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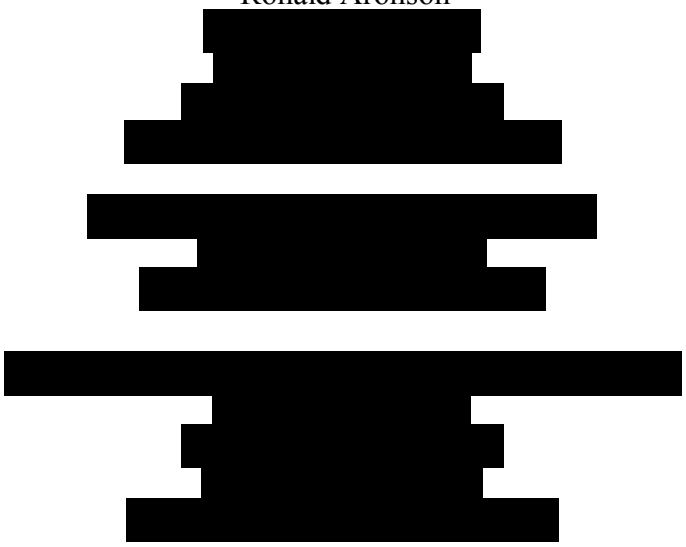
Clinical Protocol CV185316

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

Revised Protocol No.: 04
Incorporates amendment(s): 07 and Administrative Letters 03 and 04

Medical Monitor

Ronald Aronson



Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

DOCUMENT HISTORY

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
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

Document	Date of Issue	Summary of Change
		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.
Administrative Letter 01	30-Jun-2015	Removing the version number from of the Investigator Brochure
Original Protocol	19-Mar-2015	Not applicable

SYNOPSIS

Clinical Protocol CV185316

Protocol Title: 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

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Oral apixaban 5 mg or 2.5 mg tablets given BID or oral vitamin K antagonist (VKA) tablets given once daily (titrated for INR goal of 2.0 to 3.0) for the 6 month treatment period . Blinded 81 mg aspirin tablets or blinded aspirin placebo tablets given once daily for the 6 month treatment period.

Study Phase: Phase 4

Research Hypothesis:

- Apixaban is non-inferior to VKA on the combined outcome of International Society on Thrombosis and Haemostasis (ISTH) major bleeding and clinically relevant non-major bleeding (CRNM) in patients with non-valvular atrial fibrillation (NVAF) who develop acute coronary syndrome (ACS) and/or require percutaneous coronary intervention (PCI) with concomitant antiplatelet therapy.
- Single antiplatelet therapy with a P2Y12 inhibitor is superior to dual antiplatelet therapy with a P2Y12 inhibitor and aspirin on the combined outcome of ISTH major bleeding and/or clinically relevant non-major bleeding in patients with NVAF who develop ACS and/or require PCI with concomitant anticoagulant therapy.

Objectives:

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 and clinically relevant non-major bleeding in patients with NVAF who develop ACS and/or undergo PCI with planned 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 and clinically relevant non-major bleeding in patients with NVAF who develop ACS and/or undergo PCI with concomitant anticoagulant therapy.

Secondary Objectives:

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 clinically relevant non-major (CRNM) bleeding
- The composite of all-cause death and all-cause re-hospitalization
- Death, stroke, myocardial infarction, stent thrombosis, or 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:

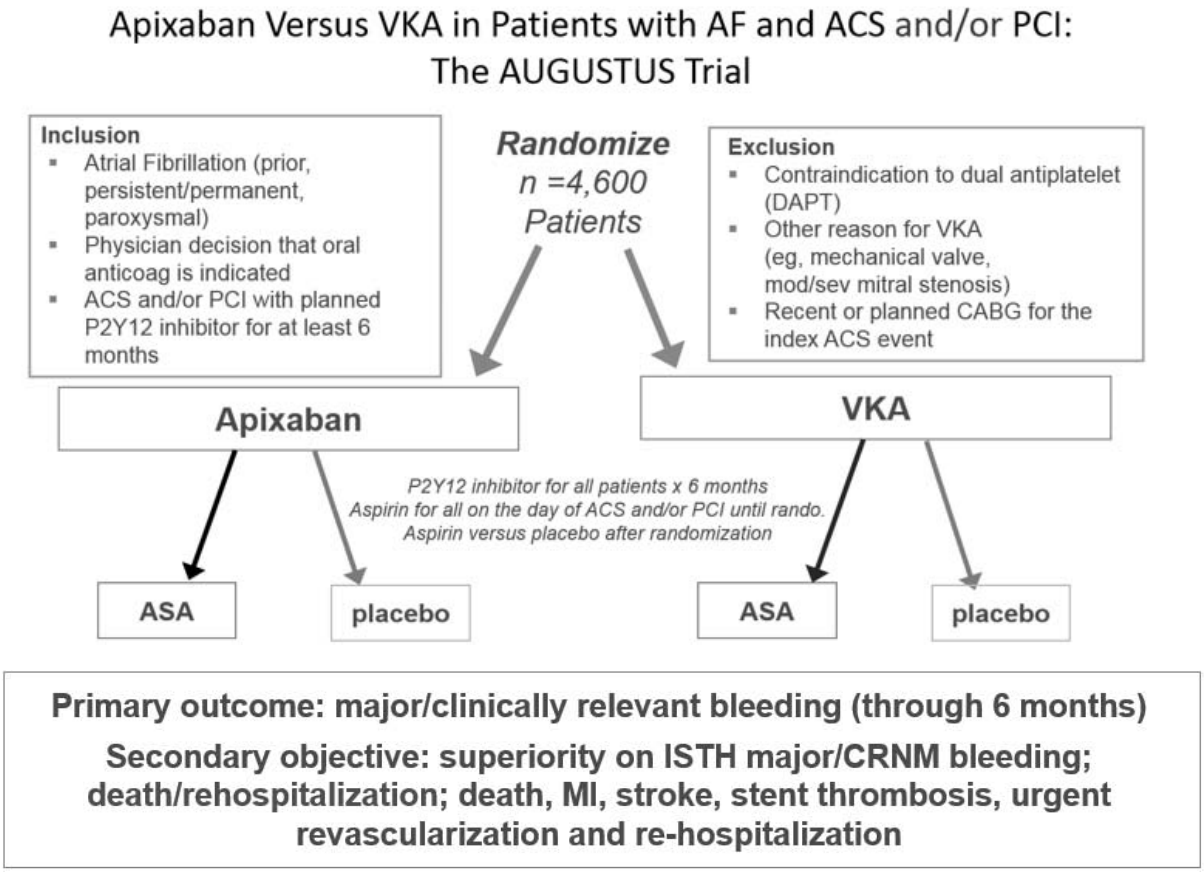
- The composite of all-cause death and all-cause re-hospitalization
- Death, stroke, myocardial infarction, stent thrombosis, or urgent coronary revascularization

[redacted]

Study Design:

Patients with a recent ACS and/or undergoing PCI with NVAF and planned treatment with P2Y12 inhibitor and oral anticoagulation for at least 6 months 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 oral anticoagulant 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 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 aspirin placebo. Randomization will be stratified by indication at enrollment (ACS vs. PCI).

Overall, the trial will include approximately 1/3 of patients with a recent ACS.



The randomized treatment period will be 6 months. In-person study visits will occur at 1, 3 and 6 months with a 30 day post treatment follow up visit. Phone visits will occur during 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 phone contacts will be scheduled in both the apixaban and VKA arms if in-person visits do not occur.

Study Population:

Males and females 18 years of age (or age of majority) or older with either active or a history of non-valvular atrial fibrillation or flutter with the planned or existing use of an oral anticoagulant for prophylaxis of thromboembolism. In addition, participants must have had, within the prior 14 days, an acute coronary syndrome (ST-elevation myocardial infarction [STEMI], non-ST-elevation myocardial infarction [NSTEMI], or unstable angina with plans for at least 6 months of treatment with an approved P2Y12 inhibitor) and/or PCI (with or without stents) with plans for at least 6 months of treatment with an approved P2Y12 inhibitor.

Key Exclusion Criteria Include:

- Conditions other than atrial fibrillation that require chronic anticoagulation (eg, prosthetic mechanical heart valve)
- Severe renal insufficiency (serum creatinine > 2.5 mg/dL [221 micromol/L] or a calculated creatinine clearance < 30 mL/min
- Patients with any history of intracranial hemorrhage
- Any contraindications to VKA, apixaban, to intended P2Y12 inhibitors or to aspirin
- Recent or planned coronary arterial bypass graft (CABG) for their index ACS event

- Patients with known ongoing bleeding
- Patients with known coagulopathies

Study Drug: includes both Investigational [Medicinal] Products (IP/IMP) and Non-investigational [Medicinal] Products (Non-IP/Non-IMP) as listed:

Study Drug for BMS-562247		
Medication	**Potency**	**IP/Non-IP**
Acetylsalicylic acid Film Coated Tablet, 81mg	81mg	IP
Placebo for Acetylsalicylic acid Film Coated Tablet, 81mg	0mg	IP
apixaban	5mg and 2.5mg	IP
VKA	INR 2.0 - 3.0	IP
P2Y12 inhibitor	As per site's decision	Non-IP

Study Assessments and Endpoints

Statistical Considerations:

Sample Size: 4600

This is a 2 x 2 factorial design with dual primary objectives. The sample size is based on the primary set of comparisons of Apixaban vs VKA for the primary endpoint of ISTH major or CRNM bleeding.

A total of 357 primary endpoint events and 4600 subjects will provide 77% power for test of non-inferiority (NI) using a stratified log rank test of apixaban versus VKA, assuming a NI margin of 1.2, with ISTH 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, and 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 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 one-sided significance level of 0.025.

A blinded assessment of the 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 first 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 first secondary endpoint to avoid the potential of futility in this study using the pre- specified rule below:

Sample Size Adjustment for Non-inferiority and Superiority Test on the Primary and Secondary Endpoints				
Observed blinded Event Rate When 50% Patient 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

Endpoints:

Endpoint Definitions:

Primary endpoints (safety):

The primary endpoint for apixaban versus VKA is

- ISTH major or CRNM bleeding

The primary endpoint for aspirin versus aspirin placebo is

- ISTH major or CRNM bleeding

Secondary endpoints:

The secondary endpoint for apixaban versus VKA includes

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

The secondary endpoint for aspirin versus aspirin placebo includes

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

[redacted]

- [redacted]

[redacted]

Analyses:

Populations for Analyses - Data set descriptions:

The primary safety data set includes all treated subjects who receive at least one dose of study drug.

A secondary data set, the evaluable subject data set, is a set of the primary safety data set and will exclude data from subjects with relevant protocol deviations expected to affect the primary safety endpoint. Relevant protocol deviations will be pre-specified in the statistical analysis plan.

The primary safety data set and the evaluable subject data will be used to analyze the primary safety endpoints. The primary safety data set will be used to analyze other safety endpoints.

The intent-to treat population of all randomized subjects will be used to analyze all efficacy endpoints.

The primary set of comparisons between apixaban and VKA

The primary and all secondary endpoints during the treatment period will be compared between apixaban and VKA.

The 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 or 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 or 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 the superiority for the composite of ISTH major or 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 one-sided $\alpha = 0.025$ significance level.

The secondary set of comparisons between aspirin and aspirin 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.

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[redacted]

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

The investigator or BMS should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

2.3 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

BMS will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4) Obtain the IRB/IEC’s written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.

5) If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed HIPAA Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

3 INVESTIGATIONAL PLAN

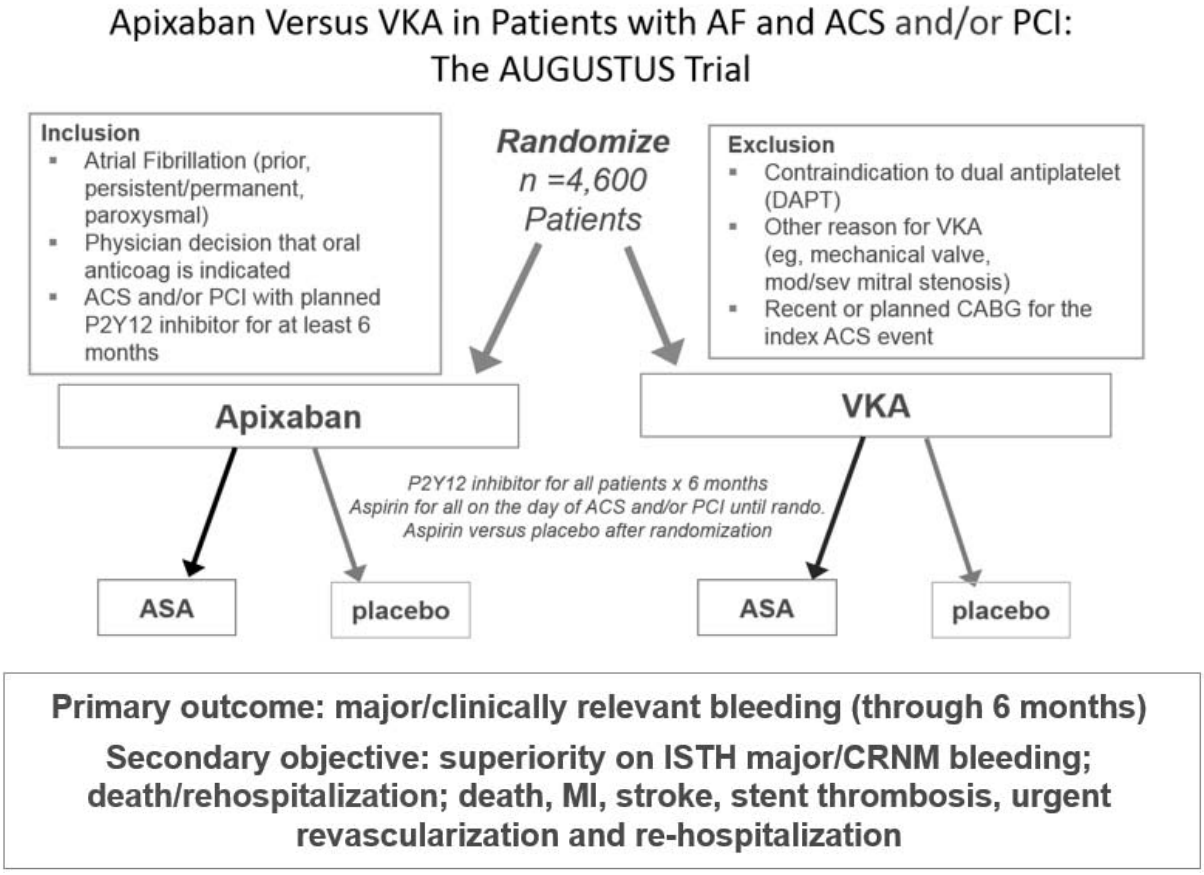
3.1 Study Design and Duration

Patients with a recent ACS and/or undergoing PCI for another indication with either active or a history of NVAF and planned treatment with P2Y12 agent and oral anticoagulation for at least six months will ideally be evaluated for eligibility during their ACS or 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 until the INR is less than 2.0. (Please refer to your country's approved label language for apixaban and VKA.)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 aspirin placebo. Randomization will be stratified by indication at enrollment (ACS vs PCI). Overall, the trial will include approximately 1/3 of patients with a recent ACS.

Approximately 690 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 study design schematic is presented in Figure 3.1-1.

Figure 3.1-1: Study Design Schematic



The study will not have a lead-in period. Screening period will be from time of consent to time of randomization.

The treatment period for all agents, including P2Y12 inhibitor, will be 6 months. In-person study visits will occur at months 1, 3, 6 (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 (via office or phone) contact will be scheduled in both the apixaban and VKA arms.

Adverse events assessments and medication compliance will be performed at study visits. Laboratory monitoring (hemoglobin, [redacted]) and diagnostic testing (ECG, brain CT or MRI, echocardiography, other imaging studies) will be assessed following suspected clinical events as per standard of care. The following events will be recorded at each visit: bleeding, stroke (ischemic and hemorrhagic), myocardial infarction, stent thrombosis, urgent coronary revascularization, and all-cause re-hospitalization.

3.2 Post Study Access to Therapy

At the end of the trial (6 months) patients will be treated according to local standards of care.

Patients will be contacted by telephone 30 days +/- 7 days after the end of treatment study visit for additional follow-up. At this contact, bleeding, death/ischemic events, antithrombotic therapy and INR values will be assessed.

At the end of the study, BMS will not continue to provide BMS supplied study drug to subjects/investigators unless BMS chooses to extend the study. The investigator should ensure that the subject receives appropriate standard of care to treat the condition under study.

As the oral anticoagulant is not blinded, investigators will be free to choose at the end of the study whether to continue the apixaban or VKA, or transition to alternative agents. Patients transitioning from apixaban to vitamin K antagonists should have frequent INR tests during the first few weeks of transition, as per local standards. Furthermore, investigators will not be routinely provided blinded aspirin/aspirin placebo assignments until after the final study results are made public.

3.3 Study Population

For entry into the study, the following criteria MUST be met.

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

a) Subjects will be required to provide a written informed consent.

2. Target Population

a) Males and females 18 years of age (or age of majority) or older with either active or a history of non-valvular atrial fibrillation or flutter with the planned or existing use of an oral anticoagulant for prophylaxis of thromboembolism for at least 6 months **AND**

b) An acute coronary syndrome (ST-elevation myocardial infarction [STEMI], non-ST-elevation myocardial infarction [NSTEMI], or unstable angina), within the prior 14 days, with planned use of an approved P2Y12 inhibitor for at least 6 months **AND/OR**

c) PCI (with or without stents) within the prior 14 days with planned use of an approved P2Y12 inhibitor for at least 6 months.

(*If both an ACS event and an elective PCI occur within the same 14 day period, the investigator has the option to define the index event for the randomization to the interactive voice/web response system. It is recommended to choose the most recent event as the index event. However, for the electronic case report form, if a patient has both an ACS and PCI within 14 days, both events can be selected.*)

3. Subject Re-enrollment:

a) This study does permit the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (screen failure).

4. Age and Reproductive Status

a) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug.

b) Women must not be breastfeeding

c) WOCBP must agree to use effective contraception for the duration of treatment with study drugs plus

i. 33 days for patients on apixaban

ii. 40 days for patients on VKA

d) Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However they must still undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. In addition, subjects and their partners should utilize two methods of contraception, such as a barrier method and hormonal method, especially for subjects randomized to VKA.

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Conditions other than non-valvular atrial fibrillation that require chronic anticoagulation (eg, mechanical heart valve)

2. Medical History and Concurrent Diseases

a) Severe renal insufficiency (serum creatinine > 2.5 mg/dL [221 micromol/L] or a calculated creatinine clearance < 30 mL/min

b) Patients with any history of intracranial hemorrhage

c) Any contraindications to VKA, apixaban, or to intended P2Y12 antagonists or to aspirin

d) Patients who have or will undergo coronary arterial bypass graft (CABG) for their index ACS event

e) Women who are pregnant, breastfeeding, or of childbearing potential and unable to use an acceptable method of birth control

3. Physical and Laboratory Test Findings

a) Patients with known ongoing bleeding

b) Patients with known coagulopathies

4. **Allergies and Adverse Drug Reaction**
   a) Known allergies or sensitivities to apixaban, VKA, aspirin, or to intended P2Y12 antagonist.
5. **Other Exclusion Criteria**
   a) Prisoners or subjects who are involuntarily incarcerated
   b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness
   c) Subjects who would have compromised ability to comply with study therapy or follow up visits
   d) Subjects who are participating in other interventional clinical trials of other drugs or unapproved devices.
6. **Current employees of Pfizer, Bristol-Myers Squibb, or PPD are excluded from participation, as well as their spouses and dependent children.**

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all inclusion criteria and no exclusion criteria.

3.3.3 Women of Childbearing Potential

A Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40mIU/mL to confirm menopause.

Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal:

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months.

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

During the 6 month treatment period, oral or parenteral anticoagulants (excluding low molecular weight heparins (LMWH or unfractionated heparins (UFH) for the purpose of bridging to VKA treatment only), including the novel oral anticoagulants (excluding apixaban for those assigned to that arm), as well as non-study aspirin, may not be given concurrently. However, transition from pre-randomization medications, such as bridging heparin, may be given at the discretion of the investigator, to overlap with study treatments.

3.4.2 Pre-Randomization Concomitant Medication

All concomitant medications from 7 days before randomization to end of study should be recorded in the electronic case report form.

3.5 Discontinuation of Subjects following any Treatment with Study Drug

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Subject's request to stop study treatment
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness.

In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

All subjects who discontinue study drug will be contacted by telephone 30 days +/- 7 days after the end of study visit as detailed in Section 3.2 and Table 5.1-2. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study drug is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate case report form (CRF) page.

3.6 Post Study Drug Study Follow up

In this study, bleeding is a key endpoint of the study. Post study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects

who discontinue study drug must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

3.6.1 Withdrawal of Consent

Subjects who request to discontinue study drug will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

3.6.2 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

Even after multiple unsuccessful contact attempts, no subject should be considered truly lost to follow-up until the final conclusion of the CV185316 study, as subjects may unexpectedly present themselves well after their scheduled final visit.

4 STUDY DRUG

Study drug includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) and can consist of the following:

Table 4-1: BMS Supplied Study Drugs for CV185316

Product Description / Class and Dosage Form	Potency	IP/ Non-IMP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
Acetylsalicylic acid film coated tablet	81 mg	IP	blinded	35 tablets/bottle White to off white, plain, round, biconvex film coated tablet	Store at 15-25°C (59-77°F). Store in a tightly closed container.
Placebo for Acetylsalicylic acid film coated tablet	0 mg	IP	blinded	35 tablets/bottle White to off white, plain, round, biconvex film coated tablet	Store at 15-25°C (59-77°F). Store in a tightly closed container.
Apixaban film coated tablet[a]	2.5 mg	IP	Open Label	30 tablets/blister wallet, yellow, round, biconvex film coated tablets with "893" debossed on one side and "2 1/2" on the other side.	Store at 15-25°C (59-77°F)
Apixaban film coated tablet[a]	5 mg	IP	Open Label	56 tablets/blister wallet, Pink, oval shaped, biconvex film coated tablets with "894" debossed on one side and "5" on the other side.	Store at 15-25°C (59-77°F)
Warfarin tablets[a]	1 mg	IP	Open Label	40 tablets/blister wallet, Pink tablets with a groove on one side and "1" on the other side.	Store at 15-25°C (59-77°F) Protect from light.
Warfarin tablets[a]	5 mg	IP	Open Label	40 tablets/blister wallet, Yellow tablets with a groove on one side and a "5" on the other side.	Store at 15-25°C (59-77°F) Protect from light.

[a] Supplied in countries where local sourcing is not permissible.

Apixaban 5 mg and 2.5 mg tablets, as well as VKA and the P2Y12 inhibitors used will be locally sourced materials (to be purchased by the sites through local commercial sources) wherever possible and not supplied by Bristol-Myers Squibb. Apixaban 5 mg and 2.5 mg tablets as well as Warfarin 1 mg and 5 mg tablets listed in Table 4-1 will be supplied in countries where local sourcing is not an option.

Locally sourced material should be kept at appropriate storage conditions in accordance with the package insert. BMS considers the blinded aspirin and blinded aspirin placebo to be Investigative Product (IP) as well as the apixaban and VKA; the P2Y12 inhibitors are considered to be non-IP study medications. For this study, apixaban/VKA and aspirin/aspirin-placebo are considered "study drugs;" the required P2Y12 inhibitors are considered background medications.

4.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations. In this study, apixaban 2.5 mg and 5 mg tablets, as well as the aspirin 81 mg tablets, aspirin placebo, and VKA are considered investigational product.

4.2 Non-investigational Product

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products. In this study, the required P2Y12 inhibitor (eg, clopidogrel) is considered non-investigational product.

4.3 Storage of Study Drug

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

Study drug not supplied by BMS will be stored in accordance with the package insert.

Please refer to Section 9.2.2 for guidance on IP records and documentation.

4.4 Method of Assigning Subject Identification

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).

4.5 Selection and Timing of Dose for Each Subject

Subjects randomized to apixaban will be dosed at 5 mg bid, unless they meet at least two of the following criteria for dose reduction to 2.5 mg BID:

- Age ≥ 80 years
- Weight ≤ 60 kg
- Serum creatinine ≥ 1.5 mg/dL (133 micromol/L)

Subjects randomized to apixaban may have their dosages increased or decreased during the 6 month treatment period if at least two of the three above criteria change during the study.

Subjects randomized to VKA should be titrated up for an INR target goal of 2.0 to 3.0. Dosages of VKA to achieve that range should be per local standards of care and per investigator clinical judgment.

Both the oral anticoagulant (apixaban or VKA) and the antiplatelet agents (blinded aspirin once daily or blinded placebo once daily) must be started within 24 hours of randomization.

4.6 Blinding/Unblinding

Apixaban or VKA will be open-label. This section will not apply to those agents.

Aspirin (or matching placebo) will be double 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.

4.7 Treatment Compliance

Drug compliance for apixaban and aspirin/aspirin placebo will be defined as between 80% to 120%. Pill counts, guided by patient-completed drug diaries, will assist completion of the appropriate eCRF pages, but actual determination of compliance will be determined by the Sponsors. Diary cards must be distributed to subjects, but completion of the cards is at the discretion of the subjects.

4.8 Destruction or Return of Investigational Product

For this study, IP (those supplied by BMS, a vendor, or sourced by the investigator) such as partially used study drug containers may be destroyed on site.

If...	Then...
IP supplied by BMS (including its vendors)	Any unused IP supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless IP containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics). If IP will be returned, the return will be arranged by the responsible Study Monitor.

If...	Then...
IP sourced by site, not supplied by BMS (or its vendors) (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

The following minimal standards must be met:

- On-site disposal practices must not expose humans to risks from the drug
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period

It is the investigator's or designee's responsibility to arrange for disposal of all empty containers.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of IP provided by BMS (or its vendors). Destruction of non-IP sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designee.

For this study, IP (those supplied by BMS or its vendors such as full or partially used study drug containers, vials, syringes) cannot be destroyed on-site. It is, however, the investigator's or designee's responsibility to arrange for disposal of all empty IP containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The return of full or partially used IP supplied by BMS or its vendors will be arranged by the responsible Study Monitor.

For subjects where the IP is not directly supplied by BMS (e.g., commercially-sourced apixaban or VKA dispensed from a pharmacy by a physician's prescription), leftover medication after the 6 month treatment period does not need to be returned to the site.

For subjects where the IP is directly supplied by BMS or one of its vendors, the site obligation is to request the subject to return the medication to the site; it is the subject responsibility, not the site's, to comply.

Please refer to Section 9.2.2 for additional guidance on IP records and documentation.

4.9 Retained Samples for Bioavailability / Bioequivalence

Not Applicable.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Baseline and Randomization (CV185316)

Procedure	Screening/ Randomization Visit	Notes
Eligibility Assessments		
Informed Consent	X	
Inclusion/Exclusion Criteria	X	
Medical History	X	Include assessment of alcohol use, tobacco use, prior VKA use, and CHADS-VASC and HAS-BLED scores
Safety Assessments		
Physical Examination	See Notes	Only if deemed necessary by treating physician. Results of examination will be documented in patient's chart, not on CRF
Vital Signs	X	Blood Pressure and Weight
Assessment of Signs and Symptoms	See Notes	Only if deemed necessary by treating physician. Results of assessment will be documented in patient's chart, not on CRF
Serious Adverse Events Assessment	See Notes	Refer to section 6.1 of the protocol for SAE definitions applying to this study.
Adverse Events Assessment	N/A	
Laboratory Tests	X	Local lab: CBC, chemistry(CHEM7 or equivalent for determination of serum creatinine), coagulation (for PT/PTT/INR) (local lab within 7 days can be used)
Urine Pregnancy Test* (*WOCBP only*)	X	*If applicable Serum pregnancy test to be performed only if urine test is positive or un-interpretable
Study Drug		
Randomize	X	
Dispense Study Drug (administer within 24 hours of randomization)	X	Those supplied by BMS or sourced by the investigator

Table 5.1-2: Short-term Procedural Outline (CV185316)

Procedure (± 7 days is allowed)	**Visit 1[a] (1 month[b])**	**Visit 2[a] (3 months[b])**	**Visit 3[a] (6 months[b])**	**Phone visits (at 2, 4, and 5 months[b])**	**Phone or In-Person Follow-up (30 day +/- 7 days after End of Treatment)**	**Notes**
Safety Assessments						
Targeted Physical Examination	X	X	X			Only if deemed necessary by treating physician
Vital Signs	X	X	X			Blood pressure and weight
Assessment of Signs and Symptoms	X	X	X		X (if in-person visit)	
Serious Adverse Event Assessment	X	X	X	X	X	Refer to section 6.1 of the protocol for SAE definitions applying to this study.
Targeted Adverse Events Assessment	X	X	X	X	X	See section 6.2
Laboratory Tests	INR for VKA	INR for VKA	INR for VKA	INR for VKA	INR for VKA	To be performed locally for VKA subjects
Urine Pregnancy Test* (*WOCBP only*)	X	X	X	X	X	*If applicable Serum pregnancy test to be performed only if urine test is positive or un-interpretable
Bleeding Assessment	CBC, if applicable	CBC, if applicable	CBC, if applicable	CBC, if applicable	CBC, if applicable	To be performed locally
Efficacy Assessments						
Death/Ischemic Events Assessment	Diagnostic studies, if applicable	Diagnostic studies, if applicable	Diagnostic studies, if applicable	Diagnostic studies, if applicable	Diagnostic studies, if applicable	To be performed locally

Table 5.1-2: Short-term Procedural Outline (CV185316)

Procedure (± 7 days is allowed)	**Visit 1[a] (1 month[b])**	**Visit 2[a] (3 months[b])**	**Visit 3[a] (6 months[b])**	**Phone visits (at 2, 4, and 5 months[b])**	**Phone or In-Person Follow-up (30 day +/- 7 days after End of Treatment)**	**Notes**
Study Drug						
Dispense Study Drug	X	X				
Drug Compliance	X	X	X	X		At Follow-up Visit, assess transition to Oral Anticoagulant (OAC)

[a] For patients who decline further treatment but still permit follow up, visits 1, 2, and 3 may be performed by telephone

[b] 30 day months

5.1.1 Retesting During Screening Period

Retesting of laboratory parameters and/or other assessments within any single Screening period will be permitted (in addition to any parameters that require a confirmatory value).

Any new result will override the previous result (ie, the most current result prior to Randomization) and is the value by which study inclusion will be assessed, as it represents the subject's most current, clinical state.

5.2 Study Materials

- Urine pregnancy kits (for WOCBP only)
- Patient education materials and site support tools
- Patient reminder cards (optional) to be used for helping patients remember to take their study medications.

5.3 Safety Assessments

No specific safety assessments other than the laboratory tests, clinical assessments of bleeding episodes, AEs/SAEs indicated in Table 5.1-1 and Table 5.1-2, are required.

5.3.1 Imaging Assessment for the Study

No radiological assessments are mandated.

5.4 Efficacy Assessments

No specific efficacy assessments are mandated. Clinical judgment should be executed in evaluating what diagnostics and tests to order to assess the study's efficacy endpoints. These suspected endpoints should be documented in the appropriate sections of the electronic case report form.

5.5 Pharmacokinetic Assessments

Not applicable.

[redacted]

5.7 Outcomes Research Assessments

Time to first all cause re-hospitalization rates would be captured.

5.8 Other Assessments

Not applicable.

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease

temporally associated with the use of study drug, whether or not considered related to the study drug.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

6.1 Serious Adverse Events

A S***erious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver abnormalities are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies). Standard medical practice in identifying and monitoring hepatic abnormalities should be followed.

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the subject's written consent to participate in the study, all SAEs must be collected and reported in a timely fashion, including those thought to be associated with protocol-specified procedures (exemptions to usual SAE reporting are described in section 6.1.1.1). All SAEs must be collected that occur during the screening period and within 30 days of discontinuation of dosing. The investigator should expeditiously report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours of awareness of the event. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the eCRF. The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

SAE Telephone Contact (required for SAE and pregnancy reporting): Refer to Contact Information list.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

6.1.1.1 Protocol Specific Exceptions to SAE Reporting

Given the body of safety data already collected on apixaban, only targeted SAE's need to be reported in an expedited fashion. These events include:

- All deaths (known and unknown cause)
- Life threatening events assessed by investigator as related to study drug (excluding endpoints)
- All SAEs that are related (as determined by investigator) to study drug (excluding endpoints)
- SAE of interest: liver injury (jaundice, hepatitis, liver failure)
- Pregnancies
- Overdose

So a fatal pneumonia event, for example, regardless of causality, would be reported in the usual expedited manner as an SAE. But a non-fatal myocardial infarction would not need to be reported as an SAE; this event would be reported in the endpoint pages of the case report form.

Beyond expedited adverse event reporting, clinically important outcome events are being systematically collected on the electronic case report form and adjudicated by the blinded clinical events adjudication committee. These events to be adjudicated include:

- All deaths and the cause of death
- All bleeding events
- All ischemic events including death, myocardial infarction, stent thrombosis, and stroke

6.2 Nonserious Adverse Events

A ***nonserious adverse event*** is an AE not classified as serious.

6.2.1 Nonserious Adverse Event Collection and Reporting

Only NSAE's that occur after the initiation of study drug and that result in **permanent** treatment discontinuation (including withdrawal from study) should be recorded in the eCRF.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. Reportable nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

(For subjects randomized to VKA treatment, INR values outside of the therapeutic range need not be reported unless associated with a clinically apparent adverse event, such as bleeding.)

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

6.4 Pregnancy

If, following initiation of the study drug, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

In the rare event that the benefit of continuing study drug is thought to outweigh the risk, after consultation with BMS, the pregnant subject may continue study drug after a thorough discussion of benefits and risk with the subject

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.5 Overdose

An overdose is defined as the accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as SAEs (see Section 6.1.1 for reporting details).

6.6 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly, except those listed those clinical endpoints in section 6.1.1.1 which are exempt from reporting.

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

When required, adjudicated events will be submitted to the Data Monitoring Committee (DMC) and Health Authorities for review on a specified timeframe in accordance with the adjudication documentation.

The external academic-led committees for this study will include an executive committee, steering committee, and clinical event adjudication committee. The executive committee will be a small body comprised of academic and sponsor representatives. The executive committee will lead the daily decision making for the study. The steering committee will be a larger body comprised of country-level academic leaders, as well as sponsor representatives, and will meet periodically at the recommendation of the executive committee. The clinical event adjudication committee will be an independent body of clinicians who are not otherwise involved with the study and will evaluate clinical events related to the study's endpoints.

The DMC will consider efficacy events, in addition to safety events, before making any study stopping recommendations to the executive committee and study sponsors, as per guidelines set forth in the DMC charter.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

This is a 2 x 2 factorial design with dual primary objectives. The sample size is based on the primary set of comparisons between Apixaban vs VKA for the primary endpoint of ISTH major or CRNM bleeding.

A total of 357 primary endpoint events and 4600 subjects will provide 77% power for test of non-inferiority (NI) using a stratified log rank test of apixaban versus VKA, assuming a NI margin of 1.2, with ISTH 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 the 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 first 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 first secondary endpoint to avoid the potential of futility in this study using the pre-specified rule below. Table 8.1-1 gives a guideline for sample size adjustment.

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

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

8.2 Populations for Analyses

The primary safety data set includes all treated subjects who receive at least one dose of study drug.

A secondary data set, the evaluable subject data set, is a set of the primary safety data set and will exclude data from subjects with relevant protocol deviations expected to affect the primary safety endpoint. Relevant protocol deviations will be pre-specified in the statistical analysis plan.

The primary safety data set and the evaluable subject data will be used to analyze the primary safety endpoints. The primary safety data set will be used to analyze other safety endpoints.

The intention-to-treat population of all randomized subjects will be used to analyze all efficacy endpoints.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

The primary endpoint for apixaban versus VKA is

- ISTH major or CRNM bleeding

The primary endpoint for aspirin versus aspirin placebo is

- ISTH major or CRNM bleeding

8.3.2 Secondary Endpoint(s)

The secondary endpoint for apixaban versus VKA includes

- Superiority on ISTH major + CRNM bleeding
- The composite of all-cause death and all-cause re-hospitalization.
- The composite endpoints of death and ischemic events (stroke, myocardial infarction, stent thrombosis, urgent coronary revascularization)

The secondary endpoint for aspirin versus aspirin placebo includes

- The composite of all-cause death and all-cause re-hospitalization
- The composite endpoints of death and ischemic events (stroke, myocardial infarction, stent thrombosis, urgent coronary revascularization)

[redacted]

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Frequency distribution and summary statistics for demographic and baseline variables will be presented by treatment group and for all subjects combined. The summaries will be tabulated for all randomized subjects.

8.4.2 Efficacy Analyses

This study does not have a primary efficacy analysis. The secondary efficacy endpoints are the composite of all-cause death and all-cause re-hospitalization and the composite of 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 use (aspirin placebo and aspirin) will be used to model the time to first occurrence of composite death and ischemic events during the 6- month treatment period. A point estimate and two-sided 95% CI for hazard ratio will be calculated. A p-value for the test of equality of rates (HR = 1) will be calculated.

8.4.3 Safety Analyses

The term "treatment period" for bleeding endpoints refers to the period between the first administration of study drug and two days after the last administration of study drug.

8.4.3.1 The primary set of comparisons between apixaban and VKA

The primary endpoint will be time to first occurrence of ISTH major or CRNM bleeding during the treatment period. Tests using non-inferiority margin will be performed using a Cox proportional hazards model including treatment group as a covariate and stratified by indication at enrollment (PCI/ACS) and antiplatelet use (aspirin and aspirin placebo). A point estimate and two-sided 95% CI for hazard ratio and a p-value for the test of equality of rates (HR = 1) will be calculated. Non-inferiority will be demonstrated if the upper bound of the two-sided 95% CI for HR is less than 1.2. Subjects without events during the treatment period will be censored.

Interaction between oral anticoagulant use (apixaban and VKA) and antiplatelet usage (aspirin or aspirin placebo) is not expected. This assumption will be examined as described in the statistical analysis plan.

The primary analysis will be based on treated subjects, and a sensitivity analysis will be performed on the intention-to-treat population.

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 or 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 or 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 or 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 one-sided $\alpha = 0.025$ significance level.

8.4.3.2 The secondary set of comparisons between Aspirin and Aspirin Placebo

The comparison between the groups treated with aspirin and aspirin placebo is critical in this population, in whom accumulating evidence suggests that omission of aspirin is associated with less bleeding than "triple" therapy without a loss in efficacy for thromboembolic events.[17,18,19]

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.

8.4.3.3 Meta-Analysis

A meta-analysis of trial-level data (WOEST, PIONEER, REDUAL, and AUGUSTUS trials) will be done outside of the clinical study report to assess the effects of treatment with different OACs and aspirin (and aspirin placebo) on clinical outcomes. The details of the meta-analysis will be written in a publication analysis plan.

8.4.4 Pharmacokinetic Analyses

Not applicable.

[redacted].

8.4.6 Outcomes Research Analyses

Time to first all cause re-hospitalization will be assessed as per secondary endpoints.

8.4.7 Other Analyses

Not applicable.

8.5 Interim Analyses

No interim analysis is planned. Ongoing review of safety will be the mandate of the DMC. Details are provided in the DMC charter.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- BMS
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

BMS representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS.

9.1.2.1 Source Documentation

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

9.1.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to BMS.

9.2.2 Study Drug Records

Records for IP (whether supplied by BMS, its vendors, or the site) must substantiate IP integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

If...	Then...
Supplied by BMS (or its vendors):	• Records or logs must comply with applicable regulations and guidelines and should include • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each subject, including unique subject identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (eg, lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form

If...	Then...
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study drug integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy. These records should include: • label identification number or batch number • amount dispensed to and returned by each subject, including unique subject identifiers • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

BMS or designee will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the paper or electronic SAE form and Pregnancy Surveillance form, respectively.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected as appropriate based on the following criteria:

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTA) governing you or your institution's participation in the study. These requirements include, but are not limited to, submitting proposed publications to BMS at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	If one form of contraception is required, Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. If two forms of contraception is required, Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. **Expanded definition** Complete abstinence as defined as complete avoidance of heterosexual intercourse is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (eg, calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence

11 LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
ACS	acute coronary syndrome
ALT	alanine aminotransferase
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AT	aminotransaminases
β-HCG	beta-human chorionic gonadotrophin
BID, bid	bis in die, twice daily
BMS	Bristol-Myers Squibb
BP	blood pressure
BUN	blood urea nitrogen
C	Celsius
CBC	complete blood count
CABG	Coronary arterial bypass graft
CFR	Code of Federal Regulations
CI	confidence interval
C1-	chloride
CLcr	creatinine clearance
CLR	renal clearance
cm	centimeter
CNS	Central nervous system
CRC	Clinical Research Center
CRF	Case Report Form, paper or electronic
CRNM	Clinically Relevant Non-major
CYP	cytochrome p-450
D/C	discontinue
DAPT	Dual antiplatelet therapy
dL	deciliter

Term	Definition
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eg	exempli gratia (for example)
ESR	Expedited Safety Report
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
g	gram
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GFR	glomerular filtration rate
h	hour
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IMP	investigational medicinal products
INR	International Normalization Ratio
IRB	Institutional Review Board
ISTH	International Society on Thrombosis and Haemostasis
IU	International Unit
IV	intravenous
kg	kilogram
L	liter
LMWH	Low Molecular Weight Heparin
LDH	lactate dehydrogenase
mg	milligram
Mg++	magnesium
min	minute
mL	milliliter

Term	Definition
mmHg	millimeters of mercury
μg	microgram
N	number of subjects or observations
N/A	not applicable
NI	Non-inferiority
NIMP	non-investigational medicinal products
NSAID	nonsteroidal anti-inflammatory drug
NVAF	Non-valvular atrial fibrillation
NSTEMI	Non-ST Elevation Myocardial Infarction
PCI	Percutaneous coronary intervention
PO	per os (by mouth route of administration)
PT	prothrombin time
PTT	partial thromboplastin time
QD, qd	quaque die, once daily
RBC	red blood cell
SAE	serious adverse event
SD	standard deviation
SOP	Standard Operating Procedures
STEMI	ST-elevation myocardial infarction
T	time
T-HALF	Half life
UFH	Unfractionated Heparin
VKA	Vitamin K antagonist
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential