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Clinical Protocol CV185158

A Phase IV, Open-Label, Multi-center Study to Evaluate the Safety of Apixaban in Indian Subjects Undergoing Elective Total Knee Replacement or Total Hip Replacement Surgery

Revised Protocol Number: 02
Incorporates amendment(s) 02

Study Director
Robert M. Knabb, PhD
[redacted]

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 02	22-Jul-2014	Incorporates Amendment(s) 02
Amendment 02	22-Jul-2014	This amendment incorporates the changes requested by the health authority of India to include 'single clopidogel use' as exclusion criteria and wording related to collection of data in case of death. Incorporate other minor changes to correct and/or clarify protocol requirements. This revision applies to all subjects and will serve in lieu of the revised protocol 01.
Revised Protocol 01	03-Jun-2013	Incorporates Amendment(s) 01
Amendment 01	03-Jun-2013	This amendment serves to revise the design of the study from a randomized, active controlled parallel group design to a single arm design by removing the enoxaparin arm. Incorporate other minor changes to correct and/or clarify protocol requirements In addition there are editorial changes throughout the document due to adaptation of the previous protocol version to the new BMS Protocol Template This revision applies to all subjects and will serves in lieu of the original protocol.
Original Protocol	12-Nov-2012	Not applicable

SYNOPSIS

Clinical Protocol CV185158

Title of Study: Protocol CV185158: A Phase IV, Open-Label, Multi-center Study to Evaluate the Safety of Apixaban in Indian Subjects Undergoing Elective Total Knee Replacement or Total Hip Replacement Surgery

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Subjects will receive oral apixaban, 2.5 mg twice daily for 12 ± 2 days in subjects undergoing TKR or 35 ± 2 days in subjects undergoing THR.

Study Phase: 4

Research Hypothesis: Apixaban 2.5 mg BID is well-tolerated for venous thromboembolism (VTE) prophylaxis in Indian subjects undergoing total hip or knee replacement.

Primary Objective: Evaluate the safety of apixaban in prophylaxis of VTE in Indian patients undergoing elective total knee or hip replacement.

Study Design: Open-label with endpoint adjudication. Subjects with planned surgery for total knee replacement (TKR) or total hip replacement (THR) will be screened for inclusion up to 14 days before surgery. Subjects will receive oral apixaban, 2.5 mg twice daily, with the first dose administered 12-24 hr after surgery, and continuing for 12 ± 2 days in subjects undergoing TKR or 35 ± 2 days in subjects undergoing THR.

During hospitalization, subjects will be observed for signs or symptoms of venous thromboembolism or bleeding. After hospital discharge, subjects will be instructed to contact the investigator for adverse events including signs or symptoms of bleeding, deep vein thrombosis (DVT) or pulmonary embolism (PE). At the end of the intended treatment period and at the end of the 30-day follow-up period, the patients will come to attend an in person visit or a phone visit if an in person visit is not planned.

SCREENING PERIOD (up to 14 days prior to surgery)

Subjects undergoing total hip replacement or total knee replacement surgery (including revisions) without known or suspected hereditary or acquired bleeding or coagulation disorders who meet the inclusion/exclusion criteria are eligible. Screening clinical laboratory samples will be collected during this period.

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ENROLLMENT (from 4 days before surgery to 24 hours after surgery)

Eligible subjects (N = 500) will be assigned to apixaban 2.5 mg PO starting 12 - 24 hours after completing skin wound closure, then BID for 35 ± 2 days for the subjects undergoing total hip replacement or 12 ± 2 days for the subjects undergoing total knee replacement. Sites will call into the IVRS system to record whether the subject's planned surgery is a hip replacement or knee replacement.

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TREATMENT PERIOD (35 days ± 2 days for THR subjects or 12days ± 2 for TKR)

Treatment Period Visits: Day 1 (day of surgery), Day 2, Day 7 ± 2, Day 12 ± 2 for TKR or Day 35 ± 2 for THR patients. The Day 7, 12 or 35 visit should ideally be an in-person visit. If this is not possible, a telephone follow-up visit will be performed.

While hospitalized, subjects will be evaluated daily for symptomatic VTE (DVT and/or PE) and bleeding events. After hospital discharge, subjects will report all AEs including, but not limited to, signs and/or symptoms suggestive of DVT or PE and bleeding, to the Investigator.

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FOLLOW-UP PERIOD (30 days after last dose of study drug)

Follow-up Visits: The follow up visit will occur 30 days after the last dose of study drug. TKR subjects will have their follow-up visit at Day 42 ± 2 days and THR subjects will have their follow up visit at Day 65 ± 2 days. The follow-up visit should ideally be an in-person visit. If this is not possible, a telephone follow-up visit will be performed.

Subjects will report all AEs, including those signs and/or symptoms suggestive of DVT and/or PE and bleeding, to the Investigator.

Study Population: Subjects Undergoing Elective Total Knee Replacement or Total Hip Replacement Surgery

Main Inclusion Criteria:

Male or female subjects over the age of 18, who are scheduled for elective total knee or hip replacement or a revision of at least one component of a total knee or hip replacement. Subjects must be willing and able to give written informed consent prior to any screening procedures.

Women of childbearing potential (WOCBP) must be using an adequate method of contraception to avoid pregnancy throughout the treatment period of the study in such a manner that the risk of pregnancy is minimized.

Main Exclusion Criteria:

WOCBP who are unwilling or unable to use an acceptable method to avoid pregnancy for the entire treatment period of the study

Women who are pregnant or breastfeeding

Known or suspected, acquired or bleeding or coagulation disorder in the subject or a first degree relative

Known coagulopathy

Active bleeding or at high risk for bleeding

Brain, spinal, ophthalmologic, or major surgery or trauma within the past 90 days

Active hepatobiliary disease

Two consecutive blood pressure readings within 15-30 minutes with supine SBP > 180 mm Hg or supine DBP > 105 mm Hg

Hemoglobin < 9 g/dL & Platelet count < 100,000/mm^3

Creatinine clearance < 30 mL/min as estimated by the method of Cockcroft and Gault

Active hepatobiliary disease, based on an ALT or AST > 2xULN or a Total Bilirubin ≥ 1.5xULN (unless an alternative causative factor [eg, Gilbert's syndrome] is identified)

Any antiplatelet agents (including clopidogrel) other than aspirin

Vitamin K antagonist or other novel oral anticoagulant (such as rivaroxaban or dabigatran)

Ongoing unfractionated heparin or low molecular weight heparin use

Use of thrombolytics within past 7 days.

Study Assessments and Primary Endpoint: The primary endpoint is the incidence of adjudicated major or clinically relevant nonmajor bleeding. Secondary endpoints include adjudicated DVT or PE and all-cause death. These primary and secondary endpoints will be assessed up to end of treatment + 2 days.

Statistical Methods: The primary objective of the study is to evaluate the safety of apixaban in prophylaxis of VTE in Indian patients undergoing elective total knee or hip replacement. The primary study endpoint is a composite of International Society on Thrombosis and Haemostasis (ISTH) major bleeding/clinically relevant non-major bleeding (CRNM) in subjects undergoing elective total knee or hip replacement at the end of treatment + 2 days.

Total of 500 subjects will be enrolled and allocated to apixaban. The sample size of the study is determined by requirement of regulatory agency rather than statistical considerations. With 500 subjects and event rate of 4.36% for ISTH major or clinically relevant non-major bleeding, the width of the 95% CI for the event rate will be (2.6%, 6.2%) and width of the CI is 3.6%.

Subgroup analyses by surgery type will also be conducted.

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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.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s).

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/process (eg, advertisements), and any other written information to be provided to subjects. The investigator or sponsor 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 sponsor 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, or, in those situations where consent cannot be given by subjects, their legally acceptable representative, are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer 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 their informed consent during the study, then 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 consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

Subjects unable to give their written consent (eg, stroke patients, or subjects with severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent

compatible with the subjects' understanding, and should they become capable, personally sign and date the consent form as soon as possible. The explicit wish of a subject unable to give his or her written consent, who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

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

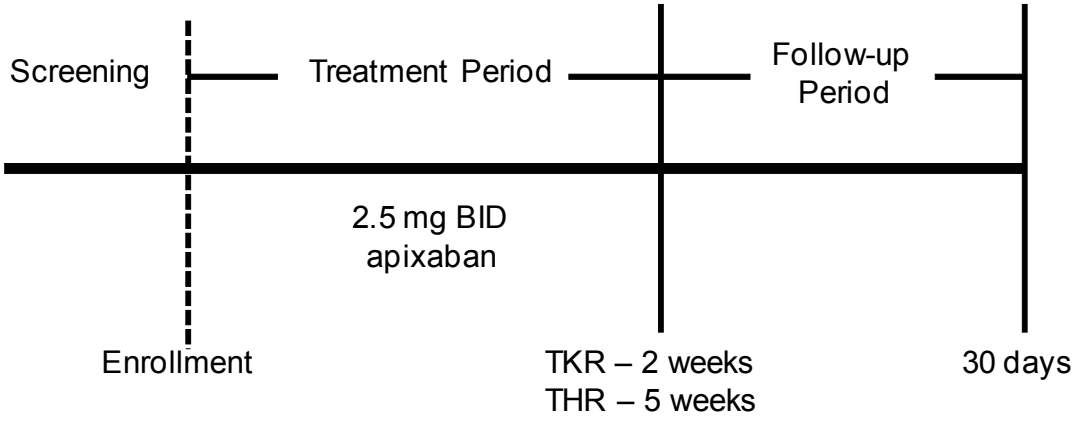
3.1 Study Design and Duration

Expected duration of the study, from first subject, first visit through last subject, last visit is approximately 8 months.

This study is designed to evaluate the safety of oral apixaban 2.5 mg BID following total knee and hip replacement surgeries. There are four study periods extending up to maximum duration of approximately 42 ± 2 days for the patients undergoing total knee replacement surgery and up to 65 ± 2 days for the patients undergoing total hip replacement surgery:

- A screening period, of up to 14 days prior to surgery
- An enrollment period: from 4 days before surgery to 1 day after surgery
- A treatment period: First dose, PO, starting 12 - 24 hours after completing skin wound closure, then BID for 35 ± 2 days for the subjects undergoing total hip replacement or 12 ± 2 days for the subjects undergoing total knee replacement.
- A 30-day follow-up period starting the day after the last dose of study medication.

Figure 3.1-1: Study Design



3.1.1 Screening

The screening period will begin with a screening visit that occurs up to 14 days prior to surgery. Subjects undergoing elective THR or TKR surgery (including revisions) who meet the inclusion/exclusion criteria are eligible for study entry.

No study-related procedure may be performed until the subject has been completely informed of the study, has freely consented to take part in the study, and has signed and dated an informed consent document approved by a licensed Institutional Review Board (IRB) or Independent Ethics Committee (IEC).

Blood sample and Urine pregnancy test will be collected for laboratory assessments.

The IVRS system will be contacted to obtain a unique subject number. Medical history, vital signs and body weight will be obtained (refer to Section 5.1 for details).

3.1.2 Enrollment

The enrollment may occur from 4 days prior to surgery to 24 hours after surgery.

Subjects who meet all the inclusion/exclusion criteria will be enrolled to the site for this visit. Subjects (N = 500) will be assigned to oral apixaban 2.5 mg BID

Blood sample and Urine pregnancy test will be collected for laboratory assessments.

Sites will call into the IVRS system for assignment to apixaban 2.5 mg; sites will indicate whether the subject is undergoing either a TKR or THR. Either hip or knee replacement patients may be enrolled in any order, but BMS may place enrollment limits on either type of surgical patient to ensure adequate enrollment of both knee and hip surgery patients in the study.

3.1.3 Treatment Period

The day of surgery is Day 1.

The first dose of apixaban will be administered 12 - 24 hours after completing skin wound closure, typically in the morning of Day 2 and then BID for 35 ± 2 days for the subjects undergoing total hip replacement or 12 ± 2 days for the subjects undergoing total knee replacement.

While hospitalized, subjects will be evaluated on Day 1, Day 2 and discharge day for suspected symptomatic VTE, bleeding events or any AEs or SAEs.

At any subsequent treatment visits (Day 7 ± 2 and Day 12 ± 2 for TKR subjects or Day 7 ± 2 and Day 35 ± 2 for THR subjects), subjects will be instructed to report to the investigator all AEs, including signs and/or symptoms suggestive of VTE and any bleeding events they experienced since their last visit. Subjects with signs and/or symptoms of VTE at any time should return to the hospital/clinic and undergo appropriate diagnostic evaluation.

If study medication is discontinued for a suspected DVT and or PE, alternative antithrombotic prophylaxis may be initiated per the Investigator's discretion and standard of care. Every effort

must be made to confirm a suspected DVT and/or PE diagnosis before discontinuing study medication and initiating treatment per the Investigator's standard of care.

Samples for laboratory assessment of hematology will be obtained on the day of discharge.

Urine pregnancy test will be performed on Day 12 for TKR subjects and on Day 35 for THR subjects.

Dosing Diaries should be collected at Day 7 & Day 12 for TKR subjects and at Day 7 & Day 35 for THR subjects.

Subjects should be encouraged to return for an in person visit on Day 7 and Day 12 for TKR and Day 7 and Day 35 for THR. Alternatively those visits would be performed by phone.

3.1.4 Follow-up Period

As appropriate and per the Investigator's discretion and standard of care, alternative antithrombotic prophylaxis may be initiated the day after the last dose of study medication.

For subjects undergoing TKR surgery, follow-up study visit will occur on Day 42 ± 2 and for subjects undergoing THR surgery, the follow up visit will occur on Day 65 ± 2. Subjects should be encouraged to return for an in person follow up visit at Day 42 (TKR) or Day 65 (THR). Alternatively those visits would be performed by phone.

Subjects will be asked to report to the Investigator, all AEs/SAEs including those symptoms suggestive of DVT and/or PE and bleeding. Suspected DVT and/or PE will be evaluated using the appropriate diagnostic assessment.

3.2 Post Study Access to Therapy

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

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) Age ≥ 18 years

b) Subjects must be willing and able to give written informed consent. Consent to participate in the study must be obtained prior to any screening procedures.

2) Target Population

a) Subjects undergoing elective total knee or hip replacement or a revision of at least one component of a total knee or hip replacement.

3) Age and Reproductive Status

a) Women of childbearing potential (WOCBP) and men must be using an acceptable method of contraception to avoid pregnancy throughout the study in such a manner that the risk of pregnancy is minimized. See Section 3.3.3 for the definition of WOCBP.

b) 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 investigational product.

c) Women must not be breastfeeding

d) Sexually active fertile men must use effective birth control if their partners are WOCBP.

3.3.2 Exclusion Criteria

1) Target Disease Exceptions

a) Known or suspected, acquired or bleeding or coagulation disorder in the subject or a first degree relative

b) Known coagulopathy

c) Active bleeding or at high risk for bleeding.

2) Medical History and Concurrent Diseases

a) Brain, spinal, ophthalmologic, or major surgery or trauma within the past 90 days

b) Active hepatobiliary disease

c) Alcohol and/or substance abuse within the past year

d) Any condition, in the opinion of the Investigator, for which surgery or administration of an anticoagulant is contraindicated.

3) Physical and Laboratory Test Findings

a) Two consecutive blood pressure readings within 15-30 minutes with supine SBP > 180 mm Hg or supine DBP > 105 mm Hg

b) Hemoglobin < 9 g/dL

c) Platelet count < 100,000/mm^3

d) Creatinine clearance < 30 mL/min as estimated by the method of Cockcroft and Gault

e) Active hepatobiliary disease, based on an ALT or AST > 2 x ULN or a Total Bilirubin ≥ 1.5 x ULN (unless an alternative causative factor [eg, Gilbert's syndrome] is identified.

4) Sex and Reproductive Status

a) WOCBP who are unwilling or unable to use an acceptable method to avoid pregnancy for the entire treatment period of the study

b) Women who are pregnant or breastfeeding

c) Women with a positive pregnancy test on enrollment or prior to investigational product administration.

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) Administration of any investigational drug currently or within 30 days prior to enrollment into this study.

6) Prohibited Treatments and/or Therapies

a) Any antiplatelet agents (including clopidogrel) other than aspirin

b) Vitamin K antagonist or other novel oral anticoagulant (such as rivaroxaban or dabigatran) during the treatment period

c) Ongoing unfractionated heparin or low molecular weight heparin use

d) Use of thrombolytics within past 7 days

e) Use of Fondaparinux

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to ensure that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

3.3.3 Women of Childbearing Potential

Women of childbearing potential include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal. Post menopause is defined as:

- Amenorrhea ≥ 12 consecutive months without another cause and a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL or
- Women with irregular menstrual periods and a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL or

  NOTE: FSH level testing is not required for women ≥ 62 years old with amenorrhea of ≥ 1 year
- Women on hormone replacement therapy (HRT).

Women who are using oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy, or are practicing abstinence or where their partner is sterile (eg, vasectomy) should be considered to be of childbearing potential.

3.4 Concomitant Treatments

Medications required for the treatment of underlying medical conditions are allowed, with the exception of those listed below.

3.4.1 Prohibited and/or Restricted Treatments

Prohibited Therapies

Prohibited medications are listed in the Exclusion Criteria (see Section 3.3.2 item 6a to 6e).

Use of pneumatic compression devices and tourniquets must be discontinued at the completion of skin wound closure and are not permitted throughout the treatment period.

Anti-thrombotic prophylaxis may be continued during the follow-up period per the Investigator's discretion and standard of care.

Restricted Therapies During the Treatment Period

Subjects are allowed to use the following therapies during the study at the investigator's discretion:

- Oral cox-2 selective (eg, celecoxib [Celebrex®]) and short-acting NSAIDs for joint pain are permitted although not encouraged (acetaminophen/paracetamol or opiods are the preferred methods for systemic pain management)
- Parenteral ketorolac or parecoxib is permitted although not encouraged (acetaminophen/paracetamol or opiods are the preferred methods for systemic pain management)
- Aspirin > 165 mg/day is prohibited
- Herbal medications are permitted, provided the subject has permission from the Investigator
- Metformin should be temporarily discontinued at the time of, or prior to, procedures in which intravascular iodinated contrast material is used and then withheld for at least 48 hours subsequent to the procedure (eg, venograms).
- Epidurals should be removed at least 5 hours prior to administration of the first dose of apixaban.

All concomitant medication use must be noted on the appropriate e-CRFs.

3.4.2 Other Restrictions and Precautions

The following precautions and restrictions must be followed to preserve study integrity and subject safety:

- Subject should comply with prescribed dosing schedule
- Subjects should be cautioned that any new prescriptions, or over-the-counter medications, including herbal medications, should be discussed thoroughly with the Investigator prior to initiation.

Study medication must be discontinued for subjects experiencing a severe adverse event, (eg, myocardial infarction) which may require the use of open-label anticoagulants (eg, LMWH), antiplatelet agents, thrombin inhibitors (eg, hirudin), glycoprotein IIb/IIIa antagonists or other antithrombotic agents, either with or without interventions (eg, percutaneous coronary intervention). The treating physician should be made aware that when study medication (apixaban) is administered at the protocol-specified doses, routine coagulation tests such as Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT) are relatively insensitive measures of activity and, therefore, unsuitable for monitoring. If treatment of a severe adverse event is indicated, the treating physician may consider using the agent(s) listed above at the lowest recommended therapeutic dose for the first 12 hours following discontinuation of study medication.

Discontinuation of Subjects from Treatment: Subjects MUST discontinue investigational product (and noninvestigational product at the discretion of the investigator) for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- 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
- Pregnancy
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Signs and/or symptoms suggestive of DVT in the operated and/or nonoperated leg which are confirmed by ultrasound and/or venography
- Signs and/or symptoms suggestive of PE which are confirmed by diagnostic assessment, eg, V/Q scan, pulmonary angiogram, CT scan (including spiral), and as indicated, additional confirmatory tests
- Subject has clinical jaundice at any time
- Subject has specific elevated liver function test (LFTs) results
- Subject has a severe adverse event that may require the use of anticoagulants, antiplatelet agents, thrombin inhibitors, glycoprotein IIB/IIIa antagonists or other thrombotic agents
- Subject has an increased risk of bleeding complications eg persistent bleeding after surgery or difficult (more than 2 failed attempts) or traumatic (bloody spinal fluid) lumbar puncture.

All subjects who discontinue should comply with protocol specified follow-up procedures as outlined in Section 5. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If a subject was withdrawn before completing the study, the reason for withdrawal must be entered on the appropriate case report form (CRF) page.

All subjects who discontinue study medication prematurely and have received at least one dose of post-surgical oral study medication should be encouraged to return for an in person visit on Day 7, Day 12 (TKR) or Day 35 (THR) and follow up visit at Day 42 (TKR) or Day 65 (THR). Alternatively those visits would be performed by phone.

Subjects who require a revision of their hip or knee replacement during the study's treatment period should have their apixaban stopped at least 48 hours before their revision surgery.

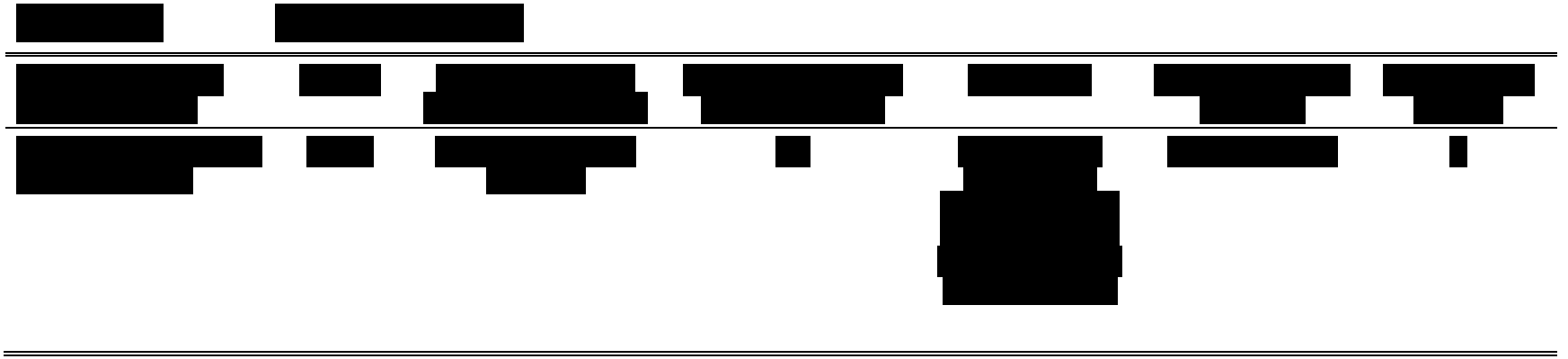
Patients who withdraw consent for treatment with study drug should still receive follow-up for adverse events and outcomes unless they withdraw consent for follow-up as well.

If a subject is lost to follow-up, every effort should be made to contact the subject and perform these procedures. At minimum the vital status should be collected.

4 TREATMENTS

All protocol-specified investigational and non-investigational products are considered study drug. The following table (Table 4.1-1) describes the study drug used.

4.1 Study Treatments



4.1.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined as follows:

A pharmaceutical form of an active substance 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) in a way different from the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form. Apixaban 2.5 mg will be the only investigational product in this study.

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 protocol, investigational product(s) is apixaban.

4.1.2 Noninvestigational 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 protocol, noninvestigational product(s) is/are: Not applicable for this study.

4.1.3 Handling and Dispensing

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 the sponsor. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact the sponsor immediately.

Storage facilities for controlled substances must be securely locked and substantially constructed, with restricted access to prevent theft or diversion, as applicable by local regulations.

Apixaban tablets should be stored at below 30°C.

4.2 Method of Assigning Subject Identification

At screening, each subject will be assigned a unique sequential number by the Interactive Voice Response System (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.

After meeting inclusion/exclusion criteria, subjects eligible for the treatment will be assigned prior to surgery to apixaban 2.5 mg by the IVRS.

4.3 Selection and Timing of Dose for Each Subject

Study medication for this study is defined as apixaban 2.5 mg tablets. Subjects will receive apixaban tablets.

- The first oral dose will be given 12 - 24 hours after completing skin wound closure, typically in the morning of Day 2, followed by BID dosing for 12 ± 2 days in subjects undergoing TKR or 35 ± 2 days in subjects undergoing THR.
- Study subjects will take one tablet in the morning and one tablet in the evening.

4.4 Blinding/Unblinding

Not applicable.

4.5 Treatment Compliance

Prior to leaving the hospital, subjects or their caregivers will be instructed on timing and proper methods of study medication administration

4.6 Destruction and Return of Study Drug

4.6.1 Destruction of Study Drug

If study drugs (those supplied by the sponsor or sourced by the investigator) are to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for the disposal, procedures for proper disposal have been established according to applicable regulations, guidelines and institutional procedures, and appropriate records of the disposal have been documented. The unused study drugs can only be destroyed after being inspected and reconciled by the responsible BMS Study Monitor.

4.6.2 Return of Study Drug

Study drug will not be returned. All unused and/or partially used study drug may be destroyed on site providing the site has an applicable standard operating procedure on file.

If the site is not able to destroy the study medication, the Study Monitor should be contacted to organize the study drug return.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Procedural Outline for TKR Subjects (CV185158)

Procedure - TKR Subjects	Screening Visit	Enrollment	Treatment Period					Follow up Period	Notes
Days	Pre-Surgery 1-14	Pre-Surgery -4 days to +24 hours	Surgery Day 1	Day 2	Hospital Discharge	Day 7 ± 2 days	Day 12 ± 2 days	Day 42 ± 2 days	
Informed Consent	X								
Inclusion/Exclusion Criteria	X								
Medical History	X								
Weight & Age & Gender	X								
Vital Signs (SBP/DBP & HR)	X								
Contact IVRS	X	X							At screening, after obtaining signed informed consent form, contact IVRS to obtain subject number; At enrollment, contact IVRS for assignment to apixaban 2.5 mg
Dispense Study Medication			X						
Discharge Instructions					X				
Review Medication Compliance					X	X	X		
AE/SAE Assessment		X	X	X	X	X	X	X	Lab: for SAE's related to liver failure/jaundice/hepatitis: local lab hepatitis panels and full LFT's (AST, ALT, T.Biliruin, D. bilirubin, GGT, AP, PT/aPTT/INR) must be performed; for bleeding related

Table 5.1-1: Screening Procedural Outline for TKR Subjects (CV185158)

Procedure - TKR Subjects	Screening Visit	Enrollment	Treatment Period					Follow up Period	Notes
Days	Pre-Surgery 1-14	Pre-Surgery -4 days to +24 hours	Surgery Day 1	Day 2	Hospital Discharge	Day 7 ± 2 days	Day 12 ± 2 days	Day 42 ± 2 days	
									SAE's, analysis of CDC, PT/aPTT/INR must be performed by the local lab.
Symptomatic VTE Assessment		X	X	X	X	X	X	X	
Local Lab: Serum Creatinine LFT's (AST, ALT,TBILI) & CBC	X	X							
Local Lab: Hb	X	X			X				
Dosing Diaries to be collected						X	X		
Pregnancy Test	X	X			X		X		WOCBP only

Table 5.1-2: Screening Procedural Outline for THR Subjects (CV185158)

Procedure - THR Subjects	Screening Visit	Enrol-lment	Treatment Period					Follow up Period	Notes
Days	Pre-Surgery 1-14	Pre-Surgery -4 days to +24 hours after surgery	Surgery Day 1	Day 2	Hospital Discharge	Day 7 ± 2 days	Day 35 ± 2 days	Day 65 ± 2 days	
Informed Consent	X								
Inclusion/Exclusion Criteria	X								
Medical History	X								
Weight & Age & Gender	X								
Vital Signs (SBP/DBP & HR)	X								
Contact IVRS	X	X							At screening, after obtaining signed informed consent form, contact IVRS to obtain subject number; At enrollment, contact IVRS for assignment to apixaban 2.5 mg
Dispense Study Medication			X						
Discharge Instructions					X				
Review Medication Compliance					X	X	X		
AE/SAE Assessment		X	X	X	X	X	X	X	Lab: for SAE's related to liver failure/jaundice/hepatitis: local lab hepatitis panels and full LFT's (AST, ALT, T.Biliruin, D. bilirubin, GGT, AP, PT/aPTT/INR) must be performed; for bleeding

Table 5.1-2: Screening Procedural Outline for THR Subjects (CV185158)

Procedure - THR Subjects	Screening Visit	Enrol-lment	Treatment Period					Follow up Period	Notes
Days	Pre-Surgery 1-14	Pre-Surgery -4 days to +24 hours after surgery	Surgery Day 1	Day 2	Hospital Discharge	Day 7 ± 2 days	Day 35 ± 2 days	Day 65 ± 2 days	
									related SAE's, analysis of CDC, PT/aPTT/INR must be performed by the local lab.
Symptomatic VTE Assessment		X	X	X	X	X	X	X	
Local Lab: Serum Creatinine LFT's (AST, ALT,TBILI) & CBC	X	X							
Local Lab: Hb	X	X			X				
Dosing Diaries to be collected						X	X		
Pregnancy Test	X	X			X		X		WOCBP only

5.2 Study Materials

BMS will supply the sites with the following materials:

- Daily dosing diaries to be used to record study medication taken
- Subject discharge instruction cards
- Electronic case report forms
- Sample source documentation worksheets
- Patient Emergency card.

5.3 Safety Assessments

Bleeding is the primary safety outcome measure. Bleeding AEs/SAE/s will be assessed by the investigator at every post-surgery visit. At discharge from the hospital, impress upon the subject and/or caregiver the importance of contacting the Investigator immediately if subject experiences signs of clinically over bleeding during the treatment period or the follow-up period. These bleeding AEs/SAEs will be evaluated by the clinical events adjudication committee.

Acute clinically overt bleeding is defined as new onset, visible bleeding or signs or symptoms suggestive of bleeding with confirmatory imaging techniques which can detect the presence of blood (eg, US, CT, MRI).

All acute clinically overt bleeding events will be adjudicated by the ICAC as a major bleeding event, a clinically relevant nonmajor bleeding event or neither.

The definition of major bleeding described below is adapted from the International Society on Thrombosis and Hemostasis (ISTH) definition.

Major Bleeding Event is defined as a bleeding event that is:

- Acute clinically overt bleeding accompanied by one or more of the following:
- A decrease in hemoglobin (Hb) of 2 g/dL or more over a 24-hour period
- A transfusion of 2 or more units of packed red blood cells
- Bleeding that occurs in at least one of the following critical sites:
  - Intracranial
  - Intra-spinal
  - Intraocular (within the corpus of the eye; thus, a conjunctival bleed is not an intraocular bleed)
  - Pericardial
  - An operated joint and requires re-operation or intervention
  - Intramuscular with compartment syndrome
  - Retroperitoneal.
- Bleeding that is fatal.

Clinically Relevant Nonmajor Bleeding event is defined as a bleeding event that is:

- Acute clinically overt bleeding
- Does not satisfy additional criteria required for the bleeding event to be defined as a major bleeding event and meets at least one of the following criteria.
- Epistaxis (nose bleed):
  - Subject seeks medical attention from a physician
  - Subject visits an emergency room
  - Bleeding requires an intervention, eg, nasal pack
  - Single bleeding episode persists for 5 minutes or more.
- Gastrointestinal Bleed:
  - Vomit containing frank blood or coffee ground material which tests positive for blood
  - Endoscopically confirmed bleeding
  - Frank blood per rectum or melenic stools.
- Hematuria:
  - Overt, spontaneous bleeding
  - Bleeding (bloody urine) persists for 24 hours or more after instrumentation.
- Bruising/ecchymosis:
  - Any bruise which is assessed as "unusual" (eg, greater than expected following surgery).
- Hemoptysis:
  - Expectoration of blood or blood-stained sputum.
- Hematoma:
  - Overt blood collection associated with the surgical wound

    Presence of a hematoma is demonstrated radiographically, eg, US, CT, MRI, and a drop in hemoglobin is present with no external evidence of bleeding.

Fatal Bleeding Event is defined as a bleeding event that the ICAC determines is the primary cause of death or contributes directly to death.

5.4 Efficacy Assessments

No specific diagnostics are required for evaluating asymptomatic VTE's. However, patients with signs or symptoms suggestive of deep vein thrombosis (DVT) or pulmonary embolism (PE) must be evaluated with the clinically appropriate imaging techniques, including compression ultrasound (CUS) or venography for suspected DVT, or VQ scanning or spiral CT for suspected PE. Additional diagnostics performed outside the efficacy assessments and outside SAE reporting need not be part of the study report but should be maintained as part of the medical record.

An independent events adjudication committee will evaluate these reports of VTEs as well as of deaths. All deaths will be adjudicated regardless of whether they seem related to VTE's or not. In

case of death, all efforts should be made to determine the cause of death which is aligned to the BMS process on data collection, obtaining autopsy reports or verbal information from family.

5.4.1 Primary Efficacy Assessment

The composite of VTE/all cause death will include all adjudicated symptomatic pulmonary embolisms and deep vein thromboses. Statistical details will be described in the Statistical Analysis Plan as a separate document.

5.4.2 Secondary Efficacy Assessments

Not Applicable.

5.5 Other Assessments

VTE's that are discovered as part of incidental findings (such as CT scans for other parts of the body), will not be counted towards the efficacy endpoint but will be adjudicated and reported separately.

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

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 ***serious AE (SAE)*** is any untoward medical occurrence that at <u>any dose</u>:

- 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.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (eg, any organism, virus or infectious particle, pathogenic or non-pathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies.)

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 "important medical event" or event life threatening)
- 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 for purpose other than remedying ill health state and was 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, care-giver respite, family circumstances, administrative).

6.1.1 Serious Adverse Event Collection and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 30 days of discontinuation of dosing. The investigator should report any SAE occurring after these time periods 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 status of seriousness.

If the investigator believes that an SAE is not related to the 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. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). When using paper forms, the reports are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: See Contact Information list.

SAE Facsimile Number: See Contact Information list.

For studies capturing SAEs/pregnancies 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): See 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 BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization. In case of death, all efforts should be made to determine the cause of death which is aligned to the BMS process on data collection, obtaining autopsy reports or verbal information from family.

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

The collection of nonserious AE information should begin at initiation of study drug.

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, or those that are present at the end of study treatment as appropriate. All identified 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 Abnormalities

The following laboratory 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 abnormality that required the subject to have the study drug discontinued or interrupted
- Any laboratory abnormality that required the subject to receive specific corrective therapy.

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

6.4 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). 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 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 the sponsor. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.5 Overdose

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

6.6 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1 for reporting details).

Potential drug induced liver injury is defined as

1. AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND

2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

7.1 Data Monitoring Committee

Not Applicable.

7.2 Independent Central Adjudication Committee

The Independent Central Adjudication Committee (ICAC) will be responsible for validating outcome events as specified in the protocol and according to guidelines using standardized criteria.

The ICAC reviews and adjudicates all suspected symptomatic DVT, PE, major bleeds, clinically relevant non-major bleeds, minor bleeds, thrombocytopenia and causes of death.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

The sample size of the study is determined by requirement of regulatory agency rather than statistical considerations. With 500 subjects in the apixaban arm and event rate of 4.36% for ISTH major or clinically relevant non-major bleeding, the width of the 95% CI for the event rate will be (2.6%, 6.2%) and width of the CI is 3.6%.

8.2 Populations for Analyses

The term “treatment period” refers to the period between the first administration of study medication (post-surgery oral apixaban) and two days after the last administration of study medication (end of treatment). The “treatment period” will be the basis for the summaries of

safety and efficacy. Summaries of safety and efficacy data will include all subjects receiving any study medication.

8.3 Endpoint Definitions

Primary Endpoint:

The primary study endpoint is a composite of International Society on Thrombosis and Haemostasis (ISTH) major bleeding/clinically relevant non-major bleeding (CRNM) in subjects undergoing elective total knee or hip replacement at the end of treatment + 2 days, where ISTH major bleeding is

- Fatal or
- Bleeding in a critical organ, such as brain, spine, eye, retroperitoneum, joint, heart sac, or skeletal muscle (and resulting in compartment syndrome), or
- Bleeding that results in a fall of hemoglobin of 2 g/dL or more or transfusion of 2 units or more of packed red cells or whole blood within 24 hours

and CRNM bleeding is bleeding that

- Is clinically acute and overt
- Does not satisfy criteria as a major bleed but requires medical intervention, such as a visit to a physician's office, emergency room, or urgent care center for epistaxis.

Secondary Endpoints:

The secondary endpoint will be: The composite of VTE/all cause death at the end of treatment + 2 days, where VTE is the combination of deep vein thrombosis and non-fatal pulmonary embolism.

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. Key demographic and baseline variables to be summarized include: age, gender, race, vital signs (systolic blood pressure, diastolic blood, pressure, and heart rate), medical history, knee or hip replacement surgery experience, intra-operative details, and post-surgical patient care characteristics. The summary will be presented for all subjects.

8.4.2 Efficacy Analyses

The event rates and their 95% confidence intervals of composite of venous thromboembolism (VTE) and all cause death during the treatment period will be summarized. Subgroup analyses by surgery type will also be conducted.

8.4.3 Safety Analyses

Bleeding is the primary safety outcome measure. The event rate of adjudicated major bleeding or clinically relevant non-major bleeding events during the treatment period will be summarized. Subgroup analyses by surgery type will also be conducted.

An additional analysis will summarize all adjudicated major bleeding or clinically relevant non-major bleeding occurring during the treatment period, which begins with the first dose of study medication.

In addition, an analysis of major or clinically relevant non-major bleeding events will look at the bleeding events that occur prior to the administration of apixaban. Additional details will be provided in the Statistical Analysis Plan.

The incidence of adverse events and of marked abnormalities in clinical laboratory tests will be summarized by treatment group for both the treatment and follow-up period.

All adverse events that are serious or that result in discontinuation of study therapy will be described in depth. K-M estimator will be used to estimate the rate of early discontinuation due to any reason.

8.4.4 Other Analyses

Not Applicable.

8.5 Interim Analyses

Not Applicable.

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
- Bristol-Myers Squibb
- 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 an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

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.

9.1.3 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 the sponsor, 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

It is the responsibility of the investigator to ensure that a current disposition record of investigational product (those supplied by the sponsor) is maintained at each study site where study drug is inventoried and dispensed. 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 ID 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
- non-study disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to the sponsor
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product (IP) dispensing/accountability, as per the Delegation of Authority Form.

BMS 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 reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

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. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by the sponsor.

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 a qualified physician who is an investigator or subinvestigator. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. 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 the sponsor. 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 considering 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 the sponsor. Any publications or abstracts arising from this study require approval by the sponsor prior to publication or presentation and must adhere to the sponsor's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to the sponsor at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. Sponsor shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

10 GLOSSARY OF TERMS

Term	Definition
Adverse Reaction	An adverse event that is considered by either the investigator or BMS as related to the investigational product
Unexpected Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator Brochure for an unapproved investigational product)
Expected Adverse Event	An event that is described or mentioned in the applicable (current version) or the prescribing information for the drug (eg, Investigator Brochure for an investigational product, approved local label for a marketed product).
Serious Adverse Event	Serious adverse event defined as 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; 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.). For reporting purposes only, BMS also considers the occurrence of pregnancy, overdose (regardless of association with an AE), and cancer as important medical events.
Investigational Product	An investigational product, also known as investigational medicinal product in some regions, is: A pharmaceutical form of an active substance* being tested or used as a reference in a clinical study, including products already with a marketed

Term	Definition
	authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form. * The only investigational product is apixaban.
Noninvestigational Product	Support, escape (rescue) or diagnostic medications (marketed form), concomitant medications.

11 LIST OF ABBREVIATIONS

Term	Definition
ACC	American College of Cardiology
AE	adverse event
ALT	alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BA/BE	bioavailability/bioequivalence
BID	twice daily
BMI	Body Mass Index
BMS	Bristol-Myers Squibb
BUN	blood urea nitrogen
CBC	complete blood count
CHF	Congestive heart failure
CK	creatine kinase
CK-MB	Creatine kinase MB subunit
CFR	Code of Federal Regulations of the United States of America
CRNM	clinically relevant non-major bleeding
CRP	C-reactive protein
CT	Computer tomography
CUS	compression ultrasound
DBP	Diastolic blood pressure
DSMB	Data Safety Monitoring Board
DVT	deep-vein thrombosis
ECG	electrocardiogram
e-CRF	electronic case report form
ERC	Ethics Review Committee
ESR	Expedited safety report
FSH	follicle-stimulating hormone
GGT	gamma-glutamyl transpeptidase

Term	Definition
HAV	hepatitis A virus
Hb	hemoglobin
HbsAg	hepatitis B surface antigen
HBC	hepatitis B core antigen
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	Human Immunodeficiency Virus
HRT	hormone replacement therapy
ICAC	Independent Central Adjudication Committee
IEC	International Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
ITT	intent-to-treat
IVRS	Interactive Voice Response System
kg	kilogram
LFT	liver function test
LMWH	low molecular weight heparin
MedDRA	Medical Dictionary for Regulatory Activities
MCV	Mean Corpuseular Volume
MH	Mantel-Haenszel
MCH	Mean Corpuseular Hemoglobin
MCHC	Mean Corpuseular Hemoglobin Concentration
MI	myocardial infarction
MRI	Magnetic Resonance Imaging
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
PCI	percutaneous coronary intervention
PE	pulmonary embolism
PO	Per os (Latin by mouth)
PT	Prothrombin time
RBC	Red blood cell

Term	Definition
QD	once daily
SAE	serious adverse event
SBP	Systolic blood pressure
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
THR	Total hip replacement
TKR	total knee replacement
ULN	Upper limit of normal
US	Ultrasound
VKA	Vitamin K antagonist
VTE	Venous thromboembolism
V/Q	Ventilation perfusion scan
WBC	White blood cell
WOCBP	women of childbearing potential