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Clinical Protocol CV185687

Relative Bioavailability of Apixaban (BMS-562247) 0.1-mg Sprinkle Capsules Compared with 0.5-mg Tablets in Healthy Participants

Medical Monitor
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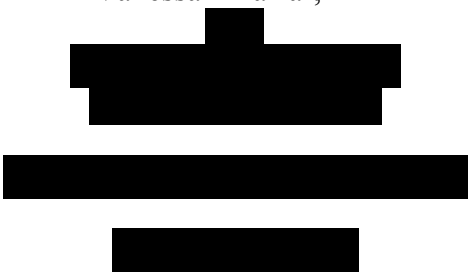


DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Original Protocol	21-Mar-2018	Not applicable

TABLE OF CONTENTS

1 SYNOPSIS

Not applicable.

2 SCHEDULE OF ACTIVITIES

Study assessments and procedures are presented in Table 2-1 and Table 2-2.

Table 2-1: Screening Procedural Outline (CV185687)

Procedure	Screening Visit (Day -28 to Day -2)	Admission Visit (Day -1)	Notes
Eligibility Assessments			
Informed Consent	X		A participant is considered enrolled only when a protocol-specific informed consent is signed.
Inclusion/Exclusion Criteria	X	X	
Medical History	X	X	A complete medical history will be obtained during screening. Interim medical history on Day -1. Include any toxicities or allergy related to previous treatments.
Report to Study Site		X	
Safety Assessments			
Physical Examination	X	X	The physical examination performed on Day -1 should be done within 24 hours of dosing on Day 1. Starting on Day –1, standard baseline medical dermatology photographs of areas affected by rash will be taken. If there are any changes with the affected areas or new areas of rash are detected, additional photographs will be obtained.
Physical Measurements	X	X	Height and weight at screening; weight only on Day -1. Body mass index will be calculated at screening and on Day -1.
Vital Signs	X	X	Includes body temperature, respiratory rate, and sitting blood pressure and heart rate. Blood pressure and heart rate should be measured after the participant has been sitting for at least 5 minutes.
12-Lead ECGs	X	X	12-lead ECGs should be recorded after the participant has been supine for at least 5 minutes.
Clinical Laboratory Tests	X	X	Includes blood and urine samples. Full clinical laboratory tests will be done including coagulation parameters (aPTT, INR, and PT) will be measured. Participants are required to fast for at least 8 hours prior to

Table 2-1: Screening Procedural Outline (CV185687)

Procedure	Screening Visit (Day -28 to Day -2)	Admission Visit (Day -1)	Notes
			the collection of specimens for clinical laboratory tests. Results of screening clinical laboratory tests must be available prior to admission to the clinic on Day -1. Results of clinical laboratory tests performed on Day -1 must be available prior to dosing on Day 1. See Section 9.4.4.
Serology	X		Results must be reviewed prior to admission to the clinic on Day -1. See Section 9.4.4.
Urine Drug Test	X	X	Includes alcohol and cotinine. Results of screening urine drug tests must be available prior to admission to the clinic on Day -1. Results of urine drug tests performed on Day -1 must be within 24 hours and reviewed prior to dosing on Day 1. See Section 9.4.4.
Pregnancy Test (serum)	X	X	All women. Results of pregnancy tests must be available prior to admission to the clinic on Day -1. The pregnancy test on Day -1 must be within approximately 24 hours, and results must be available prior to dosing on Day 1. Serum pregnancy tests must be reported in a quantitative result.
Follicle Stimulating Hormone	X		Postmenopausal women only. Refer to Appendix 4.
Adverse Event Reporting			
Monitor for SAEs	X	X	All SAEs must be collected from the date of participant's written consent until 30 days post discontinuation of dosing or participant's participation in the study if the last scheduled visit occurs at a later time.

aPTT = activated partial thromboplastin time; ECG = electrocardiogram; INR = international normalized ratio; PT = prothrombin time; SAE = serious adverse event

Table 2-2: On Treatment Procedural Outline (CV185687)

Procedure	D1	D2	D3	D4	D5	D6	D7	D8 (Study Discharge)[a]	Notes
Safety Assessments									
Physical Examination				X				X	Day 4 physical examination targeted for skin will be performed within 24 hours of dosing on Day 5. Starting on Day –1, standard baseline medical dermatology photographs of areas affected by rash will be taken. If there are any changes with the affected areas or new areas of rash are detected, additional photographs will be obtained.
Physical Measurements								X	Weight only.
Vital Signs	X				X			X	Vital signs will be obtained prior to dosing on Days 1 and 5. See note in screening procedures.
12-Lead ECGs					X			X	12-lead ECGs on Day 5 will be obtained prior to dosing. See note in screening procedures.
Clinical Laboratory Tests				X			X		Includes blood and urine samples. Full clinical laboratory tests will be done including coagulation parameters (aPTT, INR, and PT) will be measured on Days 4 and 7. Results of clinical laboratory tests performed on Day 4 must be available prior to dosing on Day 5. See note in screening procedures and Section 9.4.4.
Pregnancy Test (serum)				X			X		Serum pregnancy testing must be done within approximately 24 hours of Day 5. Results must be reviewed prior to dosing on Day 5. Serum pregnancy tests must be reported in a quantitative result.

Table 2-2: On Treatment Procedural Outline (CV185687)

Procedure	D1	D2	D3	D4	D5	D6	D7	D8 (Study Discharge)[a]	Notes
Adverse Event Reporting									
Monitor for Nonserious AEs	X	X	X	X	X	X	X	X	Nonserious AEs will be collected from the initiation of study treatment (Day 1) until 3 days after the last dose of study treatment.
Monitor for SAEs	X	X	X	X	X	X	X	X	See note in screening procedures.
PK Assessments									See Table 9.5-1. An additional PK sample may be collected in the event of discontinuation due to an AE.
Serial Blood PK Sampling	X	X	X	X	X	X	X	X	See Section 9.5.
Clinical Drug Supplies									
Randomize	X								Randomization will occur prior to study drug administration.
Apixaban Administration	X				X				See Section 7.
Other Assessments									
Palatability Assessment	X				X				For both treatments. Palatability assessment will be completed immediately (within 5 minutes) after administration of the apixaban 0.5-mg tablet and 0.1-mg sprinkle capsule dosages. Refer to Appendix 6.

[a] Evaluations performed prior to study discharge or for participants who are prematurely discontinued.
AE = adverse event; aPTT = activated partial thromboplastin time; D = Day; ECG = electrocardiogram; INR = international normalized ratio; PK = pharmacokinetic; PT = prothrombin time; SAE = serious adverse event

In the event multiple procedures are required at a single time point, the 12-lead electrocardiogram (ECG) may be obtained up to 15 minutes earlier, vital signs may be obtained up to 10 minutes earlier or later, and the clinical laboratory blood sample may be obtained up to 5 minutes earlier than the nominal time point, ensuring the pharmacokinetic (PK) samples can be collected on time. For predose procedures, vital signs within 30 minutes of dose, 12-lead ECG within 45 minutes, and predose PK collected within 15 minutes of dose. Vital signs and 12-lead ECG measurements should be performed before clinical laboratory and PK blood samples are collected.

3 INTRODUCTION

Factor Xa (FXa) plays a pivotal role in the coagulation cascade at the junction of the intrinsic and extrinsic pathways of the coagulation system. Inhibition of FXa is expected to exert anticoagulant and antithrombotic effects by decreasing the conversion of prothrombin to active thrombin, thereby diminishing thrombin-mediated activation of the coagulation process, including fibrin formation and platelet activation. Apixaban is an orally active, selective, reversible inhibitor of FXa and is approved for prevention of venous thromboembolism in patients who have undergone elective knee or hip replacement surgery, for stroke prevention in nonvalvular atrial fibrillation, and for treatment of venous thromboembolism and prevention of recurrent venous thromboembolism [USPI[1] and SmPC[2]].

[redacted]

3.3 Benefit/Risk Assessment

Since this is not an efficacy treatment study, there is no direct benefit to the participants participating in this study other than contributing to the research of a product.

The potential risk to participants from apixaban in this study is expected to be minimal. Approved apixaban doses are 2.5 mg twice daily (BID) in venous thromboembolism prevention in orthopedic patients, 5 mg BID in atrial fibrillation, and 10 mg BID for 7 days followed by 5 mg BID in venous thromboembolism treatment. In healthy participants, single and multiple oral doses of apixaban up to 25 mg BID for 7 days and 50 mg once daily for 3 days were well-tolerated. In this study, single 2.5-mg doses of apixaban will be administered under medical supervision; each single dose will be separated by a washout period of at least 4 days. To ensure safety, participants with potential risk factors for bleeding will be excluded; this includes any history or evidence of abnormal bleeding or coagulation disorders, intracranial hemorrhage, or abnormal bleeding or coagulation disorders in a first degree relative.

Apixaban did not directly impair fertility or early embryonic development in rats and was not teratogenic in mice, rats, or rabbits at area under the concentration-time curve (AUC) multiples $\leq 6.9 \times$ the human AUC at 20 mg (10 mg BID). However, the reproductive risk of apixaban has not been evaluated in humans. Therefore, women of childbearing potential (WOCBP) who are unwilling or unable to use an acceptable method of contraception (Appendix 4) to avoid pregnancy for at least 4 weeks prior to dosing, during the study, and 33 days after the last dose of study treatment in such a manner that the risk of pregnancy is minimized will be excluded. In addition, male participants must agree to use an acceptable method of contraception during the entire study and for 93 days after the last dose. Male participants must not donate sperm during the entire study and for 93 days after the last dose.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary • To assess the bioavailability of apixaban 0.1-mg sprinkle capsules relative to apixaban 0.5-mg tablets, both administered orally in healthy participants	• Cmax, AUC(INF), AUC(0-T)
Secondary • To assess the safety and tolerability of apixaban • To assess the PK of apixaban 0.1-mg sprinkle capsules • To assess the PK of apixaban 0.5-mg tablets	• Incidence of nonserious AEs, SAEs, and AEs leading to discontinuation; and results of vital signs, 12-lead ECGs, physical examinations, and clinical laboratory tests • Tmax, T-HALF, Frel
[redacted] 0.1-mg sprinkle capsules	[redacted]

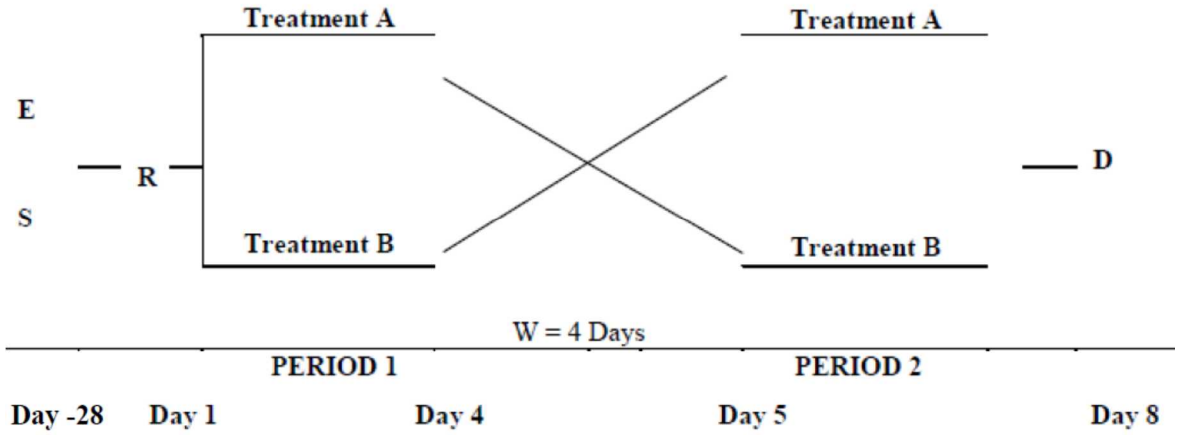
5 STUDY DESIGN

5.1 Overall Design

This is a Phase 1, open-label, randomized, 2-period, 2-treatment crossover study in healthy participants. Healthy male or female participants as determined by medical history, physical examination, vital signs, 12-lead ECG, and clinical laboratory tests will be eligible to participate in the study. Participants will undergo screening evaluations to determine eligibility within 28 days prior to study treatment administration. On Day -1, participants will enter the clinical facility and be confined for the duration of the study, until discharge on Day 8. Prior to dosing on Day 1 of Period 1, participants will be randomly assigned to 1 of 2 treatment sequences (AB or BA, where Treatment A is 5 × 0.5-mg apixaban tablets and Treatment B is 25 × 0.1-mg apixaban sprinkle capsules) in a 1:1 ratio. Participants will receive a single oral dose of apixaban on Days 1 and 5. There will be a 4-day washout period between doses. Treatments A and B will be prepared in the pharmacy.

The study design schematic is presented in Figure 5.1-1.

Figure 5.1-1: Study Design Schematic



D = Study Discharge; E = Enrollment; R = Randomization; S = Screening; Treatment A = 5 × 0.5-mg apixaban tablets; Treatment B = 25 × 0.1-mg apixaban sprinkle capsules; W = Washout

Physical examinations, vital sign measurements, 12-lead ECG, and clinical laboratory evaluations will be performed at selected times throughout the study. Participants will be closely monitored for adverse events (AEs) throughout the study. Blood samples will be collected for up to 72 hours after study drug administration for PK analysis. Approximately 240 mL of blood will be drawn from each participant during the study.

Participants will complete a palatability assessment (Appendix 6) immediately (within 5 minutes) after administration of the apixaban 0.5-mg tablet and 0.1-mg sprinkle capsule dosages, on both Day 1 and Day 5.

5.1.1 Data Monitoring Committee and Other External Committees

Not applicable.

5.2 Number of Participants

Sample size determination is discussed in Section 10.1. Approximately 30 participants (15 participants per treatment arm) are expected to be treated for this study in order to achieve approximately 28 evaluable participants (Section 10.2).

5.3 End of Study Definition

The start of the trial is defined as first visit for the first participant screened. End of trial is defined as the date of the last health status follow-up contact made to a participant discharged from the study. Study completion is defined as the final date on which data for the primary endpoint was or is expected to be collected, if this is not the same.

The approximate duration of this study will be 36 days, including a 28-day screening period.

[redacted]

[redacted]

6 STUDY POPULATION

For entry into the study, the following criteria MUST be met prior to dosing on Day 1. No exceptions will be granted.

6.1 Inclusion Criteria

1) Signed Written Informed Consent

a) The signed informed consent form.

2) Type of Participant and Target Disease Characteristics

a) Healthy participants as determined by no clinically significant deviation from normal in medical history, physical examination, 12-lead ECGs, vital signs, and clinical laboratory tests including coagulation parameters.

b) Body mass index (BMI) of 18.0 to 30.0 kg/m^2, inclusive. Body mass index = weight (kg)/[height(m)]^2.

c) Participant Re-enrollment: This study permits the re-enrollment of a participant who has discontinued the study as a pretreatment failure (ie, has not been treated). If re-enrolled, the participant must be re-consented if outside of screening window (along with verification of eligibility).

3) Age and Reproductive Status

a) Males and Females, ages 18 to 45 years, inclusive.

b) Women of childbearing potential must have a negative quantitative serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within approximately 24 hours prior to the start of study treatment. Serum pregnancy tests will be performed at screening and Day -1.

c) Women must not be breastfeeding.

d) Women of childbearing potential must agree to follow instructions for method(s) of contraception for the duration of treatment with study treatment apixaban plus 5 half-lives of study treatment apixaban (~3 days) plus 30 days (duration of ovulatory cycle) for a total of 33 days post-treatment completion (Appendix 4).

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (Appendix 4) for the duration of treatment with study treatment apixaban plus 5 half-lives of study treatment apixaban (~3 days) plus 90 days (duration of sperm turnover) for a total of 93 days post-treatment completion. In addition, male participants must be willing to refrain from sperm donation during this time.

f) Azoospermic males are exempt from contraceptive requirements. Women of childbearing potential who are continuously not heterosexually active are also exempt from contraceptive requirements, and still must undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP and male participants who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise on the use of highly effective methods of contraception, (Appendix 4) which have a failure rate of < 1% when used consistently and correctly.

6.2 Exclusion Criteria

1) Medical Conditions

a) Any significant acute or chronic medical illness.
b) History of chronic headaches, defined as occurring 15 days or more a month, over the previous 3 months.
c) History of orthostatic instability or recurrent dizziness.
d) History of gastroesophageal reflux disease, dyspepsia, protracted nausea, or chronic diarrhea.
e) History of cholecystectomy.
f) History of colitis.
g) History of upper gastrointestinal ulcer disease within 6 months, or current symptomatic or recent (within 3 months of dosing) gastrointestinal disease and gastrointestinal bleeding.
h) History of Gilbert's Syndrome.
i) Any major surgery within 4 weeks of dosing, or planned within 2 weeks after completion of the study.
j) Any gastrointestinal surgery that could impact upon the absorption of study treatment.
k) Donation of blood to a blood bank or in a clinical study (except a screening visit or follow-up visit) within 4 weeks of study treatment administration (within 2 weeks for plasma only).
l) Blood transfusion within 4 weeks of study treatment administration.
m) Inability to tolerate oral medication.
n) Inability to be venipunctured and/or tolerate venous access.
o) Use of tobacco- or nicotine-containing products (including, but not limited to, cigarettes, pipes, cigars, chewing tobacco, nicotine patches, nicotine lozenges, or nicotine gum) within 6 months prior to study treatment administration.
p) Recent (within 6 months of study treatment administration) drug or alcohol abuse as defined in Diagnostic and Statistical Manual for Mental Disorders (DSM) IV, Diagnostic Criteria for Drug and Alcohol Abuse (Appendix 5).
q) History or evidence of abnormal bleeding or coagulation disorders, hypermenorrhea, intracranial hemorrhage, or abnormal bleeding or coagulation disorders. This includes a family history of bleeding diathesis in a first degree relative (eg, hemophilia).
r) History of head injury in the last 2 years, intracranial tumor or aneurysm or known abdominal aneurysm, hemorrhoids with rectal bleeding.

s) Any other sound medical, psychiatric and/or social reason as determined by the investigator.

2) Prior/Concomitant Therapy

a) Inability to comply with restrictions and prohibited treatments as listed in Section 7.7.1.

3) Physical and Laboratory Test Findings

a) Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination, vital signs, 12-lead ECG, or clinical laboratory determinations beyond what is consistent with the target population. See Section 6.4.1 for retesting information.

b) Sitting blood pressure: systolic blood pressure < 90 mmHg or > 140 mmHg or diastolic blood pressure < 50 mmHg or > 90 mmHg, confirmed by repeat.

c) Any of the following on 12-lead ECG prior to study treatment administration, confirmed by repeat:

i) Heart rate < 50 beats per minute on both 12-lead ECG and while measuring vital signs

ii) PR ≥ 210 msec

iii) QRS ≥ 120 msec

iv) QT ≥ 500 msec

v) Fridericia's corrected QT interval (QTcF) ≥ 450 msec

d) Any of the following clinical laboratory test results outside of the ranges specified below prior to study treatment administration, confirmed by repeat:

i) Platelet count < lower limit of normal (LLN)

ii) Activated partial thromboplastin time (aPTT) > upper limit of normal (ULN)

iii) Prothrombin time (PT) > ULN

iv) International normalized ratio (INR) > ULN

v) Alanine aminotransferase (ALT) > ULN

vi) Aspartate aminotransferase (AST) > ULN

vii) Total bilirubin > ULN

viii) Serum creatinine ≥ 1.5 mg/dL

ix) Hemoglobin < lower limit of normal (LLN)

x) Hematocrit < LLN

xi) Creatine kinase > 4 times the ULN

xii) Uric acid > ULN

e) Positive urine screen for drugs of abuse including cotinine and alcohol.

f) Positive blood screen for hepatitis C antibody, hepatitis B surface antigen, or human immunodeficiency virus (HIV)-1 and -2 antibody.

4) Allergies and Adverse Drug Reaction

a) History of allergy to apixaban, FXa inhibitors, or related compounds.

b) History of any significant drug allergy (such as anaphylaxis or hepatotoxicity).

c) History of any adverse reaction to anticoagulants or antiplatelet agents that resulted in excessive bleeding requiring medication intervention.

5) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: under certain specific circumstances a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply and Bristol-Myers Squibb (BMS) approval is required.

b) Participants who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

c) Inability to comply with restrictions and prohibited activities/treatments as listed in Section 6.3.

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

6.3 Lifestyle Restrictions

6.3.1 Meals and Dietary Restrictions

1) Participants are not permitted to consume any food or beverages containing grapefruit or other citrus fruit or citrus juice from 3 days prior to Day -1 through the duration of the study.
2) Participants may not drink water 1 hour before and after study treatment administration except with dosing. Water may be consumed ad libitum at other times.
3) Participants are required to fast (nothing to eat or drink except water) for 8 hours prior to and until 4 hours after study treatment administration on Days 1 and 5.
4) On dosing days, a standard lunch will be served approximately 4 hours postdose. A standard dinner will be served approximately 8 hours postdose. A standard light snack will be served approximately 12 hours postdose. Meal content must be identical on Days 1 and 5.
5) On days other than dosing, a standard breakfast, lunch, dinner, and light snack will be served. The food content of meals may vary during the washout period.

6.3.2 Caffeine, Alcohol and Tobacco

1) Participants are not permitted to consume caffeine-containing beverages from 3 days prior to the first dose until study discharge.
2) Participants are not permitted to consume alcohol-containing beverages from 3 days prior to the first dose until study discharge.
3) Tobacco or nicotine-containing products are not permitted throughout the study (see Section 6.2 Medical Conditions).

6.3.3 Activity

1) Participants are to refrain from strenuous exercise, contact sports, and sunbathing from at least 3 day(s) prior to the first dose until study discharge.
2) Participants are required to remain in the clinical facility from Day -1 until study discharge.

3) Participants should maintain an upright (seated or standing) position for at least 4 hours postdose on Days 1 and 5. Participants should remain under direct observation by study staff during these times.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any serious AEs (SAEs).

6.4.1 Retesting During Screening or Lead-In Period

Participant Re-enrollment: This study permits the re-enrollment of a participant who has discontinued the study as a pretreatment failure (ie, participant has not been randomized/has not been treated). If re-enrolled, the participant must be re-consented.

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

The most current result prior to randomization is the value by which study inclusion will be assessed, as it represents the participant's most current clinical state.

Laboratory parameters and/or assessments that are included in Table 2-1, Screening Procedural Outline may be repeated in an effort to find all possible well-qualified participants. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

7 TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo or medical device intended to be administered to a study participant according to the study randomization or treatment allocation.

- Apixaban, 2.5 mg (5 × 0.5-mg tablets) (Investigational Product [IP])
- Apixaban, 2.5 mg (25 × 0.1-mg sprinkle capsules) (IP)

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

- All products, active or placebo, being tested or used as a comparator in a clinical trial
- Study required premedication
- Other drugs administered as part of the study that are critical to claims of efficacy (eg, background therapy, rescue medications)
- Diagnostic agents: (such as glucose for glucose challenge) given as part of the protocol requirements must also be included in the dosing data collection

An IP, also known as IMP 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.

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-IPs.

Table 7-1: Study treatments for CV185687

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging/Appearance	Storage Conditions (per label)
Apixaban (BMS-562247) Film-Coated Tablet	0.5 mg	IP	Open label	Tablets in a bottle	Refer to label on container
Apixaban (BMS-562247) Sprinkle Capsule	0.1 mg	IP	Open label	Capsules in a bottle	Refer to label on container

Note: Procedures for preparation and administration of the apixaban 0.5-mg tablet and 0.1-mg sprinkle capsule dosages will be provided in the pharmacy manual.

7.1 Treatments Administered

The selection and timing of dose for each participant is as follows:

Table 7.1-1: Selection and Timing of Dose

Study Treatment	Unit Dose Strength(s)/Dosage Level(s)	Dosage Formulation Frequency of Administration	Route of Administration
Apixaban 0.5-mg tablets (Treatment A)	5 × 0.5 mg	Single dose on Day 1 or Day 5	Oral
Apixaban 0.1-mg sprinkle capsules (Treatment B)	25 × 0.1 mg	Single dose on Day 1 or Day 5	Oral

In the morning on Days 1 and 5, each participant will receive a single oral dose of apixaban after fasting for at least 8 hours. Participants will fast for at least 4 hours after study treatment administration on Days 1 and 5.

Treatment A will be administered as 5 × 0.5-mg apixaban tablets; the tablets will be dissolved in water, and the entire apixaban solution must be consumed. Procedures for preparation and administration of the 5 × 0.5-mg apixaban tablets will be provided in the pharmacy manual.

Treatment B will be administered as 25 × 0.1-mg apixaban sprinkle capsules; the capsules will be opened and contents will be emptied into water, and the entire apixaban solution must be consumed. Procedures for preparation and administration of the 25 × 0.1-mg apixaban sprinkle capsules will be provided in the pharmacy manual.

Treatments A and B will be prepared in the pharmacy. Preparation and administration should occur within the established stability window. Additional details are available in the pharmacy manual.

The time of dose administration will be called “0” hour.

Restrictions related to food and fluid intake are described in Section 6.3.

7.2 Method of Treatment Assignment

Participants will be randomized in a 1:1 ratio to 1 of 2 treatment sequences according to a computer-generated randomization scheme prepared by PPD.

Study treatment will be dispensed at the study visits as listed in Schedule of Activities (Section 2).

Enrolled participants, including those not dosed, will be assigned sequential participant numbers starting with 00001, (eg, 00001, 00002, 00003.... 00010). Those enrolled participants meeting inclusion and exclusion criteria will be eligible to be randomized. Randomization numbers will be assigned prior to dosing.

Participants will not be replaced if they are discontinued from the study secondary to an AE unless the AE can be determined to be unrelated to treatment. The Sponsor (or designee) may replace

participants for other reasons. If a participant is replaced after dosing then the replacement participant will be assigned the original participant's number plus 100. The replacement participant will receive the same treatments as the participant being replaced but a new randomization number will be assigned to him or her. For example, Participant 4 would be replaced by Participant 104.

7.3 Blinding

This is an open-label study, blinding procedures are not applicable.

7.4 Dosage Modification

Modifications of the dosage schedule may not be made without a written amendment to the protocol.

7.5 Preparation/Handling/Storage/Accountability

The IP should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that IP is only dispensed to study participants. The IP must be dispensed only from official study sites by authorized personnel according to local regulations.

The product storage manager should ensure that the study treatment 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 treatment arise, the study treatment should not be dispensed and contact BMS immediately.

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

Investigational product documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

Further guidance and information for final disposition of unused study treatment are provided in Appendix 2 and as specified by the study team.

7.5.1 Retained Samples for Bioavailability / Bioequivalence

Not applicable.

7.6 Treatment Compliance

Study drug will be administered in the clinical facility. After administration of apixaban, including rinses if applicable, an examination of the oral cavity is required to verify that a participant has swallowed the entire apixaban solution. A mouth check should be performed after the final amount of apixaban solution has been taken. The participant should drink the entire apixaban solution (Treatment A or B) including any rinses as appropriate.

[redacted]

7.8 Treatment After the End of the Study

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

8 DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

Participants MUST discontinue IP (and non-IP at the discretion of the investigator) for any of the following reasons:

- Participant's request to stop study treatment. Participants who request to discontinue study treatment 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 participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information
- Any clinical 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 participant
- Termination of the study by 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. (Note: Under specific circumstances, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply and BMS approval is required.)
- Inability to comply with protocol
- Discretion of the investigator

Discontinuation of the study treatment for abnormal liver tests should be considered by the investigator when a participant meets one of the conditions outlined in Section 9.2.7, or if the investigator believes that it is in best interest of the participant.

Refer to the Schedule of Activities for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed (Section 2).

In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. In the event a normal healthy female participant becomes pregnant during a clinical trial, the study treatment must be discontinued immediately. In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

All participants who discontinue study treatment should comply with protocol specified follow-up procedures as outlined in Section 2. The only exception to this requirement is when a participant 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 treatment is discontinued prior to the participant's completion of the study, the reason for the discontinuation must be documented in the participant's medical records and entered on the appropriate CRF page.

8.1.1 Post Study Treatment Study Follow-up

Participants who discontinue study treatment may continue to be followed.

8.2 Discontinuation from the Study

Participants who request to discontinue study treatment 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 participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.

- Participants 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 treatment 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 participant 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.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.3 Lost to Follow-Up

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of **three** documented phone calls, faxes, or emails as well as lack of response by participant to one registered mail letter. All attempts should be documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain 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 participant's informed consent, then the investigator may use a Sponsor retained third-party representative to assist site staff with obtaining participant'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 participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities (Section 2).
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities.

9.1 Efficacy Assessments

Not applicable.

9.2 Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue before completing the study.

Contacts for SAE reporting specified in Appendix 3

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

The collection of nonserious AE information should begin at initiation of study treatment until the time points specified in the Schedule of Activities (Section 2). Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the participants.

Sections 5.6.1 and 5.6.2 in the IB represent the Reference Safety Information to determine expectedness of SAEs for expedited reporting. Following the participant'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 must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the CRF section.
- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in Appendix 3.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of this being available.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor.

The method of evaluating, and assessing causality of AEs and SAEs and the procedures for completing and reporting/transmitting SAE reports are provided in Appendix 3.

9.2.2 Method of Detecting AEs and SAEs

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. Care should be taken not to introduce bias when collecting AE and/or SAEs. Inquiry about specific AEs should be guided by clinical judgement in the context of known AEs, when appropriate for the program or protocol.

9.2.3 Follow-up of AEs and SAEs

- Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Appendix 3).
- Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study treatment and for those 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.

All SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3).

Further information on follow-up procedures is given in Appendix 3.

9.2.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a product under clinical investigation are met.
- An investigator who receives an investigator safety report describing SAEs or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the IB and will notify the Institutional Review Board/Independent Ethics Committee, if appropriate according to local requirements.

Sponsor or designee will be reporting AEs to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and US Food and Drug Administration (FDA) Title 21 of the Code of Federal Regulations, Parts 312 and 320. A SUSAR (Suspected, Unexpected Serious Adverse Reaction) is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

9.2.5 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant 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 Appendix 3.

In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy.

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 Sponsor or designee. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

9.2.6 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form electronic, as appropriate. Paper forms are only intended as a back-up option when the electronic system is not functioning.

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

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).

9.2.7 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 drug-induced liver injury (DILI) event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 9.2 and Appendix 3 for reporting details).

Potential DILI is defined as:

1) Aminotransaminases (ALT or AST) elevation > 3 times 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 aminotransaminases 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.

9.2.8 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, 12-lead ECGs, 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.

9.3 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 9.2).

For this study, any dose of apixaban greater than 2.5 mg within a 24-hour time period will be considered an overdose.

9.4 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities (Section 2).

Only data for the procedures and assessments specified in this protocol should be submitted to BMS or designee on a CRF. Additional procedures and assessments may be performed as part of standard of care; however, data for these assessments should remain in the participant's medical record and should not be provided to BMS, unless specifically requested by BMS.

9.4.1 Physical Examinations

Refer to Schedule of Activities (Section 2).

9.4.1.1 Rash Photography

Starting on Day -1, standard baseline medical dermatology photographs of areas affected by rash will be taken. If there are any changes with the affected areas or new areas of rash are detected, additional photographs will be obtained. Photographs will not be needed if there is no evidence of rash or no change in the affected areas.

9.4.2 Vital Signs

Refer to Schedule of Activities (Section 2).

9.4.3 Electrocardiograms

Refer to Schedule of Activities (Section 2).

9.4.4 Clinical Safety Laboratory Assessments

Investigators must document their review of each laboratory safety report.

A local laboratory will perform the analyses and will provide reference ranges for these tests.

Results of clinical laboratory tests performed on Day -1 and Day 4 must be available prior to dosing on Days 1 and 5, respectively.

Hematology	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Coagulation (at screening, Day -1, Day 4, and Day 7)	
aPTT	
INR	
PT	
Serum Chemistry	
AST ALT Total bilirubin Direct bilirubin (reflex if elevated total bilirubin) Alkaline phosphatase Lactate dehydrogenase Creatinine Blood Urea Nitrogen Uric acid (screening only) Fasting glucose	Total Protein Albumin Sodium Potassium Chloride Calcium Phosphorus Creatine kinase (screening only)
Urinalysis	
Protein	
Glucose	
Blood	
Leukocyte esterase	
Specific gravity	
pH	
Microscopic examination of the sediment if blood is detected on the initial analysis	
Serology	
Serum hepatitis C antibody, hepatitis B surface antigen, HIV-1 or -2 antibody (screening only)	
Other Analyses	
Urine for drugs of abuse including cotinine and alcohol (screening and Day -1)	
Serum pregnancy test (women only: at screening, Day -1, Day 4, and Day 7)	
Serum follicle-stimulating hormone (postmenopausal women only; screening)	

9.4.5 Suicidal Risk Monitoring

Not applicable.

9.4.6 Imaging Safety Assessment

Not applicable.

9.4.7 Physical Measurements

Refer to Schedule of Activities (Section 2).

9.4.8 Medical History

Refer to Schedule of Activities (Section 2).

9.4.9 Adverse Event Monitoring

Participants will be closely monitored throughout the study for AEs and will not be discharged from the study until the investigator has determined that AEs have either completely resolved or are not of clinical significance.

9.5 Pharmacokinetics

Pharmacokinetics of apixaban will be derived from plasma concentration versus time. The PK parameters to be assessed include the following to the extent that data permit their calculation:

Cmax	Maximum observed plasma concentration
Tmax	Time of maximum observed plasma concentration
AUC(0-T)	Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration
AUC(INF)	Area under the plasma concentration-time curve from time zero extrapolated to infinite time
T-HALF	Terminal plasma half-life
Frel	Relative bioavailability

Individual participant PK parameter values will be derived by noncompartmental methods by a validated PK analysis program. Actual times will be used for the analyses. Table 9.5-1 lists the sampling schedule to be followed for the assessment of apixaban PK. Further details of blood collection and processing will be provided to the site in the procedure manual.

Table 9.5-1: Pharmacokinetic Sampling Schedule

Study Day of Sample Collection	Event	Time (Relative To Dosing) Hour: Min	PK Blood Sample for Apixaban
1 and 5	predose	00:00	X
		00:15	X
		00:30	X
		01:00	X
		02:00	X
		03:00	X
		04:00	X
		05:00	X
		06:00	X
		09:00	X
		12:00	X
2 and 6		24:00	X
		36:00	X
3 and 7		48:00	X
		60:00	X
4 and 8		72:00	X

The plasma samples will be analyzed for apixaban by a validated liquid chromatography tandem mass spectrometry assay. The lower limit of quantification of apixaban is 1 ng/mL. In addition, plasma samples will be archived for potential metabolite analysis, if the need arises and to the extent possible.

The Study Director should be consulted before any requests for PK re-analysis.

Detailed instructions for the pharmacokinetic blood collection, labeling, processing, storage, and shipping will be provided to the site in the procedure manual.

9.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.7 Pharmacogenomics

Not applicable.

[redacted]

9.8.1 Additional Research Collection

This protocol will include residual sample storage for additional research.

Additional research is required for all study participants, except where prohibited by IRBs/ethics committees, or academic/institutional requirements. Where one or more of these exceptions occurs, participation in the additional research should be encouraged but will not be a condition of overall study participation.

- If the IRB/ethics committees and site agree to the mandatory additional research retention and/or collection, then the study participant must agree to the mandatory additional research as a requirement for inclusion in the study.
- If optional participation is permitted and approved, then the study participants may opt out of the additional research retention and/or collection.

This collection for additional research is intended to expand the translational R&D capability at BMS, and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. It may also be used to support health authority requests for analysis, and advancement of pharmacodiagnostic development to better target drugs to the right patients. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression and response to treatment etc.

Sample Collection and Storage

All requests for access to samples or data for additional research will be vetted through a diverse committee of the study Sponsor's senior leaders in Research and Development (or designee) to ensure the research supports appropriate and well-defined scientific research activities.

Residual plasma from PK collections (Table 9.8.1-1) will also be retained for additional research purposes.

[redacted]

The manager of these samples will ensure they are properly used throughout their usable life and will destroy the samples at the end of the scheduled storage period, no longer than fifteen (15) years after the end of the study or the maximum allowed by applicable law.

Transfers of samples by research Sponsor to third parties will be subject to the recipient's agreement to establish similar storage procedures.

[redacted]

Further details of sample collection and processing will be provided to the site in the procedure manual.

Table 9.8.1-1: Residual Sample Retention for Additional Research Schedule

Sample Type	Time points for which residual samples will be retained
Plasma PK	All

[redacted]

9.9 Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters will not be evaluated in this study.

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

The similarity of the bioavailability will be concluded if the 90% confidence interval (CI) for the ratio of geometric means of apixaban 0.1-mg sprinkle capsules relative to apixaban 0.5-mg tablets are wholly contained within 80% and 125% for Cmax and AUC. The following table shows the power provided with data from 28 PK evaluable participants based on different assumptions of difference between the bioavailability of apixaban 0.1-mg sprinkle capsules and apixaban 0.5-mg tablets.

True Geometric Mean Ratio	Power of Cmax	Power of AUC(0-T)	Power of AUC(INF)	Overall Power
1	99%	99%	99%	97%
1.02	99%	99%	99%	97%
1.04	98%	99%	99%	96%
1.06	96%	99%	99%	94%
1.08	91%	99%	99%	89%
1.1	83%	99%	99%	81%

As an example, if there is a 10% difference between the bioavailability of apixaban 0.1-mg sprinkle capsules and apixaban 0.5-mg tablets, then data from 28 PK evaluable participants will provide approximately 83%, 99%, and 99% power to conclude similar bioavailability for Cmax, AUC(INF), and AUC(0-T), respectively. The overall power for this hypothesis is approximately 81%.

These calculations use the approach described by Diletti et al.[6] and assume Cmax and AUC are log normally distributed with intra-subject coefficient of variation (CV%) of 18% for Cmax and

12% for AUC, as estimated from apixaban Study CV185111[4] and Study CV185292[7]. To allow for possible dropouts, a total of 30 participants are planned to be randomized to obtain at least 28 PK-evaluable participants.

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who signed the informed consent
Randomized	All participants who are randomized to a sequence of treatments.
Treated	All participants who received at least 1 dose of study treatment. This population will be used for the safety analyses.
Pharmacokinetic	All participants who received at least 1 dose of study treatment and had any available concentration-time data. Pharmacokinetic listings and PK parameter calculations will be based on this population.
Evaluable PK	All participants who had adequate PK profiles for accurate estimation of PK parameters and had no protocol deviations considered to affect the PK assessments. All available derived PK parameter values will be included in the PK data set and reported, but only participants with evaluable PK will be included in the summary statistics and statistical analysis.

10.3 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will describe the selection of participants to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. Below is a summary of planned statistical analyses.

10.3.1 Demographics and Baseline Characteristics

Frequency distribution of gender, ethnicity, and race will be tabulated. Summary statistics for age, body weight, height, and BMI will be tabulated.

10.3.2 Efficacy Analyses

Not applicable.

10.3.3 Safety Analyses

Endpoint	Statistical Analysis Methods
The occurrence of nonserious AEs, SAEs, AEs leading to discontinuation or death; results of clinical laboratory tests, vital sign measurements, 12-lead ECGs, and physical examinations; and marked abnormalities in clinical laboratory test results	All recorded AEs will be listed and tabulated by system organ class, preferred term, and treatment. Adverse events which occur on or after the first dose of study treatment, within 3 days after the last dose of study treatment for nonserious AEs, and 30 days after the last dose of study treatment for SAEs will be included in summary statistics. Adverse events leading to discontinuation or death will be listed. Vital sign measurements, 12-lead ECGs, and clinical laboratory test results will be listed. Any abnormal physical examination findings will be listed. The number and percentage of participants with marked clinical laboratory abnormalities will be summarized. Electrocardiogram recordings will be evaluated by the investigator and abnormalities, if present, will be listed.

10.3.4 Pharmacokinetic Analyses

Endpoint	Statistical Analysis Methods
Cmax, AUC(INF), and AUC(0-T)	Analyses will be performed on the natural logarithms of Cmax, AUC(INF), and AUC(0-T) using linear mixed-effects model with treatment and period as fixed effects and measurements within participant as repeated measures. Point estimates and 90% CIs for treatment differences on the log scale derived from the model will be exponentiated to obtain estimates for ratios of geometric means and CIs on the original scale. Summary statistics will be tabulated for all PK parameters by treatment. Geometric means and coefficient of variations will be presented for Cmax, AUC(INF), and AUC(0-T). Individual treatment ratios for PK parameters will be provided in listings and summarized. Plots of individual ratios, geometric least square mean ratios, and corresponding 90% CIs from the statistical analysis model will also be provided. In addition, the geometric mean ratios and corresponding 90% CIs of Cmax, AUC(INF), and AUC(0-T) will be presented in forest plots.
Tmax, T-HALF, and Frel	Summary statistics will be tabulated for all PK parameters by treatment. Arithmetic mean and standard deviation will be presented for T-HALF; median and range will be presented for Tmax. Individual Tmax differences will be provided in listings and summarized. Geometric means and coefficient of variations will be presented for Frel.

10.3.5 Interim Analyses

Not applicable.

12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC(INF)	area under the plasma concentration-time curve from time zero extrapolated to infinite time
AUC(0-T)	area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration
BID	twice daily
BMI	body mass index
BMS	Bristol-Myers Squibb
CI	confidence interval
Cmax	maximum observed plasma concentration
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form, paper or electronic
DILI	drug-induced liver injury
DSM IV	Diagnostic and Statistical Manual of Mental Disorders (4^{th} Edition)
ECG	electrocardiogram
F	bioavailability
FDA	US Food and Drug Administration
Frel	relative bioavailability
FXa	Factor Xa
HIV	human immunodeficiency virus
IB	Investigator Brochure
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
LLN	lower limit of normal
PK	pharmacokinetics

Term	Definition
PT	prothrombin time
SAE	serious adverse event
T-HALF	terminal plasma half-life
Tmax	time of maximum observed plasma concentration
ULN	upper limit of normal
WOCBP	women of childbearing potential

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

The term 'Participant' is used in the protocol to refer to a person who has consented to participate in the clinical research study. The term 'Subject' used in the eCRF is intended to refer to a person (Participant) who has consented to participate in the clinical research study.

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines Good Clinical Practice (GCP)
- as defined by the International Council for Harmonisation (ICH)
- in accordance with the ethical principles underlying European Union Directive 2001/20/EC
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- applicable local requirements

The study will be conducted in compliance with the protocol. The protocol and any amendments and the participant informed consent will receive approval/favorable opinion by Institutional Review Board/Independent Ethics Committee (IRB/IEC), and regulatory authorities according to applicable local regulations prior to initiation of the study.

All potential serious breaches must be reported to Sponsor or designee 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).

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, participant 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, Sponsor or designee 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.

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and if applicable, also by local health authority) 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 relevant approval/favorable opinion(s) the deviation or change will be submitted, as soon as possible to:

- IRB/IEC
- Regulatory Authority(ies), if applicable by local regulations (per national requirements)

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and if applicable, also by local health authority must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the participant: (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).

FINANCIAL DISCLOSURE

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

INFORMED CONSENT PROCESS

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 participant volunteers to participate.

Sponsor or designee 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:

- Provide a copy of the consent form and written information about the study in the language in which the participant is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
- Allow time necessary for participant or participant's legally acceptable representative to inquire about the details of the study.
- Obtain an informed consent signed and personally dated by the participant or the participant's legally acceptable representative and by the person who conducted the informed consent discussion.
- 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.

If informed consent is initially given by a participant's legally acceptable representative or legal guardian, and the participant subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the participant.

Revise the informed consent whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant or the participant's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the participant'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 participant records.

For minors, according to local legislation, one or both parents or a legally acceptable representative must be informed of the study procedures and must sign the informed consent form approved for the study prior to clinical study participation. The explicit wish of a minor, 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.

Minors who are judged to be of an age of reason must also give their written assent.

Subjects unable to give their written consent (eg, stroke or subjects with or severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The participant must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this participant become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a participant who is unable to give his or her written consent, but who is capable of forming an opinion and assessing 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.

SOURCE DOCUMENTS

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.

STUDY TREATMENT RECORDS

Records for study treatments (whether supplied by BMS, its vendors, or the site) must substantiate study treatment 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 participant, including unique participant 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.
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 treatment integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy.

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

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 Sponsor or designee 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 electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by Sponsor or designee.

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, 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. Subinvestigators in Japan may not be delegated the CRF approval task. 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 Sponsor or designee training requirements and must only access the BMS electronic data capture tool using the unique user account provided by Sponsor or designee. User accounts are not to be shared or reassigned to other individuals.

MONITORING

Sponsor or designee 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. Certain CRF pages and/or electronic files may serve as the source documents.

In addition, the study may be evaluated by Sponsor or designee 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 Sponsor or designee.

RECORDS RETENTION

The investigator (or head of the study site in Japan) 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 or designee, whichever is longer. The

investigator (or head of the study site in Japan) must contact BMS prior to destroying any records associated with the study.

BMS or designee will notify the investigator (or head of the study site in Japan) 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, study site, IRB). Notice of such transfer will be given in writing to BMS or designee.

RETURN OF STUDY TREATMENT

For this study, study treatments (those supplied by BMS, a vendor, or sourced by the investigator) such as partially used study treatment containers, vials, and syringes may be destroyed on site.

If	Then
Study treatments supplied by BMS (including its vendors	Any unused study treatments supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics). If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors) (examples include study treatments sourced from the site's 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 study treatments provided by BMS (or its vendors). Destruction of non-study treatments sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designee.

CLINICAL STUDY REPORT AND PUBLICATIONS

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

For this single site protocol, the Principal Investigator for the site will sign the clinical study report.

The data collected during this study are confidential and proprietary to Sponsor or designee. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTAg) governing [Study site or Investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to Sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTAg.

APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

ADVERSE EVENTS

Adverse Event Definition:
An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study treatment 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 treatment, whether or not considered related to the study treatment.

SERIOUS ADVERSE EVENTS

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening (defined as an event in which the participant 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) 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)
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 participant 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 9.2.7 for the definition of potential DILI.)

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study treatment 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 9.2.5 for reporting pregnancies).

EVALUATING AES AND SAES

Assessment of Causality
The causal relationship to study treatment 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 treatment administration and the AE. Not related: There is not a reasonable causal relationship between study treatment administration and the AE. The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Follow-up of AEs and SAEs
If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same investigator term(s) initially reported.) If an ongoing SAE changes in its intensity or relationship to study treatment or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report. All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study treatment, 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 must be recorded 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. In the event the electronic system is unavailable for transmission, paper forms must be used and submitted immediately. 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.**

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state 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 > 40 mIU/mL to confirm menopause.

Note: 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.

- 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. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal.

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILDBEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 5 weeks (33 days) after the end of study treatment, plus 30 days.

Local laws and regulations may require use of alternative and/or additional contraception methods.

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b] • Intrauterine device (IUD)[c] • Intrauterine hormone-releasing system (IUS)[c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence

NOTES:

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.

[c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Less Than Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of >1% per year when used consistently and correctly.*
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal Sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal(coitus interruptus) • Spermicide only • Lactation amenorrhea method (LAM)

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILDBEARING POTENTIAL

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until the end of relevant systemic exposure defined as 93 days after the end of treatment in the male participant.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 93 days after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 93 days after the end of treatment.

- Refrain from donating sperm for the duration of the study treatment and for 93 days after the end of treatment.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.5 and the Appendix for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting

APPENDIX 5 DIAGNOSTIC CRITERIA FOR DRUG AND ALCOHOL ABUSE

The following is taken from DSM-IV:

Diagnostic Criteria for Psychoactive Substance Dependence

A maladaptive pattern of substance use, leading to clinically significant impairment or distress as manifested by 3 (or more) of the following, occurring at any time in the same 12-month period:

1. Tolerance, as defined by either of the following:
   a) A need for markedly increased amounts of the substance to achieve intoxication or desired effect,
   b) Markedly diminished effect with continued use of the same amount of the substance.
2. Withdrawal, as manifested by either of the following:
   a) The characteristic withdrawal syndrome for the substance,
   b) The same (or closely related) substance is taken to relieve or avoid withdrawal symptoms.
3. The substance is often taken in larger amounts or over a longer period than was intended.
4. There is a persistent desire or unsuccessful efforts to cut down or control substance use.
5. A great deal of time is spent in activities necessary to obtain the substance (eg, visiting multiple doctors or driving long distances), use the substance (eg, chain-smoking) or recover from its effects.
6. Important social, occupational or recreational activities are given up or reduced because of substance use.
7. The substance use is continued despite knowledge of having a persistent or recurring physical or psychological problem that is likely to have been caused or exacerbated by the substance (eg, current cocaine use despite recognition of cocaine-induced depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption.)

Criteria for Severity of Psychoactive Substance Dependence

Mild: Few, if any, symptoms in excess of those required to make the diagnosis, and the symptoms result in no more than mild impairment in occupational functioning or in usual social activities or relationships with others.

Moderate: Symptoms or functional impairment between “mild” and “severe”.

Severe: Many symptoms in excess of those required to make the diagnosis, and the symptoms markedly interfere with occupational functioning or with usual social activities or relationships with others.

In Partial Remission: During the past 6 months, some use of the substance and some symptoms of dependence.

In Full Remission: During the past 6 months, either no use of the substance, or use of the substance and no symptoms of dependence.

Diagnostic Criteria for Psychoactive Substance Abuse

A. A maladaptive pattern of psychoactive substance use, leading to clinically significant impairment or distress as manifested by 1 (or more) of the following, occurring at any time in the same 12-month period:

   1. Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (eg, repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school, neglect of children or household).
   2. Recurrent substance use in situations in which it is physically hazardous (eg, driving an automobile or operating a machine when impaired by substance use).
   3. Recurrent substance-related legal problems (eg, arrests for substance-related disorderly conduct).
   4. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (eg, arguments with spouse about consequences of intoxication, physical fights).

B. The symptoms have never met the criteria for substance dependence for this class of substance.