by the IVRS to receive VKA or subjects who received VKA but were assigned by the IVRS to receive apixaban (either dose).

7.3 Study Population

All summary tables will be presented by Apixaban /VKA, aspirin/placebo separately if applicable, and combination of treatment groups (apixaban/aspirin, apixaban/aspirin placebo, VKA /aspirin, VKA /aspirin placebo).

The number of subjects enrolled into the study, and the number of subjects enrolled but not randomized together with the reasons for not being randomized will be summarized. The reasons for not being randomized will be taken from the CRF pre-randomization status page.

The summaries described below will also be presented by indication at enrollment (PCI/ACS).

The number of randomized subjects and the number of subjects discontinuing during intented treatment period together with the reasons for discontinuation will be summarized by treatment group. The reasons for discontinuation will be taken from the end-of-treatment visit page of CRF. The frequency of subjects enrolled in each country and in each site will be tabulated by randomized treatment group and for all randomized subjects combined.

The summary of VKA categories by warfarin and non-warfarin will be presented as well. The non-warfarin VKAs will be broken down by subcategories.

7.3.1.1 Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized by randomized treatment group, using the Randomized Population for oral anticoagulant and Randomized Population for antiplatelet. All summaries will be further tabulated by indication at enrollment (PCI/ACS). Continuous variables will be summarized using means, standard deviations, minima, maxima and quartiles, and categorical variables will be summarized using absolute and relative frequencies.

The following demographic and baseline characteristics will be summarized

- Indication at enrollment (where applicable)

- Apixaban dose at randomization
- Geographic region
- Age
- Age group (< 65, 65-<80, ≥80 years)
- Gender
- Race
- Ethnicity (for US only)
- Weight
- Weight group (≤ 60, > 60 kg)
- Serum Creatinine
- CHADS2 Score
- CHADSVASC2 score
- HASBLED score
- Hypertension
- Heart failure
- Diabetes Mellitus
- P2Y12 Concomitant medication
- Prior warfarin/ VKA status
- Prior use of Antiplatelet (where applicable)
- Prior Oral anticoagulant (where applicable)

7.4 Extent of Exposure

7.4.1 Study Therapy

The summaries described below will be tabulated for the Treated Populations. All summaries will be tabulated by treatment group and by indication at enrollment (PCI/ACS).

Length of exposure to study drug is defined as the number of days the subject is known to be on study drug. The distribution of the length of exposure to study drug will be presented by treatment group; this distribution will be presented by taking into account days without dosing. The distribution categories will be <30 days, 30 to <60 days, 60 to <90 days, 90 to <120 days, 120 to <150 days, 150 to <180 days, ≥ 180 days.

The length of exposure to study drug will also be summarized by treatment group using means, standard deviations, medians, minima and maxima. The total patient-days of exposure to study drug (say, T) will be presented for each treatment group and is defined as:

$$\sum_{i=1}^{N_T} \text{Length of exposure (days) for subject } i,$$

where N_T represents the number of subjects receiving treatment T.

Treatment compliance (TC) will be summarized for apixaban and aspirin/placebo. The TC will be calculated using the following formula (assuming that either on the first day or the last day subjects only receives one dose of apixaban):

$$TC = \frac{\text{number of tablets taken}}{(\text{Number of days from first to last dose of study drug} - 1) \times n + 1} \cdot 100\%$$

Where n=1 for aspirin/placebo (QD), and n=2 for apixaban.

The frequency of subjects with at least 80% compliance with apixaban and aspirin/placebo will also be summarized.

7.4.2 INR Control

The summaries described below will be tabulated for the Randomized Population for oral anticoagulant.

For subjects who receive VKA, INR control is a more appropriate measure of compliance than pill count. The assessment of INR control will be based on all available INR values.

INR values will be summarized by visit (see Sections 8.3). These summaries will also be graphically displayed using a box plot.

The proportion of time (counted from first INR value recorded on or after dosing on Day 10 until the day of discontinuation of study drug without considering interruptions) in which subjects have an INR in the following ranges will be summarized:

- INR < 2.0, 2.0 ≤ INR ≤ 3.0, INR > 3.0

The frequency of subjects with INR in the 2.0-3.0 range for ≥ 60%, ≥ 65%, ≥ 70%, ≥ 75%, or ≥ 80% of time will also be summarized.

Only subjects who have received study drug for at least 10 days will be included in these time-related summaries.

The INR control measure, proportion of time in each INR interval, is calculated using Rosendaal's method which assumes that the INR value between two measurements varies linearly from the first value to the second value.

- let INR_i and INR_{i+1} be the two consecutive INR values
- let D_i and D_{i+1} be the dates associated with these two consecutive INR values, $[(D_{i+1} - D_i)=k, k>1]$
- assuming the linear increase or decrease between the two consecutive INR measurements, the unit change per day in INR is $m=(INR_{i+1} - INR_i)/ (D_{i+1} - D_i)$
- the estimated INR value for the date after D_i (D_i+1) will be $INR_i + (m*1)$
- likewise, the estimated INR value for the date (D_i+2) will be $INR_i + (m*2)$, etc.; the estimated INR value on the date immediately prior to D_{i+1} will be $INR_i + (m*(k-1))$.

Using Rosendaal's method[1], each subject will have an INR measurement every day, either actual or by estimation through linear interpolation. The proportion of time subjects have an INR within an interval is the number of days with INR in the interval divided by the total number of days.

7.4.3 Concomitant Medications

The summaries described below will be tabulated for the Treated Populations. All summaries will be tabulated by treatment group and by treatment group and indication at enrollment (PCI/ACS).

The frequency of subjects receiving P2Y12 concomitant medication will be summarized by treatment group and medication class.

The length of exposure to P2Y12 administered concomitantly with study drug will be summarized (using means, standard deviations, medians, minima and maxima) by treatment group. The summaries will be presented by drug name.

7.5 Efficacy

There is no primary efficacy analysis for this study. All analyses described in this section will be performed on the Randomized Populations during Intended Treatment Period, and events will be confirmed by adjudication. The numbers of efficacy events will be summarized by combination of treatment groups (apixaban/aspirin, apixaban/aspirin placebo, VKA /aspirin, VKA /aspirin placebo).

Censoring scheme for time to efficacy event analyses: subjects who do not experience an efficacy endpoint event will be censored at the earlier of the date of end of Intended Treatment Period, death date (when death is not part of the endpoint), or last-contact date (for subjects who withdraw consent to be followed up or are lost to follow-up) at the end of Intended Treatment Period.

7.5.1 The comparison between apixaban and VKA

7.5.1 .1 Secondary Efficacy Endpoints

The secondary efficacy endpoints are time to first occurrence of composite of all-cause death (will use “death” in later sections) and all-cause re-hospitalization and composite death and ischemic events (stroke, myocardial infarction, stent thrombosis, urgent coronary revascularization).

A Cox proportional hazards model including treatment group as a covariate and stratified by indication at enrollment (PCI/ACS) and antiplatelet (aspirin/placebo) will be used for randomized subjects for oral anticoagulant during Intended Treatment Period. A point estimate and two-sided 95% CI for hazard ratio will be calculated. A p-value for the test of equality (HR = 1) will be calculated based on the hierarchical testing strategy.

[redacted]

7.5.2 The comparison between aspirin and placebo

7.5.2 .1 Secondary Efficacy Endpoint

The secondary efficacy endpoints are time to first occurrence of all-cause death and all-cause re-hospitalization and composite death and ischemic events (stroke, myocardial infarction, stent thrombosis, urgent coronary revascularization).

A Cox proportional hazards model including treatment group as a covariate and stratified by indication at enrollment (PCI/ACS) and anticoagulant treatment group (apixaban/VKA) will be used for randomized subjects for antiplatelet during Intended Treatment Period. A point estimate and two-sided 95% CI for hazard ratio will be calculated. A p-value for the test of equality (HR = 1) will be calculated based on the hierarchical testing strategy, similar to the analyses for apixaban vs. VKA.

[redacted]

7.6 Safety

All analyses described in this section will be performed on the Treated Populations during treatment period, and bleeding events will be confirmed by adjudication. The numbers of safety events will be summarized by combination of treatment groups (apixaban/aspirin, apixaban/aspirin placebo, VKA /aspirin, VKA /aspirin placebo).

Censoring scheme for time to event analyses of safety endpoints: subjects who do not experience a safety endpoint event will be censored at the earlier of 2 days after discontinuation of study drug, death date, or last-contact date (for subjects who withdraw consent to be followed up or are lost to follow-up) at the end of the treatment period.

7.6.1 The comparison between apixaban and VKA

7.6.1.1 Analysis of Primary Safety Endpoints

NI and Superiority Tests

All analyses described in this section will be performed on the treated subjects for oral anticoagulant during the treatment period using safety censoring scheme (considering study drugs apixaban/VKA).

The primary objective of the study is to determine if apixaban is NI to VKA for the primary safety endpoint (confirmed ISTH major bleeding and CRNM bleeding). Following the sequential testing strategy outlined in Section 7.1, if non-inferiority for the primary safety endpoint is demonstrated at the one-sided 0.025 significance level then superiority of apixaban relative to VKA for the primary safety endpoint will be tested at the one-sided 0.025 significance level.

The analysis of primary safety endpoint will be performed using a Cox proportional hazard model including oral anticoagulant treatment group (apixaban/VKA) as a covariate and stratified by indication at enrollment (PCI/ACS) and antiplatelet (aspirin/placebo). The treatment effect will be

measured by the estimated HR and two-sided 95% CIs for HR. The non-inferiority will be demonstrated if the upper bound of two-sided 95% CIs for HR is less than 1.2.

The proportional hazards assumption will be checked by examining the plots of the log(-log(survival)) versus survival time for each stratum included in the Cox proportional hazards model.

Interaction between oral anticoagulant (apixaban/VKA) and antiplatelet (aspirin/placebo) is not anticipated, but this assumption will be examined within Cox model including stratification variable indication at enrollment (PCI/ACS), and terms of oral anticoagulant treatment group (apixaban/VKA), antiplatelet (aspirin/placebo), and oral anticoagulant (apixaban/VKA) by antiplatelet (aspirin/placebo) interaction. If quantitative interaction is significant (two sided p-value < 0.1), then qualitative interaction will be assessed using Gail and Simon test (1985)[2].

Event rates will be estimated and Kaplan-Meier curves will be plotted for the time from first dose of study medication to first occurrence of ISTH major or CRNM bleeding, by treatment group, by treatment group and indication at enrollment (PCI/ACS), and by treatment group and antiplatelet treatment group.

7.6.1.2 Sensitivity Analyses for Key Measures

To assess the impact of relevant protocol deviations on the NI assessment, the NI test will also be performed on the Evaluable Population during treatment period.

Sensitivity analysis of primary safety endpoint will be performed using randomized subjects for oral anticoagulant during treatment period as well.

7.6.1.3 Subgroup Analyses

All analyses described in this section will be performed on the Treated Population for oral anticoagulant during treatment period using the safety censoring scheme.

Table 7.6.1.3 shows the subgroups of interest for analyses of primary safety assessment. If the value of the grouping variable cannot be determined for a subject, the subject will be excluded from the corresponding subgroup analysis. For each subpopulation analysis, if, in any treatment group, the number of events is ≤ 10 for a subgroup, then the grouping variable will not be included in the test of treatment by subpopulation interaction.

Table 7.6.1.3: Subgroups of Interest for Primary Safety Assessments

Grouping Variable	Subgroups
indication at enrollment	PCI ACS
Apixaban dose*	2.5 mg BID 5 mg BID
Geographic region	North America Latin America Europe

Table 7.6.1.3: Subgroups of Interest for Primary Safety Assessments

Grouping Variable	Subgroups
	Asia/Pacific
Age	< 65 years old ≥65 to < 80 years old ≥ 80 years old
Gender	Male Female
Race	White Black / African American Asian Other
Ethnicity (for US only)	Hispanic/Latino Not Hispanic/Latino
Weight	≤ 60 kg > 60 kg
Serum Creatinine	< 1.5 mg/dL ≥1.5 mg/dL
CHADS2 Score	≤ 1 2 ≥ 3
CHADSVASC2 scores	Low (0[male] or 1 [female]) Moderate (1 [male]) High (≥ 2)
HASBLED score	≤ 1 2 ≥ 3
Diabetes Mellitus	Yes No
Hypertension requiring pharmacological treatment	Yes No
Heart Failure	Yes No
Concomitant med (which P2Y12 agent was the subject on)	Clopidogrel Prasugrel Ticlodipine Ticagrelor
Prior warfarin/VKA status at least 2 months prior to the study	Experienced Naive
Antiplatelet	Aspirin

Table 7.6.1.3: Subgroups of Interest for Primary Safety Assessments

Grouping Variable	Subgroups
	Aspirin placebo

*the control for apixaban 2.5 mg will be subjects in the VKA group who meet criteria of apixaban dose adjustment (see section 1); other VKA subjects will be the control for the subjects taking apixaban 5 mg.

Each of these subgroups will be analyzed using a Cox proportional hazards model stratified by indication at enrollment (not applicable for the first subgroup listed) and antiplatelet (aspirin/placebo) (not applicable for the last subgroup listed) with terms for treatment group. The estimated HR and two-sided 95% CIs will be calculated to assess the treatment effect within each of the subgroups. The p-value for the test of the treatment by grouping variable interaction will be presented based on a Cox proportional hazards model stratified by indication at enrollment (not applicable for the first subgroup listed) and antiplatelet (aspirin/placebo) (not applicable for the last subgroup listed with terms for treatment group,) with terms for treatment group, and the grouping variable and treatment by grouping variable interaction.

7.6.1.4 Secondary Safety Analyses

The secondary safety endpoint will be superiority on time to first occurrence of confirmed ISTH major and CRNM bleeding, and the detailed analysis is as in the previous section.

[redacted]

7.6.2 The comparison between aspirin and placebo

The analyses for the primary and secondary endpoints for aspirin vs aspirin placebo will be similar to the analyses for apixaban vs. VKA. A hierarchical testing strategy at the one-sided $\alpha = 0.025$ significance level will be used for a separate secondary set of comparisons between aspirin and aspirin placebo. All analyses described in this section will be performed on the Treated Population

for antiplatelet therapy during the treatment period using the safety censoring scheme (considering study drugs aspirin/placebo).

7.6.2.1 Primary Safety Analysis

The primary safety endpoint will be time to first occurrence of confirmed ISTH major or CRNM bleeding. A point estimate and two-sided 95% CIs for hazard ratio using a Cox proportional hazards model including antiplatelet (aspirin/placebo) as a covariate, stratified by indication at enrollment (PCI/ACS) and oral anticoagulant treatment group (apixaban/VKA) using the treated subjects for antiplatelet during treatment period. A p-value for the test of equality (HR = 1) will be calculated based on the hierarchical testing strategy.

7.6.2.2 Subgroup Analyses

Table 7.6.2.2 shows the subgroups of interest for analyses of primary safety assessment. If the value of the grouping variable cannot be determined for a subject, the subject will be excluded from the corresponding subgroup analysis. For each subpopulation analysis, if, in any treatment group, the number of events is ≤ 10 for a subgroup, then the grouping variable will not be included in the test of treatment by subpopulation interaction.

Table 7.6.2.2: Subgroups of Interest for Primary Safety Assessments

Grouping Variable	Subgroups
indication at enrollment	PCI ACS
Apixaban dose*	2.5 mg BID 5 mg BID
Geographic region	North America Latin America Europe Asia/Pacific
Age	< 65 years old ≥65 to < 80 years old ≥ 80 years old
Gender	Male Female
Race	White Black / African American Asian Other
Ethnicity (for US only)	Hispanic/Latino Not Hispanic/Latino
Weight	≤ 60 kg > 60 kg

Table 7.6.2.2: Subgroups of Interest for Primary Safety Assessments

Grouping Variable	Subgroups
Serum Creatinine	< 1.5 mg/dL ≥1.5 mg/dL
CHADS2 Score	≤ 1 2 ≥ 3
CHADSVASC2 scores	Low (0[male] or 1 [female]) Moderate (1 [male]) High (≥ 2)
HASBLED score	≤ 1 2 ≥ 3
Diabetes Mellitus	Yes No
Hypertension requiring pharmacological treatment	Yes No
Heart Failure	Yes No
Concomitant med (which P2Y12 agent was the subject on)	Clopidogrel Prasugrel Ticlodipine Ticagrelor
Prior warfarin/VKA status at least 2 months prior to the study	Experienced Naive
Oral anticoagulant	Apixaban VKA

*the control for apixaban 2.5 mg will be subjects in the VKA group who meet criteria of apixaban dose adjustment (see section 1); other VKA subjects will be the control for the subjects taking apixaban 5 mg.

Each of these subgroups will be analyzed using a Cox proportional hazards model stratified by indication at enrollment (not applicable for the first subgroup listed) and oral anticoagulant treatment group (apixaban/VKA) (not applicable for the last subgroup listed) with terms for treatment group. The estimated HR and two-sided 95% CIs will be calculated to assess the treatment effect within each of the subgroups. The p-value for the test of the treatment by grouping variable interaction will be presented based on a Cox proportional hazards model stratified by indication at enrollment (not applicable for the first subgroup listed) and oral anticoagulant treatment group (apixaban/VKA) (not applicable for the last subgroup listed) with terms for treatment group, and the grouping variable and treatment by grouping variable interaction.

7.6.2.3 Secondary Safety Analyses

There is no secondary safety endpoint.

[redacted]

7.6.3.1 Adverse Events

Only NSAE's that occur after the initiation of study drug and that result in permanent treatment discontinuation will be recorded in the eCRF. All AEs that lead to treatment discontinuation are coded and grouped into Preferred Terms (PT) by System Organ Class (SOC), using the Medical Dictionary for Regulatory Activities (MedDRA). Listings and summaries will be based on the resulting SOCs and PTs.

All reported SAEs will be listed, indicating the subject id, treatment group, age, gender, race, day of onset relative to start of dosing, resolution date, investigator-assessment of relationship to study drug, investigator-assessment of intensity of event, action taken regarding study drug and whether treatment was required for the event.

Summary information (the number and percentage of subjects) regarding SAEs (for serious and non-serious events) will be tabulated by SOC, PT and treatment group for:

- deaths (outcome of an SAE)
- SAEs
- AEs leading to study drug discontinuation

All reported AEs and SAEs during follow-up period will be summarized and listed as well.

7.6.3.2 Laboratory Data

Lab data are not systematically collected in the study. All reported marked lab abnormalities during treatment period will be listed.

7.6.3.3 Vital Signs

Vital signs are not systematically collected in the study.

7.7 Pharmacokinetics/Pharmacodynamics

There will be no pharmacokinetic/pharmacodynamic analysis in this study.

7.8 Outcomes Research Assessments

Time to first all cause re-hospitalization is assessed per secondary endpoint.

7.9 Interim Analyses

No interim analysis was planned. A blinded assessment of the primary endpoint event rate was performed after 50% of subjects have completed the study. The analyses focused on the aggregate event rate and the sample size may be increased if the aggregate event rate was lower than anticipated. Ongoing review of the safety will be the mandate of the data monitoring committee (DMC). Details are provided in the DMC charter.

8 CONVENTIONS

8.1 Safety Data Conventions

Except as noted in Section 7.6, safety data will be handled according to the BMS safety data conventions (described in "Analysis of Safety Data - Reference to CT SOP 109"). This document includes descriptions on how to analyze AE data as well as how to handle partial dates, missing dates, and unknown end dates when analyzing safety data.

For the analyses of efficacy and bleeding endpoints, imputation of missing or partial dates for efficacy and bleeding events will follow the convention outlined in "Analysis of Safety Data - Reference to CT SOP 109", but rather than using the hierarchy "first active study medication date, consent date, visit date corresponding to the visit at which the event was reported", should instead use the following hierarchy

- "first active study medication date, randomization date, consent date" for efficacy and bleeding endpoints other than death
- "last contact date" for death.

8.2 Baseline Measurements

For laboratory measure will follow GBS standard.

8.3 Day Ranges for Analysis of Time Points

Subjects do not always adhere strictly to the visit schedule timing in the protocol. The day ranges for the analyses of INR measurements are defined in the following table. Values associated with each nominal visit (except for the follow-up period) will be considered from first day of dosing until 2 days after discontinuation of VKA.

Table 8.3: Day Ranges for Analysis of INR Measurements

Nominal Visit	Target Day	Day Ranges
Month 1	Day 30	Days 11 - 45
Month 2	Day 61	Days 46 - 76
Month 3	Day 91	Days 77 - 106

Nominal Visit	Target Day	Day Ranges
Month 4	Day 121	Days 107 - 136
Month 5	Day 152	Days 137 - 167
Month 6	Day 183	Days 168 - 198

8.4 Multiple Measurements

INR Values

If multiple INR values are captured in the CRF within the same nominal visit, the INR value obtained on the day closest to the target day for that nominal visit will be used; in the case of a tie, the measurement obtained at the earlier date and time will be used in the summaries.

9 CONTENT OF REPORTS

The results of this study will be presented in a standard BMS Clinical Study Report (CSR). The complete list of analysis described for the CSR will be generated in the Data Presentation Plan (DPP).

[redacted]